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Editorial

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Should We Report Unusual Presentations of Malignancies?

When a dog bites a man it is not news; but if a man bites a dog it is news. Cancer usually has a well defined presentation and metastatic path but sometimes cancer can have unusual presenting features leading to delay in diagnosis and treatment.

Whenever we read or see anything it leaves an impression on our mind which stores it for future reference. Reading about such unusual cases opens our minds to think beyond the obvious. Such reports also tell us about the prognosis and treatment approach of these unusual cases.

When do we call it an unusual presentation of cancer?

Different age of presentation

There are geographic and racial variations of presentations of certain cancers such as CML presents at least one decade early in India, but besides this certain cancers may present at an unusual age.

Prostate cancer a disease of elderly males has also been reported three decades early in men between 35-50 years of age and Joachim Weischenfeldt, et al have found that these young onset prostate cancer appear to be specifically triggered by androgens and involve genetic alterations that differentiate them from prostate cancer developing in the older men.¹ Gabe Canales, a public relations executive from Houston, Texas, after being diagnosed with prostate cancer at the age of 35, founded the Blue Cure Foundation, that promotes awareness for prostate cancer and their slogan is “not just an old man's cancer”. Many other malignancies may rarely present at an earlier age such as Myelodysplastic Syndrome or Colorectal Cancer developing in children. The reverse may also be seen, such as adult onset Wilm's tumour (3%) or Retinoblastoma which are primarily seen in children less than 5 years of age. In such cases the prognosis is different and the treatment is also not well established due to lack of meaningful clinical trials in such small number of patients.

Unusual presenting site of cancer leading to unusual presenting features

Malignancies presenting with paraneoplastic syndromes may have unusual presentations but rarely deviation from the usual presentation may be due to a

primary malignancy arising at an unusual site or an unusual metastasis which may be the presenting feature. Two examples of the former type are reported in this issue. Primary diffuse large B-cell lymphoma of the urinary bladder by Goyal et al, and oral teratoma with a yolk sac component: a case report by Ghadvi et al.^{2,3}

The usual histology of urinary bladder cancer is transitional cell carcinoma and less than 10% cases may have squamous cell cancer, adenocarcinoma, sarcoma or small cell carcinoma. Secondary bladder cancers are reported following treatment of NHL with cyclophosphamide and NHL may involve urinary bladder but primary lymphoma of the urinary bladder is a rare event.⁴ Wide use of FDG PET in combination with CT scan in staging NHL, many such cases may eventually be diagnosed as secondary involvement of urinary bladder with NHL.

Teratomas that are derived from embryonic cells may occur in the midline structures as well as in other organs such as liver and are usually benign. Among the oral teratomas, majority arise from nasopharynx and hard or soft palate, there are very reports of teratoma arising from cheek – buccal mucosa.^{5,6} But the teratoma reported by Ghadvi et al³ arose from the buccal mucosa and the recurrent nature suggested malignant transformation with presence of yolk sac element.

Unusual histologic subtype

Unusual histology also, sometimes makes diagnosis difficult. The difference in histology changes the prognosis as well the approach to treatment.

The case report by Parida et al highlights two unusual features.⁷ First, it is a rare histologic variant of diffuse large B cell lymphoma, T cell rich B cell lymphoma with <10% malignant B cells, which can be misdiagnosed as Hodgkin's disease or peripheral T cell lymphoma, but unlike them it is more aggressive and has worse prognosis. Second, is the unusual site of involvement i.e. thyroid; although TCRBCL are known to have predilection for unusual sites; involvement of the thyroid is rare.

Teratoid Wilm's Tumor is a rare histologic variant

of Wilm's Tumor which has also been reported to be associated with raised tumor markers such as Alpha Feto Protein.⁸ Teratoid Wilms' Tumor: An Unusual Variant of Nephroblastoma reported by Gohel et al⁹ is also such an example. The recommended treatment is surgery and advanced cases are difficult to treat because of relative resistance to chemotherapy and radiotherapy.

The Great Mimicker

Our knowledge is not based only on information gleaned from text books but it is a sum total of all the cases that we have seen or heard or read about over the years. Therefore teachers with more experience are those who have seen and treated more unusual cases. Based on these past experiences they may come up with unexpected but correct diagnosis. This is more relevant in India as we have a great mimicker - Tuberculosis.

When I look back at all the unusual diagnosis that I have seen, there are some that stand out in memory. A young girl with monocytic leukemoid reaction that was reported as acute myeloid leukemia and was cured with AKT (this was before the era of immunological diagnosis of leukemia when we relied mainly on morphology and cytochemistry). A 65 year old lady with bilateral cystic adenexal mass, CA 125 of 1000 U/ml and straw coloured ascitic fluid with inflammatory cells but also few cells reported as adenocarcinoma; who is now disease free at 7 years after being treated with AKT (She had refused any type of further intervention including biopsy).

These are very rarest of the rare, but having an inquisitive and open mind helps us in making the correct diagnosis. The era of Internet has flooded us with information and it has also made access to such reports easy, so we can enrich ourselves from the experiences of others. Hence, if we see anything unusual during our practice we should report it diligently and add to the ever growing medical literature and maybe the unusual will not remain unusual for long!

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Shri Madanmohan Ramanlal

GCRI Luminary Award 2012-2013

Dr Pankaj M Shah, MD,
 Vice President Gujarat Cancer Society (GCS)
 Advisor to Chairman, GCS
 Prof. Emeritus Medical Oncology, GCRI
 Trustee : Sadvichar Parivar
 Former Hon. Director, The Gujarat Cancer & Research Institute (GCRI)



Four Decades at GCRI - Sharing Joys and Dreams

(Commentary on oration)

The oration by Dr. Pankaj M. Shah, former Director, GCRI, Professor and head of department, Medical Oncology, currently special Advisor to Chairman, GCS and ever a teacher; was a nostalgic journey of development of GCRI spanning four decades. There were vintage photographs both from personal life as well from the early years of inception of GCRI. Most of the milestones were covered with pictorial evidence including Dr. Shah's joining order of 1st January 1973.

It started with paying tribute and offering gratitude to those who had helped in shaping his life and career - his parents, family, Dr. T.B. Patel (former Director, GCRI) and Shri Jitendra Mehta (who had given him 50 pounds and woolen clothes to go to Germany and UK for training in 1973).

Development of GCRI

Dr. Shah traced his career starting as a nuclear medicine physician. He went to Germany for training on chemotherapy in 1973. His career grew along with GCRI. The foundation stone of GCRI was laid in 1962 by H.E. Governor of Gujarat Shri Nawab Mehdi Nawaz Jung which became an autonomous Cancer Hospital in 1972. Initial facilities consisted of nuclear medicine, radiotherapy, surgical oncology and diagnostic facilities from 1965. Other departments were added later like gynaecological oncology in 1972 and medical oncology in 1973 under the leadership of Dr. Pankaj Shah (founder head). Other developments under the visionary leadership of Dr. Shah were development of pediatric oncology (1992) and bone marrow transplant unit (2002). GCRI also has an active and dynamic research division with state of the art facilities even for molecular research.

Academics and research

Dr. Shah was and will always be a teacher and an eternal student. When post graduate training in MD medicine and later DM medical oncology started at GCRI many senior physicians visited regularly to interact with the students and enrich them with their

knowledge. The most notable of them was Dr. Kinariwala who also brought bone marrow needles and lung biopsy needles when they were not freely available in India. The morning teaching sessions with post graduate students initiated by Dr. Shah have become a regular feature over the past 25 years. GCRI actively participates in GCS, National and International clinical trials that include reputable collaboration with NCI, US and INDOX (UK). GCRI was Headquarters of Indian Society of Medical and Paediatric Oncology (ISMPO) for 10 years. Dr. Shah has taken leadership in professional organizations-AMA, APA, APG, ISMPO, ISHBT and organized more than 20 conferences.

An Administrator/Leader/Entrepreneur

Since 1992 Dr. Shah joined the administration team. Dr. Shah received hospital management training from IIM Bangalore, Weston Park Hospital, Sheffield –British Council where Dr. Neil became a permanent friend.

Other feather in the cap of this dynamic director were the development of Community Oncology Center at Vasna which has cancer related health check -up and a permanent exhibition on cancer and Development of Madanmohan Ramanlal Urban health center. He always acknowledged his competent and supportive coworkers and gave them due credits.

Public acknowledgment of donors

Dr. Shah paid tribute to all the donors who made it possible for GCRI to reach its present status, a few memorable donors are: Ramniklal Kinariwala and Kinariwala family, Madanmohan Ramanlal family, Hitendra Desai, B. J. Medical College Allumini, USA, (40000\$), 90 years old lady from very poor back ground, Lalitchandra Dalal, Pranalal Bhogilal Dastan farm, Archan Trivedi, Akant, Arun, Dr. Hemendra - Help India and Pankajbhai Patel - are unmatched. His historic moment in life at the end of administrative services was signing MOU with Government of Gujarat for getting land for GCS Medical College.

Social/ Public service- cancer awareness and Anti Tobacco Campaign

GCRI also conducts various movements to increase awareness about causes of cancer (tobacco), stressing on early detection and curability of cancer. This was done during various festivals such as kites with anti tobacco messages during Utarayan, Rakhi with messages during Rakshabandhan, Greeting cards during Diwali festival, Tableaus during Independence and Republic Day parade. Organizing various functions like drawing competition, workshop on tobacco hazards (1st of it's kind was organized in 1998) and taking part in talk shows on radio and TV. Many celebrities were also invited to spread this message such as Shaktiman, Pooja Bhatt, Sonu Nigam, Gulzar, Kapil Dev, Parthiv Patel, Archan Trivedi, Aishwarya Majmudar. Organizing lectures in schools, colleges, institutions as a part of anti tobacco drive. Joining hands with various religious leaders and sects to increase awareness among their followers and arranging regular prayer meetings at GCRI (Sanskar Chowk). Publishing Gutka Samachar (newspaper), various booklets and humorous stories (Rang Vyang). Organizing various rallies at strategic places like railway stations.

Keeping pace with time & modern technology

Never a person to be left behind, Dr. Shah always encouraged keeping pace with modern technology. We were first to have our website in 1994 www.cancerindia.org. Telemedicine centre at GCRI was established for tumor boards, web conferences and telecasting workshops and conferences from other states. He dreamt of Computerization and a paperless office. GCRI joined hands with State Government. and actively participated in Vibrant Gujarat, with Indian Council of Medical Research, New Delhi for Cancer Atlas. He was instrumental in designing Health Passport and he actively promoted Health Cancer Insurance. He is actively involved in Comfort for care givers through a website called - Hoomfindia.org.

કેન્સર શું ના કરી શકે ?
આ રોગનું ના ગજુ એ કે,

પ્રેમને પંગુ કરે,
ના આશના મિનારા તોડી શકે,
ના શ્રદ્ધાને લૂણો લગાડી શકે,
શાંતિને હણવા એની હામ નહિ,
ના છીનવી શકે ચિરંતર મૈત્રીને,
મથુર સ્મૃતિ ભંડાર લૂંટી ના શકે,
ભીતરની ભવ્ય હિંમતને ન ચૂપ કરે,
આતમ પર ત્રાટકવાની ત્રેવડ નહિ,
ના શાશ્વત જીવને ખંડિત કરે,
આતમબળના કિલ્લાની તો ક્રંગરી ય ના
ખેરવી શકે,

- અજ્ઞાત સ્ત્રોત

Honours and awards:

- **Honoured with Dr. B.C. Roy Award** by the President of India, Her Excellency Smt. Pratibha Patil for valuable contribution in the field of Medical Education
- Presidential Address on Management of Acute Lymphoblastic Leukemia - Standard Risk, XXXIV Annual Conference of Indian Society of Hematology and Blood Transfusion and XVIII Annual Conference of Bombay Hematology Group December 17-19, 1993
- Role of Physicians in the Management of Cancer Patients, Association of Physicians of Gujarat, 16th Annual Conference, Jamnagar, Jan. 1995 (Nathubhai Patel and Rasiklal Shah Sarvajani Hospital)
- Community and Oncology - B.N.Mehta Oration Ahmedabad Medical Association 1996
- Economics of Cancer Care: Santosh Mitra Oration - Indian Society of Hematology and Blood transfusion-2000 Hyderabad
- Key note Address: Advances in chemotherapy of Solid Tumors - Indian Cooperative Group Meeting - Pune 12/July 2001
- Multiple Myeloma Indian Scene- J.B.Chatterjee Oration- Indian Society of Hematology and Blood Transfusion to be delivered at Calicut, 25th October 2002
- Role of Family Physician in Cancer Care- annual day oration Rajkot Cancer Society 2004
- Key Note Address - Head and Neck cancer - At Head and Neck Oncology Meet, Goraj, 2007
- Annual Oration at Indian Society of Medical and Pediatric Oncology biennial meeting-Patana 2008 Tobacco control Gujarat Efforts -
- Galaxy Oncology Annual Oration –New Delhi-Breast Cancer Systemic therapy from bench to bed - May 2010
- Presentation on GCRI : IndoAmerican group of oncologist meeting Chicago May 2010

*Cancer Can Not Do
Cancer is so limited-*

*It cannot cripple love
It cannot shatter hope
It cannot corrode faith
It cannot destroy peace
It cannot kill friendship
It cannot suppress memories
It cannot silence courage
It cannot invade the soul
It cannot steal eternal life
It cannot conquer the spirit*

- Source Unknown

Recent Trends in HIV Infections: A Review

Goswami Parijath N
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Department of Microbiology

Summary

Infection with HIV will lead to AIDS with different severity in different individuals, with rapid progression to long term of delay in progression. Any nations investment in HIV prevention has contributed to dramatic reductions in annual number of new cases. Over a period of more than thirty decades(1980-2013) there are a lot of changing trends in the prevalence of HIV, strategies of testing, variability of host immune response, exposure to microbial or environment co factors etc. This review focuses on the current trends of HIV infection and AIDS globally and nationally, epidemiology of the infection, laboratory markers, routine HIV testing and informed consent, revised recommendation for HIV testing and whether Consent is necessary in each case and HIV testing and results of GCRI.

Keywords : HIV, Revised strategy, WHO

HIV belong to a family of Retroviridae and sub-Family of Lentiviridae and Genus Lentivirus (Figure1). The epidemic has had a devastating impact on societies, economies and infrastructures. In countries most severely affected, life expectancy has been reduced by as much as 20 years. Young adults in their productive years are the most at-risk population. HIV and AIDS in Asia cause a greater loss of productivity than any other disease. There is drastic change in the progress of the disease , initially being epidemic and now pandemic over the period of years.

The purpose of this review was to know:

1. The current scenario of the HIV infections and AIDS around the world and in India.
2. To know whether there are any revised strategies for HIV testing.
3. Evolution of revised recommendations of HIV testing.
4. Prevalence of HIV infection in patients attending the GCRI for their treatment for cancers.

Global situation and trends¹

Since the beginning of the epidemic, almost 70 million people have been infected with the HIV virus and about 35 million people have died of AIDS. At the

end of 2011, Globally, 34.0 million [31.4-35.9 million] people were living with HIV . An estimated 0.8% of adults aged 15-49 years worldwide are living with HIV, although the burden of the epidemic continues to vary considerably between countries and regions. Sub-Saharan Africa remains most severely affected, with nearly 1 in every 20 adults (4.9%) living with HIV and accounting for 69% of the people living with HIV worldwide (Figure 2).

HIV/AIDS in India-Recent Study²

While the National AIDS Control Organisation estimated that 2.39 million people live with HIV /AIDS in India in 2008-09, a more recent investigation by the Million Death Study Collaborators in the British Medical Journal (2010) estimates the population to be between 1.4-1.6 million people.

The last decade has seen a 50% decline in the number of new HIV infections. According to more recent National AIDS Control Organisation data, India has demonstrated an overall reduction of 57 percent in estimated annual new HIV infections (among adult population) from 0.27 million in 2000 to 0.11 million in 2011, and the estimated number of people living with HIV was 2.08 million in 2011.

Epidemiology

Despite being home to the world's third-largest population suffering from HIV/AIDS (with South Africa and Nigeria having more), the AIDS prevalence rate in India is lower than in many other countries. In 2007, India's AIDS prevalence rate stood at approximately 0.30% the 89th highest in the world. The spread of HIV in India is primarily restricted to the southern and north eastern regions of the country and India has also been praised for its extensive anti-AIDS campaign. There are concerns about the role of intravenous drug use and prostitution in spreading

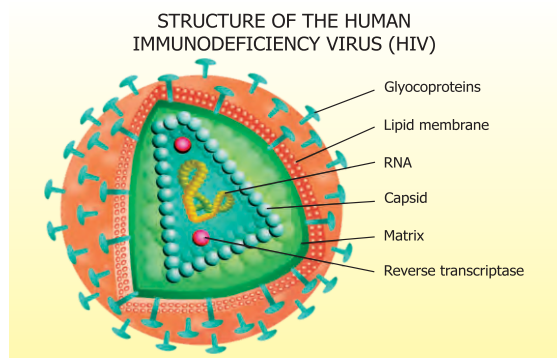


Figure 1: Structure of HIV

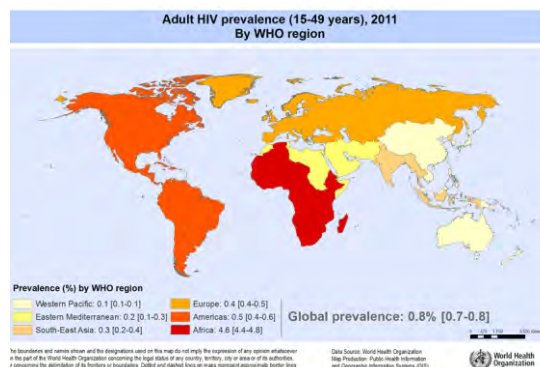


Figure 2: HIV prevalence 2011; WHO data

AIDS, especially in north east India and certain urban pockets.

The states with high HIV prevalence rates include Manipur (1.40%), Andhra Pradesh (0.90%), Mizoram (0.81%), Nagaland (0.78%), Karnataka (0.63%) and Maharashtra (0.55%).

The adult HIV prevalence in India is declining from estimated level of 0.41% in 2000 through 0.36% in 2006 to 0.31% in 2009. Adult HIV prevalence at a national level has declined notably in many states, but variations still exist across the states. A decreasing trend is also evident in HIV prevalence among the young population of 15–24 years. The estimated number of new annual HIV infections has declined by more than 50% over the past decade.

Routine HIV testing according to NACO^{3,4}

It is known that HIV/AIDS is not like other infectious diseases which is far more complex because HIV infection cannot be diagnosed clinically in asymptomatic individuals, is life long, outcome is invariably fatal and no cure or vaccine is so far available.

Since, commonly HIV/AIDS is acquired through sexual contact, individuals known to be HIV infected are stigmatized and discriminated. A number of moral, ethical, legal and psychosocial issues are related with a positive HIV status. So, anyone attempting to assess the HIV status of an individual must be conversant with these issues, strategies/ algorithms of HIV testing, protocols of testing, rationale of using test kits, correct method of informing the client, counselling, importance of confidentiality, technical and other pitfalls and quality assurance to name some.

Counselling should be undertaken to motivate the individual to tell the spouse/family and induce behaviour change

In only 50-93% of cases primary HIV infection is symptomatic with a variety of symptoms ranging from influenza-like or mononucleosis-like illness to more severe neurological symptoms which can persist from a few days to as long as two months.

Acute stage is followed by a long asymptomatic phase. Important point to understand is that laboratory diagnosis is the only method of determining the HIV infection status of an individual during the acute and the long asymptomatic period.

Purpose of HIV testing^{3,4}

Information is useful for prophylaxis, medical management and treatment of HIV and related illnesses.

- To assure blood safety and donation safety.
- To assess the efficacy of targeted intervention in a defined cohort.
- To monitor trends of epidemic (sentinel surveillance etc.).
- Identification of asymptomatic individuals

(practising high risk behaviour).

- To plan personal and family's future if the result is positive.
- To motivate for behaviour modification through counselling amongst those who test negative and who practise high risk behaviours.
- To induce behaviour change and prevent transmission by counselling in those who test positive.
- To diagnose clinically suspected cases.
- For peace of mind of individuals practising high risk behaviour.

Informed consent^{3,4}

HIV testing for the purpose of identification of an individual must always be undertaken after pre test counselling and informed consent. Testing without informed, written and explicit consent has proven to be counter productive and has driven the HIV positive individuals underground. This makes institution of prevention and intervention measures more difficult. Pre test counselling also empowers the individual to face the HIV test result.

Confidentiality^{3,4}

The confidentiality of the test result (both negative as well as positive) should be strictly maintained in all cases. This is to respect the privacy and rights of the individuals and to protect them from discrimination, victimization and stigmatization. The test result, name of the individual, etc. must never be discussed loosely. The test report must be placed in a sealed envelope and submitted to the clinician who requisitioned the test. The envelope should be marked "confidential". The records in the laboratory must also be kept secure to prevent access by unauthorised persons. The results are never communicated via telephones/fax/email etc.

Revised recommendations by CDC for HIV testing at health care settings - Why?^{5,6}

These recommendations for HIV testing are intended for all health-care providers in the public and private sectors. The recommendations address HIV testing in health-care settings only. They do not modify existing guidelines concerning HIV counselling, testing, and referral for persons at high risk for HIV who seek or receive HIV testing in nonclinical settings (e.g., community-based organizations, outreach settings, or mobile vans). The objectives of these recommendations are:

- to increase HIV screening of patients, including pregnant women, in health-care settings;
 - Foster earlier detection of HIV infection;
 - Identify and counsel persons with unrecognized HIV infection and link them to clinical and prevention services;
 - and further reduce perinatal transmission of HIV.
- These revised recommendations update previous

recommendations for HIV testing in health-care settings.^{5,6}

Major revisions from previously published guidelines are as follows:^{5,6}

Patients in all health-care settings

- HIV screening is recommended for patients in all health-care settings after the patient is notified that testing will be performed unless the patient declines (opt-out screening).
- Persons at high risk for HIV infection should be screened for HIV at least annually.
- Separate written consent for HIV testing should not be required; general consent for medical care should be considered sufficient to encompass consent for HIV testing.
- Prevention counseling should not be required with HIV diagnostic testing or as part of HIV screening programs in health-care settings.

Background of revised recommendation of HIV testing^{5,6}

Informed consent:

A process of communication between patient and provider through which an informed patient can choose whether to undergo HIV testing or decline to do so. Elements of informed consent typically include providing oral or written information regarding HIV, the risks and benefits of testing, the implications of HIV test results, how test results will be communicated, and the opportunity to ask questions.

Opt-out screening:

Performing HIV screening after notifying the patient that

- 1) the test will be performed and
- 2) the patient may elect to decline or refer testing.

Evolution of HIV testing revised recommendations in health-care settings^{5,6}

In 1985, when HIV testing first became available, the main goal of such testing was to protect the blood supply. No effective treatment existed, and counselling was designed in part to ensure that persons tested were aware that the meaning of positive test results was uncertain. During the next 2 years, the implications of positive HIV serology became evident, and in 1987, the United States Public Health Service issued guidelines making HIV counselling and testing a priority as a prevention strategy for persons most likely to be infected or who practiced high-risk behaviours and recommended routine testing of all persons seeking treatment for STDs, regardless of health-care setting. "Routine" was defined as a policy to provide these services to all clients after informing them that testing would be conducted.

In 1993, CDC recommendations for voluntary HIV counselling and testing were extended to include hospitalized patients and persons obtaining health

care as outpatients in acute-care hospital settings, including emergency departments. So, included basic information regarding the medical implications of the test, the option to receive more information, and documentation of informed consent.

In 1994, guidelines for counselling and testing persons with high-risk behaviours specified prevention counselling to develop specific prevention goals and strategies for each person (client-centered counselling).

In 2001, CDC modified the recommendations for pregnant women to emphasize HIV screening as a routine part of prenatal care, simplification of the testing process so pretest counselling would not pose a barrier, and flexibility of the consent process to allow multiple types of informed consent. CDC recommended that HIV testing be offered routinely to all patients in high HIV-prevalence health-care settings. In low prevalence settings, in which the majority of clients are at minimal risk, targeted HIV testing on the basis of risk screening was considered more feasible for identifying limited numbers of HIV-infected persons.

In 2003, CDC introduced the initiative of advancing HIV Prevention, developed new Strategies for a Changing Epidemic. Two key strategies of this initiative are:

- To make HIV testing a routine part of medical care on the same voluntary basis as their diagnostic and screening tests and
- To reduce perinatal transmission of HIV.

In its technical guidance, CDC acknowledged that prevention counselling is desirable for all persons at risk for HIV but recognized that such counselling might not be appropriate or feasible in all settings. Due to time constraints or discomfort with discussing their patients' risk behaviours caused some providers to perceive requirements for prevention counselling and written informed consent as a barrier, the initiative advocated streamlined approaches. In March 2004, CDC convened a meeting of health-care providers, representatives from professional associations, and local health officials to obtain advice concerning how best to expand HIV testing, especially in high-volume, high-prevalence acute-care settings wherein consultants recommended simplifying the HIV screening process to make it more feasible and less costly and advocated more frequent diagnostic testing of patients with symptoms. Further in April and in November 2005, CDC brought out final revision of these recommendations and in March 2006 further refined these on the basis of comments from these constituents.

Recommendations for adults and adolescents

CDC recommends that diagnostic HIV testing and opt-out HIV screening be a part of routine clinical care in all health-care settings while also preserving the patient's option to decline HIV testing and

ensuring a provider-patient relationship conducive to optimal clinical and preventive care. The recommendations are intended for providers in all health-care settings. The guidelines address HIV testing in health-care settings only; they do not modify existing guidelines concerning HIV counselling, testing, and referral for persons at high risk for HIV who seek or receive HIV testing in non clinical settings such as community-based organizations, outreach settings, or mobile vans.

Screening for HIV infection

In all health-care settings, screening for HIV infection should be performed routinely for all patients aged 13-64 years. Health-care providers should initiate screening unless prevalence of undiagnosed HIV infection in their patients has been documented to be <0.1%. In the absence of existing data for HIV prevalence, health-care providers should initiate voluntary HIV screening until they establish that the diagnostic yield is <1 per 1,000 patients screened, at which point such screening is no longer warranted. All patients initiating treatment for TB should be screened routinely for HIV infection. All patients seeking treatment for STDs, including all patients attending STD clinics, should be screened routinely for HIV during each visit for a new complaint, regardless of whether the patient is known or suspected to have specific behaviour risks for HIV infection.

Consent and pre-test information

Screening should be voluntary and undertaken only with the patient's knowledge and understanding that HIV testing is planned. Patients should be informed orally or in writing that HIV testing will be performed unless they decline (opt-out screening). Oral or written information should include an explanation of HIV infection and the meanings of positive and negative test results, and the patient should be offered an opportunity to ask questions and to decline testing. With such notification, consent for HIV screening should be incorporated into the patient's general informed consent for medical care on the same basis as are other screening or diagnostic tests; a separate consent form for HIV testing is not recommended. If a patient declines an HIV test, this decision should be documented in the medical record.

Similarities and differences between current and previous recommendations for HIV testing

Aspects of these recommendations that remain unchanged from previous recommendations are as follows:

1. HIV testing must be voluntary and free from coercion. Patients must not be tested without their knowledge.
2. HIV testing is recommended and should be routine for persons attending STD clinics and those seeking treatment for STDs in other clinical

settings.

3. Access to clinical care, prevention counseling, and support services is essential for persons with positive HIV test results.

Aspects of these recommendations that differ from previous recommendations are as follows:

1. Screening after notifying the patient that an HIV test will be performed unless the patient declines (opt-out screening) is recommended in all health-care settings.
2. Specific signed consent for HIV testing should not be required.
3. General informed consent for medical care should be considered sufficient to encompass informed consent for HIV testing.
4. Persons at high risk for HIV should be screened for HIV at least annually.
5. HIV test results should be provided in the same manner as results of other diagnostic or screening tests.
6. Prevention counselling should not be required as a part of HIV screening programs in health-care settings. Prevention counselling is strongly encouraged for persons at high risk for HIV in settings in which risk behaviours are assessed routinely (e.g., STD clinics) but should not have to be linked to HIV testing.
7. HIV diagnostic testing or screening to detect HIV infection earlier should be considered distinct from HIV counselling and testing conducted primarily as a prevention intervention for uninfected persons at high risk

Additional considerations for HIV screening

Test Results

Communicating test results:

- The central goal of HIV screening in health-care settings is to maximize the number of persons who are aware of their HIV infection and receive care and prevention services. Definitive mechanisms should be established to inform patients of their test results.
- HIV-negative test results may be conveyed without direct personal contact between the patient and the health-care provider.
- HIV-positive test results should be communicated confidentially through personal contact by a clinician or nurse.
- Because of the risk of stigma and discrimination, family or friends should not be used as interpreters to disclose HIV-positive test results to patients.
- Active efforts are essential to ensure that HIV-infected patients receive their positive test results and linkage to clinical care, counselling, support, and prevention services.

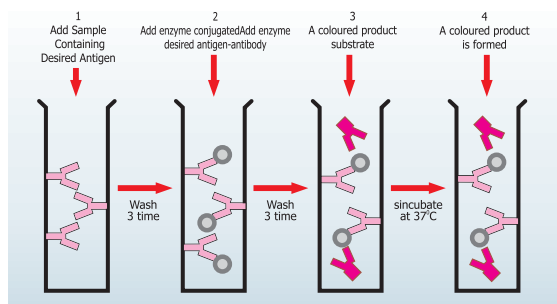


Figure 3: ELISA test

Documenting HIV test results:

Positive or negative HIV test results should be documented in the patient's confidential medical record and should be readily available to all health-care providers involved in the patient's clinical management.

Method of testing:

Detection of anti-HIV antibodies is the mainstay of testing for HIV and diagnosis of HIV. Tests to detect specific HIV antibodies can be classified into^{5,6}

1. Detection of HIV specific antibodies
2. Screening tests (ELISA/EIA and Rapid)
3. Supplemental tests (ELISA/EIA and Rapid/Western Blot)

HIV testing and results at GCRI:

The GCRI is the state-of-the-art diagnostic and therapeutic centre where services to the patients of all types of origin and financial background suffering from cancer is given. It conducts OPD and indoor activities for diagnosis, staging, treatment and monitoring disease progress. Around 979,786 patients per year are taking treatment suffering with solid tumours, Haematologic malignancies and gynaecologic cancers. These patients undergo HIV testing and are informed about the test and a written consent form is filled. The screening test is performed by serological test called ELISA (Figure 3) in the Microbiology Department.

The overall prevalence rate of sero positivity of HIV infection in patients taking treatment for different cancers is 0.66%. (Figure 4). In the earlier study conducted by our department 2011 showed that the prevalence rate of HIV in patients was 0.77%.⁷ In 2012-13 the prevalence of HIV in Gynaec Oncology is 1.11%, in Medical Oncology it is 0.88%, in surgical Oncology it is 0.59%, followed by 0.54% in other units like Orthopaedics, Urology, Neurooncology and 0.12% in Paediatric Oncology.

Therefore, the testing of HIV for all patients attending GCRI for the diagnosis and treatment of cancers is as per the revised recommendations of CDC

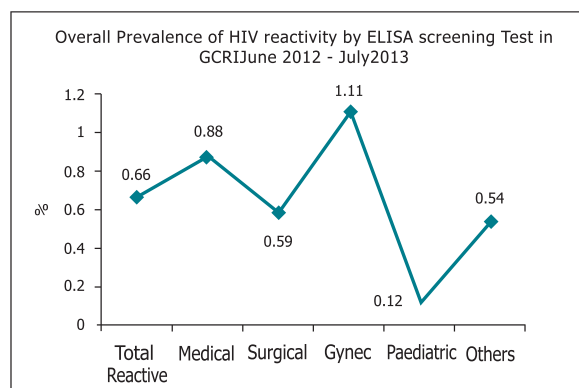


Figure 4: Prevalence of HIV in cancer patients by screening method

(testing all patients attending GCRI) as well as NACO and NABL 15189 guidelines (where in the consent form is filled and signed). Patient is explained about the HIV test and consent form is filled and the signatures of the patient as well as the doctor is made. After the test is sero positive by screening test (ELISA) the patient's serum is re-tested in duplicate, and confirmed by 2 different methods i.e. Immunochromatography and Enzyme Linked Fluorescence Assay. In case of invariable results or request by treating doctor the western blot assay is performed using nitrocellulose strips.

Abbreviations: NACO- National AIDS Control Organisation, HIV-Human Immuno deficiency virus, STDs- sexually transmitted diseases, ELISA- enzyme linked immunosorbant assay,

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A Review on Genetic Susceptibility towards Oral Cancer Risk among Indian Population

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Summary

Oral cancer is the major health burden in India. Recently, an increasing trend of oral cancer incidence especially in the younger population are reported from Gujarat, the western part of India, which is mainly due to different forms of tobacco consumption. Moreover, not all the tobacco habituates develop oral cancer; this disparity is mainly attributed to differences in genetic susceptibility of the individuals. Therefore, the association of genetic polymorphism with etiology of oral cancer needs to be explored thoroughly. In the studies on genetic polymorphisms and oral cancer risk among Indians, it is observed that the most commonly studied genes for oral cancer risk assessment include carcinogen metabolizing enzymes. Apart from these, genetic polymorphisms in cell cycle related and DNA repair genes are much explored in recent years. Studies representing single polymorphism may remain insufficient to validate an association between gene polymorphism and oral cancer risk. However, there is a great dearth of reports from India focusing on gene-gene and gene-environment association. Thus, studies that concomitantly consider multiple genetic and environmental factors involved in oral carcinogenesis are needed not only to establish the contribution of these factors to oral cancer development but also to understand their putative interactions. The data generated might be helpful in construction of genetic risk profiles which will help to delineate the individuals that are at higher risk of developing this disease. Identifying molecular markers associated with individual's vulnerability to oral cancer due to tobacco exposure might prove to be useful as early indicators of risk. Such molecular markers may be ultimately useful for preventive purposes and risk assessment of oral cancer.

Keywords: Oral cancer, Genetic polymorphism, Cell cycle, DNA repair, Carcinogen metabolizing enzymes

Oral cancer in India: Magnitude of problem

Oral cancer; the leading malignancy in India accounts for nearly one-third of all cancer cases. In 2008, 69,820 new oral cancer cases were registered in India which also represent one-third of oral cancer cases reported worldwide.¹ Moreover, 47,653 deaths due to oral cancer were registered in 2008 from India which signifies it as a major health hazard. As reported by GLOBOCAN 2008, this malignancy is highly prevalent in Gujarat, Western India. In particular, this region is exhibiting a serious trend of increased rate of oral cancer in the younger age groups.² Various cancer registries have documented that the higher incidence of oral cancer is due to wide spread habits of tobacco consumption in complex patterns, in particular smokeless tobacco in the Indian population. According to Global Adult Tobacco Survey, India (2009-2010), 46.2% males and 11.3% females were

tobacco users in Gujarat, out of which, 57.1% and 87.6%, respectively were smokeless tobacco users. If we focus on incidence of tobacco users developing oral cancer, it is not proportionate to the numbers consuming tobacco. This implies that all tobacco habituates do not develop oral cancer and this underlies the importance of genetic predisposition.

Genetic factors involved in oral carcinogenesis

The widely accepted multi-step model of oral carcinogenesis has documented the step-wise transition and progression from hyperplasia, to dysplasia, to carcinoma in situ and finally to invasive carcinoma with accompanying genomic alterations (Figure 1).³ It is hypothesized that the carcinogens present in tobacco cause DNA damage including modified DNA base and strand breaks which give rise to mutations and unregulated cell growth, which leads to cancer. The ability of a cell to proliferate in the presence of DNA damage would also increase the risk of the accumulation of gene mutations. DNA repair once escaped and unnoticed by the DNA repair proteins can lead to somatic mutations in important cell cycle regulatory proteins. Proper functioning of cell cycle regulatory proteins is a potent barrier to cancer cells, as it triggers cell cycle arrest or apoptosis if the DNA damage is un-repairable. Thus, alterations in functioning of tobacco metabolizing enzymes, DNA repair enzymes and cell cycle regulatory proteins may contribute to oral cancer risk (Figure 2). The sequential progression of malignancies has been linked to the presence of genomic instability and the appearance of extensive genomic alterations. Since 1987, our laboratory is actively engaged in oral cancer research. We have documented several noteworthy molecular events in oral cancer progression which are summarized in Table 1.⁴⁻¹⁸ Our studies have reported that several genomic and proteomic alterations have been associated with oral cancer pathogenesis. Moreover, these alterations have significant clinical utility in oral cancer diagnosis, treatment monitoring and prognosis.

Moreover, predisposition to cancer, due to inherited genetic factors, has an enormous impact on the development of the disease. Individual variations

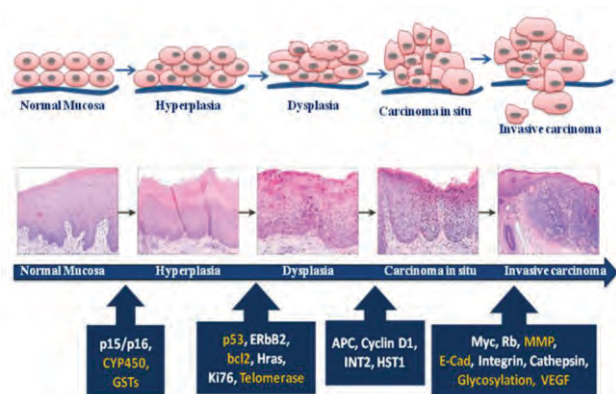


Figure 1: Multistep model of oral carcinogenesis

in cancer risk have been associated with specific variant alleles of different genes that are present in a significant proportion of the normal population.¹⁹ Recent studies have suggested that genetic polymorphisms may underlie some of the causes and events involved in carcinogenesis of oral cancer.²⁰ It is now widely accepted that the initiation and development of tumors are determined by a delicate balance of environmental and host factors. Furthermore, genetic variations in form of SNPs in large number of genes involving pathways of tobacco metabolism, DNA repair and cell cycle as possible susceptibility factors associated with oral cancer risk, have received great deal of attention worldwide. In the current era of “omics”, molecular epidemiological studies of cancer provide the potential for elucidating the carcinogenic cascade at the molecular level. Identification of susceptible subsets of the population, based on polymorphisms in genes involved in carcinogenesis, can delineate those factors that might increase cancer risk among individuals. Thus, present review attempts to summarize studies on association between genetic polymorphisms in genes involving pathways of tobacco metabolism, DNA repair and cell cycle and oral cancer risk among Indian population.

Carcinogen metabolizing genes

The Phase I and Phase II xenobiotic metabolizing enzymes (XMEs) have received a great deal of attention as possible genetic susceptibility factors for a variety of cancers. The XMEs are potentially involved in either the activation (Phase I) or detoxification (Phase II) of chemical carcinogens in tobacco. Inter-individual variations in the expression of detoxifying enzymes in the target organs and tissues may, therefore, be a key factor in resistance to chemical insult. Polymorphisms in the genes that code for these enzymes may alter expression or function, thus increasing or decreasing the activation or detoxification of carcinogenic compounds. The toxicological outcome of exposure, absorption and activation/deactivation of carcinogens is delicately balanced. Therefore, genetic variations in XMEs

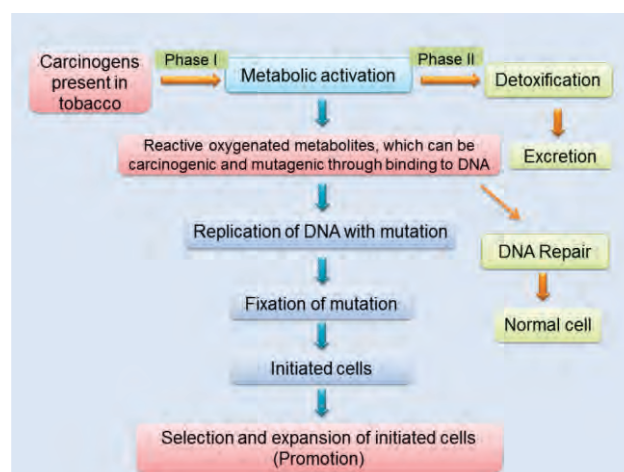


Figure 2: Sequence of events in tobacco related carcinogenesis

represent a major risk factor in the tendency to develop tumors.²¹ The variants of these genes are not directly responsible for transformation but can influence the rate at which mutations occur and/or accumulate in a cell. Therefore, identification of the polymorphisms in the genes encoding XMEs might shed some light on the mechanisms involved in the etio-pathogenesis of this cancer in the population. The most commonly studied carcinogen metabolizing genes in Indian populations are members of CYP (*CYP1A1*, *CYP2E1*) and GST (*GSTM1*, *GSTT1*) families. Functionally important polymorphisms are known to exist in tobacco metabolizing enzymes which results in altered risk to oral cancer. These functionally important polymorphisms in *CYP1A1* (*CYP1A1*2A*, *CYP1A1*2C*) and *CYP2E1* (*CYP2E1*5B*) have been studied for the association with oral cancer risk in Indian population (Table 1). However, reports for *CYP1A1*2A* and *CYP2E1*5B* have been contradictory among various region of India (Table 1).²²⁻²⁶ Recent meta-analysis on *CYP1A1*2A* and *CYP2E1*5B* suggested that these two polymorphisms might be a risk factor for oral carcinoma, particularly among Asians.^{27,28} There is only single study for *CYP1A1*2C* from India which has suggested that *CYP1A1*2C* is associated with increased oral cancer risk.²⁹ Meta-analysis by Zhuo et al (2012) suggested that *CYP1A1*2C* might modify the susceptibility to oral cancer among Asians.³⁰ Most of the studies on *GSTM1* and *GSTT1* null genotype from various regions of India have shown contradictory results (Table 2).^{22-24,29,31,32} However, recent meta-analysis on *GSTM1* and *GSTT1* suggest that Null genotype of *GSTM1* and *GSTT1* are associated with oral cancer development in Asian population.³³⁻³⁵ Further, it is also documented that *CYP1A1*2A*, *CYP2E1*5B*, *GSTM1* and *GSTT1* null genotype may modulate oral cancer risk in presence of tobacco habits.^{23,31}

Table 1: Our noteworthy studies on oral cancer susceptibility and progression

Marker studied	Results	Reference
<i>CYP1A1</i> , <i>GSTM1</i> , <i>GSTT1</i> polymorphism	Increased oral cancer risk was observed in patients having deletion of <i>GSTM1</i> and/or <i>GSTT1</i>	Singh RD, 2013 ⁴
<i>p53</i> polymorphisms	<i>p53</i> polymorphism, especially Arg72Pro in exon 4 could significantly modify the risk of oral cancer development	Patel KR, 2013 ⁵
Serum and salivary total sialic acid and α -L-fucosidase activity	Salivary TSA/TP ratio and α -L-fucosidase activity were elevated in higher magnitude than serum levels in patients with oral precancerous conditions (OPC) and oral cancer patients	Vajaria BN, 2013 ⁶
Glycoprotein electrophoretic profiling	A 230 kDa glycoprotein consistently appeared in individuals only with tobacco habits and an increasing trend of this 230 kDa along with 192 kDa, 170 kDa, 116 kDa and 44kDa glycoproteins were observed from controls to patients with OPC to oral cancer	Vajaria BN, 2012 ⁷
Plasma MMP-2, MMP-9, TIMP-1, TIMP-2	MMP-9, TIMP-1 and TIMP-2 were significantly elevated in oral cancer patients as compared to controls and correlation with stage, differentiation and infiltration	Singh RD, 2011, 2010 ^{8,9}
Nitrite, Nitrate, superoxide dismutase and catalase	Nitrite and nitrate were higher while SOD and catalase activity were lower in oral cancer patients as compared to controls	Patel JB, 2010 ¹⁰
<i>GSTM1</i> polymorphism and telomere length	Shorter telomere lengths were observed in patients with <i>GSTM1</i> polymorphism and a link between absence of <i>GSTM1</i> gene and telomere length alterations	Sainger RN, 2009 ¹¹
Salivary IL-8 and IL-8 mRNA	Salivary IL-8 mRNA and protein were significantly elevated in oral cancer patients by use of electrochemical sensor for multiplex biomarkers detection	Fang Wei, 2009 ¹²
E-cadherin and Sialyl Lewis-X	E-cadherin truncation and sLex overexpression in oral precancerous tissues helps to predict metastatic potential of tumors	Shah MH, 2009 ¹³
Antioxidant enzymes, thiol and <i>GSTM1</i> polymorphism	Antioxidant enzymes were significantly higher whereas glutathione peroxidase and thiol were lower in patients as compared with habitual controls. Individuals with <i>GSTM1</i> null genotype are at higher risk of oral cancer development	Patel BP, 2008 ¹⁴
Fucose, fucoprotein, Fucosyltransferase and α -L-fucosidase	All the levels in serum were significantly higher in patients with oral precancerous conditions and oral cancer	Shah MH, 2008 ¹⁵
Total sialic acid, α -2,3 and α -2,6 sialoproteins and sialyltransferase	All the levels were significantly higher in patients with OPC and oral cancer patients and suggested its utility in early detection, prognostication and treatment monitoring of oral cancer	Shah MH, 2008 ¹⁶
Lipid peroxidation, antioxidants and thiol	Patients with higher lipid peroxidation and decreased thiol and antioxidant status showed poor overall survival in oral squamous cell carcinoma	Patel BP, 2007 ¹⁷
Urinary nicotine, NO ₂ and NO ₃	The levels were significantly elevated in tobacco habituates, patients with OPC and oral cancer patients as compared with non-habituates sub-group	Patel JB, 2007 ¹⁸

Cell cycle related genes

One source of the cell-cycle checkpoint variation might come from genetic polymorphisms in cell-cycle control genes. Only a few have been studied in tobacco-related cancers, including *p53*, *p73*, *CCND1* and *MDM2* among Indians (Table 3). Tumor

suppressor gene *p53* play important role in cell cycle control, apoptosis and cellular senescence. Most commonly studied polymorphism is Arg>Pro substitution in codon 72 of exon 4 in *p53* gene. There are evidences that the codon 72 polymorphism has a profound effect on the primary structure of *p53*

Table 2: Studies on genetic polymorphisms in carcinogen metabolizing enzymes and oral cancer risk from India

Gene	Polymorphism	Region	Results	Controls/Cases	Authors
CYP1A1	CYP1A1*2A	North -East	No association		Chatterjee et al 2009 ²²
		West	Increased oral cancer risk	798/627	Anantharaman et al 2011 ²³
		South	Increased oral cancer risk	150/150	Shukla et al 2012 ²⁴
	CYP1A1*2C	South	No association	132/157	Balaji et al 2012 ²⁵
CYP2E1	CYP2E1*5B	South	Increased oral cancer risk	60/98	Sreelekha et al 2001 ²⁹
CYP2E1	CYP2E1*5B	West	Reduced oral cancer risk	700/423	Anantharaman et al 2011 ²³
		North -East	No association	-	Chatterjee et al 2009 ²²
GSTM1	Deletion	West	Increased oral cancer risk	799/654	Anantharaman et al 2011 ²³
			Increased oral cancer risk	450/297	Buch et al 2002 ³¹
		South	No association	150/150	Shukla et al 2012 ²⁴
			No association	60/98	Sreelekha et al 2001 ²⁹
		North	No association	87/40	Sharma et al 2006 ³²
		North -East	No association	-	Chatterjee et al 2009 ²²
GSTT1	Deletion	West	Reduced oral cancer risk	788/592	Ananthraman et al 2011 ²³
			No association	450/297	Buch et al 2002 ³¹
		South	No association	60/98	Sreelekha et al 2001 ²⁴
		North	Increased oral cancer risk	87/40	Sharma et al 2006 ³²

protein and its biochemical and biological activities.^{36,37} p73 binds to the p53 responsive elements and transactivates an overlapping set of p53 target genes implicated in G1/S cell cycle arrest and apoptotic cell death.³⁸ Two linked G>A and C>T polymorphisms occur in a region of the transcript that could theoretically affect the p73 gene expression perhaps by altering the translational initiation.³⁹ Cyclin D1 (*CCND1*) plays a critical role in the transition from G1 to S phase of the cell cycle. Overexpression of *CCND1* has been commonly observed in human cancers.⁴⁰ A870G polymorphism of this gene has been reported to be associated with increase frequencies of alternative splicing.⁴¹ MDM2 is an important feedback negative regulator of p53 gene, thus polymorphisms in *MDM2* also affect cancer risk. A naturally occurring G to T sequence variation in the *MDM2* gene, referred to as single nucleotide polymorphism (SNP) 309 increases the binding affinity of the transcriptional activator Sp1 resulting in high level of MDM2 protein expression and the subsequent attenuation of the p53 pathway.⁴² There are only few reports which have assessed the role of these p53 polymorphisms in oral cancer from India. Among them, most of reports are on Arg72Pro polymorphism of p53 gene. All studies from India did not find any association between Arg72Pro polymorphism and oral cancer risk.⁴³⁻⁴⁶ Francisco et al (2011) suggested that ethnicity, allelic frequency, histological and anatomical sites may modulate the penetrance of Arg72Pro in cancer susceptibility.⁴⁷ However, recent meta-analysis on Arg72Pro polymorphism of p53 did not suggest any association between the p53 Arg/Pro polymorphism and oral cancer risk even after stratifying by ethnicity.⁴⁸ There is only one study from north region of India on

CCND1 polymorphisms which has suggested no association between this polymorphism and oral cancer risk.⁴⁹ On the other side, recent meta-analysis suggested that it may be associated with an increased risk of developing oral cancer in the Asian population.⁵⁰ There is only one study on *MDM2* 309 G>T promoter polymorphism which has suggested that this polymorphism independently could not modify the risk of oral cancer but modulate cancer risk in combination with p53 and p73 polymorphisms.⁵¹ The study also suggested that two linked G>A and C>T polymorphisms in p73 could significantly modify oral cancer risk. Further, meta-analysis by Hu et al (2012) suggested that the p73 G4C14-to-A4T14 polymorphism may be associated with an increased risk of cancer in most cancer types and ethnicities.⁵² Polymorphisms of p73 and *MDM2* were also associated with oral cancer risk when stratified according to tobacco habits.⁵¹

DNA repair genes

DNA repair capacity (DRC) is substantially varied within human population. Defects in DRC may lead to genetic instability and carcinogenesis. A growing number of literatures have suggested that polymorphisms in DNA repair genes may alter protein function and contribute to the inter-individual differences in DRC and, therefore, may modulate cancer risks. At least four pathways of DNA repair operate on specific types of damaged DNA, and each pathway involves numerous molecules. Base Excision Repair (BER) pathway operates on small lesions such as oxidized or reduced bases, fragmented or non-bulky adducts, or those produced by methylating agents. The Nucleotide Excision Repair (NER) pathway repairs bulky lesions such as

Table 3: Studies on genetic polymorphisms in cell cycle related genes and oral cancer risk from India

Gene	Polymorphism	Region	Results	Controls/Cases	Authors
<i>p53</i>	Arg72Pro	West	No association	153/72	Tandle et al 2001 ⁴³
		East	No association	26/110	Nagpal et al 2002 ⁴⁴
			No association	348/310	Mitra et al 2005 ⁴⁶
		North	No association	20/44	Katiyar et al 2003 ⁴⁵
<i>CCND1</i>	A870G	South	No association	142/176	Sathyan et al 2006 ⁴⁹
<i>p73</i>	G4C14-to-A4T14	East	Increased oral cancer risk	348/310	Misra et al 2009 ⁵¹
<i>MDM2</i>	309 G>T	East	No association	348/310	Misra et al 2009 ⁵¹

Table 4: Studies on genetic polymorphisms in DNA repair genes and oral cancer risk from India

Gene	Polymorphism	Region	Results	Sample size	Authors
<i>XRCCI</i>	Arg194Trp	West	No association	798/655	Ananthraman et al 2011 ²³
		South	Increased oral cancer risk	110/110	Ramachandran et al 2006 ⁵³
		East	No association	389/310	Majumdar et al 2007 ⁵⁴
	Arg399Gln	West	No association	798/651	Ananthraman et al 2011 ²³
		South	Increased oral cancer risk	110/110	Ramachandran et al 2006 ⁵³
		East	No association	389/310	Majumdar et al 2007 ⁵⁴
	Arg280His	South	No association	110/110	Ramachandran et al 2006 ⁵³
		East	No association	389/310	Majumdar et al 2007 ⁵⁴
	<i>hOGGI</i>	Ser326Cys	West	No association	791/646
<i>XPD</i>	Lys751Gln	West	Reduced oral cancer risk	788/617	Ananthraman et al 2011 ²³
		South	Increased oral cancer risk	110/110	Ramachandran et al 2006 ⁵³
		North	No association	389/310	Majumdar et al 2007 ⁵⁴

pyrimidine dimers, other photo-products, larger chemical adducts, and cross-links. Genes involved in the BER and NER pathways have been extensively studied worldwide for cancer risk. In India, variants of the following genes were examined in epidemiological studies: BER genes (*XRCCI* and *OGGI*); NER genes (*XPD*) for oral cancer risk (Table 4). X-ray repair cross complementary 1 (*XRCCI*) is involved in the core processes of single-strand break repair and base excision repair. Polymorphisms in *XRCCI*, including Arg194Trp, Arg280His and Arg399Gln have been studied in Indian population. Most of reports are on Arg194Trp and Arg399Gln. However, reports on these two polymorphisms of *XRCCI* in India exhibited contradictory results. Two studies from east and north regions suggested that these two polymorphisms have no association with oral cancer risk. On the other hand, another study from southern India suggested increased risk association between these two polymorphisms and oral cancer (Table 4).^{23,53,54} Recent meta-analysis on Arg194Trp polymorphism of *XRCCI* suggested its strong association with oral cancer risk especially in Asians.⁵⁵ *OGGI* catalyzes the removal of 8-hydrodeoxy-guanine (8- OHdG), which has been considered as a key biomarker of oxidative DNA damage. Ser326Cys polymorphism in *OGGI* is extensively studied worldwide. However, there is only one study from India which suggested no association between

Ser326Cys polymorphism and oral cancer risk.²³ Xeroderma Pigmentosum type D (*XPD*), a member of the NER pathway, also acts as part of transcription factor complex, TFIIH. *XPD* Lys751Gln has been extensively studied for oral cancer risk in Indian population. All the studies have reported contradictory results (Table 3).^{23,53,54} Arg399Gln and Lys 751Gln polymorphisms of *XRCCI* and *XPD* respectively were associated with oral cancer risk when stratified according to types of tobacco habits.^{23,54}

Our ongoing research work on tobacco metabolizing enzymes' gene polymorphisms and *p53* gene polymorphisms have revealed promising results. *CYP1A1* (*CYP1A1*2A* and *CYP1A1*2C*), *GST* (*GSTM1* and *GSTT1*) and *p53* (16 bp duplication in intron 3, Arg72Pro in exon 4 and G>A in intron 6) gene polymorphisms were determined in 122 oral carcinoma cases and 127 controls from Gujarat, Western India. The results documented that the *GST* gene polymorphism modified the susceptibility to oral cancer. Moreover, individuals with variant genotypes of *CYP1A1* and *GST* genes along with tobacco habits were at significant risk for developing oral cancer. Arg72Pro in exon 4 could also significantly modify the risk of oral cancer development in this population.^{4,5}

As oral cancer is a complex polygenic disease, various gene–gene interactions, for which the single

effect might be low, may cause significant effects when analyzed in combination.⁵⁶ The outcome of the carcinogen exposure is determined by balance in the activity of Phase I and Phase II enzymes along with cell cycle related proteins and DNA repair enzymes. SNPs of these pathway genes in combination might render an individual more sensitive or resistant for a given level of carcinogens.⁵⁷ Further, gene environment interactions also modulate the risk towards oral cancer. The polymorphisms in combination with environmental exposures have been hypothesized to confer a differential risk of cancer for individuals carrying these genetic variants.⁵⁸ However, most of the studies on Indian population still remain inconclusive. It has been speculated that both ethnic back-ground and lifestyle differences contribute to the differences in predisposing genetic factors to cancer development.⁵⁹ Geographic/region and ethnic differences in the frequency distribution have been established for the candidate genes. The molecular epidemiological studies have emphasized the ethnic identification for epidemiological studies as equally crucial and indispensable.^{58,60,61} This fact is very crucial for country like, India where wide variations in ethnicity and life style factors exist. Moreover, studies on gene-gene interaction and gene-environment association are inadequate.

Concluding remarks

Germ-line mutations highlight its importance in predicting an Individual's risk for cancer as well as in understanding the underlying mechanisms of carcinogenesis. If the genetic elements that predispose to oral cancer are known, it might be possible to construct a genetic risk profile which may be helpful in delineating the subpopulation that would benefit from cancer screening programs. Genetic diagnostic tests that identify high-risk individuals may also lead to direct medical or lifestyle interventions. This risk stratification method could thus help in improving intervention strategies by minimizing the screening of low-risk individuals and focusing on individuals who are at higher risk. For estimation of total attributable risk of susceptibility genes, it is vital to systematically evaluate them in a single study, ideally in a homogenous population where the potential bias of case-control study can be minimized. Thus, comprehensive studies on genetic susceptibility and oral cancer risk from various region of India are the demand of the day.

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“Earth provides enough to satisfy every man's needs, but not every man's greed.”

Mahatma Gandhi

A Retrospective Study to Assess Safety and Efficacy of Nimotuzumab, A Monoclonal Antibody against EGFR in Combination with Chemo Radiotherapy or Radiotherapy alone in Patients with Head and Neck Cancers

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Summary

Patients with advanced inoperable squamous cell carcinoma of the head and neck (SCCHN) have poor outcome with radiotherapy alone (RT). EGFR (Epidermal Growth Factor receptor) is over-expressed in >90% SCCHN. Nimotuzumab is a humanized monoclonal antibody, a validated oncotherapeutic-targeting Epidermal Growth Factor Receptor (EGFR). Nimotuzumab is approved for advanced head and neck cancer along with radiotherapy in neo-adjuvant settings and there are ongoing trials of Nimotuzumab with radiotherapy in adjuvant therapy of head and neck malignancies. To investigate the safety and efficacy of concurrent Nimotuzumab in combination with chemo radiotherapy of SCCHN. In between August 2011 to August 2012, all patients of SCCHN, stage II-IVa; treated with Radiotherapy and Nimotuzumab 200 mg intravenous over 60 minute every week, with or without cisplatin were taken. Out of 29 patients included in this study, 19 patients received Nimotuzumab in form of curative concurrent chemoradiotherapy (CRCT) and 10 patients received Nimotuzumab in adjuvant CRCT setting. Complete response was seen in 68.4% (13 out of 19 patients) of patient receiving neoadjuvant chemoradiotherapy. Out of 10 patients who received adjuvant Nimotuzumab with radiotherapy, 7(70%) were in complete remission at 6 months. Out of 29 cases, 8(27.5%) cases developed mucosities, 4(13.7%) developed hypoproteinemia and asthenia, 1(3.44%) developed dry mouth. Our study concluded that concurrent use of Nimotuzumab with Radiotherapy or chemoradiotherapy is safe. It enhances radiation and chemotherapy responses.

Keywords: Nimotuzumab, monoclonal antibody, EGFR, concurrent chemoradiotherapy, head and neck cancer

Introduction

An estimated 263,900 diagnoses and 128,000 deaths from oral cavity cancer occurred, world wide in 2008. This study will focus on the most common histology of malignancy arising in the head and neck, squamous cell carcinoma, which highly expresses the epidermal growth factor receptor protein.¹ Enhanced production of growth factors that actively support cell growth or over expression of their cognate growth factor receptors on the cell membranes to which these growth factors bind; give the cancer cells capacity for autonomous and dysregulated proliferation. Both these phenomena are responsible for activation of downstream signaling pathways that ultimately lead to the proliferation of cancer cells, induction of

angiogenesis and metastasis. Majority of human epithelial cancers exhibit marked over expression of growth factors [e.g., epidermal growth factor (EGF), transforming growth factor α (TGF α)] and receptors of the EGFR family.²

Four EGFR specific agents have received regulatory approval. Cetuximab for metastatic colorectal cancer (mCRC) and squamous cell carcinoma of the head and neck (SCCHN), Gefitinib for advanced or metastatic non-small-cell lung cancer (mNSCLC), Erlotinib for advanced or metastatic pancreatic cancer and NSCLC, and Panitumumab for mCRC.² Nimotuzumab, a humanized IgG1 monoclonal antibody targeting EGFR, has shown activity in various phase II/III trials in head and neck malignancies. Preliminary data indicate that therapeutic levels of Nimotuzumab can be reached without dermatological toxicity, which is the common side-effect of the other anti-EGFR directed therapies.³ There are ongoing trials of Nimotuzumab with radiotherapy in adjuvant therapy of head and neck malignancies.⁴ We present our initial experience of Nimotuzumab given concurrently with RT with or without Cisplatin.

Objectives

A retrospective, single center study to assess safety and efficacy of Nimotuzumab with chemotherapy and radiotherapy or radiotherapy alone in patients with histologically documented squamous cell carcinoma of head and neck was conducted at GCRI Ahmedabad. Primary objective of study was to evaluate safety of Nimotuzumab with radiotherapy in squamous cell carcinoma of head and neck and secondary objective was to assess response and disease status at 6 months.

Materials and Methods

This study was based on a retrospective analysis of 29 consecutive patients with previously untreated,

Table 1: WHO response grading system

Category	Response on examination or imaging
Complete response of the primary tumor	Complete disappearance of all detectable disease at the primary site to visual inspection and imaging studies
Complete response of the nodal disease	Complete disappearance of all nodal disease on clinical examination and imaging studies
Complete composite response	Complete disappearance of loco regional disease.
Partial response	Tumor reduction by at least 50% of the sum of the product of perpendicular diameters of all measurable lesions on endoscopy and imaging studies without any appearance of new lesions.

stage II to IVa primary squamous cell carcinoma of the head and neck without distant metastases. The age range was from 18 years up to 84 years and performance status of 0 to 1. All patients underwent RT with Nimotuzumab with or without cisplatin from August 2011 to August 2012 at GCRI, Ahmedabad. Detailed patient's evaluation prior to treatment included complete medical history with attention paid to disease-related signs and symptoms, and tobacco or alcohol abuse, clinical examination, complete blood count, basic blood chemistry, and liver and renal function tests, chest x-ray, liver ultrasound, and fiber optic endoscopy with biopsy, fine-needle aspiration biopsy in cases with detectable neck adenopathy and computed tomography (CT) scanning. Patients were staged according to the classification of the American Joint Committee on Cancer Staging (AJCC). All patients had received 200 mg of Nimotuzumab infusion over 60 minutes once weekly with radiotherapy. Some patients also received chemotherapy with this modality (50mg of cisplatin infusion once a week). Hydration and antiemetic were given according to standards of care. Complete blood count and biochemical analysis of serum urea and creatinine were done every week. Evaluation of tumor response was performed 1 month after the completion of CRCT by physical examination, fiber optic endoscopy, and CT or MRI of the primary site and the neck. Endoscopy under anesthesia and/or biopsy for any clinical abnormality or radiological abnormality if found was performed to confirm the suspicious residual lesion. Response to treatment was documented by the World Health Organization (WHO) response grading system (Table 1).⁵ Patients who received adjuvant Nimotuzumab based therapy

Table 2: WHO scale for oral mucosities

Grade 0	No oral mucosities
Grade 1	Erythema and soreness
Grade 2	Ulcers, able to eat solids
Grade 3	Ulcers, requires liquid diet (due to mucosities)
Grade 4	Ulcers, alimentation not possible (due to mucosities)

were followed up every 3 month.

Patients were followed up every month after treatment to evaluate any acute or chronic toxicity. Oral mucosities were graded according to WHO scale for oral mucosities (Table 2).⁶ All patients enrolled in study were advised Betadine gargles and healthy diet to prevent mucosities.

Results

Out of 29 patients, who were enrolled in this study, 25 were male and 4 were female. Age of patients ranged from 18 years to 84 years. Out of 29 cases, 7 cases were of carcinoma base of tongue, 5 were of carcinoma buccal mucosa, 6 were of carcinoma tongue, 4 were of carcinoma vocal cord, 2 were of carcinoma pyriform fosse, and 1 each of carcinoma tonsil, carcinoma post cricoids, carcinoma

Table 3: Characteristics of patients

Variables	No. of patients (%)
Gender	
Male	25(86.2)
Female	04(13.7)
Age (years)	
< 60	23(79.3)
> 60	06(20.6)
Disease sites	
Base of tongue	07(24.1)
Buccal mucosa	05(17.2)
Tongue	06(20.6)
Vocal cord	04(13.7)
Pyriform fosse	02(6.89)
Others	05(17.2)
TNM staging	
Stage II	02(6.89)
Stage III	08(27.5)
Stage IV	19(65.5)
Histopathological grading of squamous cell carcinoma	
Poorly differentiated	02(6.89)
Moderately differentiated	21(72.4)
Well differentiated	06(20.6)

Table 4: Outcome of patients treated with curative and adjuvant CT-RT with Nimotuzumab

	Patient treated with curative CT-RT	Patients treated with adjuvant CT-RT
Patient number	19	10
Residual disease	2/19(10.5%)	-
Recurrence at 6 month	04/17(23.5%)	3/10(30%)

Table 5: Therapy related toxicity

Toxicity	No.of patients (%)
Mucosities	08(27.5%)
Hypoproteinemia and asthenia	04(13.7%)
Dry mouth	01(3.44%)

posterior pharynx, carcinoma upper esophagus, Malignancy of unknown origin in neck. Out of 29 enrolled patients 2 had poorly differentiated squamous cell carcinoma, 21 had moderately differentiated and 6 were of well differentiated squamous cell carcinoma (Table 3).

Table 4 depicts that response was seen in all patients (19/19) who received neoadjuvant chemoradiotherapy. Seventeen patients out of 19 patients were in complete remission and 2 had partial response. Of these 17 patients, 4 patients showed recurrent disease at 6 months. Out of 10 cases who received adjuvant treatment, 3 patients had recurrence at 6 months. These inferior loco regional control can be attributed to advance stage (stage IV) in all patients (6/6) included in studies. No case of distant relapse was documented within study duration.

Out of 29 cases, 8(27.5%) cases developed mucosities, 4(13.7%) developed hypoproteinemia and asthenia, 1(3.44%) developed dry mouth and 16(55.1%) patients did not developed any complications. Out of 8 cases with mucosities, 7 patients had grade 2 mucosities only. One patient had grade 3 mucosities, who also received radiotherapy dose 66Gy. Out of 29 cases 6 were of age more than 60 years. All this 6 elderly patients tolerated CT-RT with Nimotuzumab well, 3 had mucosities which was grade-2 in severity, 1 patient had mucosities, infection and asthenia (Table 5). Nimotuzumab is not studied in age more than 80 years, but in present study one patient with age of 84 years received Nimotuzumab with RT and tolerated it well without any major complications except mucosities of grade 2 severities.

Discussion

Cancer cell proliferation involving EGFR dysregulation can happen by receptor over expression, growth factor independent dimerization processes, autocrine growth factor loops and deficiency of specific phosphatases.² EGFR

Table 5: Comparison with other study

Studies	RR at 6 months
Melarkode S. et al ²	100%
Present study	100%

dimerization induces intracellular tyrosine kinase mediated phosphorylation of the cytoplasmic domain of the receptor, which in turn provides docking sites for adaptor proteins and signaling enzymes. This results in a receptor mediated activation of downstream signaling protein kinases involved in cellular events such as proliferation and survival. This signaling matrix is redundant as a result of the involvement of multiple ligands, receptor homo- or hetero-dimerization and an abundance of intracellular downstream effectors.² New data describes possible mechanisms of innate and acquired resistance to EGFR inhibitors, such as over expression of insulin-like growth factor, Ras, Braf and PTEN mutations. Combination therapies using EGFR inhibitors along with drugs acting on other key receptors and downstream signaling molecules involved in tumorigenesis could reduce incidence of innate and acquired resistance.²

Over the past few years, two EGFR specific agents (Cetuximab and Nimotuzumab) have also received regulatory approval for SCCHN. Gefitinib has also been used along with radiotherapy in HNSCC at our institute and the overall response rate in Gefitinib group was 69% (unpublished data).⁷

Nimotuzumab is a humanized IgG1 isotype monoclonal antibody targeted to EGFR receptor.² Terminal deoxynucleotidyl transferase dUTP nick end labeling staining revealed a five-fold increase in the apoptotic index of the nimotuzumab treated tumors. Nimotuzumab could also be cytolytic on target tumors by its capacity to cause Antibody dependent cell mediated cytotoxicity and complement dependent cytotoxicity.² Nimotuzumab is presently approved for the following types of cancer – as for example SCCHN, in India, Cuba, Argentina, Colombia, Ivory Coast, Gabon, Ukraine, Peru and Sri Lanka; for glioma (pediatric and adult) in Cuba, Argentina, Philippines and Ukraine and for nasopharyngeal cancer in China.² It has been granted orphan drug status for glioma in USA and for glioma and pancreatic cancer in Europe.¹ According to phase II study in Japan, the combination of Nimotuzumab with platinum-based chemotherapy and concurrent thoracic RT is feasible and shows promising activity for locally advance NSCLC.⁸

Over all response rate (RR) in curative CT-RT group, in Melarkode S. et al² study was 100%, which correlates with results of present study.

The Nimotuzumab related adverse events are asthenia, dizziness, vomiting, loose stools, fever,

chills, hypertension, rash, urticaria and infusion related reaction as notified in different studies.⁹ In present study, toxicities documented were mucosities (grade 2 mainly), hypoproteinemia, asthenia. Nimotuzumab containing regimens were highly effective and safe.

Conclusion

This study suggested that Nimotuzumab exhibited a very safe profile and it can be a promising add-on therapy to the existing standard of care in patients with advanced SCCHN.

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Solution to Crossword Puzzle-III

	¹ S	² C	³ R	³ E	³ E	³ N	³ I	³ N	³ G										
⁴ P		H		X															
A		O		T						⁵ A	L	C	O	⁶ H	O	L			
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A				A						P			⁹ F	I	S	H			
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¹⁰ H	I	¹¹ V		¹² E	G	F	R			E	N							¹⁴ C	
Y		A		B						O	E								H
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D		R				N	O			O									Y
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Congratulations to the winner:

Dr. Jahnvi Gandhi
Junior Lecturer, Pathology

Answers:

ACROSS:

1. SCREENING
5. ALCOHOL
7. PARTIAL
9. FISH
10. HIV
12. EGFR
13. MEN
15. SUV
17. SLOAN
19. TONGUE
20. CALCIMIMETIC
21. LEUCOCORIA

DOWN:

2. CHOP
3. EXTRA
4. PARATHYROID
5. APPLE
6. HRSG
8. ASTROCYTOMA
11. VAS
12. EBV
13. MELANOMA
14. CHLAMYDIA
16. CANCER
17. SEMINOMA
18. BRCA2

Infections in Patients with Cancer - GCRI (Gujarat Cancer and Research Institute) Experience

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Assistant Professor¹, Resident², Professor and Head³
Department of Microbiology

Summary

Infection is a frequent and serious complication for many cancer patients. Bone marrow and hematopoietic stem cell transplantation and use of intensive chemotherapeutic regimens, have added substantially to the number of patients who are able to survive neoplastic disorders but do so with seriously impaired host defense mechanisms that compromise their ability to resist or contain infections. The spectrum of bacterial infection continues to change, requiring continued vigilance, and the development of antibiotic policy. The objective of study was: 1. to know the infection rate of patients at GCRI (Gujarat Cancer and Research Institute) 2. To know the antibiogram of our isolated strains and to formulate antibiotic policy for hospital. This retrospective analysis carried out from January to June 2013, to know the prevalence of infections (Bacterial & Fungal) in cancer patients. Out of total 52321 patients attending the hospital, 2910 different samples were received in the microbiology laboratory for a period of 6 months (Jan 13- July 13). Out of them 852 samples were cultures positive. Infection rate was highest in urology 4.84% (3/62) followed by paediatric department 4.68% (108/2309) and lowest in radiotherapy department 0.74% (15/2035). Amongst the total isolates, bacterial isolates were 92 % (789/852) and 8% (63/852) were fungal isolates. Amongst the bacterial isolates, amongst gram negative bacilli were 71% (561/789) and 29 % (228/852) were gram positive cocci. *E.coli* (30.16%), *S.aureus* (16.43%) and *Candida tropicalis* (30.15%) were the commonest organisms isolated. Antibiogram of GNBs (Gram Negative Bacilli) and GPCs (Gram Positive Cocci) were produced. For GNBs, Tigecyclin shows 25.4% resistance and Amikacin shows 30.4%. For GPCs, Teicoplanin shows 4% resistance, Moxifloxacin 17% and Gentamycin 33%. Data generated by vital 3 compact for mechanism of antimicrobial resistance was noted.

Keywords: Infection, Neoplastic disorders, Antibiogram

Introduction

Infection continues to be a significant problem in patients with cancer. Recent advances in medical technology, such as bone marrow and hematopoietic stem cell transplantation and the use of intensive chemotherapeutic regimens, have added substantially to the number of patients who are able to survive neoplastic disorders but do so with seriously impaired host defense mechanisms that compromise their ability to resist or contain infections. The spectrum of bacterial infection continues to change. Newer opportunistic pathogens are being recognized with increasing frequency.¹ The emergence of antimicrobial resistance in common bacterial pathogens during the past decade is also of great concern.^{2,3} Fungal, viral, and protozoal infections are becoming increasingly common in immunosuppressed patients, are difficult to recognize and treat in a timely manner, and are often refractory to therapy.^{4,5} Time is critical

for the successful management of these patients, and delays in the administration of appropriate therapy can jeopardize a favorable outcome. Because of the difficulty in treating many of these infections, attempts at reversing the immunologic deficit and strategies for infection prevention are of the utmost importance.⁶

In severely immunosuppressed patients, the usual signs and symptoms associated with infection may be altered, suppressed, or even absent. Therefore, it is often not possible to make a specific diagnosis, and empiric therapy is generally administered in high-risk patients who are suspected of having an infection. A thorough knowledge of the many factors that predispose these patients toward the development of infections is essential.^{7,8}

Factors responsible for increased susceptibility to infections:

Many factors increase the susceptibility of immunosuppressed cancer patients to infections like, 1. Neutropenia, 2. Cellular Immune Dysfunction, 3. Humoral Immune Dysfunction, 4. Bone Marrow Transplantation, 5. Local Factors, and 6. Intravascular Devices. Each of these factors is associated with a unique set of infections, although there is some overlap between predisposing factors and certain infections. Also, multiple predisposing factors might exist in the same patient, widening the spectrum of potential infections. Recognition of these factors enables the astute clinician to make an accurate prediction of the potential pathogen(s) in a particular patient or setting and to institute appropriate empiric therapy promptly. Table 1 lists the predominant defects in host defense mechanisms associated with various cancers and the infections most commonly seen as a consequence of those defects.

Neutropenia remains the most common predisposing factor for infection in cancer patients.^{9,10} Both the degree and the duration of neutropenia influence the development of infection. The risk of infection does not begin to increase until the neutrophil count decreases to levels below 1,000/ml of blood (Figure 1). This risk increases substantially as the neutrophil count decreases further. Neutropenic patients often fail to develop the characteristic signs

Table 1: Host defense mechanisms associated with various cancers and the infections⁹

Disease	Predominant Defect	Predominant Infections
Acute leukemia, Aplastic anemia	Neutropenia	Gram-positive cocci, gram-negative bacilli, Candida, Aspergillus, Fusarium, Trichosporon
Hairy cell leukemia	Neutropenia, impaired lymphocyte function, monocytopenia	Gram-negative bacilli, gram-positive cocci, mycobacteria (including nontuberculous)
Chronic lymphatic leukemia, multiple myeloma	Hypogammaglobulinemia	Encapsulated organisms. Streptococcus pneumoniae; Haemophilus influenzae; Neisseria meningitidis
Hodgkin's disease, AIDS	Impaired T-lymphocyte response	Pneumocystis, Cryptococcus, mycobacteria, Toxoplasma, Listeria, Cryptosporidium, Candida, Cytomegalovirus
Bone marrow transplant recipient	Neutropenia, increased activity of suppressor T lymphocytes	Gram-positive cocci, gram-negative bacilli, cytomegalovirus, Candida, Aspergillus, herpes viruses
Breast cancer	Tissue necrosis	Gram-positive cocci, gram-negative bacilli
Lung cancer	Local obstruction, tissue necrosis	Gram-positive cocci, gram-negative bacilli, anaerobes
Gynecologic malignancy	Local obstruction, tissue necrosis	Mixed aerobic and anaerobic enteric flora

and symptoms of infection, since they are unable to mount an adequate inflammatory response.¹¹ Infection can disseminate widely and rapidly in patients with severe neutropenia. Nearly all episodes of bacteremia and disseminated fungal infection complicating neoplastic diseases arise in patients with neutrophil counts of less than 100/ml. The frequency of infection in acute leukemia is higher among patients whose neutrophils have reduced bactericidal capacity in vitro than among patients whose neutrophils function normally.¹²

Defects in the T lymphocyte and/or mononuclear phagocytic system result in an increased susceptibility to infection. Cell-mediated immunity plays a primary role in protecting against intracellular pathogens.¹³ Surgically implanted central venous catheters are utilized extensively in patients who require frequent vascular access. These catheters (Hickman, Broviac, and long lines) can have up to three lumens, greatly facilitate a variety of functions, including the drawing of blood, and may remain in the same location for prolonged periods, ranging from several weeks to months. Three separate types of device-related infection have been described: infection of the entry site, tunnel infection, and catheter-related bacteremia or fungemia.¹⁴

Bacterial infections

The variety of bacterial infections continues to change as newer antimicrobial agents become available and as therapeutic interventions for neoplastic diseases continue to evolve. During the past 7 to 10 years, there has been resurgence in gram-positive infections and a decrease in documented gram-negative infections.^{1,15-17} Although the exact reasons for this epidemiologic shift remain unclear, and several factors may be partly responsible. The most important factor is the increased use of catheters (i.e., central venous, peripheral, arterial), resulting in a parallel increase in catheter-related infections. Also, the use of antimicrobial regimens directed predominantly against gram-negative pathogens may reduce the incidence of (or the recovery of) such organisms from culture specimens. The predominant organisms which cause infections are as follows:

1. Enterobacteriaceae: The emergence of resistance to beta-lactam antimicrobial agents as a result of the production of type 1 and extended-spectrum beta-lactamases (ESBL) is of great concern.

2. Pseudomonas aeruginosa: It has been a leading cause of infection in the immunocompromised host and is associated with significant morbidity and mortality. The majority of *Pseudomonas* infections occur in patients with severe neutropenia.

Table 2: Shows details of total patients attending hospital and overall infection rate (Excluding patients treated on clinical grounds)

Unit	Total Patients attending hospital	Total sample receive in lab	Culture Positive	Infection rate (%) (No. of Infection)	GNB (Gram Negative Bacilli)	%	GPC (Gram Positive Cocci)	%	Fungus	%
Medical	13777	1212	249	1.81	162	65	71	28	16	6
Surgery	27955	636	333	1.19	184	55	88	26	26	8
Paediatric	2309	631	108	4.68	58	53	43	39	7	6
Gynec	4837	280	103	2.13	76	73	21	20	6	6
Radio Therapy	2035	41	15	0.74	4	26	8	53	3	20
Neuro Logy	859	48	25	2.91	15	60	6	24	4	16
Urology	62	4	3	4.84	3	100	0	0	0	0
Ortho paedic	487	58	16	3.29	11	68	4	25	1	6
Total	52321	2910	852	1.62	513	60	241	28	63	7

3. Acinetobacter Species: They are opportunistic pathogens and usually cause disease in debilitated patients and those with severe underlying conditions, including cancer. Recent data indicate that, *A. baumannii* remain the predominant species isolated from clinical specimens.¹⁸ Multi-drug resistance is common among these organisms and may complicate the treatment of serious infections.¹⁸⁻²¹

4. Staphylococcus Species: During the past 15 years, a marked increase in the incidence of infections caused by gram-positive organisms has been reported from most major cancer treatment centers. The majority of these are caused by *Staphylococcus* species. Among them MRSA and VRSA are of great concern.

5. Enterococcus Species: Infections caused by VRE (Vancomycin Resistance Enterococci) are much more common in patients with severe neutropenia. VRE are associated more often with recurrent infections, higher rates of refractory infections, and higher rates of serious morbidity and mortality.²²

Fungal infections

Fungal infections began to emerge as a significant problem among cancer patients once effective antibacterial agents became available and immunocompromised patients were surviving for prolonged periods. Most fungal infections occur in patients with hematologic neoplasms.²³ Observation in recent years is the increasing frequency of systemic fungal infections in patients undergoing initial remission induction chemotherapy for acute leukemia and lymphoma.

Frequently, this has been attributed to the widespread use of broad-spectrum antibiotics. Candidiasis and Aspergillosis are the commonest infection.

However, the recognition, prevention, diagnosis,

and treatment of infections in cancer patients will continue to challenge us in the foreseeable future, as we work towards the larger goal of eliminating cancer. Therefore we intended to have an:

1. Awareness regarding the prevalence of these infections in GCRI
2. Antibigram of isolated organisms
3. To formulate antibiotic policy

Materials and Methods

This is a retrospective analysis carried out from January to June 2013, to know the prevalence of infections (Bacterial and Fungal) in cancer patients attending different oncology units like medical, surgery, gynecology, paediatric, neurology, orthopedic, radiotherapy etc. for various treatment and diagnostic invasive procedures having signs or symptoms suggestive of any infection. The clinical history of patients was recorded. Between this periods a total of 2910 different samples like peripheral and catheter blood, urine, stool, sputum, broncho alveolar lavage (BAL), tissue, frank pus, wound swab and etc. were received in microbiology laboratory for bacterial/fungal culture and sensitivity from different units of the hospital.

All samples were subjected for microscopy and culture and sensitivity (bacterial and fungal) using standard bacteriology and mycology techniques (CLSI 2013 guidelines²⁴) on Fully automated bacteriology system (VITEK 2 Compact, Biomerieux, France) using different ID (Identification) and AST (Antibiotic Susceptibility testing by Minimum Inhibitory Concentration) kits procured from Biomerieux, France. CLSI 2013 M100-19 guidelines were used for MIC interpretation and NATURAL RESISTANCE guidelines used for therapeutic interpretation. Also AES (Advanced Expert System) parameter was used for analysis of test result and

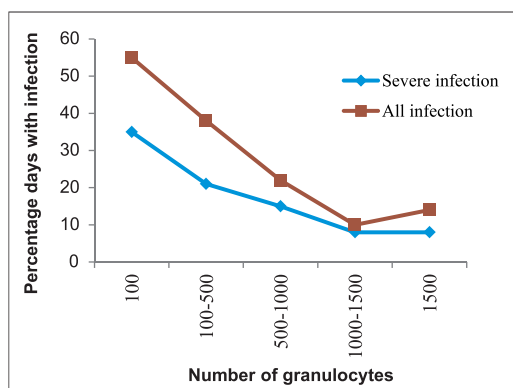


Figure 1: Relations between granulocyte count and infection in patients with acute leukemia. Percentage of days spent with infection is inversely related to the level of circulating granulocytes

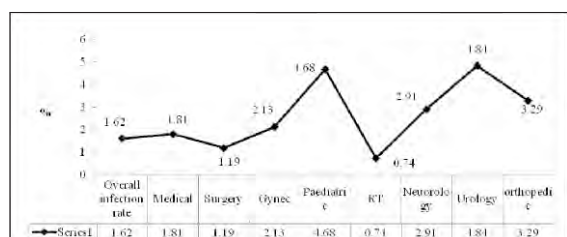


Figure 2: Department wise infection rate

detection of resistant organisms. Semi automated blood culture system (BACTEC 9050, Becton Dickinson) was used for blood (peripheral and catheter) samples.

Different strains of ATCC (American Type Culture Collection,) were used for quality control of identification and sensitivity in Vitek 2 Compact. ATCC strains were procured from Microbiologics, USA. The frequency of Quality Control was performed on monthly bases as per recommended guidelines.

Vitek 2 GN –QC set (containing *E.coli* ATCC 25922 & 35218, *P.aeruginosa* ATCC 27583, *Klebsiella pneumoniae* ATCC 700603), Vitek -2 AST-QC set (containing *Enterococcus faecalis* ATCC 51299), Vitek 2 GP-QC (containing *S.aureus* ATCC 25923) and *Candida krusei* ATCC 6258 for fungal culture and sensitivity, *Enterococcus faecalis* ATCC 51299 for VRE and high level gentamicin resistance, *S.aureus* ATCC 29213 and *E.coli* ATCC 35218 for beta lactamase production, *Klebsiella pneumoniae* ATCC 700603 for ESBL production and *S.aureus* ATCC BAA977 for inducible clindamycin resistance were used.

Statistical analysis

Data were entered and analyzed in WHONET 5.6 software (Developed by Department of Essential drugs and Medicines Policy in collaboration with Center for the surveillance of Antibiotic Resistance, WHO-Geneva, Switzerland). Infection rate is

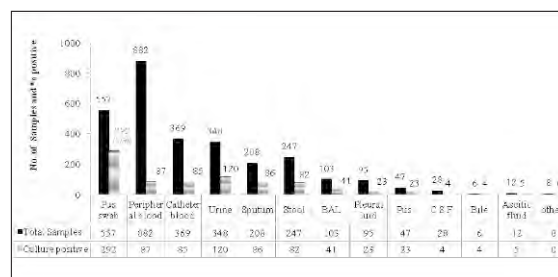


Figure 3: Positive cultures (N=852/2910)

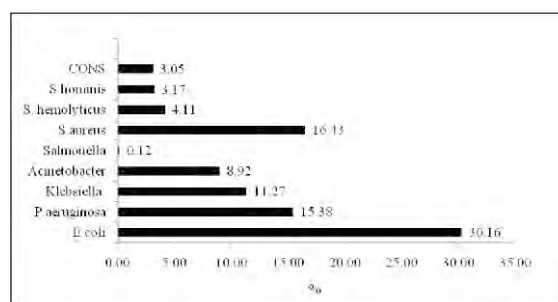


Figure 4: Bacterial isolates (N=789/852)

expressed as the number of patients with an infection per hundred numbers of patients attending hospital. Statistical analysis was performed using WHONET 5.6 and SPSS statistical software.

Results

Between January to June 2013, total of 2910 different sample were received in laboratory from different units of the hospital.

Out of total 52321 patients, 2910 different samples were received for a period of 6 months, 852 were culture positive (Table 2). Overall infection rate was 1.62 % (number of infection/100 patients). Infection rate was highest in urology 4.84% (3/62) followed by 4.68% (108/2309) in paediatric department, 3.29 % (16/487) in orthopedics, 2.91% (25/859) in neurology, 2.13% (103/4837) in gynecology, 1.81% (249/13777) in medical oncology, 1.19% (333/27955) in surgery department and lowest in radiotherapy department 0.74% (15/2035) (Figure 2). Amongst different samples, Peripheral blood, pus swab, catheter blood and urine. Pus swab (52%), Bile (66%) were more positive. Peripheral blood and C.S.F. samples were less positive (Figure 3). the analysis showed that; bacterial isolates were 92 % (789/852) and fungal isolates were 8 % (63/852). Amongst bacteria isolated, gram negative bacilli were 71 % (561/789) and gram positive cocci were 29 % (228/852). *E.coli* (30.16%) was the commonest organism isolated in all GNBs and *S.aureus* (16.43%) commonest in all GPCs. In fungal isolates, *Candida tropicalis* (30.15%) was the commonest isolates (Figure 4, 5).

Figure 6 shows antibiotic resistance pattern of isolated gram negative bacilli from different samples.

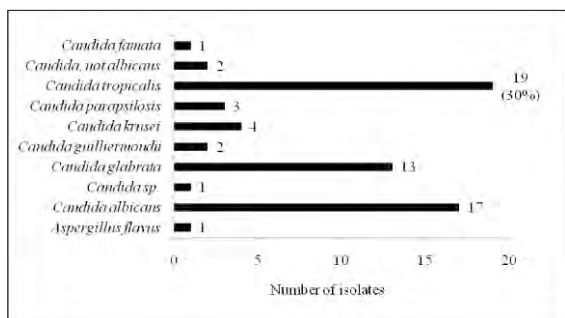


Figure 5: Fungal isolates (N=63/852)

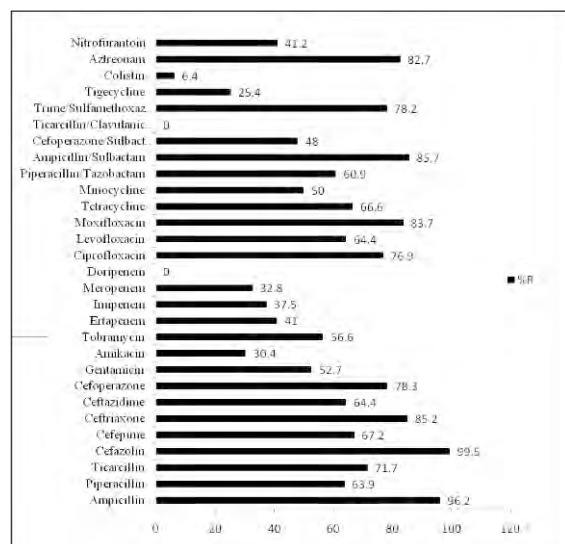


Figure 6: Antibiotic resistance pattern of GNBs by MIC (N=561/852)

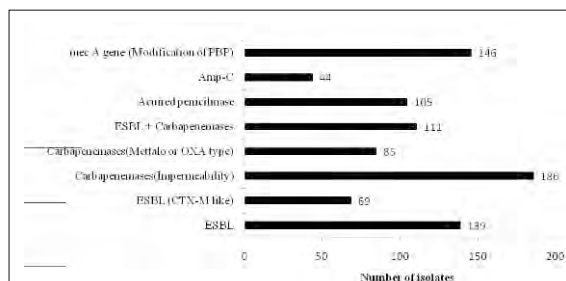


Figure 8: Resistance Mechanism in GNBs & GPCs by automated ID-AST system

It is seen that resistance of bacteria to penicillin group of antibiotics ranged from 63-96% to 3rd and 4th generation cephalosporin showed range of 64-99%, aminoglycosides showed 30-56%, and 32-41% showed resistance to Carbapenem group of antibiotics. GNBs showed resistance ranging from 64-83% to fluoroquinolones. Combination of Beta lactam and beta lactamase inhibitor showed resistance ranging from 48-85.7%. 75% and 70% of GNBs were sensitive to Tigecyclin and Amikacin respectively. 100% of the GNBs were sensitive to Doripenem. Figure 7 shows antibiotic resistance pattern of isolated gram positive cocci from different samples. It is seen that resistance of bacteria to penicillin group of

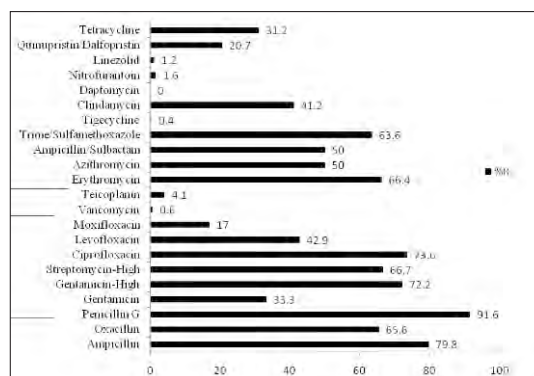


Figure 7: Antibiotic resistance patterns of GPCs by MIC (N=228/852)

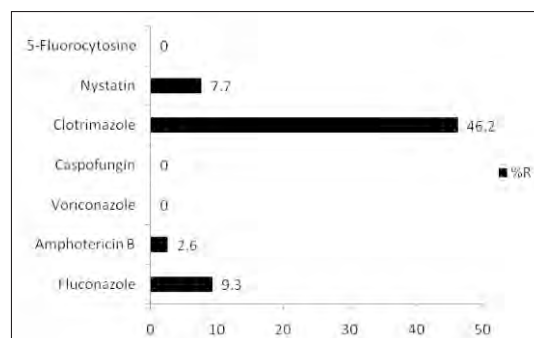


Figure 9: Antifungal Resistance Pattern by MIC method (N=63)

antibiotics ranged from 80-91%. High level resistance to Gentamicin and streptomycin in enterococci was 66% and 72% respectively. Resistance of GPC to aminoglycosides showed 33-72% and resistance from 17-73% to fluoroquinolones. 50-63% of gram positive cocci showed resistance to BL-BLIs (β lactam and β lactamase inhibitors). They also show resistance of 41% and 33% to clindamycin and gentamicin respectively. 100%, 99.4%, 98.2% and 95.9% of GPCs are sensitive to Daptomycin, Vancomycin, Linezolid and Teicoplanin respectively. Figure 8 shows different resistance mechanisms responsible for drug resistance in isolated bacteria. Amongst gram positive cocci, the number of cocci producing Amp-C is 44, mec-A gene expression is 146 and acquired penicillinase is 105. In the gram negative bacilli, there were several different mechanisms responsible for drug resistance, production of different enzymes like Extended Spectrum of Beta Lactamases (ESBL), Carbapenemases and impermeability to antibiotics. Amongst them Carbapenemases impermeability was in 186 isolates, followed by ESBL production. Certain isolates showed mixed pattern of resistance like ESBL and Carbapenemases in 111 strains. Figure 9 shows Antifungal resistance pattern of yeast isolates (candida spp.) from different samples, which showed, 46% resistance to Clotrimazole, followed by fluconazole (9.3%) and Nystatin (7.7%) and newer drug, caspofungin is 100% sensitive.

Discussion and Conclusion

Infection is a serious complication for many cancer patients. The bacterial infection continues to change, requiring continued monitoring the antimicrobial susceptibility of these isolates, and laying down the antibiotic policy. The emergence of newer pathogens, such as vancomycin-resistant enterococci, ESBL producer, multidrug resistance *Acinetobacter* are becoming increasingly difficult to treat due to the acquisition of resistance to commonly used antimicrobial agents.

In the present study, overall infection rate is 1.62%, whereas in another study conducted by C.wattal's et.al, the patient flow is of general category and their infection rate was 1.2% (1873infections/156083 patients).²⁵ Amongst different units' highest infection rate was found in urology department. But sample volume was very less in urology, so it is statically insignificant. Second highest was in paediatric department (4.68%).

Out of total 852 isolates, 60% were gram negative bacilli (GNBs), 28% gram positive cocci (GPCs) and 7% were *Candida* spp. In C.wattal's study,²⁵ 70% were gram negative bacilli, 20% gram positive cocci and 10% were fungus. In our hospital *E.coli* (30%) was the commonest isolate in GNBs, *S.aureus* (14%) in GPCs and in C.wattal's study *E.coli* was 28% and *S.aureus* 14%.

The GNB's resistance profile are similar to that of the analysis conducted by Dr. C.wattal et al Tigecyclin and Amikacin show lower resistance to GNBs, they can be the choice of treatment. Antibiotics like cefipime and ceftriaxone are currently contraindicated to use as 67-85 % of isolates are resistant. Resistance to Carbapenem group is increasing because of Carbapenemase production and impermeability to drug. Therefore of all the Carbapenems, Doripenem should be the first choice to treat infections followed by meropenem, imipenem and ertapenem. Colistin may be used in infection caused by multi drug resistance *Pseudomonas* species.

GPCs isolated shows 50% to 80% resistance to penicillin group of antibiotics, while C.wattal study analysis also noted the same pattern. High-level gentamycin resistance in enterococci was 72% in our hospital, while 100% in his study analysis. We have seen normal gentamycin resistance is 33%. It is stated that whenever the enterococci shows high level resistance it is indicated that when it is instituted with penicillin group of antibiotics it does not give synergistic bactericidal activity. Therefore gentamycin even though sensitive in-vitro will not be sensitive in-vivo. The antibiotics like Teicoplanin, Moxifloxacin can be used in the treatment of infections caused by GPCs.

As what is seen in the analysis of our work, the different types of resistance mechanisms noted are mec-A gene expression in *S.aureus*, Carbapenem impermeability in GNBs, carbapenemases and ESBL production etc. We need to be vigilant enough to start treatment with antibiotics as per the AST given through our reports, and the sensitivities performed in Microbiology is by MIC method. It is also seen that the *Candida* spp. have started becoming resistant to anti-fungal drugs like Clotrimazole being 54% sensitive. Thus, fluconazole and amphotercin B can still be considered as the choice of treatment, as it shows lower resistance.

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“What we are doing to the forests of the world is but a mirror reflection of what we are doing to ourselves and to one another.”

Mahatma Gandhi

Myths and Facts about Cancer- Cancer can be Cured!

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Department of Medical and Pediatric Oncology

February 4th is celebrated as the World Cancer Day and it gives a chance to raise our collective voices in the name of improving general knowledge around cancer and dismissing misconceptions about the disease. This year the theme of the World Cancer Day 2013, i.e. February 4, 2013 was to focus on “Dispel damaging myths and misconceptions about cancer, under the tagline “Cancer-Did You Know?”¹

Knowledge is a powerful weapon to fight against the cancer. Unfortunately, there are many myths around cancer prevailing in the community and among the medical fraternity as well. It is very imperative to squash all those myths about cancer because it is the major obstacle to cure of the cancer. The very purpose of this article is to squash all those 'popular beliefs' about cancer and to spread awareness about cancer and its outcome.

Myth: Cancer is a death sentence¹ The belief about cancer that it is incurable disease; it is fatal disease, cancer equals to 'cancel' and cancer means 'death warrant'.

Fact: Many cancers, which were once considered a death sentence, now can be cured and for many more people, their cancer can be treated effectively. Advances in understanding risk and prevention, early detection and treatment have totally revolutionized the management of cancer leading to improved outcomes for patients. With few exceptions, early stage cancers are less lethal and more treatable than late stage cancers. Cancer is treatable and curable provided detected early, diagnosed properly and treated optimally by an expert. Many factors influence the cure of cancer. Cure rate of various common cancers and the conditions require to cure the cancers are described in detail in this article.

Myth: Cancer is just a health issue¹

Fact: Cancer is not just a health issue. It has wide-reaching social, economic, development, and human rights implications. Cancer constitutes a major challenge to development, undermining social and economic advances throughout the world. Approximately 47% of cancer cases and 55% of cancer deaths occur in less developed regions of the world. The situation is going to get worse by 2030, if current trends continue cancer cases will increase by 81% in developing countries. Cancer is both a cause

and an outcome of poverty. Cancer negatively influences families' ability to earn an income, with high treatment costs pushing them further into poverty. At the same time, poverty, lack of access to education and healthcare increases a person's risk of getting cancer and dying from the disease.

Myth: Cancer is a disease of the wealthy, elderly and developed countries¹

Fact: Cancer is a global epidemic. It affects all ages and socio-economic groups; with developing countries bearing a disproportionate burden. Cancer is a global issue and becoming an increasing public health problem in poorer countries. Cancer now accounts for more deaths worldwide than HIV/AIDS, tuberculosis and malaria combined. Of the 7.6 million global deaths from cancer in 2008, more than 55% occurred in less developed regions of the world. By 2030, 60-70% of the estimated 21.4 million new cancer cases per year are predicted to occur in developing countries.

Myth: Cancer is my fate¹

Fact: With the right strategies, a third of the most common cancers are preventable. Prevention is the most cost-effective and sustainable way of reducing the global cancer burden in the long-term. Global, regional and national policies and programme that promote healthy lifestyles can substantially reduce cancers that are caused by risk factors such as alcohol, unhealthy diet and physical inactivity. Improving diet, physical activity and maintaining a healthy body weight could prevent around a third of the most common cancers. Based on current trends, it is estimated that tobacco use can kill one billion people in the 21st century. Addressing tobacco use, which is linked to 71% of all lung cancer deaths, and accounts for at least 22% of all cancer deaths is therefore critical. Chronic infections estimated to cause approximately 16% of all cancers globally, with this figure rising to almost 23% in developing countries. Several of the most common cancers in developing countries such as liver, cervical and stomach cancers are associated with infections with hepatitis B virus, the human papillomavirus, and the bacterium *Helicobacter pylori* respectively. Exposure to a wide range of environmental causes of cancer in our personal and professional lives, including exposure to

Table 1: Warning signals of cancer ²⁻⁷

Adult	Children
C - Change in bowel/bladder habit	Continued, unexplained weight loss
A - A sore that does not heal.	Headaches with vomiting in the morning
U - Unusual bleeding from any orifice	Increased swelling or persistent pain in bones or joints, sometimes accompanied by limping
T - Thickening/Lump anywhere in the body	Lump or mass in abdomen, neck or elsewhere
I - Indigestion/Inability to swallow or inability to breathe	Development of a whitish appearance in the pupil of the eye or sudden changes in vision
O - Obvious change in a mole/wart	Recurrent fevers not due to infections
N - Nagging cough, hoarseness of voice	Excessive bruising or bleeding (often sudden)
	Noticeable paleness or prolonged tiredness

Table 2: Various control measures for prevention of cancer ⁵⁻⁷

Control Measures	Prevention of Cancers
1 Control of tobacco and alcohol	Cancers of Oral Cavity, Pharynx, Larynx, Lung and Oesophagus
2 Personal hygiene	Cervix, Penis
3 Prevention of radiation exposure	Leukaemia
4 Prevention of occupational exposure to industrial carcinogens	Benzene Leukaemia Asbestos Mesothelioma of Pleura Benzidine Bladder
5 Immunization i.e.Hepatitis-B vaccine	Primary Liver cancer
6 Prevention of air pollution	Lung cancer
7 Treatment of precancerous lesions	Cervical, Oral, Colon cancers
8 Legislation to control tobacco, alcohol, air pollution etc.	Oral, Lung and Esophagus cancers
9 Education to motivate people to seek early diagnosis and treatment	All types of cancers

indoor air pollution, radiation and excessive sunlight are also major preventable causes of cancer

Myth: Cancer is a single disease

Fact: Cancer is a heterogeneous group of disorder. There are more than 200 different types of cancer, identified based on their organ of origin and morphological characteristics. Each of these cancers has its own natural history, biological behavior, unique therapy, response to therapy and outcome. It is imperative to diagnose each cancer precisely based on the morphology with the aid of immunohistochemistry, immune phenotyping, cytogenetic and molecular diagnostics.

Myth: Cancer is hereditary²

Fact: It is true that some cancers are genetic but this does not mean that one will definitely develop cancer because of their heredity. Only few cancers are hereditary, however remaining more than 90% of cancers are not hereditary. It is believed that those having family history of cancer among the first and second-degree relatives are more prone to develop cancer but the transmission rate is very low and ultimately, it is the individual's susceptibility that

determines the development of cancer even in the setting of a positive family history. Cancer such as breast, colon, and ovary are few of the cancers that can pass down genetically.

Myth: Cancer is infectious and contagious²

Fact: Basically, cancer is a disease of the cell. It is caused by an alteration in the genetic material i.e. DNA unit of the cell, leading to changes in the oncogenes and proto-oncogenes which ultimately transforms normal cell into the cancerous cell. Cancer is uncontrolled growth of the cells, which accumulates and results into tumor. Therefore, cancer cannot be infectious and contagious.

Myth: Early detection of cancer is not possible

Fact: It is possible to detect cancer in early stage. It is possible to detect in very early i.e. precancerous stage means 'in situ' cancer or microinvasive stage. Sometimes, cancer is preceded by various 'warning signals' (Table 1) which can help in the early diagnosis of cancer. Astute observation and awareness on part of the physician can diagnose cancer in early stage. Moreover, there are various successful screening methods available with the help of which many

common cancers like breast, lung, prostate, cervix, and head and neck can aid in early diagnosis. For cancers having hereditary predisposition, genetic testing are available that can help in predicting risk for cancer to progeny. Persons who are at high risk for developing cancer can opt various treatment options like chemoprevention, prophylactic surgeries and close surveillance to prevent development of cancer in the future.

Myth: Cancer is not preventable²

Fact: Cancer prevention is a reality. It is possible to prevent cancer adopting healthy life styles, modifying the risk factors, chemoprevention and prophylactic surgeries whenever appropriate. 'It is better to stay away from trouble rather than to get out of trouble'. There are various control measures for prevention of various types of cancer (Table 2).

Myth: Surgery alone can cure the cancer

Fact: Surgery is very important component in the comprehensive management of cancer and surgery alone may cure cancer in highly selected cases however, surgery alone is not sufficient treatment in many cancers. This is partly because majority of time, cancers are diagnosed in very late stage and so subsequent treatment therapy in the form of adjuvant chemotherapy, radiation therapy, or both is needed. So it becomes imperative to seek opinion of medical oncologists to determine the need for the further treatment. Moreover, surgery has very limited role in the management of various hematological malignancies.

Myth: Chemotherapy cannot cure the cancer, is always very painful and causes many side effects

Fact: Chemotherapy alone is curative in acute leukemia, aggressive lymphomas, multiple myeloma, chronic leukemia, germ cell tumor, and choriocarcinoma. Chemotherapy is not free from side effects but most of the side effects are self-limiting, tolerable and reversible. With the availability of good supportive care like growth factors, cyto-protective agents, antibiotics and blood component therapy, most of the side effects are manageable.

Myth: Cancer is not treatable in advanced stage

Fact: Patients with presenting with advanced stage cancer should offered treatment. Cancer treatment improves the quality of life. It may prolong the survival. It may cure the cancer in selected situations. Germ cell tumor, Choriocarcinoma, Hodgkin's lymphoma and all hematological malignancies are some of the cancers, which are possible to cure, even in the advanced stage.

Myth: Cancer does not affect children

Fact: In general, older individual are more prone to develop cancer because of aging process but with changing life styles younger are equally susceptible to develop cancer. Cancer in children is not uncommon. There is a separate Pediatric oncology division at the Gujarat Cancer Research Institute, which registers approximately 1000-1200 Pediatric cancer cases every year.

Myth: Ayurvedic medicine is safe and can cure cancer

Fact: Allopathic medicines are widely used across the globe, extensively tested in the controlled clinical trials, it is very effective and the results are reproducible. While in case of ayurvedic medicines, there are no such scientific proofs available for its efficacy and safety, in such circumstances; in absence of robust evidence, it is very difficult to believe that ayurvedic medicine can cure the cancer especially in the era of evidence-based medicine.

Myth: Positive attitude can cure the cancer²

Fact: It is good to have positive attitude. Positive attitude helps in coping up with cancer diagnosis, its treatment and its consequences. It improves the overall outlook of cancer treatment. However, positive attitude alone cannot cure the cancer because cancer is something more than 'Mind over matter'.

Cure in cancer: A reality? or an illusion?

With recent advances and availability of many therapeutic options, cure in cancer is not at all an illusion; gradually it is becoming a reality. Various treatment modality used and cure rate of various common cancers are shown Table 3.

Cancer can be cured, but conditions apply!⁵⁻⁷

Many factors determine the cure of cancer. Curative nature of cancer is the inherent property of many cancers while certain cancer is incurable by nature. Nonetheless, even among curative cancers, many factors that influence the cure of the cancer. We consider them as conditions or prerequisite for achieving the cure, these are

Condition 1: Early detection, it is very important to detect cancer in early stage. It is easy to treat cancer in early stage. It requires less efforts and success rate is very high. Detection and treatment of cancer in advanced stage results in the dramatic fall in cure rate, despite adequate treatment. Early stage cancer is relatively easy, to treat requires less intensive treatment and success rate is very high.

Table 3: Treatment modality used and cure rate of various common cancers ⁵⁻⁷

SN	Common cancer	Treatment modality	Disease free survival at 5 years
1	Acute Lymphoblastic leukemia	Combination chemotherapy with some form of central nervous system prophylaxis	5-85%-85%for children
2	Brain Tumor	Complete resection confers good prognosis, helps in tissue diagnosis, symptom relief and cytoreduction. It is curative in low-grade tumour. Radiation therapy is useful in adjuvant / palliative setting and for tumours at inaccessible site. Chemotherapy improve the survival and helps to reduce the use of radiation.	90% for low grade astrocytomas with complete surgical resection 25%for high-grade tumor with incomplete surgical resection.
3	Ewing's Sarcoma (bone and soft tissue malignant tumor)	Surgical resection followed by chemotherapy and radiation therapy. Organ or limb sparing surgery is preferred and possible in majority of cases with the help of chemotherapy.	70% for non- metastatic disease 30%for metastatic disease
4	Gestational trophoblastic disease	Usual treatment is chemotherapy	80-100% for low risk disease 70-80% for high-risk disease
5	Germ cell tumor	Complete surgical resection is the mainstay of treatment followed by 4-6 cycles of adjuvant chemotherapy to the majority of patients	>90 % , for stage I and II while 80% for stage III and IV
6	Hepatoblastoma	Complete surgical resection is the mainstay of treatment followed by adjuvant chemotherapy for 4-6 courses. For unresectable disease, neoadjuvant chemotherapy followed by surgery and post-operative chemotherapy is preferred.	90-100% for stage I, 90% for stage II, 69% for stage III, 40% for stage IV
7	Hodgkin's Lymphoma	Combination chemotherapy ABVD (Adriamycin, Bleomycin, Vinblastin and Dactinomycin), Radiotherapy for bulky disease/ involved field	>90%for stage I and II more than 70% for stage III and IV
8	Lung cancer	Surgical resection is treatment of choice in early stage followed by radiation therapy and chemotherapy. In advanced stage, palliative chemotherapy and targeted therapy is useful.	60-70% for stage I, 30-50% for stage II, 10-30%for stage IIIA, 5-10% for stage IIIB & IV
9	Neuroblastoma	Surgical resection is preferred whenever possible. Radiotherapy with chemotherapy for bulky tumor and high-risk disease require high dose chemotherapy with autologous stem cell transplantation.	80-90% for stage I 60-80% for stage II 30-50% for stage III 7% for stage IV
10	Osteosarcoma	Usual treatment is surgical resection and chemotherapy. Limb sparing surgery is preferred and possible in majority of cases with the help of chemotherapy.	55-85%for non metastatic disease 20-30% for metastatic disease
11	Retinoblastoma	Both vision and eye can be salvageable with various local treatments like laser photocoagulation or focal radiotherapy along with chemo reduction to facilitate the local treatment. It is almost incurable if detected in advanced stage and vision cannot be salvageable.	90% for early stage 10-30% for advanced stage
12	Rhabdomyo sarcoma	Surgical resection followed by chemotherapy and radiation therapy. Organ or limb sparing surgery is preferred and possible in majority of cases with the help of chemotherapy.	72- 92% for stage I 65-75% for stage II 60% for stage III 50%for stage IV
13	Wilms' tumour	It is treated with surgical resection followed by chemotherapy and radiation therapy as per the stage and histology	94-98% for favorable histology, early stage , 82-88% for favorable histology, advanced stage, 70-80% for unfavorable histology, early stage, <50% for unfavorable histology, advanced stage

Condition 2: Proper diagnosis, it is mandatory to plan optimum treatment and to achieve cure. As we know that cancer is not a single disease. It is heterogeneous group of disorders with different biology, clinical behavior and outcome. It is obligatory to diagnose exact morphological types, genetic type and molecular subtype of each cancer for proper treatment decision. To understand this we can take help of example of acute leukemia. Acute leukemia are of two types, acute myeloid leukemia (AML) and acute lymphoid leukemia (ALL). Treatment of both leukemia is very different. AML have eight different subtypes from AML M0 to AML M7. Treatment of M3 subtype is different from non-M3 subtype. Non-M3 subtypes have two subtypes i.e. favorable and unfavorable group depending upon their cytogenetic profile. Those having favorable cytogenetic do not require stem cell transplantation but in unfavorable cytogenetic, cure rate is very low without stem cell transplantation. Same thing in with ALL too, treatment of ALL-L3 is different from ALL L1 and L2. In non-L3 ALL, it is very important to look for the Philadelphia (Ph) chromosome, because the treatment of Ph positive ALL is different from Ph negative ALL. This example highlights the proper diagnosis and tailoring the treatment accordingly.

Condition 3: Optimum treatment, it includes proper surgery as per principles of oncology, adequate clinical and pathological staging, proper dosing and scheduling of chemotherapeutic agents (maintaining

their dose intensity and density), adherence to the protocol and compliance, and completion of treatment.

Condition 4: Treatment by an expert, only oncologist, who is formally trained, should treat cancer. Surgical oncologist should preferably perform surgery. It has been studied in ovarian cancer that, survival is inferior if general gynecologist performs surgery as compared to gynecologic oncologists. There are laid down principles of cancer surgery and it should be strictly followed to achieve the desire cure rate. Medical oncologists must plan and execute the chemotherapy treatment. They are well versed in the planning and handling the issues related to the chemotherapy treatment and its toxicities.

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“If we surrendered to earth's intelligence we could rise up rooted, like trees.”

Rainer Maria Rilke,
Rainer Maria Rilke's the Book of Hours: A New Translation with Commentary

T-Cell-Rich B-Cell Lymphoma of Head and Neck Region with Waldeyer's Ring Involvement: A Case Report

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Summary

T-cell-rich B-cell lymphoma (TCRBCL) is a recently described variant of diffuse large B-cell lymphoma characterized by a predominance of reactive T-cells and a minority of neoplastic large B cells. It is a rare entity, accounting for approximately 1 to 2% of all non-Hodgkin's lymphomas. Morphologically it closely resembles with nodular lymphocyte predominant Hodgkin's lymphoma and peripheral T-cell lymphoma (PTCL). It has both nodal and extranodal presentation. Primary TCRBCL of head and neck region with waldeyer's ring involvement is an extremely rare presentation and only few cases has been reported. We report the case of a 74 year old man presented with cervical lymphadenopathy and waldeyer's ring involvement.

Keywords: T-cell-rich B-cell lymphoma, Non-Hodgkin's lymphoma, Waldeyer's ring, DLBCL, Extranodal lymphoma

Introduction

Diffuse large B-cell lymphoma is the largest subtype of non-Hodgkin's lymphomas, and is characterized by frequent extra nodal presentation. T-cell-rich B-cell lymphoma (TCRBCL) is an uncommon morphologic variant of diffuse large B-cell lymphoma (DLBCL) representing 1 to 3% of all DLBCLs. Most patients with TCRBCL present with nodal disease involving various sites of body. Extranodal involvement of liver, soft tissue, spleen, nasopharynx, mediastinum and bone has been reported.¹

Here we report a case of T-cell-rich B-cell lymphoma (TCRBCL) with thyroid gland and waldeyer's ring involvement.

Case Report

A 74-year-old man presented with history of pain in throat, dysphagia and hoarseness of voice since one month. Physical examination revealed left side cervical lymphadenopathy without any organomegaly. Laboratory evaluation including CBC, RFT and LFT were normal except mildly elevated LDH. Computerized tomography (CT) scan neck and para nasal sinuses (PNS) showed diffuse infiltrative soft tissue lesion in lateral and posterior pharyngeal wall, tonsillar fossa and nasopharynx (waldeyer's ring) with obliteration of oropharyngeal lumen. PET-CT confirmed the conglomerated cervical lymphadenopathy and involvement of waldeyer's ring, thyroid gland with erosion of thyroid cartilage.

Biopsy of lymph node showed predominant population of small lymphocytes and admixed with these, there were scattered large cells with prominent nucleoli resembling Lymphocytic and histiocytic (L&H) variants of Reid-Sternberg cells (RS). The immunohisto-chemical analysis revealed the large cells to be positive for LCA, CD20, CD79a, CD30 (B-cells) and negative for CD15, ALK-1, EMA, Cyclin-D1. The small lymphocytes were positive for CD2, CD3(T-cell). These histological and immunohisto-chemical findings led to diagnosis of TCRBCL.

The patient is presently receiving Rituximab based chemotherapy (R-CEOP regimen) and is doing well until now. This is a rare presentation as it primarily involves head and neck region with extranodal involvement.

Discussion

T-cell-rich B-cell lymphoma (TCRBCL) is a rare variant of diffuse large B-cell lymphoma accounting for 1 to 2% all cases. Most patients present with nodal disease, although extranodal involvement also occurs.^{2,3} The common extranodal sites reported are liver, soft tissue, bone, stomach, intestine, bone marrow and nasopharynx. TCRBCL predominantly involving head and neck region with waldeyer's ring involvement rarely reported.^{2,3}

Histological characteristics of TCRBCL is predominant population of reactive small T cells with a minority of neoplastic B-cells. The neoplastic large B-cells constitute less than 20% to 25% of the total cellular population. T-cell component, by definition, must be greater than 50% at minimum. It has morphologic features similar to peripheral T-cell lymphoma (PTCL) and lymphocyte predominant hodgkin's disease (LPHD).^{4,5}

It has been seen that immunohistochemistry provides the best adjunct to morphologic diagnosis in TCRBCL. Early diagnosis of this entity is important to ensure proper treatment.⁶ Since the morphology of the neoplastic cells in TCRBCL resembles L&H variants of RS cells, differential diagnosis between TCRBCL and LPHD is necessary. Although L&H variants usually display a positive staining for CD45

and CD20, but negative staining for CD15, the relatively high content of CD57+ T lymphocytes and their rosette like arrangement around the neoplastic (RS) cells are typically seen in LPHD.

Conclusion

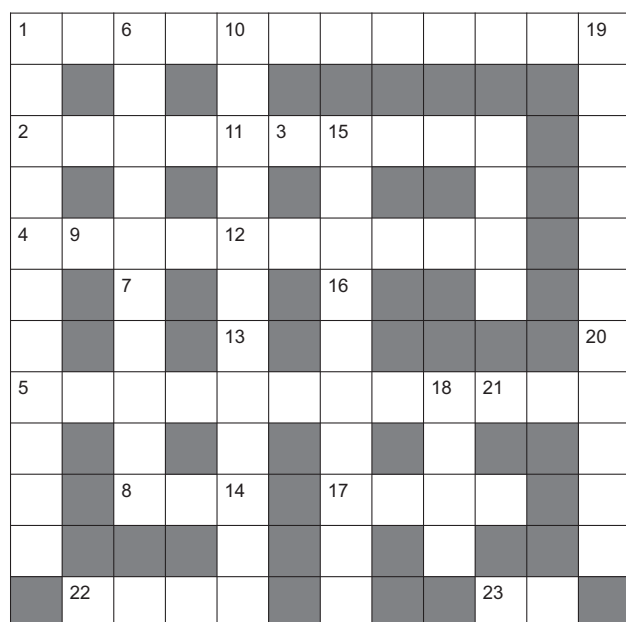
We report a rare case of TCRBCL of head and neck region with thyroid gland and waldeyer's ring involvement. The correct diagnosis was made on the basis of morphology and immunohistochemistry. Differentiation from PTCL and LPHD is important as it morphologically resembles with them. It should be treated in the same manner as an aggressive non-Hodgkin's lymphoma.

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Crossword Puzzle-IV

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ACROSS

- 1) Which is the most common bone tumour in adults (12)
- 2) Which is the premalignant condition preceding invasive cancer (9)
- 3) Hepatocellular carcinoma is common in which race (5)
- 4) Dr Harold Varmus is the director of which institute (3)

- 5) Drug used to treat her2 positive breast cancer (11)
- 8) Tumour marker for Choriocarcinoma (3)
- 9) Most common nephrotoxic platin (9)
- 17) OCP can be used in which skin lesion (4)
- 21) Gene responsible for CML located in chromosome number 9 (3)
- 22) Protocol used for neuroblastoma (4)
- 23) Regimen used for CLL (2)

VERTICAL

- 1) Most common antiemetic used for moderate emesis (11)
- 6) Male reproductive organ (6)
- 7) Most common endocrinal paraneoplastic syndrome associated with small cell lung carcinoma (5)
- 10) Substance put in oil immersion lens (3)
- 11) Score used to differentiate between leukemia and leukemoid reaction (4)
- 12) Questionnaire designed to help, assess the management and performance of programs (4)
- 13) Name of one of radiation Trial (4)
- 14) Recent Noble Prize in physics is for which particle (3)
- 15) Lux is an example of (4)
- 16) Name of a fast food (5)
- 17) Crizotinib acts on which gene (3)
- 18) One of the protocol for relapsed DLBCL (4)
- 19) One of element responsible for mesothelioma (7)
- 20) Synonym for distributed computing over a network (5)

Primary Diffuse Large B-Cell Lymphoma of the Urinary Bladder

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Summary

Primary lymphoma of the urinary bladder is rare; primarily, it is extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT-lymphoma). There are few case reports of primary diffuse large B-cell lymphoma (DLBCL) of the urinary bladder, accompanied by diffuse wall thickening of the bladder. Here, we report a case of primary DLBCL of the bladder in a 75-year-old male patient, with diabetes mellitus, coronary artery disease and diabetic nephropathy.

Keywords: Lymphoma, Diffuse large B-cell lymphoma, Urinary bladder

Introduction

Involvement of urinary bladder in lymphoma is rare, and it represents 0.2% of primary and 1.8% of secondary lymphomas. Primary bladder lymphoma is mainly extranodal marginal zone B cell lymphoma of mucosa-associated lymphoid tissue (MALT-lymphoma) and less than 20% of cases are diffuse large B-cell lymphoma (DLBCL). In most cases of primary lymphoma of the bladder, the tumor is observed as a nodule in the bladder wall. There are few case reports of primary DLBCL of the bladder, accompanied by diffuse wall thickening of the bladder. Here, we report a case of primary DLBCL of the bladder with diffuse wall thickening in a 75-year-old male patient, presented with complaints of hematuria and low grade fever.

Case Report

A 75-year-old man with comorbidities like diabetes mellitus, coronary artery disease and diabetic nephropathy since 10 years for which he was on regular treatment presented with complaints of hematuria, low grade fever and general fatigue for one month presented to urologist. There was no past history of recurrent cystitis. On general physical examination, anemia, lymphadenopathy or hepatosplenomegaly was not found. Urine routine and microscopy was suggestive of hematuria and proteinuria. An abdominal sonography demonstrated minimal dilatation of pelvicalyceal system in both kidneys with slightly thickened bladder wall (7 - 9

mm). Transurethral resection of bladder thickening was done. Biopsy was suggestive of high grade lymphoma. Immunohistochemistry was positive for CD20 and LCA and negative for Vimentin and AE-1 suggestive of DLBCL (Figure 1 and 2). Bone biopsy was normal. FDG PET-CT scan demonstrated no FDG avid lesion in the bladder and in other organ. Hence, the final diagnosis was primary diffuse large B-cell lymphoma (DLBCL) of the bladder i.e. Stage IE.

On laboratory evaluation, he had markedly elevated levels of blood urea nitrogen (52 mg/dl), creatinine (2.81mg/dl) and LDH (1531 U/ml). Creatinine clearance was below 30 and uric acid was 5.9 mg/dl while other hematological parameters like LFT and coagulation profile were normal. 2D Echo was suggestive of LVEF 55%.

In view of advance age and significant comorbidities like diabetes, coronary artery disease, diabetic nephropathy he was treated with nonanthracycline based chemotherapy. He received three courses of Rituximab, Cyclophosphamide, Etoposide, Vincristine, Prednisolone (R-CEOP) with Growth factor (G-CSF) support. Dose of chemotherapy was modified as per creatinine clearance. Patient tolerated chemotherapy well and no major side effect like myelotoxicity, febrile neutropenia, infections and noninfectious complication (cardiac, renal) related to chemotherapy were observed. However, patient was lost to follow up after 3 courses of chemotherapy.

Discussion

Primary lymphoma of the bladder is a rare disease, first described by Eve in 1885,¹ representing less than 0.2% of extra nodal lymphomas.² Patients with bladder lymphomas can be divided into 3 groups, according to their clinical presentation: a) primary cases in bladder, b) cases occurring in bladder as a manifestation of systemic disease, and c) secondary cases, with clinical history of malignant lymphoma recurring in bladder. Among cases of bladder

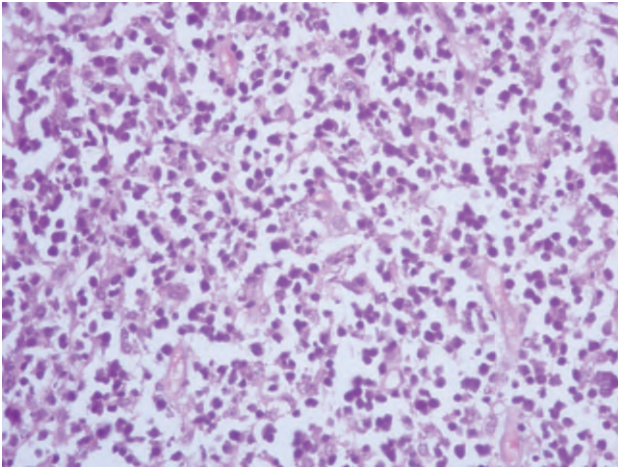


Figure 1: Large round cell in discohesive pattern with background of Apoptosis (H and E staining, $\times 40$)

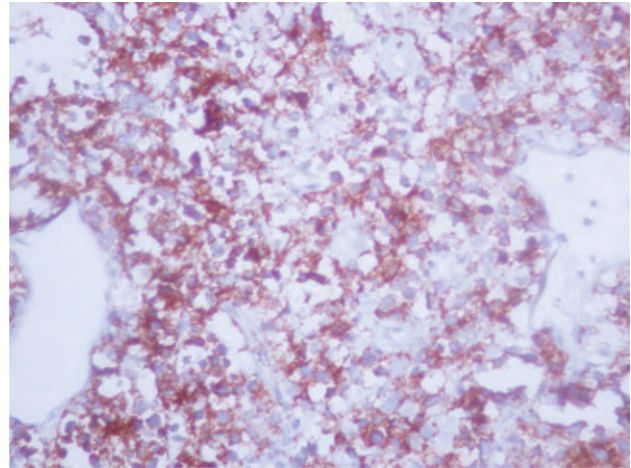


Figure 2: Membranous CD20 positivity for the atypical lymphoid cells ($\times 40$)

lymphoma, approximately 17% occur in primary form, 47% in non-localized form, and 36% in secondary form.³ MALT-type lymphomas are the most common form of primary involvement of the bladder. Primary lymphoma of the bladder affects women 6.5 times more than men, with a mean age of 64 years ranging from 20 to 85 years.⁴ Al-Maghrabi et al in 2001, studied 84 cases of primary bladder lymphoma.⁵

The major symptoms of primary bladder lymphoma are hematuria, urinary frequency and dysuria. A history of chronic cystitis, approximately 20% has been shown to be a preceding feature in some cases.⁴ However, in the present case, there was no past history of recurrent cystitis. Systemic lymphoma should be excluded by clinical and radiological finding. The most common images in the case of primary bladder lymphoma are nodule formation in the bladder wall. Few patients may also present with thickening of bladder wall. In our case, there was thickening of bladder wall. Hydronephrosis is uncommon feature in primary bladder lymphoma. PET scan demonstrated no FDG avid lesion in the bladder as well as in other organs. There are few cases of primary lymphoma of the bladder, where the wall was diffusely thickened by tumor involvement.^{4,6-8}

Diagnosis of bladder lymphoma is confirmed by histopathological examination in our case it was low grade lymphoma. Approximately 20% of B-cell bladder lymphoma is high grade⁹ and most such high grade bladder lymphomas are the DLBCL type.¹⁰ In this case, biopsy was positive for CD20 and LCA, indicating a diffuse large B-cell lymphoma. AE-1 and Vimentin negativity rules out possibility of carcinoma.

Previously, chemotherapy, radiotherapy and surgery were preferred as a single or combination therapy to treat patients with primary lymphoma of the bladder.^{2,5,9,11} The most commonly used

chemotherapy protocol is R-CHOP for primary B-cell lymphoma of the bladder.⁵ Due to the patient's age, cardiac dysfunction and renal dysfunction, we substituted etoposide for doxorubicin and three courses of R-CEOP chemotherapy were given. The omission of doxorubicin in patients who are frail, have poor baseline cardiac function may compromise outcome.¹² However, the recent introduction of rituximab may allow for improved outcomes without the use of doxorubicin. The 5-year time to progression was similar for patients treated with R-CEOP compared to patients in the R-CHOP control group, 57% versus 62%, respectively ($p=0.21$). The 5-year overall survival was lower for patients receiving R-CEOP compared with the R-CHOP control group (49% versus 64%, $p=0.02$), reflecting the underlying co-morbidities and frailty of this population.¹² There is no consensus regarding the treatment of primary lymphoma of bladder. Patient with high grade lymphoma should be considered to have systemic disease and therefore require chemotherapy.

Since our patient presented with high grade lymphoma of the bladder, we chose systemic chemotherapy and not radiation and surgery. Radiotherapy might have been chosen if the lymphoma would have been low grade and localized in the bladder. The role of surgery is controversial, as it is possible that the lymphoma will relapse in the other organs and surgical extraction of the bladder definitely reduces the quality of life. The prognosis of primary high grade lymphoma of the bladder is more favorable because, by definition, they are, at the time of diagnosis, confined to a single organ, and this difference justifies investigation to exclude systemic lymphoma if a high grade lymphoma is diagnosed in a biopsy.¹³

Conclusion

Primary diffuse large B lymphoma of bladder is a rare disease and it may present as diffuse wall thickening of bladder. Thorough staging workup with PET-CT scan should be done to rule out systemic or secondary lymphoma. It is important to differentiate it from low grade lymphoma by morphology and immunohistochemistry as treatment management may change. Rituximab based chemotherapy is an effective treatment for high grade bladder lymphoma and one may consider substitution of anthracycline with etoposide in patient with cardiac dysfunction and advanced age.

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“A nation that destroys its soils destroys itself. Forests are the lungs of our land, purifying the air and giving fresh strength to our people.”

Franklin D. Roosevelt

Splenic Infarcts Following Treatment with Filgrastim - An Unusual Complication

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Summary

We report a case of acute lymphoblastic leukemia (ALL) with baseline splenomegaly (pretreatment) on chemotherapy having splenic problems while on treatment with filgrastim for chemotherapy related neutropenia. We suggest strict adherence to cautious prescription of filgrastim with 'five microgram per kilogram per day' dosage for a maximum of 14 days per month with an extra vigilance for patients with pretreatment splenomegaly. We have documented the decreased level of antithrombin III with filgrastim related adverse effect, which is open for further confirmation of association.

Keywords: Filgrastim, Splenic infarcts, Leukemia

Introduction

Splenic problems are known complications of filgrastim therapy. Filgrastim therapy is often unavoidable supportive therapy in chemotherapy related neutropenia. Physicians often come across patients having baseline splenomegaly who are candidates for chemotherapy and subsequent filgrastim therapy. We discuss one of such situations which shows the importance of optimum dose of filgrastim therapy in such cases.

Case Report

A fifteen year old male weighing 34 kg, presented with breathlessness and fatigue since one month. He had recent history of multiple blood transfusions inspite of no previous history of bleeding. Patient was conscious, oriented and all his vital parameters were normal. On general examination, he was found to have severe palor, no icterus, lymphadenopathy, cyanosis, oedema or clubbing. He had bone tenderness. On systemic examination, cardiovascular system, central nervous system and respiratory system were normal but per abdominally he revealed moderate splenomegaly i.e. 5 cm palpable below costal margin. He had no past or family history of any medical illness.

Complete blood count (CBC) on first presentation showed, haemoglobin (Hb) - 4.4 g/dl, total leucocyte count (TLC) - 23000/ μ l with 28 % blasts, platelet count (PLC) - 1000/ μ l, with normal liver (LFT) and renal function tests (RFT). On bone marrow examination the morphologic picture was hypercellular marrow, 89 % blasts, high nucleus/

cytoplasmic ratio, altered myeloid/ erythroid ratio, lack of megakaryocytes, morphologically suggesting acute lymphoblastic leukemia (ALL). On immunophenotyping (IPT), the blasts mainly expressed B lymphoid markers CD79a (92%), CD 19 (99%), CD22 (33%) and Tdt (88%) along with CD34 (79%), HLADR (98%) and CD 10 (99%). Co-expression of CD34/CD22 was 23%, CD 34/CD 19 was 77 % CD 10/CD22 was 33 % and CD 10/19 was 99 %. He was diagnosed to have pre-pre B cell ALL. Philadelphia chromosome test was negative by fluroscent insitu hybridisation (FISH) method. Ultrasonography showed splenomegaly with spleen size of 8 centimetres.

Initially he was treated with first phase of induction (I-1) of MCP 841 protocol of ALL therapy with daunorubicin, vincristin, steroids, L-asparaginase and intrathecal methotrexate. Leucocyte counts gradually decreased. While receiving chemotherapy, 8th day first phase of induction (I-1) was awaited, the patient had epistaxis and had to be hospitalized. On examination, the patient had fever, pansinusitis, pleural effusion, hemoperitonium, gross ascitis and hepatosplenomegaly (spleen size was 16 cm). Further, on stool culture E.coli was detected. Biochemistry tests revealed pancytopenia with grade-4 neutropenia (absolute neutrophil count i.e. ANC<500/ μ l), deranged liver function, with hypoalbuminemia. This episode lasted for 11 days. The patient was treated with sensitive antibiotics and filgrastim (300 μ g daily for 11 days).¹ Chemotherapy was restarted. Injections of L-asparaginase were administered on 22nd day of induction. The patient had repeat episode of abdominal pain and loose motions, hence pancreatitis was suspected but serum amylase level was normal. He recovered from this episode with conservative treatment and tolerated further chemotherapy till the end of I-1. Post I-1 bone marrow was in remission. Cerebrospinal fluid cytology was negative for malignant cells.

Second phase of I-2 was delayed for 15 days due to one more episode of gastroenteritis which required antibiotic treatment. Imaging revealed spleen size 13 cm with two splenic infarcts (62x24x53 mm;



Figure 1: CT scan image of this patient showing splenomegaly with multiple splenic infarcts

35x27x50 mm) and few mesenteric nodes. Sickling test was negative and osmotic fragility was normal. I-2 was started and followed as per protocol. 15th day of second phase of I-2, day 15 was delayed for 10 days due to 6-mercaptopurine induced grade-4 neutropenia and treated with filgrastim (150µg for 6 days). I-2 was completed after recovery of counts.

Reinduction (RI) also delayed for 5 days due to grade 4 neutropenia. Reinduction started on TLC - 2000/µL. RI, day 8 was delayed for 5 days due to persistent leucopenia and grade 4 neutropenia. Again this was treated with (filgrastim 300µg for 4 days). RI, day 22 was similarly delayed for 10 days due to grade 4 neutropenia. Eventually reinduction completed.

Consolidation (CDN) chemotherapy treatment started and filgrastim (300µg, 7 days) was supported due to expected delayed count recovery. Patient admitted on CDN day 10 with febrile neutropenia (which progressed further to grade-4) and deranged LFT. He was treated with antibiotics and filgrastim (300µg for 5 more days). At presentation his Hb 2.3g/dl, TLC 5500/µl, PLC 71000/µl, total bilirubin 2.75mg/dl (indirect 2.21 mg/dl), and international normalized ratio (INR) 3.25. Imaging revealed splenomegaly of 18 cm with multiple infarcts.

Here we ruled out L-asparaginase as cause of splenic infarctions by reviewing the temporal profile of the events which started before receiving L-asparaginase. After stabilisation we did work up for thrombophilia profile which was normal except mild decrease in antithrombin III level. (INR-1.33, activated partial thromboplastin time i.e APTT-32.2 second for patient /32.1 second for control, lupus anticoagulant was absent, factor V 1691-normal, factor II 20210-normal, MTHFR 677-normal, protein C-normal, protein S-normal, antithrombin III-70 % the reference interval being 80-120). Thus we concluded in this case that the cause for recurrent splenic problems was attributable to filgrastim. The exact mechanism of splenic enlargement, infarction and rupture is not described in available literature but

may be correlated to extramedullary hematopoiesis. We have documented mild decrease in antithrombin III level, which needs to be carefully confirmed in similar other settings.

This patient reverted from critical status with antibiotics and supportive treatment. Filgrastim was excluded from treatment prescription. At present the patient is pursuing smoothly for one year with maintenance regimen. Still, splenomegaly persists however; the intercurrent events of abdominal pain related to recurrent splenic infarctions did not recur.

Discussion

Overall most commonly observed adverse effect of filgrastim is mild-to-moderate bone pain after repeated administration and local skin reactions at the site of injection. Those with sickle cell disorders may suffer sickle cell crisis after receiving filgrastim therapy. Other adverse effects comprise spleen rupture, serious allergic reactions, alveolar hemorrhage, acute respiratory distress syndrome (ARDS), and hemoptysis.^{2,3}

Splenomegaly is frequently observed at pretreatment baseline in severe neutropenia patients and is commonly noticed early in the course of treatment with filgrastim. The clinical trials monitored spleen size by physical examination and one phase III trial by imaging studies. Palpable splenomegaly was documented at baseline in 15% of study patients and in 30% of patients on filgrastim. Computed tomography or magnetic resonance imaging showed a median increase in spleen volume of 38% over the first 5 months of filgrastim treatment (range, 2 to 148%). Spleen volume then tended to plateau around 18 months and around 2.5 years it decreased toward pretreatment values. Registry data confirmed the common finding of pretreatment splenomegaly, reported at baseline in 18% of patients with congenital neutropenia. During the first year of filgrastim therapy, the prevalence increased to 38.2% and remained near this level (27 to 45%) through 10 years of therapy. Splenomegalies have been correlated with the underlying disease, its progression, severe infection, or may be associated with leukemic transformation.⁴

According to CalOptima Injectable Medication Guideline and NCCN guidelines for Filgrastim, the recommended dose of filgrastim for cancer patients receiving chemotherapy is 5µg/kg/day and maximum number of doses for filgrastim are 14 doses per month.^{5,6}

Conclusions

From this case we could be able make many inferences. First, the prescription of filgrastim in pediatric and adolescent patients should be given after

weighing the risk and benefits in each individual patient because we have less data of filgrastim use in this age group in acute lymphoblastic leukemia. Second, filgrastim should be prescribed cautiously using '5 µg/kg/day' schedule and even the maximum duration of treatment for neutropenia should be restricted upto maximum 14 days. Third, to prevent filgrastim related adverse effects, extra vigilance are required in presence of baseline splenomegaly. Fourth, the mechanism of filgrastim related adverse effects, which is not explained in literature could be related to decrease in antithrombin III level and needs further confirmation.

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“To waste, to destroy our natural resources, to skin and exhaust the land instead of using it so as to increase its usefulness, will result in undermining in the days of our children the very prosperity which we ought by right to hand down to them amplified and developed.”

Theodore Roosevelt

Oral Teratoma With a Yolk Sac Component: A Case Report

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Summary

Teratomas are tumours of germ cell derivation consisting of tissues from all the three germ cell layers. They are the most common extragonadal germ cell tumours (EGCTs) in childhood. EGCTs of head and neck accounts for 4% of all GCTs and 6% of teratomas. Yolk sac component arising from germ cell tumour is a distinct entity. This paper presents a 4 year old male child who reported with painless swelling which was present since birth but rapidly increased in size over a period of 4 months, in the left cheek region. Histopathological examination confirmed it to be a teratoma with yolk sac component.

Keywords: Extragenadal teratoma, Yolk sac, Alpha Feto Protein

Introduction

Teratoma is composed of tissues from all three germinal layers including mature and immature elements with predominance of ectodermal and mesodermal derivatives.¹ This neoplasm is more frequently present in the gonads than in extragonadal regions. Extragenadal germ cell tumours are more frequently seen in the retroperitoneal area, the presacral region and the anterior mediastinum.² Less frequent sites are: brain, pineal gland and head and neck. Soft tissues of neck, thyroid, superficial facial structures, oral cavity, nasopharynx and orbit are the common sites of involvement in the head and neck.³

Teratoma with malignant transformation refers to a form of germ cell tumour in which a somatic teratomatous component becomes morphologically malignant and develops aggressively. The histology of the somatic malignant elements most commonly includes carcinoma and various types of sarcoma. We report a rare case of oral teratoma that had malignant transformation of the yolk sac component in a young child.

Case Report

A 4 year old boy presented on 21st November 2011 with swelling in left cheek region which was present in smaller size since birth and had rapidly increased over a period of 4 months. His father gave history of excision of swelling 2 months back by a doctor at his place, histopathology of the excised sample showed derivatives from various germ layers like areas of respiratory epithelium, salivary gland and myxoid tissue. 1 month after excision, the swelling grew again rapidly; FNAC was performed at a local pathology laboratory which suggested teratocarcinoma. On examination during first presentation at our

institute on November 2011, there was a 3 cm x 3 cm swelling on the lower and outer quadrant of maxilla which was hard in consistency with normal overlying skin and temperature (Figure 1). There were palpable left submandibular lymph nodes that were soft and non tender.

Radiographic examination with MRI-PNS showed a 4.5 cm x 2.8 cm x 3.1 cm sized well defined mass in the left buccal space involving subcutaneous tissue and extending into both upper and lower gingivo-buccal spaces, inferiorly extending into submandibular gland, posteriorly involving the retro-molar trigone with multiple enlarged nodes at level 1A, bilateral level 1B and 2.

The FNAC slides reviewed at our institute also suggested teratocarcinoma. The levels of tumour markers for GCT such as alpha feto protein, beta hCG and LDH were 6469 ng/ml, 0.1 IU/ml and 649 U/l, respectively. The parents were informed about the aggressiveness of the lesion and the need for immediate surgical treatment.

The child underwent wide local excision and cervical lymph node level 1 and 2 dissection in the neck. Histopathology revealed yolk sac tumour with clear margins and uninvolved lymph nodes; the post operative tumour markers were alpha fetoprotein: 319.2, beta hCG: 0.1 and LDH: 649. Hence, patient was advised chemotherapy in form of cisplatin, etoposide and bleomycin (PEB). The markers normalised after 3 cycles of PEB chemotherapy regimen and he was treated with 2 more cycles of chemotherapy (Table 1). Six months post treatment, MRI-PNS was repeated, which suggested a normal MRI study with minimal post operative soft tissue enhancement in RMT and buccal space and patient was kept under strict surveillance since April 2012. His last follow-up on 21 February 2013 confirmed continuing complete remission clinically and biochemically.

Discussion

Teratoma is a tumour of variable maturity and organization. Its elements represent differentiation from all three embryonic germ layers. In the present case, derivatives from various germ layers were observed like areas of respiratory epithelium, salivary



Figure 1: Swelling on the lower and outer quadrant of maxilla

gland and myxoid tissue in the excised tissue.

The presentation of teratomas can be as broad as their histologic appearance⁴. The most common site of primary tumours is gonads but about 5% of germ cell tumours appear in some extra cranial site in head and neck region⁵. They are classified as mature, immature and malignant from the standpoint of histologic appearance and future behaviour. They greatly vary in maturity and oncogenic potential. The synchronous presence of embryonal, fetal and adult elements is possible in a tumour mass and also indicates the level and type of differentiation.¹ Immature neuroectodermal elements are the easiest immature tissues to recognize and quantitate.⁶ Teratomas may be classified as mature and immature based on the presence of immature neuroectodermal elements on histological findings. Survival and risk of recurrence are also related to the degree of immature component.⁷

The prognosis for children with yolk sac tumours remains guarded with successful management depending on early diagnosis and aggressive adjuvant therapy. Histologically yolk sac tumour cells resemble cells of endodermal sinuses of rat yolk sac. Microscopic appearance of tumour is variable, but usually includes malignant endodermal cells. Schiller Duval bodies, when present, are pathognomonic.

Immunohistochemistry is helpful in the diagnosis and diagnostic markers include placental alkaline phosphatase, alpha fetoprotein; although they lack in sensitivity and specificity. Other markers like cytokeratin and epithelial membrane antigen also show positivity in a large number of cases. However SALL4 has shown 100% sensitivity with 94% cells staining positively.⁵ AFP can usually be detected in tumour tissue, serum, CSF and urine. Clinically AFP is not only useful for diagnosis of yolk sac tumours but it is also the ideal post operative tumour marker for prognostic assessment.

Yolk sac tumour also occurs as malignant foci within teratoma and biopsy occasionally may not reveal yolk sac component but only teratoma as in our case where earlier biopsy suggested teratocarcinoma, however elevated AFP may suggest it's presence and vice versa biopsy may only show yolk sac component and teratomatous component may not be sampled. Yolk sac tumours commonly occur in association with

Table 1: Biochemical response of chemotherapy

No. of cycle	Date (ng/ml)	alpha fetoprotein
1	29-11-2011	64.69
2	19-01-2012	19.22
3	09-02-2012	04.56
4	02-03-2012	04.17
5	22-03-2012	03.58

immature teratomas.⁸ Our case most likely represents a yolk sac tumour which had arisen from a mature teratoma. Therapy is primarily surgical excision. The tumour is not radiosensitive but adjuvant multi-agent chemotherapy improves survival. Prognosis is however poorer for children with extra gonadal as compared to gonadal germ cell tumours.⁹

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Teratoid Wilms' Tumor: An Unusual Variant of Nephroblastoma

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Summary

Teratoid Wilms' tumor is an unusual variant of nephroblastoma in which heterologous tissue like adipose tissue, glial tissue, muscle, cartilage or bone predominates. Classical Wilms' tumor is a chemosensitive and radiosensitive tumor. Teratoid Wilms' tumor is a chemoresistant and radioresistant tumor and surgical resection is the treatment of choice. We report a case of teratoid Wilms' tumor in a 2-year-old female with liver and lung metastases. It showed failure of response to preoperative chemotherapy and radiotherapy. She underwent surgical resection and is on post-operative chemotherapy.

Keywords: Teratoid, Wilms' tumor, Nephroblastoma

Introduction

Teratoid Wilms' tumor, a rare variant of nephroblastoma, has a predominance of heterologous elements. To date less than 30 cases of teratoid Wilms' tumor have been reported in the literature.¹⁻³ Metastasis is seldom reported in teratoid Wilms' tumor. Our patient presented with lung and liver metastases.

Case report

A two year-old girl presented with palpable mass on the right side of abdomen for one month. No history of hematuria or constitutional symptoms was present. Physical examination revealed mild pallor, but no hypertension. A firm, ballotable mass with smooth surface was palpable in the right lumbar region and insertion of fingers was possible between the intercostal margin and the mass.

All routine investigations were normal except anemia (Hemoglobin 8.2 gm/dl). Contrast-enhanced computed tomography (CECT) scan (Figure 1) showed large heterogeneous lesion in the right kidney measuring 79x93x91mm, abutting inferior surface of right lobe of liver with loss of fat plane. Multiple hypodense lesions were seen in right lobe of liver largest measuring 63x50 mm. Right lung showed pleural based soft tissue opacities in posterior segment of right upper lobe of about 20x16x15mm suggestive of metastasis. Her biopsy from kidney was suggestive of blastemal type of Wilms' tumor with favorable histology.

She was treated with chemotherapy (DD4A protocol with vincristine, doxorubicin and actinomycin -D). Twelve weeks after chemotherapy, CT scan revealed, no change in the size of renal mass (Figure 1B), however, a partial response in lung and liver metastases was noted. Post chemotherapy, the renal mass was inoperable as it was encasing IVC and hence she was further treated with radiotherapy (12Gray/6#). In spite of radiotherapy, on post radiotherapy CT scan, the disease was found stable (Figure 1C). Therefore, right radical nephrectomy with ureterectomy and trucut biopsy of liver lesion was performed.

Gross pathological examination of specimen showed well circumscribed growth of 11x9.5x5.5 cm³ (Figure 2) (225 gm) involving entire kidney with multiple microcystic areas was found with rim of normal renal parenchyma at periphery of tumor. Renal capsule, perinephric fat, ureter, renal artery and renal vein were free of tumor.

Microscopic examination (Figure 3) revealed teratoid Wilms' tumor involving the entire right kidney with predominantly hyaline material and mesenchymal component including skeletal muscle, adipose tissue, squamous epithelium (1-2%), minimal tubular and tiny bone component. Blastemal component of Wilms' tumor was absent suggestive of post chemotherapy effect. There was no lympho vascular permeation and capsule was free of tumor. Cut end of renal artery, renal vein and ureter were free of tumor. Tru cut biopsy of liver lesion was also free of tumor.

Her α -feto protein (AFP) level was normal. Postoperative recovery was uneventful along with normal ultrasonogram.

She was restarted on chemotherapy (DD4A protocol) and has received week 15 of the chemotherapy protocol.

Discussion

Wilms' tumor is perfect example of a neoplastic process that fully recapitulates embryogenesis at the

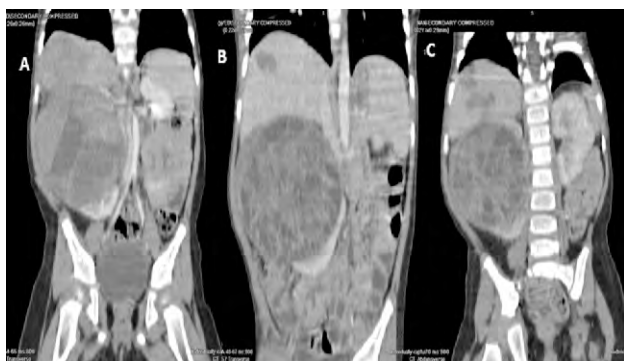


Figure 1: CT scan of patient showing right renal heterogeneous mass and liver metastasis: A- pre-treatment, B- post chemotherapy, C-post radiotherapy (showing no response on tumor size)



Figure 2: Gross examination and cut section-tumor involving entire kidney approximately 11x9.5x5.5 cm³ having grey white, firm, smooth appearance

morphologic and molecular level. Embryonic tumor is typically composed of variable admixture of blastematos, epithelial and stromal components.

Variend et al⁴ described that Wilms' tumor can include heterologous elements in addition to these components. Fernandes et al⁵ defined teratoid Wilms' tumor that contains heterologous elements comprising more than 50% of the tumor mass. To date, less than 30 cases of teratoid Wilms' tumors have been reported,¹⁻³ and about 38% of cases are bilateral.⁶ In the present case, the tumor was unilateral and the contralateral kidney was normal. Raised α fetoprotein level is reported in occasional cases.⁷⁻⁹ However, in the present study it was normal.

The pathogenesis of this entity is still debated; it is likely that it originates from totipotent primitive metanephric blastema. The variable presence of intracellular matrix proteins may influence the presence, extent, and diversity of heterologous differentiation. Commonly found teratoid elements representing aberrant mesenchymal differentiation are skeletal muscle, smooth muscle, adipose tissue, glial tissue, cartilage and bone; and rarely squamous epithelium.⁸

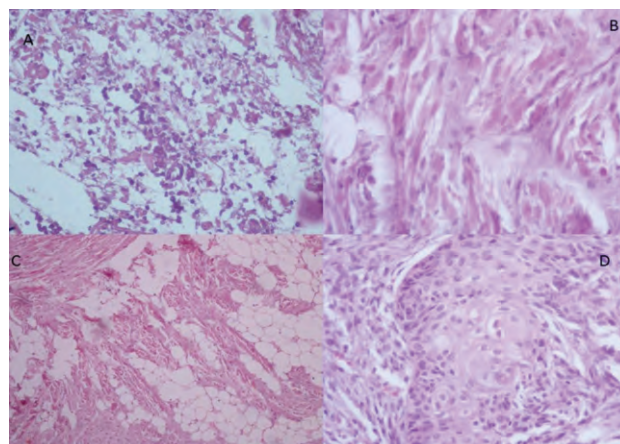


Figure 3: A- Pretreatment tumor biopsy suggestive of malignant round small cell tumor of primitive nature suggestive of blastemal component of Wilms' tumor. Other components are not present. B,C,D-Post chemo and radiotherapy tumor showed no blastemal component, B - showing skeletal muscle, C- adipose tissue, D-squamous epithelium

The differential diagnosis of teratoid Wilms' is intrarenal teratoma, metastatic germ cell tumor, and retroperitoneal infiltration of teratoma. In our case, blastemal pattern of Wilms' tumor was seen and no adnexal structures or organogenesis was found ruling out intrarenal teratoma. Normal ovaries excluded metastatic ovarian germ cell tumor. Renal capsule was also free of tumor ruling out retroperitoneal infiltration of teratoma.

Behavior of teratoid Wilms' tumor is usually not aggressive with a favorable outcome and less metastatic potential.^{2,11} Classical Wilms' tumor is highly chemo and radiosensitive tumor making them an essential component of the treatment. Treatment of teratoid Wilms' tumor has not yet been established because of its rarity and varying tumor components.^{12,15} Teratoid Wilms' tumor is relatively resistant to chemotherapy and radiotherapy; hence, surgery is the treatment of choice.^{2,3,11-13} Resistance to chemotherapy and radiotherapy is thought to be due to the presence of well-differentiated heterologous components.^{12,13,15} Failure to respond to preoperative chemotherapy was observed in our patient and similar findings have also been reported.¹⁶

However, few authors recommend chemotherapy in these cases regardless of the tumor size, stage, age at diagnosis, and the histological appearance tumor.¹⁴ According to one of the reports in literature, out of 15 cases of teratoid Wilms' tumor, chemotherapy was given in nine cases and only one case showed cytoreductive response.⁶

Both surgeons and pathologists should be aware that the treatment of this rare variant should be focused on total surgical removal of the tumor. As there is still controversy regarding treatment, further,

research should be carried out before concluding a tight treatment protocol in these cases.

Conclusion

Teratoid Wilms' tumor is very rare tumor with resistance to chemotherapy and radiotherapy. One should be vigilant for this variant when there is no response to preoperative chemotherapy and radiotherapy, and should proceed with surgery as complete/total resection is the treatment of choice.

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“Environmental degradation is an iatrogenic disease induced by economic physicians who treat the basic malady of unlimited wants by prescribing unlimited growth.... Yet one certainly does not cure a treatment-induced disease by increasing the treatment dosage.”

Herman E. Daly,
Steady-State Economics: Second Edition With New Essays

Summaries of Published Articles

01. Anesthetic Management of a Patient with Wolff-Parkinson-White Syndrome for Modified Radical Mastectomy- A Case Report

Jansari Amita H, Sanghavi Priti R, Jadav Deepa N, Tank Tanmay V, Patel Bipin M
Department of Anesthesiology

Summary

Wolff Parkinson White syndrome (WPW) is an uncommon cardiac disorder having an aberrant pathway between atria and ventricles. It may pose problem for anesthesiologist during general anesthesia due to sudden development of tachyarrhythmia which may result in deleterious hemodynamic changes. We are reporting a known case of WPW syndrome for modified radical mastectomy under general anesthesia. Management of the present case is an important pearl to revisit management of WPW syndrome. The perioperative management should be tailored according to the nature of surgery and the clinical presentation of the patient.

GCS MCJ Med Sci 2013; II: 40-42

02. Propofol and Thiopentone Admixture-Effect on Pain on Injection, Pulse, Blood Pressure and Recovery in Day Stay Unit

Shah Kinna G, Sanghavi Priti R, Shah Bhavna C, Patel Bipin M, Sharma Gaurav
Department of Anesthesiology

Summary

This study examined some pharmacodynamics of two admixtures of Propofol and Thiopentone. 100 patients of ASA I and II were divided in four groups. Group P50: Propofol 1% (5 ml) + Thiopentone 2.5% (5 ml), Group P75: Propofol 1% (7.5 ml) + Thiopentone 2.5% (2.5 ml), Group P100: Propofol 1% (10 ml) + Lignocaine 2% (1 ml), Group T: Thiopentone 2.5%. Thiopentone resulted in more rapid induction (45.64±7.4 seconds) of anaesthesia than any other group. The Group P50 (Thiopentone+ Propofol 50%) was found to be superior to Group P100 in reducing pain on injection. The fall in systolic blood pressure was significantly less in P50 (10%-20%) group compared to group P75 (20%-30%) and Group P100 (25%-40%). Recovery was early in P100 group (2.92±1.1 min). Admixture of Thiopentone+ Propofol as P50 results in additive hypnotic effect, a less pain on injection and reduced hypotensive response. Group P50 was found more economic compared to Propofol alone.

Asian Archives of Anaesthesiology and Resuscitation 2011; 73; 2092-2095

Summaries of Presentations at Clinical Meetings

01. Lu-177 (Lutetium-177) Scan and Therapy for Neuroendocrine Tumour

Tiwari Rasna
Department of Nuclear Medicine

Summary

Somatostatin receptor imaging (SRI) with [¹¹¹In-DTPA0] octreotide has proven its role in the diagnosis and staging of gastroenteropancreatic neuroendocrine tumors (GEPNETs). Newer radiolabeled somatostatin analogs which can be used in positron emission tomography (PET) imaging, and which have a higher affinity for the somatostatin receptor, especially receptor subtype-2, have been developed. It would be desirable, however, if one radiolabeled analog became the new standard for PET imaging, because the current application of a multitude of analogs implies a fragmented knowledge on the interpretation of the images that are obtained in clinical practice. In our view, the most likely candidates for such a universal PET tracer for SRI are [⁶⁸Ga-DOTA0,Tyr3] octreotate or [⁶⁸Ga-DOTA0,

Tyr3]octreotide. Treatment with radiolabeled somatostatin analogs is a promising new tool in the management of patients with inoperable or metastasized neuroendocrine tumors. Symptomatic improvement may occur with all ¹¹¹In-, ⁹⁰Y-, or ¹⁷⁷Lu-labeled somatostatin analogs that have been used for peptide receptor radionuclide therapy (PRRT). The results that were obtained with [⁹⁰Y-DOTA0, Tyr3] octreotide and [¹⁷⁷Lu-DOTA0, Tyr3]octreotate are very encouraging in terms of tumor regression. Also, if kidney protective agents are used, the side effects of this therapy are few and mild, and the median duration of the therapy response for these radiopharmaceuticals is 30 and 40 months respectively. The patients' self-assessed quality of life increases significantly after treatment with [¹⁷⁷Lu-DOTA0, Tyr3]octreotate. Lastly, compared to historical controls, there is a benefit in overall survival of several years from the time of diagnosis in patients treated with [¹⁷⁷Lu-DOTA0, Tyr3]- octreotate. These data compare favorably with the limited number of

alternative treatment approaches. If more widespread use of PRRT can be guaranteed, such therapy may well become the therapy of first choice in patients with metastasized or inoperable GEPNETs.

02. Endovascular Embolization- An Alternative and Adjuvant Treatment in Cancer Patients

Jolapara Milan

Department of Radiodiagnosis

Summary

Radiology started as a diagnostic modality, but now it has advanced and has become important therapeutic option. This is especially true in cancer patients. Transarterial chemoembolization and transarterial radioembolization are well known techniques in treatment of inoperable hepatocellular carcinoma and liver metastasis. Bland embolization is good alternative in patients with inoperable renal cell carcinoma and renal angiomyolipoma. Endovascular embolization is also very useful as adjuvant to surgery in vascular tumors. It helps to make surgery bloodless, decrease operative time and it also make some inoperable tumors operable. Portal vein embolization helps to increase volume of future remnant liver so that unresectable liver tumor becomes resectable. Endovascular embolization also helps in management of post-operative complications like bleeding and pseudoaneurysm formation. Thus radiology has come long way and endovascular embolization has now become important part of management of cancer patients.

03. Role of Targeted Therapy in Her-2 Positive Cancer Breast - GCRI Experience

Gadhvi Vikas

Department of Medical Oncology

Summary

HER2 positive carcinoma breast is an aggressive disease, less sensitive to standard cytotoxic chemotherapy and early metastasis and shorter progression free survival in metastatic setting. Many newer targeted therapy directing against HER2 is available in recent year which includes trastuzumab, lapatinib, T-DM1, axitinib, pertuzumab and is used in various combination with cytotoxic chemotherapy, hormonal therapy or alone as single agent. No significant toxicity noted with there used except cardiotoxicity and requires stringent cardiac monitoring. Of 1252 new carcinoma of breast case presented to GCRI in year 2011, 289 where Her2 positive of them only 21 patients were treated in gcri in year 2011 with her2 targeted therapy. All of them where metastatic. Drug mainly used where trastuzumab as first line therapy and lapatinib as second line therapy after progression on trastuzumab. Therapy was well tolerated with no cardiac complication. Median time to progression was 7.8

month. Cost of therapy was significantly high with expected cost of Rs 1,25,000/- to prolong one month of patients life. HER2 targeted therapy is well tolerated and effective therapy in prolonging life of patient with this aggressive disease. Cost of therapy is major hinderance in using this effective drug for large section of patient population who can be benifited from it.

04. Paraganglioma of Carotid Body: Management by Carotid Artery Excision and Polytetrafluoroethylene (PTFE) Grafting

Jain Abhishek

Department of Surgical Oncology

Summary

A 20 yr old female came with complaints of neck swelling. MRI and carotid angiography diagnosed it to be paraganglioma of Carotid Body. Tumor was excised along with a segment of internal carotid artery and PTFE grafting was done. She recovered well and was discharged. She is on regular follow up and her last examination was normal.

05. Massive Pelvic and Sacral Resection – Data of Last Five Years at GCRI

Shah Mandip

Department of Musculo-Skeletal

06. Pain and Palliative Care - Road Travelled so Far and Road Ahead

Macwan Kalpesh

Department of Pain and Palliative Medicine

Summary

Pain and Palliative Care services were started in October 2010. The service has gained momentum. OPD services, which were started in afternoon hours, have been extended in morning hours in room number 103. Number of new cases registered under palliative care has increased from 788 in 2011 in 1271 in 2012. Number of patients put on morphine and morphine consumption, an indicator for effective pain management, has increased by 61%. The services were formally transformed in “Department of Pain and Palliative Medicine” in November 2012. Pain management, symptom control and counseling about disease status, nutrition, wound care, psychosocial issues and hygiene of patients are main objectives of this department.

07. Prevalence of Inducible Clindamycin Resistance in Staphylococcus Species in Cancer Patients

Lunagariya Rahul

Department of Microbiology

Summary

Gram positive organisms are one of the leading pathogens causing skin and soft tissue infection. For these infections Clindamycin is a useful alternative

drug in Penicillin allergic patients. Routine tests for detection of Clindamycin susceptibility may fail to detect Inducible Clindamycin resistance mediated through *erm* gene resulting in treatment failure necessitating the need to detect such resistance by a reliable method. One more thing which needs attention is that those isolates which are resistant to Clindamycin (Lincosamide group) also become resistant to Macrolide and Streptogramin B group of antibiotics due to sharing of common receptor. It is a type of retrospective study where we have collected the data of Staphylococcus isolates from various clinical samples like blood, sputum, urine, pus swab, frank pus, throat swab etc. Staphylococcus isolates were identified and sensitivity was done in Vitek 2 compact machine. Inducible clindamycin test as well as Cefoxitin screen (for detection of Methicillin resistant Staphylococcus sp.) were also done in Vitek 2 Compact machine. A total of 415 Staphylococcus were isolated from various clinical samples between January to November 2012. Out of them 257 were Staphylococcus aureus and 158 were Coagulase Negative Staphylococcus (CONS). In *S. aureus*, 67/257 (26%) were Inducible Clindamycin resistant (Erythromycin resistant and Clindamycin sensitive and Inducible Clindamycin Resistant test positive) and 72/257 (28%) were Constitutive resistant (Erythromycin resistant and Clindamycin resistant). In CONS, 16/158 (10.12%) were Inducible Clindamycin resistant and 42/158 (26.58%) were constitutive resistant. As there is very high prevalence of Inducible clindamycin resistance in Staphylococcus isolates, it should be a normal clinical practice to do Inducible clindamycin resistance test in laboratory and report it. The clinician should not use clindamycin without knowledge of Inducible clindamycin resistance test as there are high chances of treatment failure particularly in MRSA infections.

08. GCRI Experience of Management of Medulloblastoma

Turakhia Suvidh

Department of Neuro-Oncology

09. Two Year Experience of Radial Artery Forearm Free Flap (FRAFF) at GCRI for Head and Neck Cancer Reconstruction

Gupta Sandip

Department of Surgical Oncology

Summary

There are various ways of reconstruction of defects created after wide excision of primary malignancy in head and neck e.g. local flaps, regional flaps, distant pedicle flaps and free flaps. Free micro vascular flap is an advanced technique of reconstruction. The FRAFF provides well-vascularized and relatively thin and pliable soft tissue. We illustrate the

versatility of the FRAFFs in 30 patients with various head and neck defects that were reconstructed after tumor ablation. We present our clinical experience in terms of postoperative functional and cosmetic results and discuss donor-site morbidity of the FRAFF.

A total of 30 patients had reconstruction with free micro vascular flap, from Jan. 2011 to Dec. 2012 at GCRI, Ahmedabad, were studied retrospectively. The medical records of 30 patients were reviewed for age, gender, histopathologic diagnosis, location of primary tumor, tumor stage, preoperative chemotherapy, and preoperative and postoperative radiotherapy. Out of 30 patients 5 were female. The mean age was 39.3 years. Of the 30 head and neck tumors, 29 were squamous cell carcinomas and 1 was squamous papilloma. The primary site of the cancer was the buccal mucosa in 21 patients, the tongue in 4, the mandibular alveolar process in 1, the maxillary alveolar process in 1, the floor of the mouth in 1, the lip 1, angle of mouth 1. The majority of the tumors that could be staged were either T1 (13 patients), T2 (11 patients), T4 (4 patients) or T3 (2 patient). No patient received preoperative chemo-radiotherapy. However, 20 patients received postoperative radiotherapy. The size of flap harvested, results of flap transfer, flap-related complications, donor site morbidity, harvest time, and clinical course were analyzed. Preoperative Allen test and Doppler study of upper limb arteries done in all patient. The donor site at the forearm covered with a split thickness skin graft. Among the 30 FRAFFs, 3 total flap losses occurred. An overall success rate of 90% (27/30). There were 6 minor complications: fistula in 3 patients, wound dehiscence in 2, and hematoma 1 in 1. Therefore, of the overall complications (30%) at the recipient site, 10% (3/30) were severe and 20% (6/30) were minor. All patients tolerated postoperative radiotherapy without evidence of wound breakdown. The donor site complications are four patients had partial loss of skin grafts, which lead to tendon exposure in 2 patients. Esthetic outcomes of donor hands were rated as acceptable in 28 patients. Analyzing the results found that FRAFF recipients had excellent postoperative speech production, good oral competency and Swallowing. Free radial artery forearm flaps provide better cosmetic and aesthetic results, provided the technical expertise is available. FRAFF in the oral cavity provide excellent postoperative results in the form of speech production and swallowing.

10. Transfusion Transmissible Infections Testing-Past, Present and Future

Kusumgar Rima

Blood Bank, Department of Pathology

Summary

Safe and effective blood is the most important aspect of any blood transfusion services. Transfusion

transmissible infection is the major threat as consequence of any blood transfusion. Testing of HIV, HBsAg, HCV, Syphilis and Malaria parasite is mandatory in India. Various methods are available for transfusion transmissible infection testing based on serology. Enzyme linked immunosorbent assay (ELISA) being the most prevalent among them. Newer techniques like chemiluminescent assay and Nucleic Acid Testing are now also available having better sensitivity and specificity. Transmission during window period can not be avoided in spite of best testing techniques used. Various studies have been done to prove efficacy of various techniques. Chemiluminescent assays are rapid and with higher sensitivity than ELISA and also cost effective in comparison to NAT testing.

11. Triple Negative Breast Cancer - 3 Year Retrospective Study at GCRI

Bomanwar Nitin

Department of Surgical Oncology

12. Sorafenib in Metastatic RCC - GCRI Experience

Patel Kaushal

Department of Medical Oncology

Summary

To confirm the antitumor efficacy of sorafenib in patients with mRCC, including review of side effect profile. This study is a retrospective analysis of patients treated at our institute. Source of data is treatment records of patients. An inclusion criterion was mRCC patients treated with sorafenib. Total 20 patients, treated in 2011-12, were reviewed. The reported data applied till may 2013. Except 1 patient, all had clear cell histology. 10 patients received dosage of 800 mg/d while rest 9 patients 400 mg/d as starting dose and one was on 600 mg. Assessment of clinical response and degree of tumour regression on imaging studies using the Response Evaluation Criteria in Solid Tumours guidelines. Primary end point was overall objective response rate (complete plus partial). Secondary end points were progression-free survival and safety. Till the date of reporting, 5 out of 20 patients are currently on sorafenib. Most common MSKCC poor prognostic marker present was interval of <1 year between diagnosis & starting of treatment (85%). Other poor prognostic factors were ≥ 2 metastatic sites (50%), anaemia (30%) & KFS<70 (25%). The objective response rate was 25% (CR+PR=0+5). Clinical benefit rate (CR+PR+SD) was 65% (n-13). Median patients in this study is 6 months, with a range of 1.5 to 11 months and median

overall survival of patients in this study is 10 months with a range of 1.5 to 16 months. Major toxicities seen were fatigue (n-10), diarrhoea (n-2) skin rash (n-7), mucositis (n- 6), and hand foot syndrome in 4 patients. Only 3 patients experienced grade ≥ 3 side effects. Side effects in patients were managed by dose reduction to 400 mg/d (3 patients), dose interruptions (2 times) and supportive care. These results confirm the efficacy and easily manageable side effect profile of sorafenib in mRCC. Response rates were well matched to other studies confirming the efficacy of sorafenib. Cost effectiveness is also one of the important factor.

13. Role of Gynec Oncologist for Comprehensive Care in Carcinoma Endometrium

Magdum Anil

Department of Gynecological Oncology

Summary

Carcinoma of endometrium is the most common gynecological malignancy in developing countries and it's incidence is increasing in India. It is managed with surgical staging. Significant number of women with carcinoma of endometrium are receiving suboptimal treatment due to incomplete staging. This study was done with an aim of evaluating impact of gynecological oncologist (GO) in management of carcinoma of endometrium. This was a retrospective analysis of all cases managed at regional cancer center (RCC) over a period of one year, 2007. Study group had patients referred to RCC after surgery done outside and control group had cases managed at RCC. Various parameters like demographics, adequacy of surgery, time interval between surgery and referral, time interval between surgery and start of adjuvant radiotherapy (RT), disease free and overall survival (DFS, OS). Out of total 71 cases managed at RCC in 2007, 31 were operated outside and referred to RCC where as 36 were operated at RCC of remaining 40 cases. Most of the patients presented with endometroid adenocarcinoma and in early stage. There was no stastically significant differenece in median age and postmenopausal status in both groups. 70.8% of study population was unstaged and was stastically highly significant (15% in control group). 25% of referred cases were without proper documentation. 38% of the study population were referred after 3 months. Those women who were operated outside had lesser compliance to adjuvant RT (73% v/s 91%) compared with control population. Gynecologic oncologist should be involved in care for women with carcinoma of endometrium as they undergo surgical staging and they are at lesser risk of receiving adjuvant RT.

Presentations at the Clinical Meetings

(January 2013 to June 2013)

Sr. No.	Date	Speaker/Department	Title
1.	12.01.13	Tiwari Rasna Nuclear Medicine	Lu-177 (Lutetium-177) Scan And Therapy For Neuroendocrine Tumour
2.	26.01.13	Jolapara Milan Radiodiagnosis	Endovascular Embolization: An Alternative & Adjuvant Treatment In Cancer Patients
3.	09.02.13	Gadhvi Vikas Medical Oncology Unit II	Role of Targeted Therapy in Her-2 Positive Ca Breast – GCRI Experience
4.	09.02.13	Jain Abhishek Surgical Unit V	Paraganglioma Of The Carotid Body: Management by Carotid Artery Excision and PTFE Grafting
5.	23.02.13	Shah Mandip Musculo-Skeletal	Massive Pelvic and Sacral Resection – Data of Last Five Years at GCRI
6.	09.03.13	Macwan Kalpesh H Pain & Palliative Care Unit	Pain And Palliative Care – Road Travelled So Far and Road Ahead
7.	23.03.13	Lunagariya Rahul Microbiology	Prevalence of Inducible Clindamycin Resistance in Staphylococcus Species in Cancer Patients
8.	13.04.13	Turakhia Suvidh Neuro-Oncology	GCRI Experience of Management of Medulloblastoma
9.	13.04.13	Gupta Sandip Surgical Unit II	Two Year Experience of Radial Artery Forearm Free Flap at GCRI for Head and Neck Cancer Reconstruction
10.	27.04.13	Kusumgar Rima Blood Bank	Transfusion Transmissible Infections Testing – Past, Present & Future
11.	11.05.13	Bomanwar Nitin Surgical Unit IV	Triple Negative Breast Cancer – 3 Year Retrospective Study at GCRI
12.	25.05.13	Patel Kaushal Medical Unit I	Sorafenib in Metastatic RCC – GCRI Experience
13.	08.06.13	Magdum Anil Gynec Oncology Unit III	Role of Gynec Oncologist for Comprehensive Care in Carcinoma Endometrium

Journal Club / Guest Lecture / Review Lecture Presentations

(January 2013 to June 2013)

No. Sr.	Date	Department Presenter/	Topic	Authors	Citation
1.	12.01.13	Jain Abhishek Surgical Unit V	Neoadjuvant Chemoradiation For Rectal Cancer - German Rectal Cancer Trial	Rolf Sauer, Heinz Becker, Werner Hohenberger et al	N Engl J Med 2004; 351: 1731-1740
2.	09.03.13	Lakhani Jay Gyaec-Oncology Unit I	Risk Of Ovarian Failure & Fertility Preserving Methods In Girls And Adolescents With A Malignant Disease	Schmidt KT, Larsen EC, Andersen CY	BJOG 2010; 117:163-174
3.	11.05.13	Parita Pandya Pathology	Clinico-pathological Profile Of Hairy Cell Leukemia: Critical Insights Gained At A Tertiary Care Cancer Hospital	Galani KS, Subramanian PG, Gadage VS et al.	Indian Journal of Pathology and Microbiology 2012; 55: 61-65
4.	08.06.13	Sunil RA Radiotherapy	Proportion Of Second Cancers Attributable To Radiotherapy Treatment In Adults: A Cohort Study In The US SEER Cancer Registries	Amy Berrington de Gonzalez, Rochelle E Curtis, Stephen F Kry et al.	Lancet Oncol 2011; 12: 353-360
5.	22.06.13	Patel Jayendra B Biochemistry Research Division	Understanding Carcinogenesis For Fighting Oral Cancer	Tanaka Takuji, Ishigamori Rikako	Journal of Oncology 2011, Article ID 603740, 10 doi:10.1155/2011/603740

Case Presentations for Morbidity, Mortality at Clinical Meetings

(January 2013 – June 2013)

Sr No	Date	Presenter / Department	Case Discussion
1	26.01.13	Prajapati Devendra Anesthesiology	Mortality Morbidity Data Presentation of Surgical and Medical Department
2	26.01.13	Jetani Amit Medical Oncology, Unit II	A Case of Cervical Lymphadenopathy (Kikuchi Disease)-Morbidity
3	23.02.13	Barkhane Ruchi Anesthesiology	Mortality Morbidity Data Presentation of Surgical and Medical Department
4	23.02.13	Gupta Sandeep Surgical Oncology, Unit II	A Case of Hepatic Carcinoid Tumor Morbidity
5	23.03.13	Prajapati Devendra Anesthesiology	Mortality Morbidity Data Presentation of Surgical and Medical Department
5	23.03.13	Raut Shreeniwas Medical Oncology, Unit III	A Case of Splenic Infarcts Following Treatment with Filgrastim-Morbidity
6	20.04.13	Barkhane Ruchi Anesthesiology	Mortality Morbidity Data Presentation of Surgical and Medical Department
7	20.04.13	Jain Abhishek, Surgical Oncology, Unit V Majumdar Rini, Anesthesiology	A Case of Radical Cystectomy-Mortality
8	25.05.13	Prajapati Devendra Anesthesiology	Mortality Morbidity Data Presentation of Surgical and Medical Department
9	25.05.13	Patel Kaushal Medical Oncology, Unit I	A Case on IFOS Induced Encephalopathy-Morbidity
10	26.06.13	Barkhane Ruchi Anesthesiology	Mortality Morbidity Data Presentation of Surgical and Medical Department
11	26.06.13	Bhumika Revar Anesthesiology	A Case of Pediatric Hepatic Resection-Mortality

About the Journal and Instructions to Author

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The following documents are required for each submission:

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- Tables (separate page, Number Arabic numerals (e.g. 1,2,3) as it comes in results)
- Figures and Illustration (separate page, JPEG format, Number Arabic numerals (e.g. 1, 2,3) as in results, if photographs of persons are used, the subjects or patients must not be identifiable).
- Legends to Figures and Illustration: Present the legends for illustrations separate page using double-spacing, with Arabic numerals corresponding to the Illustrations.
- References (separate page, Number references consecutively in the order in which they are first mentioned in the text. Identify references in the text in numerals in superscript and parenthesis).
- Acknowledgement

Units and abbreviations

Avoid abbreviations in the title and abstract. All unusual abbreviations should be fully explained at their first occurrence in the text. All measurements should be expressed in SI units. **Drug names** Generic drug names should be used.

Abbreviations of units should conform to those shown below:

Decilitre	dl	Kilogram	kg
Milligram	mg	hours	h
Micrometer	mm	Minutes	min
Molar	mol/L	Mililitre	ml
Percent	%		

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The title page should include

1. Type of manuscript (article/case report)
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Summary and Keywords: Summary no more than **250 (150 for Case Report)** words. Should have following headings: **Introduction** (state the purposes of the study or investigation), **Materials and Methods** (selection of study subjects/patients, observational and analytical methods), **Results** (give specific data and their statistical significance, where ever possible), and **Conclusion** (succinct emphasis of new and important aspects of the study or observations). Do not use symbols in the summary; rather, spell out what they stand for in full. Three to eight keywords must be included below the summary.

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Materials and Methods: Describe precisely your selection of the observational or experimental subjects (patients, including controls). Identify the methods, apparatus (including manufacturer's name and address in parenthesis), and procedures in sufficient detail to allow others to reproduce the method. Give references to established methods, including statistical methods; provide references and brief descriptions for methods that have been published but are not well-known. For new or substantially-modified methods, describe and give reasons for using them and evaluate their limitations.

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Results: Present your results in a logical sequence in the text, Tables, and Illustrations. Do not repeat in the text all the data in the Tables or Illustrations. Emphasize or summaries only important observations. Specify the statistical methods used to analyze the data. Restrict Tables and Illustrations to those needed to explain the argument of the paper and to assess its support. Where possible, use Graphs as an alternative to Tables with many entries. Do not duplicate data in Graphs and Tables.

Discussion: Emphasize the new and important aspects of the study and the conclusions that follow from them. Do not repeat in detail data or other material given in the Introduction or the Results section. Include in the Discussion section the implications of the findings and their limitations, including the implications for future research. Relate the observations to other relevant studies.

Tables: Print each Table double-spaced on a separate sheet. Number Tables consecutively in Arabic numerals (e.g. 1, 2,

3) in the order of their first citation in the text and supply a brief title, which should be shown at the top of each table.

Illustrations (Figures) and Legends for Illustrations: All Illustrations must be submitted in JPEG finished format form that is ready for reproduction. Figures should be numbered consecutively in Arabic numerals (e.g. Fig. 1, 2, 3) according to the order in which they have been first cited in the text. If photographs of persons are used, the subjects or patients must not be identifiable. Present the legends for illustrations using double-spacing, with Arabic numerals corresponding to the Illustrations.

Acknowledgements: State contributions that need to be acknowledged.

References

A list of all the references cited in the text should be given at the end of the manuscript and should be numbered consecutively in the order in which they are first mentioned in the text. Identify references in the text by Arabic numerals in superscript. Omit month and issue number. List all authors, but if the number is six or more, list first three followed by et al. The references should be cited according to the Vancouver agreement. Authors must check and ensure the accuracy of all references cited. Abbreviations of titles of medical periodicals should conform to the latest edition of Index Medicus. Some examples are shown below:

Standard Journal

You CH, Lee KY, Chey RY, et al. Electrogastrographic study of patients with unexplained nausea, bloating, and vomiting. *Gastroenterology* 1980; 79:311-314

Online journal article

Miyamoto O, Auer RN. Hypoxia, hyperoxia, ischemia and brain necrosis. *Neurology* [serial online] 2000; 54:362-71. Available at: www.neurology.org. Accessed February 23, 2000.

Chapter in a book

Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, eds. *Pathologic Physiology: Mechanisms of Disease*. Philadelphia: Saunders, 1974: 457-472

Online book or website

Garrow A, Weinhouse GL. Anoxic brain injury: assessment and prognosis. In: *UpToDate Cardiovascular Medicine* [online]. Available at: www.UpToDateInc.com/card. Accessed February 22, 2000.

In press

Lillywhite HB, Donald JA. Pulmonary blood flow regulation in an aquatic snake. *Science*. In press.

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Generally, submitted manuscripts are sent to one experienced referee from our panel. The contributor's may submit names of two qualified reviewers who have had experience in the subject of the submitted manuscript, but not associated with the same institution(s) as contributors nor have published manuscripts with the contributors.

Department of Pain and Palliative Medicine

Pain and palliative care is an integral part of cancer care, however, all these years; it was practiced by different departments of GCRI. As most of the patients coming to GCRI are in advanced stage of disease, hence, a need was felt to bring this essential treatment under one umbrella; hence the acceptance of proposal by JivDaya foundation Dallas, USA. Thus, Pain and Palliative Care services got its separate and distinct identity on 9th October 2010, a day on which World Hospice and Palliative Care Day was celebrated. JivDaya foundation Dallas, USA, an NGO working for improving quality of human lives, promised to support human resources for this initiative. Dr Geeta Joshi was nominated as Co-ordinator of Palliative Care, JivDaya foundation project.

The team made up of Dr Kalpesh Mecwan as medical officer, Natvar Dayma as counselor and Mittalkumari Chauhan as a staff nurse started attending patients under guidance of Dr Geeta Joshi. The team shared a common goal of improving quality of life of cancer patients by managing pain and symptoms and addressing psychosocial and spiritual issues. **They adopted the slogan “Sharing the Care”**, emphasizing the multidisciplinary approach to palliative care. Hence, a bonding network was established with all departments and services of the institute.

Palliative Services

The Palliative services, which initially took the form of OPD services (afternoon) has now spread out in different direction to encompass a caring support to cancer patients irrespective of disease stage and status.

- 1. OPD Services:** Initially started in Room No 11, Surgical OPD between 2:00 to 5:00 PM, that was not sufficient due to increased patient reference, therefore, also has been extended in Room No 103 in morning hours. **The aim of this service is “No Waiting, No Pending”**. We attend patients between 9:00 to 5:00 PM, all days of the weeks, except holidays.
- 2. Inpatient Services:** Inpatient reference from wards are attended for symptom management and counseling.
- 3. Hospice:** The Community Oncology Centre, Vasna houses 10 beds (Inpatient Care) for terminally ill patients, and is visited by Palliative Care team members. Wound care, Hygiene and Pain are matter of primary concern in these patients.
- 4. Home Care Team:** Palliative Care team provides home visits to registered treated cancer patients those residing within city limits but, unable to visit hospital. They are given medicines and in addition family members are counseled for care of patient by our special team including Dr B.G. Pandya, RMO.
- 5. Training and Education:** It started with training of team members, who got formal training in Palliative Care within 1st year of appointment. This included Certificate course run by Indian Association of

Palliative Care as well as practical training at other centres.

Formation of Department of Pain and Palliative Medicine

“A single step on the Moon is a giant leap forward for mankind”. This happened in GCRI; in about two years, the initiative of starting the Palliative Care began bearing fruits and the load of patients increased manifold. Hence, “The Department of Palliative Care” was established in November 2012. Dr Geeta Joshi has been appointed as Head, Pain and Palliative Medicine. The team was strengthened by appointment of Dr Ruchira Trivedi and rotation of resident doctors from various specialties.

Highlights of Department

- At present the workload is around 5000 patients/year.
- Morphine consumption has hiked from 1880.55 gm to 3301.51 gm from the year 2010 to 2012, indicating the efficient cancer pain management.
- We focus on holistic care of patients which includes pain management, symptom control, wound care, advice on nutrition, counseling on disease status, general hygiene, and various other important issues like psycho-social, financial and spiritual aspects.
- Department is involved in training of students from Medical colleges, Nursing colleges, BM Institute for mental health and Gandhi Labour institute for project-work.
- Two projects have been taken up namely Cancer Pain Prevalence Study and Radio Frequency Ablation (RFA) of Spheno-palatine Ganglia in Head and Neck cancer.
- Community Awareness Programme: Each year, World Hospice and Palliative Care Day is celebrated on 2nd Saturday of October. Department organizes programme for creating awareness about “Palliative Care” to patient's relatives and medical staff of other institutes in campus.
- Our institute is now a recognized centre for “Essentials of Palliative Care”, a certificate course run by Indian Association of Palliative Care.

Future Plan

1. We plan to start MCI approved **Post-Graduate course in Palliative Medicine**.
2. We also plan to become a **nodal center** for training, policy making on issues of Morphine availability for Palliative Care patients.
3. As we have many specialty Institutes like Kidney Institute, Cardiac Institute, and HIV/AIDS Centre etc. in our Civil Hospital Campus, this Department has a potential to be a Palliative Care Center for all Non-Communicable Diseases.

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RP (10/13)

Department of Pain and Palliative Medicine "Sharing the Care"



Rally for awareness on World Hospice Day



Three days course held GCRI by Indian Association of Palliative Care



Inauguration: Pain & Palliative Medicine Department on Nov 3, 2012



Essentials of Palliative Care CME



OPD seen by senior faculties



Pain & Palliative OPD



Home visit by home hospice team and R.M.O



Counseling of patient and relative with psychologist



Home based dressing being explained by staff nurse