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End of Life Care in Oncology Critical Care Unit: Many Questions, Few Answers

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Intensive care units provide intense care to patients suffering from critical illness and the aim of keeping the patient in ICU is to reduce morbidity and mortality associated with that episode by providing assistance with life support measures, preventing organ dysfunction and restoring health. But scenario is little different when we talk about oncology critical unit care.

The spectrum of patients admitted to oncology critical care unit comprises of hematological malignancy, advanced solid tumors and post operative patients. Wishes of such patients vary from one extreme: Doctor, do not give up to the other end of dignified death: End of Life Care (EOLc). Here, patients admitted with advanced cancer have limited life expectancy, limited organ reserve due to cancer treatment and a very little hope of cure and death is common outcome. Therefore, ICU clinician may think of the concept of death with dignity in such cases where advanced cancer is refractory to treatment, parameters of poor outcome are met as defined by physician's subjective and objective observations.

What is End of Life Care (EOLc)?

EOLc[1] is a multidisciplinary team approach towards total care for people with advanced, progressive, incurable or life limiting illness so that they can live as well as possible before they die. The process of care is not just limited to the person who is dying but extends to his/her families and caregivers. Recognizing medical futility and dying process is first step in providing EOLc.

What is dignified death?

The committee on care at the end of life of the institute of medicine concluded that a good death is "free from avoidable distress and suffering for patients, families, and caregivers; in general accord with patient's and families' wishes, and reasonably consistent with clinical, cultural, and ethical standards".[2]

What is medical futility?

The concept of medical futility remains controversial, and there is no general professional consensus about the appropriate use of futility in medical decision making.

Medical futility[3] means when physiological parameters still respond to measures but the ultimate prognosis both in terms of mortality and quality of life is grim. A term used when "Reasonable Measures" for maintenance of life are unlikely to result in "Meaningful Survival."

Physiologic futility means that an intervention will have no physiologic effect.

Qualitative futility refers to an intervention that "fails to end a patient's total dependence on intensive medical care."Quantitative futility occurs "when physicians conclude (either through personal experience, experiences shared with colleagues, or consideration of reported empiric data) that in the last 100 cases, a medical treatment has been useless.

Economic futility is not a well defined terminology but we understand a situation where the family has exhausted of all resources and requests withdrawal.

How to predict the imminent death or dying process?

A model[4] for impending death within three days in cancer patients using two objective bedside physical signs, the Karnofsky Performance Scale (KPS, an 11-point scale that ranges from 0 [death] to 100 percent (completely asymptomatic), is based upon the patient's function, oral intake, and cognitive status, and is widely used to estimate prognosis in cancer patients.

EOLc- How, when and what?

Once the futility being recognized and the dying process identified, discussions and consensus building about poor prognosis and plan to initiate EOLc discussion[5] should follow.

Physician should make an honest, accurate, early disclosure of poor prognosis of patient to family and patient if capable. Pending consensus decisions or in event of convict with the family/patient physician must continue all existing life supporting interventions and review situation periodically. Holding family meetings is required periodically. Clinicians should recognize that family members of patient are often "living with dying" as they are maintaining hope though faced with uncertainty. Though "hope" should be respected during prognostic disclosure a realistic view should be maintained. When the fully informed capable patient/family

chooses to opt for overall treatment Goal of "Comfort Care Only" option, physician should explicitly communicate standard modalities[5] of limiting life prolonging interventions. These include Do not resuscitate (DNR), withholding of life Support or non escalation, withdrawal of life support (Passive Euthanasia) and terminal sedation. Common modalities involve not initiating new therapies aimed at cure, withholding, weaning/withdrawing from mechanical ventilation, vaso-pressors, renal replacement therapy, therapeutic medications, nutrition and extubation.

Case notes should clearly reflect through faithful recording, entire or gist of all the discussions with family, decision-making process and final decision based on medical appropriateness and patient's/family's preferences. It is mandatory to have a life support limitation form duly filled and signed by two or more members of family and treating team. The documentation is must at each and every step and the moment of the process.

Living will/advanced care directives refers to a document in which a person while still competent, requests and directs that certain measures, which may be variously specified, should be adopted when he becomes incapable of taking responsibility of his own health care, i.e. by consenting to or refusing treatment. A competent adult patient has the right to insist that there should be no invasive medical treatment by way of artificial life sustaining measures / treatment. Such decision is binding on the doctors / hospital attending on such patient. It should be "informed decision" based on" free will."

Issues specific to critical care unit are patient without decision making capacity, patients in whom life support measures are withdrawn, performing CPRs, transitioning out of ICUs and attending religious spirituality. Most of the patients and families prefer to die at home if given a choice. The issues to shift the patient home are death during transition, availability of support facility at home.

What are the legal and ethical issues?

Caring for patients at the end of life is a challenging task that takes into account the patient as well as family, social, economic, legal and institutional circumstances that surround patient care.

Over centuries, clinicians have developed ethical norms regarding care of the dying including withdrawal and withholding of life-sustaining treatments. The first suggestion dates to Hippocrates' injunction[6] "to refuse to treat those (patients) who are overmastered by their disease, realizing that in such cases medicine is powerless."

From history to the contemporary modern medicine, the EOLc has not moved its way to get into standard practice because of its legal and ethical issues.

The term dignity has become highly politicized and is frequently invoked as justification for various end-of-life care practices and policies. In many circles, the term "death with dignity" is synonymous with the right to assisted suicide and euthanasia.

Fundamental doubts are 'what is dignified death? Who decides when the process of death commences? what of medical research tomorrow finds a cure to the presently terminally ill disease?. Can court fathom the problems and abuse that could happen in far-flung places?"

Supreme court[7] decided to adjudicate the legality of active and passive euthanasia and emerging concept of living will which is highly emotive and legally complicated issue. Government does not accept euthanasia as a principle and court has no jurisdiction to decide it. It's for parliament and the legislature to take a call after a thorough debate and taking in to account multifarious views.

241[st] Law for incompetent patient such as a person in "irreversible coma" or in persistent vegetative state says that the relatives, next friend, or the doctors concerned / hospital management shall get the clearance from the High Court for withdrawing or withholding the life sustaining treatment. The high court shall take a decision after obtaining the opinion of a panel of three medical experts and after ascertaining the wishes of the relatives of the patient. The high court as parens patriae will take an appropriate decision having regard to the best interests of the patient. The additional solicitor general said medical council (professional conduct, etiquette and ethics) regulations, 2002, also consented that a team of doctors could decide withdrawal of life support system from terminally ill patients after they were declared brain dead.

"Passive euthanasia", which is allowed in many countries, shall have legal recognition in our country too, subject to certain safeguards, as suggested by the 196th report and as held by the supreme court in Aruna's case[8] [(2011) 4 SCC 454)]. A two-judge SC bench in 2011 had legalized passive euthanasia in the Aruna Shanbaug case. However, a three judge bench later ruled that the 2011 verdict was based on wrong reasoning and referred it to a constitution bench for fresh adjudication on legality of passive euthanasia.[9]

Conclusion

End of life care in the oncology critical care unit is a well desired modality for patients with refractory advanced malignancy. Defining imminent death and futility are important points in decision making over and above family and patient's wish/will. Advanced directive is still considered illegal in our country. It's for parliament and the legislature to take a call after a

thorough debate and taking in to account multifarious views. The consensus building amongst the treating team, patient and care givers; explicit consent; transparency and accountability through documentation of the process are mandatory. The availability of the treatment for diseases considered incurable in past worsens our confusion. The issue of abuse is the remote places needs to be tackled. Over all, the EOLc, is highly desirable but still a contentious modality in the mist of legal, ethical and operational frame work and we need to wait for the mist to clean up.

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To raise new questions, new possibilities, to regard old problems from a new angle, require creative imagination and marks real advance in science.

Albert Einstein

Dr. T. B. Patel Oration Award Year - 2015

Professor Neerja Bhatla
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Cervical Cancer Control: The Dawn of a New Era

The history of cervical cancer control is a story of the victory of science and a remarkable example of how collaborative work between epidemiologists, scientists, gynaecologists, pathologists has come together to benefit womankind. Cervical cancer is the second most common cancer affecting women globally but there is great disparity between developed and developing countries: it is not even in the first ten cancers in the developed world. This is testimony to the fact that the oft-repeated lament about cervical cancer: "Preventable but not yet prevented!" need not be carried any further.

Many stalwarts played a great role in this achievement. Rigoni-Stern's epidemiological observations in 1850 pointed out the correlates of cervical cancer and Papanicoloau and Traut developed the art and science of cytological testing. Though an infectious etiology was long suspected, it was Harald zur Hausen who finally proved the role of the human papillomavirus, for which he received the Nobel Prize. This discovery opened the gates for the development of a whole new generation of tests based on HPV DNA testing, which are found to be more sensitive than cytology and therefore reduce the need for repeated testing. It also led very quickly to the development of prophylactic vaccines against HPV types responsible for the majority of cervical cancers, as well as genital warts.

However, technology comes with a price and we live in an India that has many Indias – the affording and the not-so-affording. For low resource situations, the role of simple visual inspection methods has been clearly delineated through the painstaking efforts of Dr Sankaranarayanan at the International Agency for Research on Cancer (IARC). Outpatient management techniques were standardised, at the same time new techniques like cold coagulation and Loop Electrosurgical Excision Procedure (LEEP) found their place alongside the older methods of cryotherapy and cold knife conization. Surgical management has also entered a new phase with minimal access radical surgery. Research is ongoing on therapeutic vaccines to reverse cervical intraepithelial neoplasia and improve outcomes in cervical cancer treatment. Each technology and innovation needs to be evaluated for its applicability to our situations, its effectiveness, cost-effectiveness, general availability, etc.

On the prophylactic HPV vaccine front too, much advancement has oocurred since the vaccines were introduced a decade ago. There is good data to support the safety and efficacy of the vaccines, as well as data from the real world on the effect on HPV prevalence and disease prevalence. Results from the IARC trial have shown that two doses of the vaccine given 6 months apart have the same immunogenicity as three doses as per standard recommendation. WHO has now recommended two doses to be administered to girls under 15 years of age. The introduction of the nonavalent vaccine has improved the spectrum of genotypes covered. Meanwhile, an Indian vaccine is now in Phase I trials already.

A new era has dawned – women should be counselled about the available options and encouraged to participate actively in the movement for preventive, promotive and curative health care. There has been a small and steady decline in the rate of cervical cancer but in no way commensurate with the rate in countries that have regular cervical cancer prevention practices. Denying opportunities for vaccination and screening places women at unnecessary risk of cervical cancer. Health care providers, policy makers, NGOs and all stakeholders should work together to implement Cervical Cancer Control. Prof. Fathallah, the former President of FIGO has said very aptly: "Women are not dying because of disease we cannot treat. They are dying because societies have yet to make the decision that their lives are worth saving." We should all pledge to save every life that we can.

Shri Madanmohan Ramanlal GCRI Luminary Award - 2015

Dr Rajendra I Dave
M.B.B.S., M.S., F.I.C.S.

Dept of Surgical Oncology,
Former HOD and Deputy Director
GCRI, Ahemedabad

Journey at the Gujarat Cancer and Research Institute

M. P. Shah Cancer Hospital, indoor facility and surgical procedures commenced in1967. From small 40 beded hospital now it has grown to a 650 beded comprehensive cancer care center with education and research wing. It serves about 10,000 patients daily with different modalities of treatment. It has all supportive services and super specialty units to serve cancer pts of Gujarat and neighbouring states. it is attached to B. J. Medical College and Gujarat University for various post graduate and super speciality degrees. So far it has trained and qualified more than 500 doctors for oncology work for society.

Surgery is the oldest modality practiced for cancer cure. Wilium Halstead, Crile, Bilroath and Kocher have performed their cancer operations and they are still successful and time tested. I am in the Dept. of Surgical Oncology since1971. I learnt basic principle of oncology from my senior teachers of India and abroad. I practiced cancer surgery of all organs since last four decades. I have seen changes taking place in diagnosis, staging and operative procedure due to advances in radiology, pathology and operative equipments. Advances in Anesthesia, preoperative evaluation, post op care and ICU facility have reduced mortality and morbidity of surgery to acceptable level. Multi modality approach and combination therapy has improved results and survival. During my tenure at Gujarat Cancer & Research Institute (GCRI), I have seen certain operations becoming rare and certain new procedures are started for the first time and carried out frequently. Supra radical approach of past is changed to conservative plan. Better cosmetic and functional result is the aim of surgical oncologist now along with complete removal of disease. He performs either single or along with help of medical or radiation oncologist or other colleague to achieve this goal. My presentation describe my experience and progress of Department of Surgical Oncology at GCRI in last four decades

Equipped with his five senses, man explores the universe around him and calls the adventure science.

Edwin Powell Hubble

Circulating Tumor Cells (CTCs) or Cancer Stem Cells (CSCs): The Unresolved Paradox as Drivers of Metastasis

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Summary

Tumor aggressiveness, relapse and metastasis are the primary causes of poor survival rates in patients with advanced stage cancer despite successful resection as well as chemotherapeutic treatment which limits the possibility of developing new therapeutic strategies. Nevertheless, circulating tumor cells (CTCs), accountable for tumor dissemination, and cancer stem cells (CSCs), essential for tumor growth maintenance, together shed light on the complex metastatic cascade. The major cause of recurrence and metastasis can be attributed to the cancer stem cells (CSCs), which are extremely resistant to chemotherapy. Moreover, CTCs and CSCs are not essentially separate subpopulations of tumor cells, because CTCs are essentially generated in the process of epithelial mesenchymal transition (EMT) and often have features characteristic of CSCs. Furthermore, EMT programming in tumor cells allows the remodelling of extracellular matrix to break the dormancy of relapse-initiating CSCs. Thus, in this review we comprehensively discuss the association of EMT with CTCs and CSCs to characterize a subpopulation of patients prone to recurrence, relapse and metastasis. Deeper understanding of the mechanisms by which EMT-transformed CTCs and CSCs initiate relapse could aid in the development of new strategies for early detection of metastasis and treatment approaches that will be translated into clinical practice.

Keywords: Epithelial mesenchymal transition, Circulating tumor cells (CTCs), Cancer stem cells (CSCs), Tumor metastasis

Introduction

Distant metastasis development is the leading cause of death worldwide. Metastatic lesions are often too widespread to be removed surgically and frequently exhibit increased resistance to chemotherapy and low therapeutic response. Thus understanding the nature of metastatic process is of key significance for curbing the global death rate due to carcinogenesis and also for the improvement of treatment. In order to progress, tumors of epithelial origin need to acquire features which enable them to: (1) detach from each other, rupture the basal membrane and dissociate from the tumor mass, (2) invade surrounding tissue, intravasate into blood or lymph vessels and (3) extravasate from vessels in distinct organs to form secondary tumor(s).[1] Epithelial mesenchymal transition (EMT) is essential for the successful spread of the metastatic cells. In this process the epithelial tumor cells gain invasiveness and migratory abilities.[2,3] EMT is believed to be responsible for tumor recurrence, relapse, and decreased drug responsiveness and thus lead to the failure of anticancer therapy. Moreover, studies have shown that stem-like cells may also arise as a result of EMT process.[4-6]

A major cause of tumor metastasis is an increasing number of circulating tumor cells (CTCs) and their downstream transformation into cancer stem cells (CSCs) which initiates recurrence.[7,8] Moreover, cases that demonstrate chemo- or radio-resistance have high numbers of EMT transformed CTCs.[9] Evidence from clinical studies also suggests that poor survival of cancer patients has been linked with EMT phenotypes in malignant cancer cells.[10-12] Accumulating evidence shows that subsets of CTCs and CSCs have characteristics of EMT phenotype and also a sub clone of CTCs can be induced to express phenotypes of CSCs.[13, 14] These findings suggest that EMT links CTCs and CSCs, enabling these cells to survive in circulation and facilitate the metastasis process. A better understanding of the reprogramming switches might lead to determination of tumor progression through EMT and also CTCs, tissue/cell dormancy and CSCs could pave the way towards clinically relevant drug targets. In this review, we discuss the concept of EMT, CSCs and also the link between them which might be the probable cause for cancer progression, relapse and metastasis. We highlight the most recent studies demonstrating the potential contributions of EMT, CTCs and CSCs leading to cancer invasion and metastasis. Thus, improving our understanding of these mechanisms may help to categorize potential targets for novel therapeutic approaches.

EMT and Cancer Metastasis

An EMT is a biological process that allows an epithelial cell, which normally interacts with basement membrane, to undergo multiple biochemical changes and enable it to attain a mesenchymal cell phenotype, with enhanced migratory capacity, invasiveness, increased resistance to apoptosis, and elevated production of extra cellular matrix (ECM) components.[15] The multistep event of EMT during cancer progression and metastasis closely resembles that observed during embryogenesis as it plays a very important role in tissue homeostasis, embryological development, wound healing and tissue development.[16] The accomplishment of the EMT process is indicated by the degradation of underlying basement membrane and the formation of a mesenchymal cell that can migrate from the epithelial layer in which it originated. A number of distinct molecular processes such as activation of transcription factors, expression of specific cell-surface proteins, reorganization and expression of

cytoskeletal proteins, production of ECM-degrading enzymes, and changes in the expression of specific microRNAs are involved in the initiation and completion of EMT. Moreover, the above mentioned factors involved in EMT are also used as biomarkers to demonstrate the passage of a cell through this process. The phenotypic plasticity of EMT is revealed by the occurrence of the reverse process- a mesenchymal-epithelial transition (MET), which involves the conversion of mesenchymal cells, to epithelial origin. Furthermore, very little is known about this process but the best studied example is the MET associated with the kidney formation and the genes involved in the process are paired box 2 (Pax2), bone morphogenetic protein 7 (Bmp7), and Wilms tumor 1 (Wt1).[17] EMT is thus a resultant effect of the crosstalk amongst several mechanisms such as E-cadherin regulation, transcriptional factors governing the E-cadherin suppression and independent activation of various oncogenic signalling molecules.[18,19]

Mechanisms of EMT

Cellular Junctions and E-Cadherin Suppression : The cell surface changes intensely as the expression of EMT-inducing genes increases. E-cadherin, a transmembrane protein and key marker of the epithelial phenotype, is responsible for anchoring neighbouring cells to one another and forming adherens junctions, with its cytoplasmic component linked to the actin cytoskeleton by α- and β-catenin. Loss of this protein is required for EMT to occur, and it promotes metastasis.[20] During EMT, E-cadherin is substituted by N-cadherin, a process referred to as 'cadherin switching'. This cadherin switching causes decrease in expression of epithelial markers, increase in expression of mesenchymal markers (Vimentin, Metalloproteases, N-cadherin), loss of cell-cell contacts and also facilitates cell migration and invasion.[21] The well-known E-cadherin repressors that act by inducing epigenetic silencing at the promoter in the form of hypermethylation and histone deactylation include Snail, Zeb and Twist.[22] The O-glycosylation of the E-cadherin protein controls the posttranslational modification at the cell surface and inhibits its transportation to the plasma membrane. After reaching the plasma membrane the protein can be inactivated by proteolytic cleavage or destabilized by phosphorylation of β-catenin. [23] The loss of E-cadherin is an integral step in EMT and without the tight adherens junctions keeping tissues together, individual cells are able to migrate, which is critical for cancer metastasis. [20,23]

Signalling and Transcriptional Factors: Several transcription factors such as Snail, Twist, Zeb etc. are up-regulated in metastatic cells that are undergoing EMT and have invasiveness characteristics as depicted in Figure 1. In the epithelial to mesenchymal transition TGF-β plays an important role in activating Snail, which in turn down-regulates cadherin-16 and HNF-1β. Moreover, TGF-β also induces apoptosis and thus cancer cells must protect themselves from this cell-death pathway. Interestingly, in addition to inducing EMT, Snail up-regulates Akt and Bcl-xL, which inhibit TGF-β-induced apoptosis in cancer cells.[24] Snail has been shown to inhibit cell cycle progression through the down regulation of Cyclin D2 while conferring resistance to apoptosis. However, in the tumor microenvironment, Snail can be activated through multiple pathways, including HIF1, HIF2, Notch (hypoxia) as well as NF-κB and TGF-β (inflammation) .[25,26] The nuclear localization of Snail1 is due to VEGF-A which is thought to be involved in EMT. Studies have shown that IGFR induces EMT through NF-κB and Snail in mammary epithelial cells and also up-regulates Zeb in prostate as well as activates latent TGF-β1 to induce EMT.[27] The expression levels of HIF-1α, a

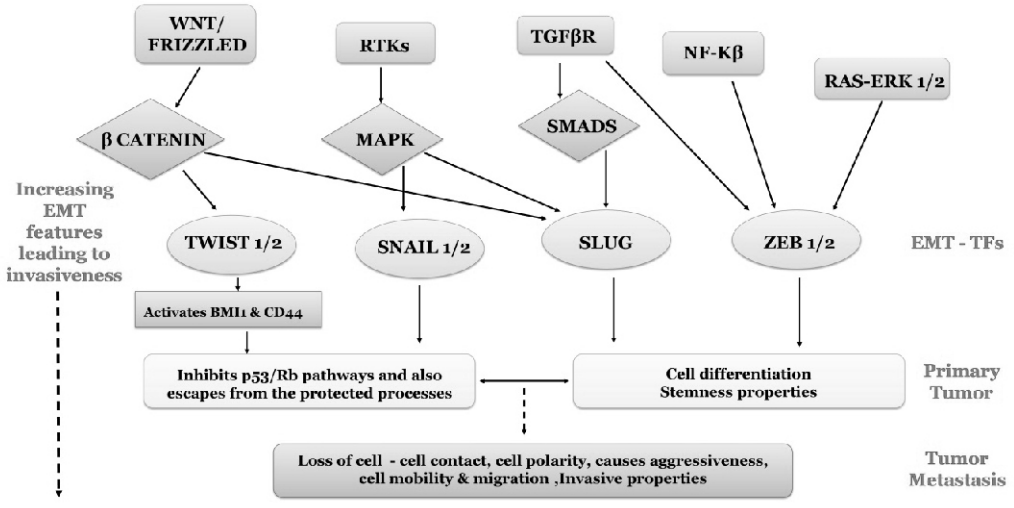

Figure 1: The molecular network of Transcription Factors and Signalling Pathways that regulate the Epithelial-Mesenchymal Transition in metastatic cells

protein that plays a central role in the development of aggressive, mesenchymal phenotypes in hypoxic and inflammatory environments, have been shown to induce IL-8, VEGF, and Twist1 expression, and thus lead to EMT.[28] Transcriptional factors like ZEB2 play a vital role in initiating the downregulation of E-cadherin while Slug and ZEB1 are critical for maintaining its repression.[29] However, the effect of E-cadherin repressors on mesenchymal markers such as Vimentin and N-cadherin still remains to be elucidated. Alternative splicing plays a significant role in EMT and this was established in a study of pancreatic cancer that found specific splice variants of CD44 in metastasized cancer cells that were not present in the primary tumor cells. Later it was found that the splicing factor, ESRP1 in epithelial cells inhibit the CD44 isoform switching from an epithelial variant to the mesenchymal variant. Additionally Snail inhibits ESRP1 during EMT thus increasing the expression of the CD44 isoform associated with dedifferentiation and invasiveness. However, CD44 is not, by any means, the only example of alternative splicing that induces and affects EMT.[30]

Cancer Stem Cells

CSCs, comprising of a small population of tumor cells, have the unique ability of self-renewal, multipotency and differentiation into cells of various lineages giving rise to heterogeneous populations, have the ability to promote tumorigenesis, are distinctive cell surface markers in the CSC population and are not expressed by normal stem cells. These unique characteristics of CSCs are responsible for disease aggressiveness, metastases, resistance to chemo-radiotherapy and high mortality rate. The first evidence for the existence of CSCs was reported by Bonnet and Dick[31] in acute myelogenous leukemia (AML), and later was shown for breast cancer and other malignancies.[32,33]

Two hypothetical models have been proposed for CSCs –the 'Stochastic model' and the 'Cancer stem cell hypothesis'. The stochastic model suggests that all the cancerous cells are equally malignant and every single cell in the population has the potential of developing a tumor under favourable circumstances, although the probability is quite low. According to this concept, during tumor progression heterogeneity within the population of cancerous cells develops due to the effect of genomic instability and accumulation of mutations and in the process of clonal selection, cells with metastatic potential disseminate and form secondary tumors. On the other hand 'Cancer stem cell hypothesis' signifies the pre-existence of functional heterogeneity within tumor cells with a distinct subpopulation of CSCs which initiate and maintain tumor growth as well as the bulk of non-tumorigenic cells.[34]

Furthermore, identification and isolation of these CSCs as potential diagnostic/ prognostic markers is increasingly becoming a priority for research purpose as well as for clinical targeted therapies. The inconsistent expression of these CSC cell surface markers at different stages and in various sub-types of tumor progression makes it difficult to recognize these markers from the bulk of tumor population. Currently, CSCs have been distinguished from the bulk of tumor population by the expression patterns of cell surface proteins and cellular activities such as drug efflux and aldehyde dehydrogenase. Hence, better characterization of CSCs may help in developing new and more effective strategies against cancer progression and invasion.[35]

CSCs and Tumor Metastasis

Alternatively, CSCs arising through an EMT process from transformed epithelial cells attain migratory and tumor-spreading properties. In an experimental study, the induction of EMT in immortalized, non-tumorigenic human mammary epithelial cells resulted in acquisition of the CD44+ CD24–low phenotype, characteristic of breast cancer stem cells.[36] CD44, a cell-adhesion molecule is the binding partner of hyaluranon (HA) whereas CD24 is a negative regulator of the chemokine receptor CXCR4, known to be involved in breast cancer metastasis. It has been shown that the CD44+/CD24 –/low subpopulation of cells is present in most (but not all) basal-like tumors, especially in BRCA1 hereditary breast cancer and is also found in few HER2- positive tumors.[37] Cells with the CD44 + /CD24 –/low phenotype were hypothesized to be stem-like cells responsible for tumor initiation in non-small cell lung cancer (NSCLC) and prostate cancer.[38] Interestingly, in pancreatic cancer, a subpopulation with a high co-expression of CD24 (CD44+/CD24+/ESA+) was identified as being tumorigenic in NOD/SCID mice. It is reported that expression of CD24, CD44 and CD133 is correlated with invasiveness and differentiation of colorectal carcinoma, but not with patient survival and outcome. Majority of the cell surface proteins (CD24, CD133, CD166) are important for cellular adherence they might probably be involved in forming new tumors.[33,39]

However, it is also crucial to identify functional markers for CSCs, such as ALDH1 (present in breast, colon, pancreatic carcinoma) or Wnt ALDH1, a marker for both normal and malignant stem cells is thought to have a pivotal role in the early differentiation of stem cells. A subpopulation of ALDH1- positive cells with prominent tumor initiating ability was found within breast cancer cells with CD44 + CD24 –/low phenotype. Additionally the expression of ALDH1 alone in breast cancer was known to be associated with poor clinical outcome.[40] Other stemness markers that are known to be involved in tumor carcinogenesis and progression include CD133, OCT-4 and NANOG-1. OCT-4, a transcription factor involved in the self-renewal of undifferentiated embryonic stem cells can reprogram unipotent stem cells to pluripotent stem cells. Significantly higher expression of OCT-4 was observed in CD44 + /CD24 – primary breast cancer cells and in ALDH1-expressing cells of the 4T1 murine breast

cancer cell line.[41,42] OCT-4 along with other transcription factor NANOG-1 is known to be involved in the pluripotent state of stem cells – and their expression is elevated in mammospheres, (cells enriched for metastatic potential). Surprisingly, the meticulous function of CD133 is not yet completely understood; however, it might be involved in cell differentiation, proliferation and epithelial-mesenchymal interaction.[43] Various stem cell markers - NOTCH1, ALDH1, SOX1, and CD44 are reported to have been expressed frequently on CD133-positive breast cancer cells and are highly tumorigenic in animal models. A study employing microarray analysis of CD44 + CD24 -/low cells versus CD44 - /CD24 + cells isolated from breast cancer tumors confirmed that these two subpopulations of cells are genetically distinct from each other, and the gene expression profile of the breast cancer stem cell fraction (CD44+/CD24-/low) resembles characteristics of stem cells. Another study by Liu et al. developed a gene signature which consisted of 186 genes differentially expressed in breast CD44 + /CD24 –/low cells and normal breast epithelium thus correlating the signature with metastasis-free and overall survival.[44]

Several studies have indicated that CSCs play a major role in tumor progression, invasion, metastasis and resistance to non-targeted therapies. Moreover, the crosstalk amongst multiple signal transduction pathways involving the various metastases associated genetic factors and CSCs plays a vital role in governing biological properties of the complex metastatic cascade.

CTCs and Tumor Metastasis

CTCs are cells which dissociate from the tumor mass and enter into the circulation. They have been detected in a majority of epithelial cancers, including those from breast, prostate, ovary, lung and colon and are extremely rare in healthy people. According to Paget's 'seed and soil hypothesis' CTCs may constitute seeds for the subsequent growth of distant metastasis in various organs.[45] However, CTCs may also be capable of self-seeding in the original organs, which leads to increased aggressiveness of the existing tumor [46], or they can settle in other organs such as bone marrow, where they are termed as disseminated tumor cells (DTCs) and can serve as a reservoir of cancer cells responsible for imminent recurrence. CTCs represent a heterogeneous population of tumor cells with the potential of forming multiple metastases. It is proved that among the cells that have detached from the primary tumor, only 0.01% can form metastases and are found in the frequencies of order of 1-10 CTC per ml of whole blood in such metastatic patients. The metastasis inefficiency can be attributed mainly to anoikis and thus explains the low survival rates of CTCs in vessels after leaving the primary tumor mass. Moreover, only some cells which extravasate in distant organs are able to proliferate, but not all established micrometastasis can overcome angiogenesis and develop into macrometastasis.[47]

CTCs, CfDNA/ctDNA known as 'liquid biopsy' is a potential alternative to invasive biopsies as a source of tumor material for the detection, isolation, characterization and monitoring of non-hematologic cancers. Despite numerous efforts and studies, CTC detection is still technically challenging, mainly due to their scantiness and biological heterogeneity and thus much clinical application of CTC is not considerably possible. Currently used approaches for CTCs isolation and detection the presence of specific proteins (CellSearch, CTC-chip, RARE, MagSweeper) and gene transcripts (ADNAtest), density (Oncoquick), size (ISET technology), electric charge, includes secretion of specific proteins (EPISPOT) and/or invasive properties.[48] Many issues such as accuracy, sensitivity, specificity of the techniques and optimal markers for CTC detection are concerning issues related to CTC detection and isolation and they still remain to be a matter of debate. Currently the most widely used approach for CTC isolation and detection relies on the epithelial molecule - EpCAM that is present in 60-100% of breast cancers.[49] However, various studies have shown that EpCAM-based CTC detection does not identify breast cancer cells belonging to a normal-like subtype, which is characterized by aggressive behaviour.[50] By using the additional surface marker CD146, which is frequently expressed on the cells that lack EpCAM the sensitivity of the assay can be overcome. Additionally it was discovered that when EMT occurs in CTCs it causes the downregulation of epithelial markers and renders CTCs undetectable posing as a major drawback for epithelial markers based isolation and detection methods.[51] Recent studies have aimed at the analysis of EMT process itself, the markers involved in EMT and also on the EMT - induced stemness of CTCs, thus suggesting that for the detection of CTCs we should not rely solely on single markers and should possibly include mesenchymal markers induced by EMT.[49] Thus advancement in the optimization and clinical validation of techniques involved in CTC isolation and detection will lead to better characterization of CTCs and deeper understanding of the mechanisms involved in their generation, survival and migration.

Recent studies have revealed that CTCs may be linked to both cancer stem cells and the EMT process, which adds additional value to the clinical utility of CTCs. Studies have reported the expression of EMT-related proteins, such as vimentin or TWIST1, in CTCs obtained from breast cancer patients.[52,53] CTCs with epithelial/mesenchymal phenotype have also been found in patients with metastatic non-small cell lung cancer (NSCLC) and metastatic prostate cancer.54 Interestingly, it is proved that mesenchymal markers on CTCs occur more frequently in metastatic breast cancer as compared to early stage breast cancer,[52] and led to prediction of worse prognosis than the expression of epithelial markers alone.[53] The over expression of EMT-inducing TFs (TWIST1, SNAIL1, SLUG, ZEB1, and FOXC2) was more frequently detected in patients with

primary breast tumor undergoing neoadjuvant therapies as compared to those who did not suggesting that neoadjuvant therapy is unable to eliminate CTCs undergoing EMT.[55] The over expression of EMT markers on CTCs was complemented with the presence of stem cells markers such as ALDH1 and CD133 in breast cancer at all stages and castration prostate cancer respectively.[56] A subpopulation of CTCs from metastatic breast cancer has been identified that expresses stem cell like CD44 + CD24 – phenotype with ALDH1. One of the major signalling axis - EGFR/HER2/PI3K/Akt which is involved in the regulation of mammary stem/progenitor cells, promotes proliferation and inhibits apoptosis are known to be activated in CTCs isolated from patients with primary as well as metastatic breast cancer.[57] Cell lines derived from DTCs of breast cancer patients show decreased expression of CK8, CK18 and CK19 and increased levels of vimentin, which resembles characteristic features of EMT. In EpCAM-enriched bone marrow samples elevated TWIST1 expression was found suggesting the occurrence of partial EMT. Furthermore, an increased tumor-initiating ability of DTCs, recognized as the stem cell phenotype (CD44 + CD24 –), was detected in both the DTC-derived cell lines and the CK19-positive DTCs isolated from the bone marrow of early-stage breast cancer patients.[58] Collectively these results suggest that the expression of stemness and EMT markers in CTCs might provide them strong metastasis-initiating properties, and render them resistant to conventional anticancer therapies. Thus, the fact that CTCs show stemness and EMT features is of fundamental importance for their reliable detection, which can further be used as a tool for developing effective cancer therapies.

EMT and CSCs

In recent years the role of CSCs and Tumor initiating cells (TICs) has been of utmost importance in cancer research.[59] CSCs are generally characterized by the expression of multiple cell surface markers, including CD44high, CD24low, and CD133high, depending on the malignancy. Interestingly, numerous studies have demonstrated that EMT activation can produce CSCs and/or disseminated cells that possess tumor-initiating properties. Moreover, Studies have shown that activation of EMT by TGF-b, Snail1, Twist1, and Zeb1 in normal human mammary epithelial cells can promote a CSC like phenotype with tumor-initiating properties.[60] Remarkably, Snail2 was found to be a crucial player in regulating normal mammary stem cells in mouse mammary epithelial cells where as Twist1 was found to be capable of suppressing CD24 expression, providing a direct link between an EMT transcription factor and CSC generation.[61] Activation of urokinase-type plasminogen activator receptor (uPAR) was found to reversibly activate EMT, and was also capable of generating CSC-like properties in breast cancer cells.[62,63] Furthermore, it is also found that basal breast cancer non-CSCs are subpopulations that can generate CSCs de novo, and plasticity of CSCs is governed by the chromatin state of the Zeb1 promoter,[64] highlighting the critical role of EMT regulators in regulating CSC plasticity during tumor progression and invasion. In breast cancer patients, the DTCs acquired from pleural effusions, were likely to have undergone EMT, with enriched CD 44high, CD 24low CSC-like population. Moreover, the tumor immune response results in EMT – associated emergence of CD 44high–CD 24low CSCs. Regardless of the strong evidence of a pro-CSC-forming role by EMT core regulators; there are experimental results that indicate EMT as having a negative influence on TICs. Celia-Terrassa et al presented that cancer cells with a distinct epithelial phenotype were enriched with highly metastatic TICs, whereas the mesenchymal-like cells lacked TICs. Additionally, forced expression of Snail1 in the epithelial cells suppressed their self-renewal and metastatic capabilities, suggesting that EMT activation may repress the tumor initiating properties of CSCs.[65] A recent study found that eliminating an EMT regulator, Prrx1, is required for the tumor-initiating ability of breast cancer cells expressing Twist1.[66] Thus, these contradictory results could be due to the difference in the genetic/epigenetic alterations in the individual cell types associated with different malignancies. Various studies are being carried out to clearly define the difference in signalling pathways regulating EMT and TICs which will provide much-needed evidence on how the EMT process and TICs are regulated.[67]

Conclusion

Metastasis is a potent threat causing mortality in patients with advanced stage cancer and remains a leading cause of cancer globally. Major complications related to metastasis include heterogeneity of tumors and difficulty of capturing residual drug-resistant tumor cells. Thus the central focus of today's research aims to identify various mechanisms involved in the metastatic process that will help in developing different clinical models to curb this disease. Clinical studies indicate that harnessing EMT-transformed CTCs and CSCs could shed light on the transition of dormant tumor cells to active aggressive cells in advance cancer patients. Future therapeutic studies pertaining to relapse should focus on EMT positive CSCs or relapse-initiating tumor cells rather than just primary tumor enriched CSCs.

The molecular and cellular elasticity of EMT-positive cells needs to be characterized to differentiate aberrant molecular pathways and heterotypic interactions with different tumor microenvironments. Moreover, ECM remodelling supports EMT in tumor cells and initiates drug resistance and relapse which can be used in the in-depth tracing of the complex cascade. However, because of the dynamic interaction between tumor microenvironments and cancer cells, EMT-positive CSCs frequently experience genetic drift and clonal evolution, so novel pharmacologic agents that

demonstrate better therapeutic efficacy as compared to the current neoadjuvant therapies need to be generated. As translational research is streamlined toward more personalized therapy, suppressing EMT-transformed CTCs and CSCs should prove useful for preventing relapse and extending the life spans of patients with recurrent cancer.

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Everything is theoretically impossible, until it is done.

Robert A. Heinlein

The Impact of Obesity on Surgery in Gynaecologic Oncology: Our Experience

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Summary

Surgery represents the mainstay in the treatment of gynecological cancers. It is believed to be more difficult in obese patients and increases the incidence of intraoperative and postoperative complications in these patients. This study was carried out to estimate the morbidity, adequacy of surgery and complication rates in obese women undergoing gynecological cancer surgery. We did a retrospective study of patients operated in a single unit in the department of gynecologic oncology from January 2009-June 2011 with BMI >27.5kg/m^2 (obese). During the study period, 20 obese patients were operated amongst which 11were of endometrial cancer, 5 were of ovarian mass, 2 were of cervical and vulvar cancer each. Mean BMI was 32kg/m^2. Mean operative time was three hours and mean blood loss was 294 ml. Lymphadenectomy was done in 66% of patients. Optimal surgery was possible in all the patients. Mean hospital stay was 17.5 days. There were no major intra-operative complications in any case. Superficial wound dehiscence occurred in seven patients. Obesity per se, without severe co-morbid diseases, is not a contraindication to surgical treatment. Such patients should not be considered for suboptimal treatment strategies. Special precautions should be taken during preoperative evaluation. A multidisciplinary approach involving experienced surgeon, anesthetist, physician, physiotherapist and intensivist is mandatory.

Keywords: Obesity, Gynecological cancer surgery, BMI

Introduction

Worldwide obesity has more than doubled since 1980. In 2008, 1.5 billion adults, aged twenty years and older, were overweight. Of these over 200 million men and nearly 300 million women were obese. The incidence of obesity in India is about 9% and is mainly concentrated in urban areas. Presently, one in six women and one in five men are overweight in India.[1] The various adverse health consequences and risks associated with obesity are summarized below: Greatly increased risk (relative risk >3) - Diabetes, hypertension, dyslipidaemia, breathlessness, sleep apnoea, gall bladder disease. Moderately increased risk (relative risk about 2-3)- Coronary heart disease or heart failure, osteoarthritis (knees), hyperuricemia and gout, complications of pregnancy- for example, pre-eclampsia. Increased risk (relative risk about 1-2): Cancer (many cancers in men and women), impaired fertility/polycystic ovarian disease, low back pain, increased risk during anaesthesia and fetal defects arising from maternal obesity.[2]

Pathophysiology of obesity and cancer: Adipose tissue is recognized as an endocrine organ that secretes multiple cytokines such as leptin and adiponectin. In cancer cell lines, adipocytokineleptin stimulates cell growth, proliferation and invasion of the cells in vitro. Contrary to leptin, adiponectin down-regulates the cancer cell growth and proliferation.[3-5] In addition there is increased peripheral aromatisation of androgens to estrone in the adipose tissue leading to a hyperestrogenic state, resulting in greater incidence of endometrial and breast cancer.[6] Body mass index (BMI) is significantly associated with higher rates of death due to cancer of the oesophagus, colon and rectum, liver, gallbladder, pancreas, kidney, non-Hodgkin lymphoma and multiple myeloma. Among those with a BMI $\geq$ 40 kg/m^2, mortality from all causes of cancer was 62% higher in women compared with those with a normal BMI. Increasing BMI is associated with an increased incidence of all cancers combined in addition to endometrial cancer, adenocarcinoma of the oesophagus, renal cancer, leukemia, multiple myeloma, pancreatic cancer, non-Hodgkin lymphoma, ovarian cancer, breast cancer in postmenopausal women and colorectal cancer in premenopausal women.[7] In addition to medical morbidity, surgery is believed to be more difficult and increases the incidence of intraoperative and postoperative complications in obese patients.

Obesity has long been considered as a potential risk factor for poor outcomes from a variety of surgical procedures, yet there have been surprisingly few studies to accurately assess the extent to which obesity affects surgical risk.[8] Indeed, three of the largest studies which examined the impact of obesity on postoperative outcome in patients have demonstrated that obesity alone is not a risk factor for perioperative morbidity or mortality.[9] Since surgery represents the mainstay in the treatment of gynecological cancers, it is important to evaluate how obesity affects the feasibility of surgery, its complication rate, and long term outcomes.

Material and Methods

This retrospective study was conducted in a single unit of department of gynecologic oncology from January 2009 - June 2011. The hospital records of all obese patients with gynecological malignancy operated during this period were reviewed. Data was retrieved from the patients' records and institutional tumor registry. Information regarding age of the patient, history, clinical examination and routine investigations and treatment, including operative procedure details, chemotherapy, and/or radiation

therapy was collected. In our study BMI was used as a measure of obesity. BMI was categorized according to WHO recommendation for Indian standards (BMI-normal 23kg/m^2, obese >27.5kg/m^2, severe obesity >32.5kg/m^2, morbid obese >37.5 kg/m^2) Operated patients with endometrial, cervical, ovarian and vulvar malignancy with BMI >27.5kg/m^2 were included in the study.

Certain surgical protocols were followed at our institute for obese patients: Extensive counselling of the patient and her relatives about the risks and potential complications, cardio respiratory evaluation, preoperative showers, careful cleaning of umbilicus, abdominal hair removal by clips and prophylactic antibiotics (cephalosporins intravenously given at the time of induction). Low molecular weight heparin for deep vein thrombosis prophylaxis was started two days before surgery and withheld twenty four hours before surgery. It was administered twelve hours after surgery and continued until discharge or for seven days, whichever came first. While operating on an obese patient, vertical midline incision was placed in fifteen (83%) patients by retracting the panniculus caudally below the symphysis pubis (Figure 1). High transverse incision was given at level of superior iliac spine in three (17%) patients. Special self-retaining Bookwalter or similar table fixed retractor was used for adequate exposure. With a morbidly obese patient, multiple assistants were required to facilitate optimal exposure. Extra-long instruments were used as these patients have a "deep" pelvis. Instruments, mops and gauzes were counted properly before closing the abdomen and if the subcutaneous sutures were not taken, a drain was placed anterior to fascia in seven (39%) patients. On an average the drain was removed between fifth to eighth postoperative days. Alternatively subcutaneous retention sutures were taken in four (22%) patients.

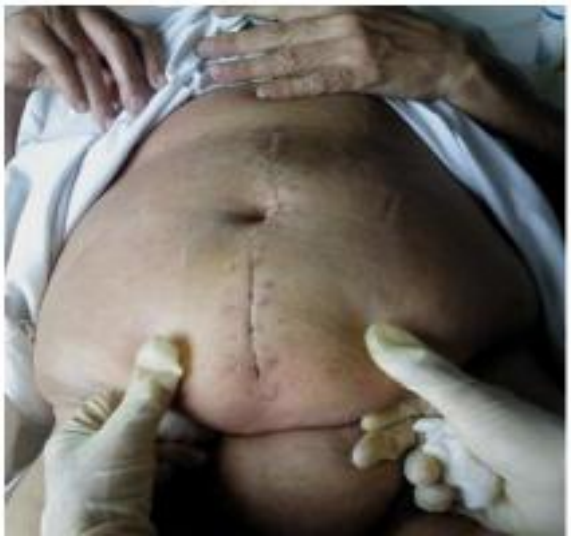

Figure 1: Stitch line in an obese patient of endometrial cancer

Post operatively, patients were closely monitored in the intensive care unit. Fluid intake and output was documented carefully. Early ambulation was encouraged. Physiotherapy, especially spirometry exercises, was mandatory. Intensive spirometry was recommended for the first few days after surgery. Thigh-high compression stockings were applied postoperatively. Multidisciplinary approach involving the gynecologist, anesthesiologist, primary care physician, intensivist and other appropriate subspecialists was done. Surgical wound was closely monitored for any signs of infection which included inflammation and collections of serous fluid, blood, pus, or a mixture of these. If retention sutures were placed, it was ensured that they were not cutting into the skin of the abdomen. Weight loss was strongly recommended after discharge.

Results

During three year period we operated on 20 obese patients amongst which 11 (55%) were of endometrial cancer, 5 (25%) of ovarian mass – (3 malignant and 2 benign), 2 (10%) of cervical and 2 (10%) vulvar cancer. Out of 15 patients with vertical incision, 7 (46%) had wound infection and 6 (40%) had superficial wound dehiscence. In rest 8 (53%) patients the wound healed well. Conversely, in those with high transverse incision 2 (67%) patients had wound infection and 1 (33 %) patient had superficial wound dehiscence.

Endometrial cancer:

Majority (55%) of the patients were of early stage and had well differentiated cancers and only 5patients required adjuvant treatment. The baseline characteristics of all these obese patients with endometrial cancer are summarized in Table 1. In our study, the mean operative time was 174 minutes with an average blood loss of 286 ml.

Ovarian cancer:

We operated upon 5 obese patients with ovarian mass. Amongst these 2 had benign ovarian mass and 3 had malignant ovarian disease. On the basis of clinical examination, radiological investigations and tumour markers we suspected malignancy and decision for laparotomy was taken for these two patients. However, frozen section reported mature cystic teratoma and benign mucinous cystadenoma in both the cases respectively. Two patients were taken for upfront surgery and one underwent interval laparotomy amongst the three malignant cases. Optimal debulking was possible in all the three malignant ovarian cancers. Four patients

Table 1 : Clinical characteristics (N=18) of obese patients

Characteristic	Endometrial cancer (N=11)	Ovarian cancer (N=3)	Cervical cancer (N=2)	Vulvar cancer (N=2)
Age (mean) (years)	56	50	46	62
Parity (mean)	3	3	4	6
Menopausal	9	3	1	2
BMI(mean) kg/m^2	33	34	30	31
Comorbidities Hypertension	9	4	1	2
Diabetes	9	4	-	-
Others (asthma, heart disease, hypothyroidism)	3	2	-	1
Stage				
I	9	1	2	-
II	1	1	-	1
III	1	-	-	1
Unknown	-	1	-	-
Lymphadenectomy	6	2	2	2
Grade				
I	6	1	-	2
II	5	1	2	-
III	0	1	-	-
DVT prophylaxis	11	3	2	2
Mean operative time (mins)	174	190	180	240
Average blood loss (ml)	286	283	240	380
Postoperative wound dehiscence	5	1	1	1
Mean post-operative hospital stay (days)	20	15	15	20

were hypertensive, three diabetic and one was a known case of diabetes, hypertension with history of multifocal neuropathy. Deep vein thrombosis prophylaxis was given in all three patients. The final histopathology report of both the patients with upfront surgery was well differentiated endometrioid carcinoma of ovary and endometrioid variety with poor differentiation respectively. The one who underwent interval laparotomy had moderately differentiated adenocarcinoma. Lymph node dissection was omitted in one patient due to morbid obesity (BMI=42kg/m^2) and poor performance status of the patient.

Cervical cancer:

Table 1 summarizes the clinical characteristics of the two obese patients with early stage cervical cancer operated upon. The aim was to ensure that these patients benefit from single modality treatment as radiation and radical hysterectomy are equally effective options in treatment of obese patients with cervical cancer stage Ib-IIa. The mean operative time was 180 minutes and mean estimated blood loss 240 ml. Lymph node dissection was done in both the patients and there were no major intraoperative complications. Mean hospital stay was 15 days and one patient had wound dehiscence. On histopathologial examination, one of these obese patients fell in intermediate risk score (squamous cell carcinoma, moderately differentiated, 4x4 cms tumor size and half thickness cervical involvement) and hence adjuvant treatment (radiotherapy) was planned. The other patient fell in low risk score (squamous cell carcinoma, moderately differentiated, 0.5x0.5 cms tumor size and less than half thickness cervical involvement) and hence no adjuvant treatment (radiotherapy) was required thus reducing the morbidity of radiotherapy in morbid obesity.

Vulvar carcinoma:

Both the patients with vulvar cancer had a mean BMI of 31kg/m^2. Both were hypertensive and one of them had associated hypothyroidism with bilateral knee arthritis. The final histopathological report showed well differentiated squamous cell carcinoma and negative resection margins in both the patients. Groin lymph nodes were negative for malignancy in both. Adjuvant treatment (radiotherapy) was planned for both.

Discussion

In obese patients, deep surgical-site infections and fascial disruptions are major sources of morbidity, contributing to prolonged hospitalization and re-hospitalization. Therefore, skin incision has to be planned meticulously. The incision may be vertical or transverse. For the vertical incision, pubis should be considered as a landmark to decide where to perform the incision. Incision should not be placed in the suprapubic fold after lifting the abdominal fat pad as the poorly vascularised skin in this area is very thin and submitted to intense maceration due to moist warm environment which promotes proliferation of numerous microorganisms. Midline incision is made by retracting the panniculus caudal below the symphysis pubis. The transverse incision should be given at level of superior iliac spine and transverse periumblical incision is given in massively obese patients when umbilical groove falls below the anterior superior iliac spine.[10]

The purpose of our study was to evaluate the feasibility and outcome of obese patients undergoing gynecologic oncology surgeries and to compare it with previous studies published in literature. Ours was a retrospective study carried out in tertiary cancer institute on 20 obese patients suspected of having gynecological malignancy undergoing surgery with a mean BMI of 32kg/m^2 which was more than studies conducted by Foley and Lee (>30kg/m^2)[11]and less than those of Chapman et al (>35kg/ m^2).[12] Endometrial cancer - A high BMI or obesity has more consistently been associated with an increased risk of endometrial cancer than any other obesity related cancers in the reviews. In our study, the mean operative time was 174 mins with an average blood loss of 286ml. This was less compared to previous studies i.e. Foley and Lee (212 minutes and 819 ml) [11] and Everret et al (189 minutes and 441ml).[13] Wound dehiscence rate (45%) was comparable to the study conducted by Foley and Lee (43%).[11]

Ovarian cancer:

In advanced stage ovarian cancer, the benefit of cytoreductive or debulking surgery that eliminates the bulk of the cancer without leaving residual disease is the most important predictor of survival. The surgery is usually aggressive and often requires bowel resections, omentectomy, removal of bulky nodes and sometimes splenectomy.[14] Thus to study the impact of obesity on the feasibility of an optimal cytoreductive surgery is of paramount importance. Wolfberg et al [15] and Christinia et al [16] reported mean operative time of 176 minutes and 280 minutes respectively which was similar 168 minutes to that in our study. The mean estimated blood loss (283ml) was quite less than other studies (724 ml and 450 ml). Wolberg et al reported a 66.5% incidence of post operative complications as compared to 45% by Christinai et al and 33.3% in our study.[15,16]

Cervical cancer:

Radiation and radical hysterectomy are equally effective options in treatment of obese patients with cervical cancer stage Ib-IIa. The main advantage of surgery over radiotherapy is the ability to preserve ovarian and vaginal function. Previous studies have concluded that radical hysterectomy and pelvic lymph node dissection are more difficult in obese patients because of increased operative time and blood loss without an increased risk of major complications or compromised survival. The decision to pursue one treatment modality over another is generally based on an assessment of comparative morbidity and patient preference.[17]

The mean operative time in this study (3 hours) was similar to that in Foley and Lee11 (2.6hours) and Chapman et al12 (3 hours). Postoperatively three patients had paralytic ileus due to low potassium levels, nine had wound infection and seven had superficial wound dehiscence which was higher compared to Foley and Lee11 who reported wound dehiscence in three patients and Chapman et al12 (wound dehiscence in six patients). Mean hospital stay in our study (17.5days) was comparable to other studies (18 days). There was single mortality which was case of carcinoma ovary with diabetes, hypertension with history of multifocal neuropathy who expired on eight postoperative day due myocardial infarction. The pitfall of this study is lack of statistical power due small sample sizes as it is a single centre observational study. So further randomized controlled trials with long term follow up would be required to evaluate the impact of obesity on outcome of surgery.

Conclusions

Surgery is considered the cornerstone in the treatment of various malignancies in gynecologic oncology. In our study, there were no major post operative complications like deep vein thrombosis or complete wound dehiscence. Thus obesity per se, without severe comorbid diseases, is not a contraindication to surgical treatment. Such patients should not be considered for suboptimal treatment strategies but should be treated in identical manner as non obese patients. Every obese patient is not a significant surgical risk, so care should be individualized and team approach should be used involving the gynecologist, anesthesiologist, primary care physician, and other appropriate subspecialists.

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What is a scientist after all? It is a curious man looking through a keyhole, the keyhole of nature, trying to know what's going on.

Jacques Yves Cousteau

Autologous Serum as Growth Factor Substitute for Isolation and Characterization of Lung Cancer Stem Cells: an In-vitro Approach

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Summary

Cancer stem cells (CSCS), comprising of a very small subpopulation of cells within the tumor mass, has been increasingly reported to be responsible for initiation, progression, relapse and metastasis. Attributed to these characteristics, lung cancer is now known to be a stem cell disease. Thus, the need of the hour is to generate inter- and intra-tumoral (LCSC) models on the basis of their cancer initiating property from a heterogeneous population and isolate lung cancer stem cells (LCSCs) by using multiple marker approach. Therefore, in the present study, heterogeneous population of LCSCs were isolated from a single cell suspension of non small cell Lung cancer (NSCLC) tissue and enriched in serum-free culture as well as in media containing patient's own serum to form pleurospheres (PS). In both conditions, PS exhibited an enhanced capacity for self-renewal and resistance towards chemotherapeutic drug; however, a significant increase was observed in the size of PS enriched in the patient's own sera after the second passage. Furthermore, results of our study demonstrated that apart from CD133, an established CSC maker in NSCLC, ALDH and EpCAM may also serve as a putative cell surface marker for lung adenocarcinoma stem cells. Thus, culturing NSCLC cells in the presence of autologous serum could serve as an effective in-vitro model for enriching LCSCs by mimicking the in-vivo microenvironment conditions and facilitating the growth for future gene and stem cell targeted therapies. Additionally, isolation and characterisation of LSCSs by using multiple marker approach proves to a better method than the conventional single marker based approach which tends to underestimate presence of other putative LCSC in NSCLC. Collectively, this approach can be used to translate the basic research findings like invasive properties, drug screening, chemo-resistance, apoptosis, immune responses, proliferation, gene expression and targeting various signalling pathways into clinical trials.

Keywords: Lung cancer stem cells, Pleurospheres, In-vitro model, CD 133, ALDH, EpCAM

Introduction

Lung cancer is one of the major causes of morbidity and mortality worldwide. It is classified into two major groups based on pathological features; small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC). Despite of the considerable progress in surgery, chemotherapy, radiotherapy and biological targeted therapy, NSCLC comprising of 80% cases remains to be one of the leading causes of cancer-related mortality worldwide. The three main subtypes of NSCLC are squamous cell carcinoma, adenocarcinoma and large-cell carcinoma. NSCLC patients continuously exhibit a very poor prognostic rate, with only 15% of 5-year survival rate post treatment. Despite having effective initial therapy, the recurrence rate ranges from 35% to 50% amongst NSCLC patients in the early stage.[1]

Moreover, the biological characteristics related to the hostile behaviour of cancer cells is driven by a subpopulation of cells within the tumour called cancer stem cells (CSCs).[2,3] Previous studies indicate that various solid tumors, such as breast,[4] colon,[5] brain gliomas,[6-8] liver[9] and prostate[10] cancers, contain a small population of CSCs that are responsible for tumor dissemination and maintenance. Features such as unlimited proliferative potential and ability to self-renew are exhibited by CSCs. They have recently been linked with initiation and progression of malignancies, therapeutic resistance (chemotherapy and radiotherapy), recurrence and metastasis.[2,11,12] It is expected that therapies specifically targeting the stem cell signalling pathways utilized by CSCs may be beneficial in battling specific types of cancer.[13] Hence, it is important to understand CSCs' biology and identify new approaches to prevent disease progression.

Currently, isolation and identification of CSCs is chiefly reliant on the presence of unambiguous cell surface markers, although the expression of such markers depends on various factors such as differentiation state of the cells and niche factors.[5,14-18] Researchers are now turning towards the identification of lung CSCs (LCSCs) which has been hindered by the lack of consistent normal lung epithelial stem cell markers.[19,20] One study has demonstrated that SCLC and NSCLC contain cells that express a cancer stem cell marker, glycoprotein prominin-1 (CD133), which is indispensable for tumor cell propagation leading to metastasis; however, its proliferative capacity is yet to be determined.[21] Conflicting results on the detection, abundance, and tumorigenicity of CD133+ tumour cells, however, specify a need to identify additional markers of LCSCs. The expression and activity of aldehyde dehydrogenases is another impending CSC

biomarker. Aldehyde dehydrogenases, a family of intracellular enzymes, participate in differentiation, cellular detoxification and drug resistance through the oxidation of cellular aldehydes.[22-24] ALDH1A1 and ALDH3A1 are two isoenzymes expressed in lung epithelial stem cell niches, over expressed in NSCLCs compared to SCLCs.[25] Collectively, these findings suggest that apart from CD133, ALDH proteins may serve as putative candidate marker for LCSCs. Apart from CD133 and ALDH, EpCAM, CD44, CD90[18,26] and CD166[27] have been widely used as LCSCs markers. Additionally, recent transgenic mouse models of lung cancer showed tumors with different oncogenotypes displaying different CSC populations that indicated the need to relate different CSC markers as well as to control if their signalling pathways are therapeutic targets for the CSC population.[28] Based on these data, we included CD133, ALDH and EpCAM as CSCs markers in this study.

The aim of this study was to isolate and cultivate CSC population from human NSCLC by pleurosphere (PS) formation assay in serum-free medium. Furthermore, these PSs were investigated for their self-renewal capacity, response to chemotherapeutic drugs and gene expression profiles of CD133, ALDH and EpCAM as CSC markers. Thus, these in-vitro models may represent as useful models for studies on NSCLC with the aim to find new therapeutic approaches.

Materials and Methods

Cell culture and lung cancer single cell suspension preparation: Lung cancer specimens were obtained from patients who underwent CT-guided biopsy at the department of radiology, GCRI. The specimens were cut into 0.5 mm sections following washing with numerous times with phosphate buffer saline with high doses of penicillin/streptomycin and amphotericin B (Hi-Media) to avoid contamination. The specimens were enzymatically digested in the presence of 0.1% collagenase IV (Hi-Media) and hyaluronidase for 1 h under 5% CO_2 at 37˚C. The remaining cell debris was removed by passing the cells through a 70 µm diameter disposable filter and centrifuged for 15 min at a speed of 400 x g. Finally, the primary human lung cancer cells were cultured in DMEM supplemented with containing 25 mM HEPES buffer, 1000 mg/l glucose, L-glutamine, sodium bicarbonate, sodium pyruvate and supplemented with 20% heat-inactivated FBS (Cellclone), 1% (v/v) minimal essential medium nonessential amino acids (Hi-Media), and antibiotic & antimycotic (Penicillin, Streptomycin & Amphotericin B; Hi-Media) in humidified atmosphere of 5% CO_2 at 37°C. The present study was approved by the ethics committee of GCRI (Ahmedabad, India). Written informed consent was obtained from the family of each patient.

Pleurosphere (PS) culture: Cells were rinsed and split with typsin-EDTA (Hi-Media) for sphere forming assay, when the cells reached 70-80% confluency. Cells were transferred to ultra-low attachment 6 well plate and cultured in serum free medium for 2-3 week. The culture media was changed every 2-3 days. Wells that contained spheres were counted using inverted phase contrast microscopy (Nikon Eclipse TS100) and the percentage of cells exhibiting sphere-forming capacity was calculated. This experiment was carried out in three independent replicates. Apart from this, cells were cultured in the presence of patient's own serum(10%) to check its effect on cells self-renewal capability as compared to serum free medium.

Stemcellness self-renewal assay: The spheres were collected by centrifugation and allowed to digest using Dispase II (20U/mL of DMEM) to get single-cell suspensions. After passing through a 40 µm filter, 250 cells/cm^2 cells in 10 ml of medium was added to non-adherent culture flasks for daughter sphere formation. The floating spheres and colonies were observed using phase contrast microscope.

Chemotherapeutic resistance assay: MTT assay was used to evaluate chemotherapy resistance of these sphere forming cells. Cells were seeded in 96 well plate to check the effect of chemotherapeutic agent gemcitabine commonly used in treatment of lung cancer patients. Cells were exposed to this drug in the range of 1 nM to 100 µM for 24 hrs to check their IC50 values as described previously.[29]

RNA extraction and RT-PCR: Sphere forming cells were taken and total endogeneous mRNA from these cells was isolated using NucleoSpin RNA kit (Macherey - Nagel) according to the manufacturer's instructions to detect the expression of various CSC markers like CD 133, ALDH and EpCAM. The quantity of RNA was determined by Qubit 2.0 Fluorometer (Invitrogen, USA) and purity was checked on FA-Gel. Total 1 µg of RNA was reverse transcribed to cDNA by incubating the reaction mixture at 42 ºC for 30 minutes, 85 ºC for 5 minutes using iScript™ cDNA Synthesis Kit (Bio-Rad) and the resulting first-strand cDNA was used as template in the qualitative polymerase chain reaction (PCR). The cDNA product was used as a template and subjected to PCR (Thermo Scientific) for 35 cycles using gene specific primers (Table 1). β -actin was used as an internal control. The PCR products were

electrophoresed on ethidium bromide stained 1.5 % agarose gel for these genes. Densitometric analysis was done to evaluate the band intensity.

Statistical analysis

All data were expressed as the means ± SEM from triplicate samples. $p < 0.05$ was considered statistically significant.

Results

Isolation of CSCs by pleurosphere (PS) formation assay: According to the CSC theory, only a small population within the tumor reveal CSC characteristics. Due to their capability to propel out toxic agents, these stem-like cells are innately resistant to chemotherapeutic agents and they are also able to grow in serum-free medium in-vitro. To isolate CSCs, single cell suspension obtained was harvested and cultured in appropriate medium. Following three days of culturing, numerous individual cells in the suspension culture were detected to survive and proliferate. After approximately one week, these cells gradually formed sphere colonies of various sizes and irregular shapes. The majority of non-sphere forming cells adhered to the well plate and grew slowly. However, almost no clear sphere colonies were observed in these cells over a period of time. Under the culture condition, sphere resembling typical PS (20-30 cells) rapidly formed (about 3 days) on the top of the monolayer of the NSCLC cells.

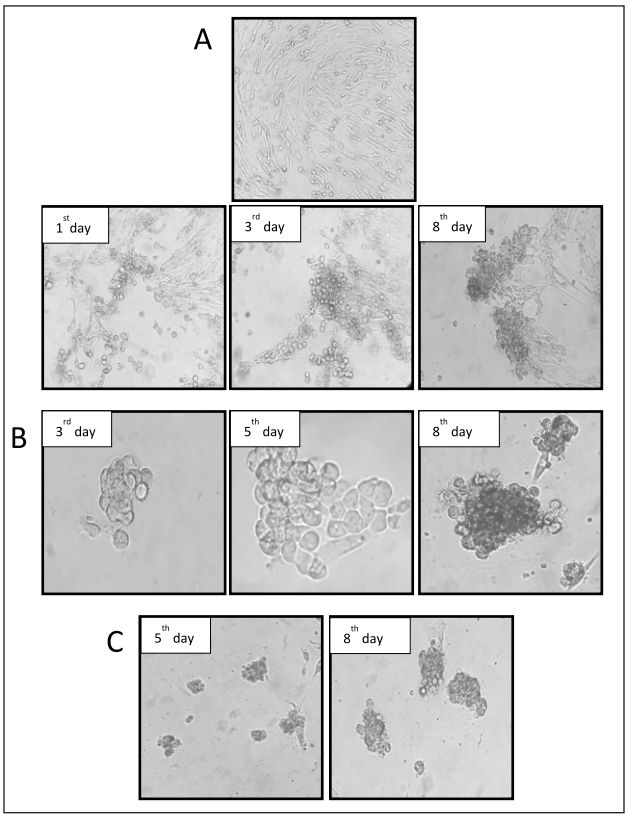

Figure 1: Representative phase contrast microscopy analysis of cultured PS (A) top, primary cultured adenocarcinoma cells in their medium. Bottom, formation of PS on top of the monolayer of adenocarcinoma cells on 1st, 3rd and 8th day (B) PS generated after 2nd passage (C) PS generated after 3rd passage

Self-renewal of cancer cell spheres: The capabilities for self-renewal and adoption of a spheroidal morphology, ascribed to the presence of CSCs, were tested by collecting the spheres generated on top of the monolayer of cultured primary NSCLC cells and culturing them after dissociation into single-cells. After 1 week of culture, the formation of tumor spheres (secondary spheres) was detected with no attached cells or less attached cells and photographed under an inverted microscope (Figure 1 and 2).

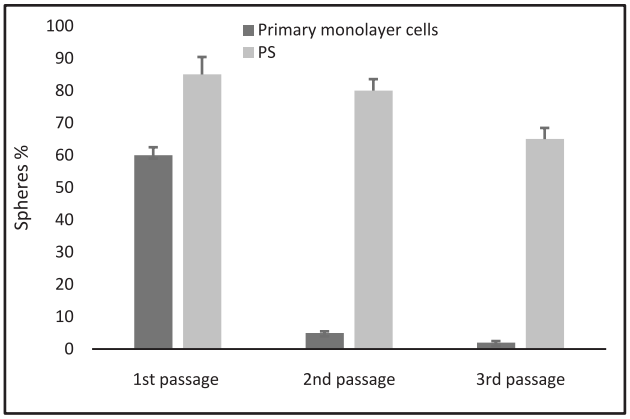

Figure 2: Pleurosphere forming assay revealed that PS exhibited an significantly enhanced capacity for self-renewal, compared with primary monolayer NSCLC cells. (1st passage: $p=0.001$; 2nd passage: $p<0.001$; 3rd passage: $p<0.001$)

Effect of autologous serum on self-renewal capacity: In addition to this, it was observed that the self-renewal potential was enhanced when the cells were cultured in the presence of patient's serum suggestive of its effect on CSC survival and disease progression, while a progressive loss of regenerative ability was observed in the cells cultured in serum free medium after subsequent passage (Figure 3).

Chemotherapy resistance study: Chemotherapeutic resistance was checked by MTT assay on PS obtained from primary NSCLC. These PS were plated in 96 well plates in order to check resistance of chemotherapeutic drugs like gemcitabine and paclitaxel. The results demonstrated that PS were resistant to gemcitabine as there was no cytotoxic effect of this drug at higher concentration of 100µM (Figure 4).

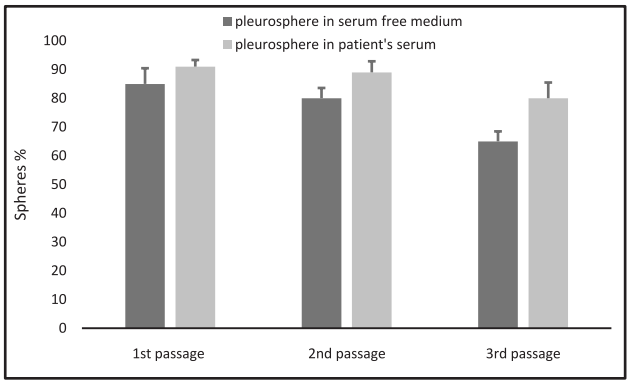

Figure 3: Effect of autologous serum on self-renewal capability of PS. Sphere % was significantly higher in media containing patient's own serum than serum-free media. (1st passage: p=0.0391; 2nd passage: p=0.0351; 3rd passage: 0.0064)

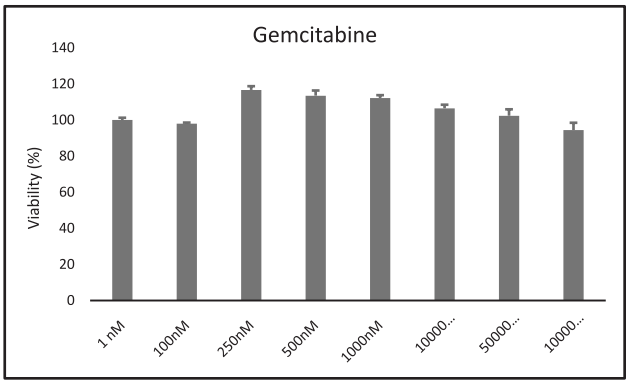

Figure 4 : Chemotherapy resistance study. There was no effect of gemcitabine on generated PS in the range of 1 nM to 100000 nM. Experiment was performed in triplicate.

Expression of CSC markers in PS: Semi-quantitative expression of CSC markers like ALDH, EpCAM and CD133 was checked in pleurospheres. It is evident from fig.2 that these LCSCs possess high ALDH and EpCAM expression with compared to CD133. The observation was further validated by comparing band intensity of these three genes. Band intensity of ALDH, EpCAM and CD133 was 38.11%, 41.62% and 20.27% respectively. The results clearly suggest that PS derived from primary NSCLC cells express high ALDH and EpCAM CSC marker as compared to CD133 (Figure 5).

Discussion

CSCs are likely to play a vital role in maintaining cancer cell populations, hence targeting their regulatory pathways could open up a new approach for cancer treatment. Lung cancer may be defined as a stem cell disease originating from the malignant transformation of adult lung stem cells, according to the CSC theory. Such altered adult stem cells are also known as LCSCs. Identification and isolation of CSCs from NSCLC cells is the first step in recognizing more specific CSCs markers in the NSCLC cell population. Consequently, our study demonstrated that generated PS have the ability to express different CSCs markers like CD133, ALDH and EpCAM, which suggests that CSCs population is heterogeneous. These PS are the putative LCSCs having self-renewal capability, which attest that they have the stem cell like phenotype.

Figure 5 : Expression of various markers (ALDH, EpCAM, CD133) in PS

Researching about LCSCs is still into the primary stages and LCSCs are not yet commercialized; thus, they are difficult to purchase. Studies of LCSCs generally involve an initial segregation step. Till date, we can isolate or enrich CSCs using flow cytometry or magnetic beads using specific cell surface markers, separation of SP (side population), by growing them in serum free medium or selection based on the drug resistance of LCSCs with various chemotherapeutic agents.[21,30,31] Nevertheless, these four separation methods have certain restrictions. For instance, Hoechst 33342 is used to isolate SP cells based on CSCs characteristics, causing cellular toxicity, therefore, limiting its further application. Additionally, dependability of cell surface marker separation using flow cytometry or magnetic beads is yet to be established as no recognized cell surface markers of LCSCs are currently accessible. Moreover, the cell sorting procedure may cause harm to the cells and the number of sorted cells may be small due to a low quantity of positive cells in the tissues. Furthermore, suspension of the culture in serum-free medium alone may only achieve preliminary enrichment of CSCs. This may cause other SP cells to be present, resulting in a culture with reduced LCSC purity and concentration that is not suitable for further research. Next, the CSC theory is still in the investigative stage where the procedure by which LCSCs triggers tumorigenesis and maintain their formation and existence, have yet to be investigated. As a result, the induction of resistant cells might have some effect on CSCs' biological properties.[32-34]

Keeping in mind that the undifferentiated LCSCs are more resilient to apoptosis and more likely able to endure serum-free conditions, the present experiment originally used single cell suspension primary cultured cells obtained from lung tumor

tissues. Afterwards, the single cell suspensions comprised of CSCs were used to generate PS. A serum-free suspension culture was used to enrich these PS, as LCSCs have characteristics such as resistance towards serum-free culture and apoptosis tolerance. After more than a week of culturing, the cells were witnessed to form spheres of different numbers of cells. Also, when the PS were cultured in the presence of the patient's own serum, they displayed a substantial increase in the number of colonies formed after the third passage compared to serum-free medium suggesting that the patient's own serum provides all the pre-requisite cytokines, growth factors and suitable microenvironment for the cancer cells to grow and sustain. Hence, these three techniques demonstrated complementary, producing an innovative method that should be further investigated, due to the short culture period, low cost and high efficiency.

The purpose of primarily used cultured cells was to define whether or not they have the characteristics of LCSCs. A present study demonstrated that following enrichment, the PS displayed strong self-renewal capacities in comparison to the attached cells. In the serum-free culture, 85% of cells formed spheres of stem cells which was considerably different from the adhered cells. In addition, attached cells did not produce any characteristic spheres during sub passage approving that there is sub-population of cells in primary cultured mix population having capability to form sphere i.e. self-renewal abilities. Furthermore, the results of the chemotherapeutic resistance study demonstrated that chemotherapeutic agent gemcitabine resistance was significantly higher in PS and is therefore a characteristic of CSCs. Aside from this, the expression of these three CSC markers differed in generated PS. In this study, it was found that LCSCs express more ALDH and EpCAM than CD133. The high expression levels of EpCAM suggest the fact that an onset of the disease presence of LCSCs can enable the early diagnosis and prognostic condition of the patients. The heterogeneous population has the ability to drive lung carcinogenesis towards aggressive and invasive pathways because of its potential to express several CSC markers at the same given time. Increased expression of ALDH was also observed in Lung adenocarcinoma, apart from EpCAM. ALDH activity has previously been linked with multiple downstream carcinogenic signalling pathways such as Notch pathway,[35] which reveal that it not only can be beneficial as a therapeutic target but also in understanding the underlying mechanism that governs the LCSCs towards initiation, progression and invasive behaviour of lung carcinogenesis. Similar to CD133, ALDH and EpCAM can also be used as candidate markers for identification and enrichment of NSCLC cells with many of the properties attributed to CSCs.

In the present study, the ultimate aim was to isolate LCSCs, the cells capable of forming PS due to their highly proliferative capability, and thus would be an ideal in vitro model for drug screening and molecular characterization for identification of potent drug targets for future therapeutics. Comparative assessment of generated PS in various stages of cancer can be studied to get clues concerning about the progress of disease and metastasis. Apart from this, there is an urgent need for information on the possible molecular mechanisms which mediates the self-renewal capability of CSCs at the genetic and proteomic level. Comparison between normal and cancer stem cells may throw a light on starting point for identifying molecules responsible for driving these mechanisms. The potential applications for LCSCs characterization include monitoring of CSCs as biomarkers of acquired resistance to new cancer therapies, recognizing new prospective therapeutic targets to directly inhibit cancer metastasis and develop high-throughput technologies for detection of LCSCs at initial stages of cancer progression with the aim of early cancer detection. The outcome of current study is suggestive of autologous serum has better growth potentiality of LCSC in-vitro as compared to FBS/FCS/serum-free media. Moreover, proteomic profiling of patients' serum may provide better insights into the growth promoting mechanism which provides a conductive in-vitro microenvironment for renewal and sustenance of the LCSCs.

Table 1: Primers used in RT-PCR analysis

Name	Forward Primer	Reverse Primer
EpCAM	CTGCCAAATGTTTGGTGATG	CTTCTGACCCCAGCAGTGTT
CD133	CCTGGGGCTGCTGTTTATTA	TACCTGGTGATTTGCCACAA
ALDH	TTGGAATTTCCCGTTGGTTA	CTGTAGGCCCATAACCAGGA
β-actin	CAGAGCAAGAGAGGCATCCT	TTGAAGGTCTCAAACATGAT

Table 2: Number and size of spheres in primary cultured NSCLC cells.

		Passage 1	Passage 2	Passage 3
Primary monolayer cells	No. of cells	30-40	None	None
	No. of sphere	15-25		
CSCs in the form of PS	No. of cells	30-40	30-40	15-25
	No. of sphere	25-40	20-25	10-15
PS in the presence of serum	No. of cells	35-40	40-50	30-40
	No. of sphere	40-50	30-40	25-30

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We don't regard any scientific theory as the absolute truth.

Kenneth R. Miller

Uncontrolled Hypothyroidism and Ovarian 'Tumors': Cases and Review of Literature

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Summary

Ovarian enlargement and ovarian cysts are associated with hypothyroidism. A decrease in ovarian volume, resolution of ovarian cysts and reversal of hyperstimulation like syndrome, has been shown to occur after the achievement of euthyroidism. The first case was of Van, Wyk and Grumbach syndrome. This syndrome is characterized by Juvenile hypothyroidism, isosexual precocious puberty, and multicystic ovarian masses with delayed bone age. In the second case an eight year girl had unilateral solid cystic enlargement of the ovary, mild ascites, raised serum LDH with severe hypothyroidism but no precocious puberty.The third patient had spontaneous ovarian hyperstimulation syndrome with severe undiagnosed hypothyroidism. She presented with enlarged adnexal masses, markedly elevated beta hCG and acute abdominal pain. We present three unusual cases in which ovarian "tumors" were associated with primary hypothyroidism in young women and prepubescent girls. They were all referred to us for surgery as cases of suspected malignant ovarian neoplasms. Ultrasonography, thyroid function tests and tumor markers were obtained in each case. In all three cases expert radiological opinion was taken for ultrasound characteristic of the ovarian lesion. Careful investigation revealed primary hypothyroidism all three cases. They were all managed with thyroid replacement therapy, counselling and very close observation. In all three cases "tumours" completely regressed with appropriate thyroid replacement therapy and inadvertent castration was avoided in these young women.

Keywords: Uncontrolled severe hypothyroidism, Ovarian Tumour like lesions, Young age

Introduction

Ovarian tumors are a common cause for gynecological surgery, often performed hastily due to the perceived risk of malignancy. However, in young girls and women, the decision to operate must be tempered with extreme caution to avoid unnecessary castration. Some ovarian lesions are a direct result of endocrine disorders and will regress with appropriate treatment, obviating the need for surgical excision. Occasionally, ovarian cysts, mimicking tumors, are reported in juvenile primary hypothyroidism though they are very rarely seen in adults. Failure to recognize hypothyroidism as the etiology of ovarian lesions could lead to inadvertent oophorectomy.

Primary hypothyroidism is a common endocrine abnormality in which thyroid hormone deficiency affects the body metabolism, leading to multiple system impairment. It may also cause reproductive endocrinology disorders. Hypothyroidism is one of the endocrine disorders associated with ovarian enlargement, multiple ovarian cysts (unilateral or bilateral) and spontaneous ovarian hyperstimulation, yet is often ignored in the evaluation of ovarian lesions.

We encounterd three such cases associated with primary hypothyroidism. The first was Van Wyk and Grumbach Syndrome, the second was a case of unilateral ovarian tumor like lesion and third was spontaneous ovarian hyperstimulation.

Hypothyroidism is usually associated with delayed puberty and rarely with precocious puberty. However hypothyroidism with precocious puberty was first described by Kendle in 1905. Van Wyk and Grumbach reported the association of multi-cystic ovaries with hypothyroidism and precocious puberty. Since than a few cases of this syndrome have been reported in pre-pubertal or adolescent girls.[1]

The studies have also shown that hypothyroidism has profound effects on ovarian size, other than simply producing ovarian cysts. Hypothyroidism is characterized by deposition of mucopolysaccharides (hyaluronic acid and chondroitin sulfate) within the connective tissue of various organs.

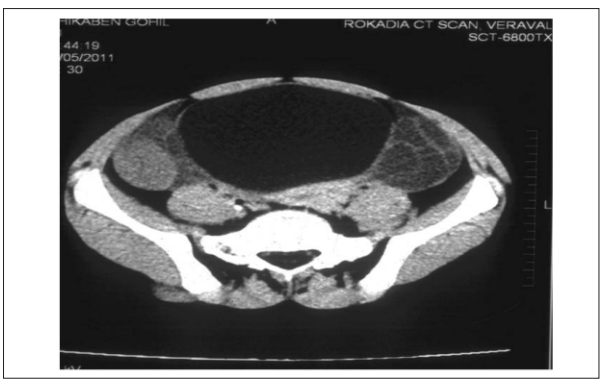

Figure 1 : Bilateral multicysticovaries

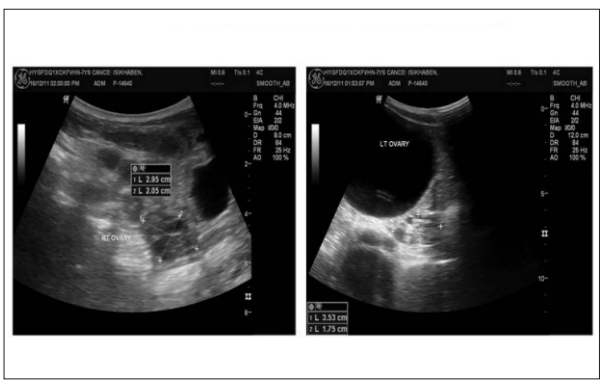

Figure 2 : Normal Ovaries after treatment

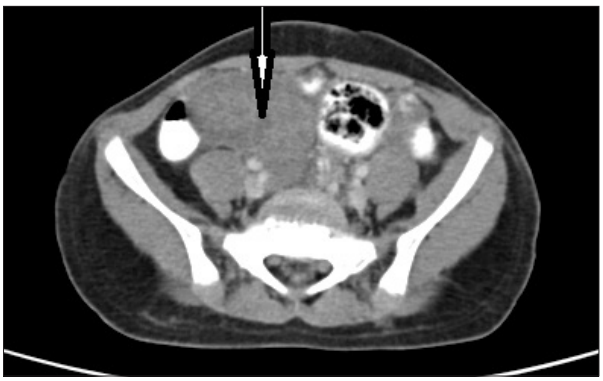

Figure 3 : unilateral ovarian lesion

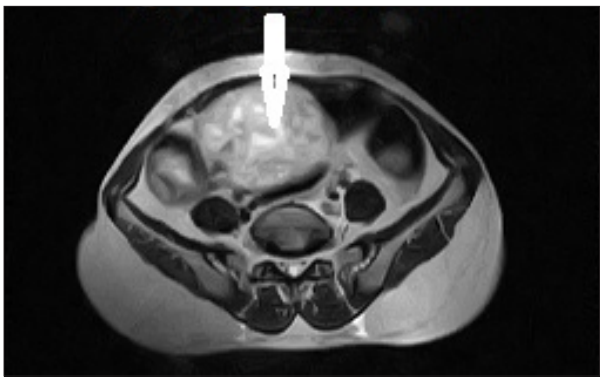

Figure 4 : Huge ovarian lesion

Similar myxedemetous changes of the ovarian stroma together with an increase in collagen content and sclerosis in severe longstanding hypothyroidism leads to an increase in ovarian volume, which can also be accompanied by cyst formation.[2]

Ovarian cysts are a common cause for gynecological surgery. The etiology of ovarian cysts can be benign or malignant neoplasms, endometriosis and inflammation, among others. Large ovarian cysts or enlargement may rarely be the result of uncontrolled severe hypothyroidism and may resolve after correction. Spontaneous ovarian hyperstimulation is one of such condition.[3]

The aim of this study is to emphasis that hypothyroidism must be considered in the differential diagnosis of pre-pubertal or adolescent girls or woman presenting with ovarian lesions. Surgical excision should be considered only when adequate thyroid replacement therapy fails to resolve ovarian enlargement

Materials and Methods

All three patients were referred to our institute for surgery, as cases of suspected ovarian malignancy. However, the young age and atypical presentation led us to suspect underlying endocrine pathology. All patients were looked for clinical features of hypothyroidism like puffiness of face, weight gain, constipation, dry skin.

Ultrasonography, thyroid function tests and tumor markers were obtained in each case. In all three cases expert radiological opinion was taken for ultrasound characteristic of the ovarian lesion. An endocrinologist evaluation was then done and a joint decision for trial of thyroid replacement therapy was taken. Serial ultrasound examination was used as the main tool to monitor the ovarian lesions. Serial thyroid function test and tumor marker assays were also performed.

In all the cases relatives were explained in detail regarding the management. Close surveillance ensured that no case of ovarian malignancy was missed. The patient and her parents were explained about the condition and need for close and regular follow up with hormonal assay and ultrasound examination. They were asked to report immediately in the event of acute abdominal pain or vomiting.

Case 1 : Van Wyk Grumbach Syndrome

A nine year old girl was referred as a case of bilateral ovarian tumor with raised CA -125 (56 U/ml). Ultrasonography and CT scan showed bilateral multicystic ovarian lesions, 5.8x4.4 cm with small hemorrhagic cyst on right side and 4.6x 3.8 cm on left side (Figure 1). The patient's parents gave history of early menarche with heavy vaginal bleeding at the age of eight and half years. She also had excessive weight gain in past few months. She had a normal appetite and good scholastic performance. There was no family history of precocious puberty or hypothyroidism.

On clinical examination she appeared overweight (25 kilogram) and also had stunted growth for her age (height 115cm, ≤ 5th percentile). She had pallor and dry skin. There was no goiter. Breast enlargement corresponded to stage I-II, with no galactorrhoea. She had no axillary and pubic hair. On abdominal examination there was no palpable mass. Her genitals were well developed for her age.

Laboratory investigations revealed severe hypothyroidism with TSH: >100 uIU/ml. Raised circulating Prolactin (78.8 ng/ml) and estradiol (36.4 pg/ml) level. FSH was normal for her age (8.56 mu/ml) and LH was at lower limit of normal value (< 0.10 mu/ml). Anti TPO levels were negative. Her radiological investigation revealed delayed bone age of 7 years. Repeat ultrasonography performed at our institute also suggested bilateral multicystic enlarged ovaries with no solid component. Thyroid ultrasound showed heterogenous echotexture in both lobe and a small cyst in left lobe of thyroid

After reviewing the literature and taking an endocrinologist opinion, Van Wyk and Grumbach Syndrome was confirmed.[4] The precocious puberty and multicystic ovarian enlargement was secondary to hypothyroidism. Thyroid replacement therapy was started with gradual increase of the dosage.

The TSH became within normal limit in two months. After six months of treatment with thyroxine there was complete resolution of the ovarian cysts

(Figure 2) and the CA-125 returned to normal. Her weight had reduced to 20 kg and height had increased to 119 cm. She had still not achieved menarche.

Case 2: Ovarian Enlargement with Severe Hypothyroidism

An eight year old girl was referred for surgery as a case of unilateral solid ovarian tumor Ultrasonography done elsewhere showed 4.8x4.6x3.3 cm solid left ovarian lesion suggestive of ovarian neoplasm with mild ascites. She had stunted growth and decreased appetite. She also had swelling all over the body since two years and abdominal distension for the past few months. There was no history suggestive of precocious puberty.

Her height was 105 cm, less than 5th percentile. On examination secondary sexual characters were not developed. She had pallor, dry skin and periorbital puffiness. There was abdominal distension but no palpable mass.

Laboratory investigations revealed severe hypothyroidism with TSH: 919.2 uIU/ml. CA -125 (100.4 U/ml) and LDH (976 IU/L) were also raised, which led us to initially suspect an ovarian dysgerminonma.

CT scan revealed 5.6x4x4.6 cm heterogeneously enhancing soft tissue density lesion with internal cystic area in right adnexal region (Figure 3). Detailed discussion with the radiologist suggested that this might be a myxematous ovarian infiltration with cystic area due to severe hypothyroidism. Ultasound guided biopsy from ovarian mass showed necrotic debris with few short spindle stromal cells only. Hence surgery was deffered and a joint decision was with endocrinologist to treat the patient conservatively with thyroid replacement therapy.

In a view of biopsy negative for malignancy before scheduling patient for surgery a detailed discussion was done with radiologist that it might be a myxematous ovarian enlargement with cystic lesion due to severe hypothyroidism. After 21 days of thyroid replacement therapy serum LDH had reduced to 725 U/L and sonography also showed reduction in the size of ovarian lesion. Seum TSH reached within normal limit in eight weeks. Her tumor markers and sonography findings became normal after three and six month, respectively.

Case 3: Spontaneous Ovarian hyperstimulation syndrome (OHSS) in a naturally conceived pregnancy

A 21-year-old lady presented with the complaints of abdominal pain and distension since few days with an ultrasonography report of 10x9.2 cm right and 4.6x2.6 cm left solid cystic complex ovarian masses.

She had spontaneously aborted a first trimester pregnancy 15 days before presenting to us. She gave past history of four consecutive first trimester abortion. All her pregnancies were naturally conceived.

On examination she was pale and short statured. Her abdomen was distended and non-tender with a huge palpable mass in the lower abdomen extending to the right iliac fossa. Repeat ultrasonography and pelvis MRI revealed a right solid cystic ovarian mass of 11.8x 5.3x 11cm and a small cystic lesion on left side. The uterus was bulky.There was no ascites (Figure 4).

Laboratory investigation showed gross hypothyroidism with TSH: 310.3 u IU/ml raised β-hCG – (69,900 mIU/ml) and CA-125 (55 U/ml) and severe anaemia (Hb: 6.5gm). LDH and α fetoprotein were normal.

Treatment for severe hypothyroidism was started as per endocrinologist advise. The initial differential diagnoses included Persistent gestational trophoblastic tumor following abortion or germ cell ovarian tumor. History of repeated spontaneous abortion pointed towards endocrinological pathology. However after reviewing the literature the diagnosis of severe hypothyroidism causing spontaneous ovarian hyperstimulation in naturally conceived pregnancy was considered. The decision was taken to treat the patient conservatively with close monitoring of β-hCG and serial ultrasonography of ovary. She was admitted to hospital for close observation.

Once the β-hCG started falling Gestational trophoblastic tumor was rule out. After this, biopsy was performed from the right ovarian mass. It revealed only blood clots, strengthening our diagnosis of of severe hypothyroidism causing spontaneous ovarian hyperstimulation. The β-hCG fell to 13,870 mIU/ml. Three weeks later ultrasonography showed regression of right ovarian solid cystic mass(8.7x5.3cm).The solid area now appeared to be echogenic suggestive of clot and the left cyst had regressed. Her β-hCG became normal after three and half months. There was complete resolution of ovarian lesions after seven months.

Result

All three patients responded dramatically after initiation of levothyroxine replacement therapy. The ovarian lesions gradually regressed and the tumour markers returned to normal. Unnecessary ovarian surgery could be avoided in these young patients with institution of appropriate thyroid replacement therapy and close observation. All three patients were advised to continue thyroid replacement therapy for their life time and regular monitoring of thyroid hormones levels.

Review of Literature and Discussion

In first case, precocious puberty and ovarian enlargement suggested an estrogen-secreting ovarian tumor such as, juvenile granulosa cell tumor. However in the case of juvenile granulosa cell tumor bone age is advanced with growth spurt. Children with precocious

puberty due to other etiologies are tall, have pubertal growth spurt and advanced bone age where as children with hypothyroidism are short statured, have delayed bone age and no concomitant growth spurt, as seen in our case.[4]

The salient diagnostic features of Van wyk Grumbach syndrome include long-standing hypothyroidism, high levels of TSH, low LH, isosexual precocity with lack of public and axillary hair, and delayed bone age along with multicystic ovarian enlargement 2. The precocious puberty is always isosexual (FSH dominated) and incomplete in this syndrome .[1,4]

The exact mechanism of the development of precocious puberty in Van Wyk and Grumbach syndrome remains speculative. High circulating levels of TSH acting directly on FSH receptors may be the actual mediator of precocity. TSH levels are consistently elevated in such patients and the tendency to manifest isosexual precocity may be directly related to the severity of TSH elevation. It is also possible that increased sensitivity of the ovaries to the circulating gonadotropins could result from the hypothyroid state directly or via increased prolactin. However, ovarian enlargement may be secondary to a myxematous infiltration.[5]

Hypothyroidism presenting during childhood with pseudoprecocious puberty and ovarian cysts is a well-defined condition, but rare in today's world. Widespread use of neonatal screening program has led to diagnosis of most of the patients of congenital hypothyroidism in the neonatal period. Van Wyk and Grumbach first reported multicystic ovaries with precocious puberty in patients with hypothyroidism in 1960. Since then sporadic cases of this syndrome have been reported in prepubertal and adolescent girls. However, very few cases have been reported in adults aged 19–26 years.[5,6]

With severe hypothyroidism, ascites is an uncommon feature, occurring in only 4% of patients6 as seen in our second case. If hypothyroidism is not appropriately treated, after few years it could cause ovarian cystic enlargement. Patients with uncontrolled hypothyroidism causing ovarian cystic enlargement may not always exhibit precocious puberty as seen in Van Wyk Syndrome. Most of the patient with severe hypothyroidism has delayed puberty. Our patient had the typical symptoms of hypothyroidism along with delay in growth and sexual development, ascites and ovarian enlargement. Association of hypothyroidism, ascites (myxedema),elevated levels of LDH and unilateral ovarian lesion is very rare. Elevation of LDH probably is due to delay of clearance, secondary to hypothyroidism as seen in our patient. Very few cases have been reported in the literature.[7]

There are very few reports of adult hypothyroid patients presenting with ovarian cysts as seen in our third case. Spontaneous OHSS (ovarian hyper stimulation) can occur both in pregnant and non-pregnant women and is extremely rare. De Leener classified spontaneous OHSS syndrome into three types based on clinical presentation and FSH receptor mutation in which Type III is related to hypothyroidism.[4] Type I is associated with the mutated FSH receptor and Type II is secondary to high levels of human chorionic gonadotropin.[3,8]

Hypothyroidism is an endocrine disorder associated with spontaneous ovarian hyper stimulation, yet it is often ignored in its evaluation of ovarian lesion.

Spontaneous OHSS usually occurs at 8-14 weeks of gestation, as seen in our patient, while iatrogenic OHSS usually occurs earlier at 3-8 weeks of gestation.[3,8] Unlike in iatrogenic OHSS, in spontaneous OHSS extravascular fluid retention may not occur and usually a hemodilution rather than hemoconcentration is seen. As in this case the blood picture showed anemia instead of hemoconcentration.[7]

The pathophysiology of spontaneous OHSS associated with hypothyroidism is not studied well. The explanations given are (a) excessive estriol via the 16-hydroxylation pathway instead of the normal 2-hydroxylation that has been demonstrated in hypothyroid patients. (b) High levels of thyroid stimulating hormone can directly stimulate ovaries in women with hypothyroidism and can cause ovarian hyperstimulation. In women with hypothyroidism, the elevated concentrations of TSH may mediate ovarian hyperstimulation because of the presence of nuclear thyroid receptors (TR and TRβ) in the granulosa cells. Mutations in the FSH receptor (FSHR) can also be a predisposition factor to OHSS. The relationship between hypothyroidism and ovarian hyperstimulation is suggested by the consistent regression of the ovarian cysts after the institution of thyroid hormone replacement therapy. [8]

Thyroid hormone replacement seems to be the best therapeutic approach, but in some patients, the complete resolution of the ovarian cysts does not occur. In cases of spontaneous OHSS associated with pregnancy and hypothyroidism, conservative surgery should be the first approach when the ovarian cysts remain in spite of adequate medical treatment. It is suggested to consider longer observational management without surgical intervention in some specific cases of OHSS .

Conclusion

Our study emphasises the need to consider hypothyroidism in the differential diagnosis of patients with ovarian lesions in order to prevent inadvertent ovarian surgery especially in young patient.[8] There are reports in the literature where young girls were operated for large cystic enlargement of ovaries and then subsequently found to have hypothyroidism. Such girls will have recurrent development of cystic ovaries even after surgery unless their thyroid deficiency is treated.[1,4]

Bilaterality, cystic appearance and clinical profile are the most important diagnostic clues that an endocrine source is the underlying pathology for the

Table 1: Responses after thyroid replacement therapy

Cases	S.TSH	Pre- treatment		Post treatment (all patient became euthyroid)	
		Ovarian Lesion	Tumor marker	Ovarian Lesion	Tumor marker
1 VWG syndrome	>100u IU/ml	Bilateral multicystic	CA-125 : 56 U/ml	Regressed completely in 6 months	CA-125 : Normal in two months
2 Ovarian Enlargement with Severe Hypothyroidism	919.2u IU/ml	Unilateral, solid – cystic enlargement	S.LDH : 976 IU/L CA-125 : 100.4U/ml	Regressed completely in 6 months	S.LDH and CA-125 : Normal in three months
3 Spontaneous OHSS	310.3u IU/ml	Bilateral,Huge multicystic	β-hCG 69,000mIU/ml CA-125 : 55U/ml	Regressed completely in 7-8 months	β-hCG Normal in three months

ovarian tumors. However it should be suspected even in patients with unilateral and/or cystic-solid enlargement of ovary with severe uncontrolled hypothyroidism as seen in our case 2 .[7] Patients with repeated abortion, menstrual irregularities, pregnancy with ovarian cyst or abdominal pain should also be evaluated for hypothyroidism.

In addition these cases also show that elevated tumor markers may occur in the absence of a malignancy.

Our patients were having long-standing hypothyroidism, with very high serum TSH levels. It is very rare to come across untreated patients with such high TSH levels. This case highlights that such patients should be treated as early as possible to avoid complications. In younger women with ovarian cysts, it is desirable to avoid unnecessary surgery so as to prevent fertility problems in the future.[9]

It is also imperative that health care providers consider hypothyroidism in the differential diagnosis of pregnant females presenting with huge multicystic ovarian tumors during pregnancy or after abortion, to avoid unnecessary and catastrophic ovarian resection. [10]

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Malignant Transformation in Dermoid Cyst: A Case Series and Review of Literature

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Summary

Malignant transformation of a mature cystic teratoma (MCT) is a very rare complication with an incidence of 1-2%.The most common form of malignant transformation of the MCT is squamous cell carcinoma. Other tumors arising in MCT include basal cell carcinoma, sebaceous tumor, malignant melanoma, adenocarcinoma, sarcoma, and neuroectodermal tumor. Adequate sampling is essential in these ovarian tumors to establish their teratomatous origin and avoid an erroneous diagnosis. We hereby report a case series of 3 cases of dermoid cyst with malignant transformation to squamous cell carcinoma and sarcoma; discuss their management and relevant literature

Keywords: Dermoid cyst, Malignant transformation, Squamous cell carcinoma.

Introduction

Malignant transformation in a mature cyst teratoma occurs in 1-2% of cases and usually not recognised preoperatively. Squamous cell carcinoma is a common secondary tumour however, sarcoma is a rarity. We hereby report a series of three cases of dermoid cyst with malignant transformation to squamous cell carcinoma and sarcoma; discuss their management and relevant literature.

Case 1

Forty-five year (P2L2) menopausal woman presented with abdominal pain since seven days. Per abdominal exam demonstrated 10×8 cm mass with restricted mobility. Bimanual exam confirmed the per abdominal findings. Ultrasonography showed 107x78 mm heterogenous mass in right adnexal region, predominantly solid with echogenic area and posterior acoustic shadowing within the mass suggestive of dermoid cyst. Few spots of calcification were also noted within the mass. Tumor markers (βhCG, AFP, CA-125) were normal.

Patient underwent exploratory laparotomy with removal of right ovarian tumor, total abdominal hysterectomy with left salpingo-oophorectomy and infracolic omentectomy.

Histopathology showed well encapsulated mature cystic teratoma of right ovary with malignant transformation, mainly spindle cells suggestive of sarcoma.

Case 2

Forty year (P3L3) premenopausal woman presented with anorexia, mass in lower abdomen and lower abdominal pain since 6 months. Per abdomen showed 10-12 cm mobile pelvic mass, more on right side. Bimanual examination revealed 10-12 cm irregular mass on right side, anterior to uterus. On per rectum nodularity was felt in pouch of Douglas. USG revealed 16x9 cm size echogenic lesion posterior to the uterus with internal calcification and posterior shadowing, possibility of dermoid cyst. Tumor markers (βhCG, AFP, CA-125) were normal.

Patient underwent exploratory laparotomy with removal of left tubo-ovarian mass, total abdominal hysterectomy, right salpingo-oophorectomy, infracolic omentectomy and left side pelvic node dissection. Histopathology revealed dermoid cyst of left ovary with capsular invasion and malignant transformation. Squamous cell carcinoma, moderately differentiated, is seen as malignant component. Pelvic node shows squamous cell carcinoma.

Patient was assigned stage IIIc and received MTX+5-FU weekly. She was lost to follow up following treatment.

Case 3

Forty-five years old (P3L3), menopausal woman, presented with abdominal pain and distension since 4 months. Per abdomen examination revealed multilobulated cystic mass occupying entire abdomen up to xiphisternum with restricted mobility. On bimanual examination mass was found separate from uterus. Per speculum and per rectum examination were unremarkable. Tumor markers (βhCG, AFP, CA-125) were normal. Ultrasonography showed a huge complex cystic mass lesion of 21x18x16 cms size seen in pelvic cavity extending superiorly to supraumbilical region with internal ill defined inhomogenous echogenicities and solid components.

Patient underwent exploratory laparotomy with removal of right ovarian tumor, total abdominal hysterectomy, left side Salpingo-oophorectomy, left side pelvic lymphnode dissection and infracolic omentectomy (Figure 1). Histopathology revealed mature cystic teratoma of left ovary with malignant transformation (squamous cell carcinoma) with intact capsule (Figures 2-4)

Discussion

Mature cystic teratoma is the most common germ cell tumor of the ovary. It composes 10–20% of all ovarian tumors and 9–16% of the cases are

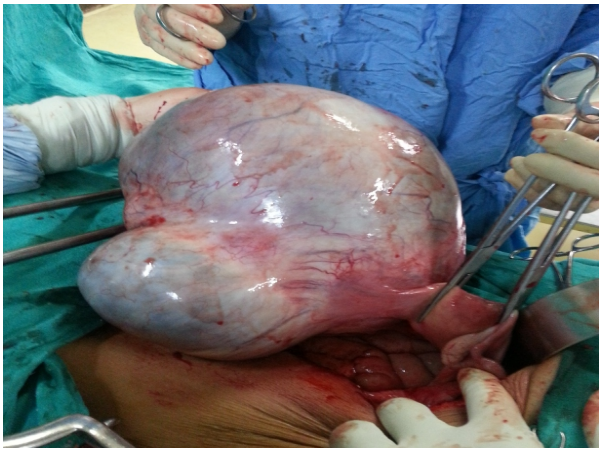

Figure 1: A large dermoid cyst arising from right ovary and occupying the whole abdomen.

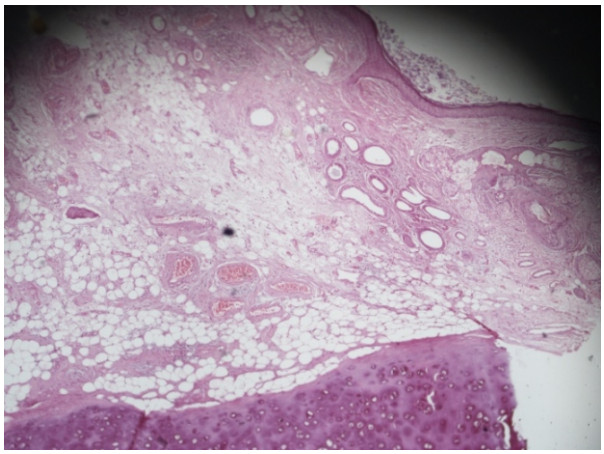

Figure 2: H & E 10x Section shows squamous epithelium with subcutaneous adnexa, fat and cartilage

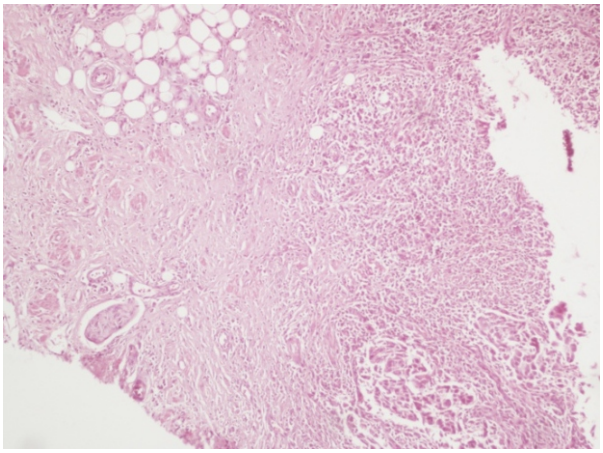

Figure 3: H & E 10x Section shows ulcerated epithelium with squamous cell carcinoma

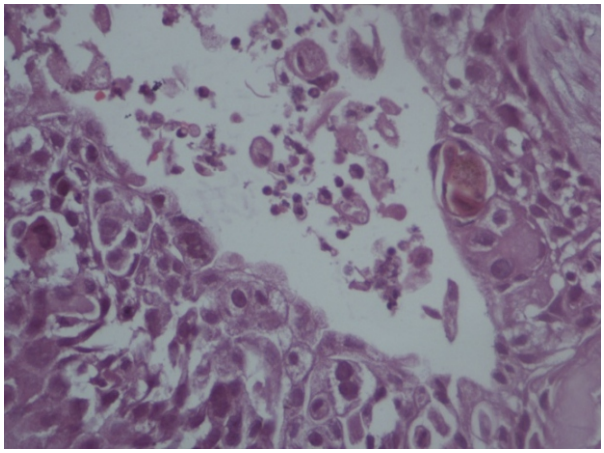

Figure 4: H & E 40x Section shows invasive cell carcinoma

bilateral.[1] It is generally a benign type of tumour however, malignant transformation can occur in 1-2% of the cases. Squamous cell carcinoma accounts for 75% cases.[2] Other tumors that can arise from dermoid cyst are adenocarcinoma, Paget disease, transitional cell carcinoma, basal cell carcinoma, small cell carcinoma and carcinosarcoma.

Malignancy should be suspected in postmenopausal women. The median age of the diagnosis is between 45-60 years and the frequency of malignant change increases with increase in age, rising to 19% in woman after menopause.[3] However malignant transformation can occur at younger age and cases have been reported in women as young as 19 years old.[4] In our series, the average age was 43.3 years and the youngest woman was 40 years old.

Various factors predicting malignancy have been studied

Tumour size has been noted to predict malignancy. Al-Rayyan et al asserted that possibility of malignancy should be strongly considered in cases of tumour size >10 cm or rapidly growing tumours.[4] In our case series, the average tumour size was 15.9cm. Several studies reported that tumour size of > 9.9 cm was 86% sensitive for malignancy.[5]

Chiang et al stated that higher concentration of serum CA-125 levels were associated with malignant transformation.[6] However in our case series, serum CA- 125 was not found to correlate with diagnosis. Doppler sonography has been found to be more useful in predicting malignancy. Vascularisation in the solid component can indicate malignancy.[7]

Management of such cases include exploratory laparotomy and frozen section with optimal debulking. When preoperative suspicion of malignancy is present, laparoscopic removal should not be attempted in order to avoid inadvertent rupture of the tumour and upstaging of the disease. For young patients desirous of fertility preservation, unilateral salpingo-oophorectomy, surgical staging and close follow up has been proposed.

Patients with stage Ia have better survival than advanced stage. Al Rayyan reported 100% five year survival for 8 patients with stage Ia cancer in their study. They further noted that irrespective of the tumour type and size, prognosis was good for FIGO stage Ia tumours.[4] One patient with stage Ia in our series, irrespective of the sarcomatous transformation is disease free at seven year of follow up. Patients with advanced disease carry poor prognosis. For squamous carcinoma arising from mature cystic teratoma, survival can markedly vary from stage I patients (76.9%), versus stage II-IV patients (11.1%), $p<0.001$.[4] The other potential predictors reported include residual tumor, rupture or spillage, tumor grade, vascular involvement and the mode of tumor infiltration.

Due to rarity of the disease, a definitive adjuvant treatment has not been yet established. Chemotherapy or radiotherapy or combined treatment has been described.[7,8]

Platinum and taxane based regimens are most commonly used. One patient in our series had stage IIIc disease according to FIGO staging and received adjuvant chemotherapy. Second look surgery for relapsed disease is prescribed and good remission can be achieved. Second line chemotherapy and radiotherapy are infrequently prescribed.

Conclusion

Malignant transformation in a mature cystic teratoma is a rarity and can occur in the form of squamous cell carcinoma or sarcoma. We recommend maintaining a high index of clinical suspicion for malignancy in women of 40 years and above age group, large tumours and increased vascularity on doppler sonography. Histopathological specimens in such cases should be adequately sampled. Optimal cytoreductive surgery is the mainstay of management. Role of adjuvant treatment is yet to be established. Survival is mainly related to stage.

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Nothing in education is so astonishing as the amount of ignorance it accumulates in the form of inert facts.

Henry Adams

Myths and Facts about Palliative Care

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Palliative care has been included in the WHO definition of Universal Health Coverage (UHC). This means that palliative care will be included in discussions as the WHO prioritizes UHC.[1]

Myths and misinformation around hospice and palliative care represent significant barriers to access palliative care services. Such misconceptions are unnecessary and lead to greater suffering. As part of the effort to achieve universal coverage of palliative care, the theme for year 2013, World hospice and palliative care day was: 'Achieving universal coverage of palliative care: Dispelling the myths'. Various hospice and palliative care set up across world has described unhelpful myths for better understanding of this specialty.

Here, I am attempting to describe few myths and fact about palliative care and use of opioids in cancer patients, which are prevalent amongst professionals, patients and caregivers.

Myth: Palliative care is given only when other treatment is over.
Fact: Palliative care integrated with active treatment of disease. Palliative care is given in addition to prescribed treatment. Our palliative care specialists will make recommendations to treating physicians about the management of pain and other symptoms. Palliative care will address other psychosocial, spiritual and financial issues of disease and its treatment. (Figure 1)

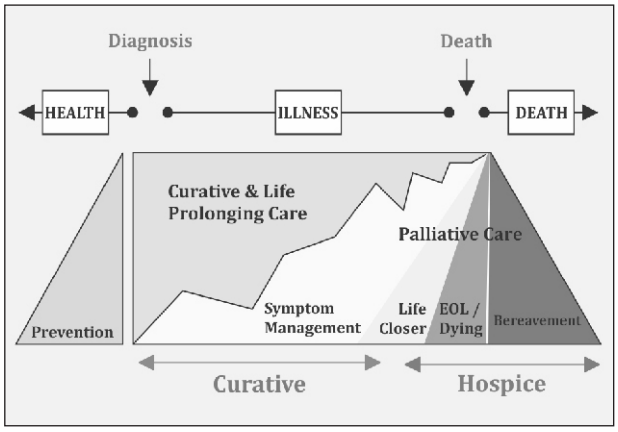

Figure 1: Palliative Care: Continuum of Care

Myth: Palliative care is given only when patient has pain or other symptoms.
Fact: Palliative care is given even when patient doesn't have physical issues. It also helps patient and care givers, to understand about disease, its treatment and prognosis. This helps patients to adhere to treatment prescribed, reduces defaulters and improve patients' compliance. Hence; palliative care can be started at diagnosis of the disease.

A study on 151 lung cancer patients who had palliative care in addition to standard treatment shows that patients receiving palliative care lived an average of nearly three months longer than those who did not have palliative care. Their quality of life was better, had 50 percent lower rate of depression even without the use of antidepressant medications.[2]

Myth: Palliative care is only nursing care and counselling.
Fact: Palliative care is medical specialty, having scientific approach to patient's pain and other distressing symptoms. Physicians trained in pain management, medicine, psychiatry, oncology or palliative care are part of team of palliative care.

Myth: Palliative care is given only in terminal stage or just before dying.
Fact: End of life care is part of palliative care. Patient and care givers should be prepared for such event, for which they should be counseled and educated right from the time when the disease is not curable. Patients suffering from life limiting illnesses should be referred to palliative care services during diagnosis or treatment for end of life care.

Myth: Palliative care is only for people with cancer.
Fact: Palliative care can benefit patients and their families from the time of diagnosis of any illness that may shorten life. HIV/AIDS, End stage renal, cardiac, and liver or lung disease are few of the conditions in which patient needs holistic care addressing their physical, psychosocial and spiritual support. However, people with these conditions are less likely to receive palliative care than people with terminal cancer, as they have intermittent acute episode of illness, followed by chronic symptoms. This means some people who can benefit from palliative care are not getting it at earlier stages of their illness.

Marie Curie published a report looking at the barriers which are preventing people with a terminal condition other than cancer from accessing the palliative care they need. The report found that there is limited understanding of what palliative care can do, who it benefits and when to introduce it. It also showed that generalist healthcare professionals do not always receive enough training in the area and therefore miss the signs when their patients need palliative care, or when they're nearing the end of their lives.[3]

Myth: Palliative care hasten death.
Fact: Palliative care does not hasten death. It provides comfort and the best quality of life from diagnosis of an advanced illness until end of life. The goal of palliative care is to relieve suffering and stop futile interventions toward end of life within ethical and legal framework.[4]

Myth: Patient who stops eating will die of starvation.
Fact: This is the worry of care givers. They feel, if patient doesn't eat, he/she will die soon. People with advanced illnesses don't experience hunger or thirst as healthy people do. People who stop eating die of their illness, not starvation. Interventions required to initiate feeding should be initiated at earlier stage of disease. Early interventions are effective at increasing nutritional intake and improving some aspects of Quality of life (QoL) in patients with cancer who are malnourished or are at nutritional risk but do not appear to improve mortality.[5]

Myth: Something has to be done to relieve all symptoms of end stage disease.
Fact: All interventions done by treating physicians and palliative care specialist should be weighed for their benefits, its impact on QoL of patient, care givers and suffering of patient. E.g. Hemodialysis in end stage renal disease or CRF in advanced cancer patient. Institute should follow prognostic indicators for care of such patients.

Myth: Palliative care means treating physician has given up and there is no hope for patient.
Fact: Palliative care ensures the best quality of life for those who have been diagnosed with an advanced illness. Hope becomes less about cure and more about living life as fully as possible. Palliative care helps to restore function, helps patients and care givers to a chronic life-limiting illness and accept the situation. Palliative care focuses on living until the end, not dying.

Myth: It is not necessary to discuss with patient about disease, end of life and death.
Fact: Discussing prognosis and end-of-life issues is an important component of care of patients with progressive life-limiting illnesses, and their families.[6,7] A well informed patient and family member are essential to participate in decision making about treatment and care. It helps to set goals and priorities and to prepare for death. Treating physician need to provide information in a way that assists patients and their families to make appropriate decisions, be informed to the level that they wish, and cope with their situation. Training of physicians and para-medical staff in communication skills is need of every healthcare set up involved in care of patients of life limiting illnesses.

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Isolated Central Nervous System Blast Crises in Chronic Myelogenous Leukemia

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Summary

Chronic myeloid leukemia (CML) is a chronic myeloproliferative disorder, currently treated with tyrosine kinase inhibitors. Uncontrolled CML eventually progresses to accelerated and blast crises, which is often medullary, and rarely extramedullary. It is extremely uncommon to have extramedullary blast crises, in the presence of major molecular response. The current case describes successful management of extramedullary blast crises of CNS in presence of major molecular response to Imatinib.

Keywords: CML, Blastic crises, Extramedullary.

Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by dysregulated production and uncontrolled proliferation of mature granulocytes. The reciprocal trans- location between chromosomes 9 and 22 results in the formation of the Philadelphia chromosome,a hallmark of this disease.[1] Imatinib mesylate is the standard of care for CML patients in whom allogenic stem cell transplant is not an option. Natural history of uncontrolled CML is triphasic, complicated by evolving into accelerated phase and eventually into blast crises. Blast crises is usually medullary and rarely extramedullary involving lymph nodes, skin, soft tissues, serosal surfaces, bones, gastrointestinal and genitourinary tract and rarely central nervous system.[2] We report a case of chronic myeloid leukemia with major cytogenic response and associated extramedullary blastic crises of central nervous system.

Case Report

A 15 years male, with chronic myelogenous leukemia (CML) in chronic phase received imatinib 400 mg/d. Achieved complete hematological response by 6 months, further achieved major cytogenetic response by fluorescent in situ hybridization (FISH) of BCR-ABL at 12 months. He continued to take Imatinib regularly, 18 months on Imatinib, patient complained of headache, loss of balance and blurring of vision. Fundus examination revealed bilateral papilloedema, suggesting increased intracranial tension (ICT). Hemoglobin level was 11.0 g/dL, WBC count was 9,600/mm^3 with normal distribution of differential count without precursor cells, and platelet count 196,000/mm^3. Brain MRI showed brain parenchyma infiltration in parietal regions with perilesional edema. Lumbar puncture demonstrated high opening pressure. The CSF cell count was two RBCs per mm^3 and total WBC 450/cumm (Figure1), with increased numbers of atypical cells 30%, altered nuclear cytoplasmic ratio and hyperchromatic nuclei. CSF immunophenotype study revealed CD10, Cd19, HLADR+ suggestive of Pre B cell origin (Figure 2). Bone marrow examination revealed CML chronic phase, and fluorescent in situ hybridization (FISH) of BCR-ABL showed no Ph+ metaphases suggesting major cytogenic response.

We started anti edema measures in the form of iv dexamethasone and mannitol to control intracranial pressure, after normalizing the raised ICT, intrathecal therapy (methotrexate, cytarabine and hydrocortisone) was given thrice weekly until CSF cytology was negative for two occasions. Patient also received imatinib 800 mg/day and therapeutic cranial radiation of 16 Gy. Further he was started on REZ protocol, [3] for relapsed acute lymphoblastic leukemia. Currently he is normal, on maintenance therapy and has resumed his day to day activity and school for six months.

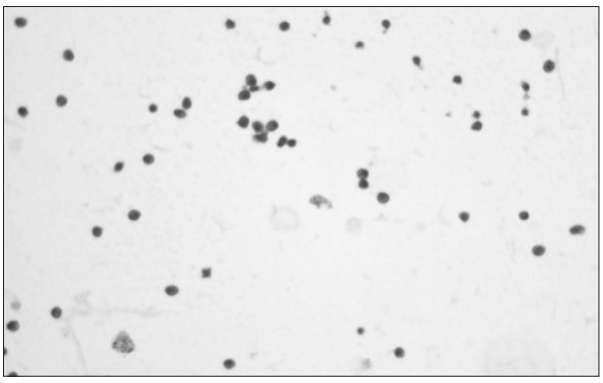

Figure 1 : CSF : Reveals increased number of atypical lymphocytes (lymphocytic pleocytosis)

Discussion

CML accounts for approximately 15 to 20% of leukemias in adults and 3% of all pediatric leukemias.[4] CML has a triphasic or biphasic clinical course: a chronic phase, which is present at the time of diagnosis in approximately 85% of patients; an accelerated phase, in which neutrophil differentiation becomes progressively impaired and leukocyte counts are more difficult to control with treatment;and blast crisis, a condition resembling acute leukemia in which myeloid or lymphoid blasts proliferate in an uncontrolled manner.[1] Most patients are asymptomatic, diagnosed on routine blood counts, of

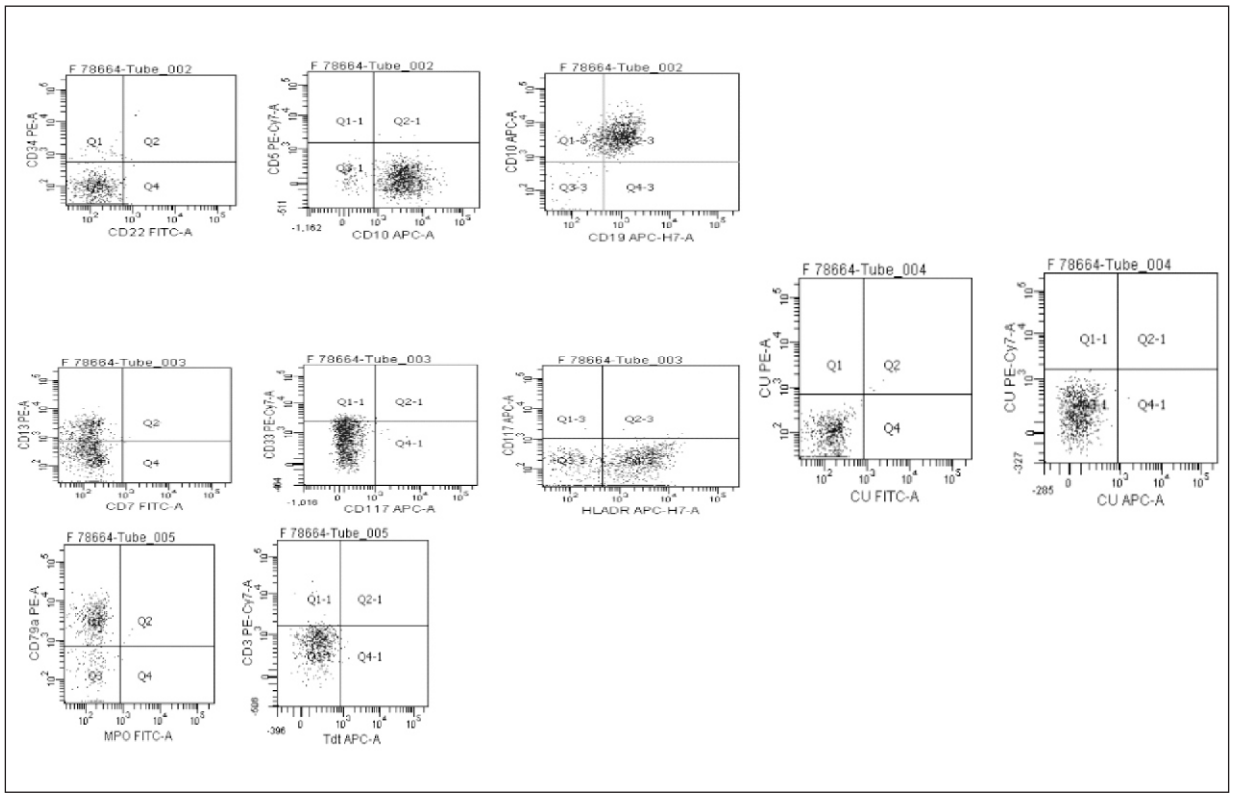

Figure 2 : Immunophenotype study of CSF: showing Cd10,CD19, HLADR+ suggestive of pre B cell origin

those with symptoms present with fatigue, splenomegaly and loss of appetite.[1] Lymphadenopathy, constitutional symptoms, and infiltration of skin or other tissues are uncommon. When present, they favor accelerated phase or blast phase of CML. Accelerated phase might be insidious or present with worsening anemia, splenomegaly, and organ infiltration. Most patients evolve into accelerated phase before blastic phase, but 20% transit directly into blastic phase. In 5-10% of the cases, the blast phase can present at extramedullary sites, lymphnodes, serosal surfaces, skin and soft tissue, breast, bone, and gastrointestinal or genitourinary tract are commonly involved, the central nervous system as a site of extra medullary blast crisis is quite rare.[2]

Tyrosine kinase inhibitors (TKI) Imatinib, Dasatinib, Nilotinib are the molecularly targeted agent that plays a major role in management of CML. These drugs competitively inhibits the inactive configration of Bcr-Abl protein tyrosine kinase by blocking the ATP binding site and thereby preventing a conformational switch to the active form.[5] It inhibits cellular proliferation and tumor formation without inducing apoptosis, thus It has become the treatment of choice of CML and has changed the natural history of disease dramatically, the 10-year overall survival from of 20 to 80–90% present era.[6] Wolff et al suggested that there was inadequate penetration of Imatinib crossing across the blood brain barrier into the CNS.[7] These were confirmed by analyzing the CSF samples, they found that it was less than 1% of plasma concentration and one-third of the concentration required to achieve 50% inhibition of cellular Bcr- Abl related tyrosine phosphorylation.[7] Several other authors also agreed that the drug concentration in CSF is less than that seen in plasma.[8] Some believe the low levels of drug in CSF is due to increased efflux of the drug from the CNS due to P-glycoprotein,[9] while others have postulated it is due to altered pharmacokinetics of Imatinib.[10]

In the past few years, there have been several reports of CML patients with CNS BP on imatinib therapy, despite achieving cytological remission, suggesting the CNS as a sanctuary site for extramedullary blast crises. [2,11,12] The presenting symptom in these patients was headache with or without neurological deficit, the median time from treatment initiation to CNS relapse was 24months, earliest 3to latest 58months.[2,11,12] Most of such cases receive triple intrathecal chemotherapy, with either escalation of on gowning TKI or second line TKI Dasatinib, with or without chemotherapy.[13]

To conclude, isolated CNS relapse is extremely rare and only limited reports are available. They can occur even after hematological and cytological remission. Strategies and treatment protocol needs to be developed to prevent and manage CNS relapse. Head ache and features of increased ICT should be evaluated aggressively, as they may

possibly be a sign of CNS relapse. Currently, there are no standard guidelines established till date, to address CNS directed therapy. Surveillance and prophylactic CNS directed therapy in patients achieving cytologic remission is likely to be suggested in future to control the sanctuary site.

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Science knows no country, because knowledge belongs to humanity, and is the torch which illuminates the world. Science is the highest personification of the nation because that nation will remain the first which carries the furthest the works of thought and intelligence.

Louis Pasteur

Successful Management of Vincristine Induced Unilateral Ptosis in an Adult

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Summary

Vincristine (VCR) is a vinca alkaloid widely used in the treatment of lymphoma, leukemia and solid tumours.VCR is neurotoxic and it usually causes peripheral neuropathy,but cranial and autonomic neuropathy are uncommon side effects. This case report describes the successful management of Vincristine induced unilateral ptosis in an adult patient of Burkitt lymphoma. Patient was given cytoreductive chemotherapy i.e. CVP (cyclophosphamide,vincristine and steroids).On post chemotherapy day-3,he developed acute onset of left eye ptosis. Patient's neurological examination revealed only unilateral ptosis with normal pupillary and corneal reflex. Other cranial nerves, peripheral nerves and other neurological findings were normal. Magnetic resonance imaging of brain and cerebrospinal fluid examination was normal. Patient was started on pyridoxine and pyridostigmine. Ptosis markedly improved after 5 days of treatment. The case has been reported in view of rarity of this complication.

Keywords: Vincristine, Ptosis, Pyridostigmine, Pyridoxine

Introduction

Vincristine (VCR) is a vinca alkaloid widely used in the treatment of leukemia, lymphoma, solid tumours etc. The neurotoxicity of Vincristine is a limiting factor for the drug administration[1]. Pathogenesis of neuropathy is primarily due to the structural changes in the microtubules of the nerves induced by vincristine which leads to interference in the axoplasmic flow/axonal degeneration and finally loss of neuronal reflexes[2]. Since VCR has low central nervous system penetration peripheral neuropathy is much more common.

Vincristine induced neurotoxicity can be divided into four groups: Peripheral neuropathy, Autonomic neuropathy, Cranial neuropathy and Encephalopathy.

Case Report

A 30 year old male diagnosed as a case of Burkitt ymphoma. He was started on cytoreductive phase chemotherapy-CVP (cyclophosphamide, vincristine and prednisolone) as a part of his treatment protocol. On post chemotherapy day-3,he developed sudden onset of unilateral ptosis in his left eye (Figure 1). Patient had no other complaints at that time. There was no past history of trauma, recent eye surgery or any neurological disease. here was not any significant drug history except VCR. His physical examination including neurological findings were normal except unilateral ptosis of left eye. Pupillary/corneal reflexes, eye movements and cranial nerve examination were normal. Ophthalmology evaluation revealed no abnormality. Laboratory investigations such as complete blood counts, serum electrolytes, uric acid, renal and liver function tests were normal except LDH which was high. His MRI brain and cerebrospinal fluid examination were normal.

There was no other cause found in this patient for unilateral ptosis and as it is a known side effect of Vincristine treatment, he was started on pyridoxine 300mg/m^2 and pyridostigmine 3mg/kg/day. After 5 days of treatment, patient had significant improvement in ptosis (Figure 2).

Discussion

VCR is a commonly used chemotherapy agent for various malignancies. Neural toxicity is a limiting factor for the administration of VCR. Neurotoxicity is usually dose and duration dependent.

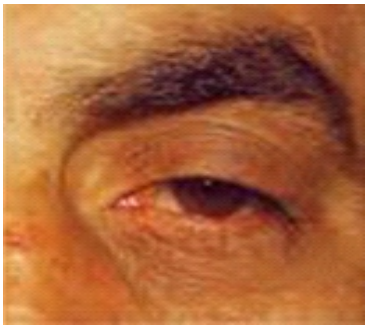

Figure 1: Vincristine induced ptosis

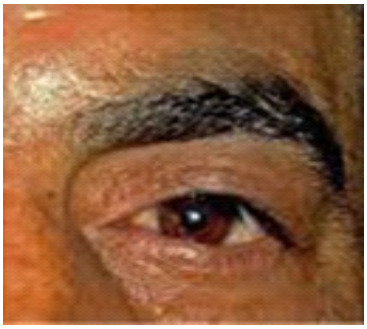

Figure 2: Significant improvement in ptosis with neuroprotective treatment

Symptoms usually appear 2-19 weeks of starting VCR3.In our patient ptosis developed after single dose and within one week of VCR. The clinical spectrum of VCR induced neuropathy includes: paraesthesia, ataxia, gait disorder, facial nerve palsy, rist and foot drop, depression of tendon reflexes, optic neuropathy, transient cortical blindness, ptosis, urinary retention, abdominal colicky pain, constipation, orthostatic hypotension etc. Neurotoxicity is usually reversible but is slow and may take several months. Toxicity is more if patient has any pre-existing diabetes mellitus, liver dysfunction, hereditary neuropathy, concomitant administration of drugs like isoniazid, erythromycin, phenytoin, and itraconazole.[4] But surprisingly in our case ptosis developed with single dose and with such a short duration without any apparent previous cause.

Definitive diagnosis of VCR induced neuropathy is related to the exclusion of other etiologies that cause similar clinical features. Findings in the present case which give support to our diagnosis are: 1.The absence of any abnormal findings on thorough ophthalmological evaluation, brain imaging and CSF examination.[2] Temporal profile and absence of any other history pointing out only VCR as a culprit.[3] The resolution of ptosis with neuroprotective treatment.

Bilateral ptosis is the usual feature of VCR induced cranial neuropathy but unilateral ptosis can also be seen as a part of cranial neuropathy.[5] Neuroprotective agents/Nerve regenerating agents e.g. Pyridostigmine and Pyridoxine have been reported through several case reports as a very effective therapy for such complications. Treatment should be continued for at least 2-4 weeks depending on the severity.[6,7]

Conclusion

Vincristine induced ptosis should always be kept as a differential diagnosis, when it is used as a part of treatment protocol. As in our case, VCR induced ptosis can be unilateral, can be seen in adult and can develop even with single dose in an early part. Neuroprotective drugs can lead to rapid and most of the times complete recovery of ptosis.

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Research is what I'm doing when I don't know what I'm doing.

Wernher von Braun

Summaries of Presentations at Clinical Meetings

01. Salivary Gland Neoplasms - An Overview of Cases at GCRI

Bakshi Saaishta
Pathology

Summary

Salivary gland tumors often pose a diagnostic challenge since they can show a striking range of morphological diversity, benign tumors have a propensity for malignant change and special stains & IHC have limited role. Cases of salivary gland neoplasms, presenting in our set up, were studied to understand their distribution and spectrum. Data of salivary gland tumors presenting to the Pathology Dept., from 1stJuly 2014 – 30thJune 2015 was retrieved. Demographic distribution and pathological spectrum of the cases were studied. Wherever possible, fine needle aspiration – biopsy – specimen findings & diagnosis were corroborated. Seventy nine cases were retrieved. Nineteen percent were benign, whereas the rest (81%) were malignant. There was a male preponderance in both. Average age of presentation was higher for malignant tumors (51yrs) as compared to benign (46 yrs). The proportion of major (53%) salivary gland tumors was slightly higher than minor (47%). Parotid tumors were the most common. Adenoid cystic carcinoma was the most common tumor type. Pleomorphic adenoma was the most common benign tumor type. A varied spectrum of both benign and malignant salivary gland neoplasms, originating from both major and minor glands were seen. Few cases presented a diagnostic challenge because of the morphological diversity inherent to the tumor type.

02. Management of knee pain

Khoja Jasmin
Physiotherapy

Summary

Knee pain or knee injuries are extremely common and there are many causes. It may be acute or chronic. It is important to make an accurate diagnosis of the cause of your knee pain or injuries. So that appropriate treatment can be directed at the cause. OA is responsible for majority of knee pain. The age prevalence was similar in both sexes, but in those aged over 45 years for prevalence was three times higher in women than in men. The role of physiotherapy in knee pain is important both conservatively and post operatively. The patient can be treated with electrotherapy modalities to reduce pain and inflammation and with stretching and strengthening exercises as per the cause. Thus by physiotherapy treatment, knee pain can be relieved and patient can be pain free in performing their daily activities in its shortest period of time. Physiotherapy department offered services for different types of pain. Out of which most prevalent is knee pain. We treated 78 staff members in 2012, 65 staff members in 2013,129 staff members in 2014. The aim of physiotherapy is to reduce pain, improve physical function, prevent disability, enhance quality of life and generalized fitness.

03. Co-relation of percent reduction in CA-125 levels with extent of interval cytoreduction and survival outcome after neo-adjuvant chemotherapy in patients with advanced stage ovarian cancer

Gupta Monisha
Gynecologic Oncology

Summary

To evaluate the role of percent fall in CA-125 levels after neo-adjuvant chemotherapy (NACT) to predict the extent of cytoreduction during interval cytoreduction and survival outcomes in patients with advanced stage ovarian cancer. To corelate a single pre-operative cut off value of CA-125 with the same end points. Using the cancer registry database from our institution, a retrospective review of patients who received NACT for advanced stage epithelial ovarian cancer (EOC) and primary peritoneal cancer (PPC) from January 2012 to July 2015 was conducted. Data was collected for demographic profile, radiographic profile and CA-125 levels before and after NACT, chemotherapy details and surgico-pathological information. Percent fall in CA-125 was categorized in 2 groups: <95% R< 95%) and > 95% (R > 95%) reduction from pre-chemotherapy to pre-operative CA-125. Also, a single pre-operative cut off value of CA-125 was taken as 100 IU/ml and, accordingly, patients were divided in to two categories. A subset of patients from January 2012 till December 2013 was followed till June 2015 for evidence of any recurrence. Women with more than 95% reduction in CA-125 levels after NACT are more likely to have complete cytoreduction. Women with pre-operative CA-125 levels of less than 100U/ml are more likely to have complete cytoreduction. More than 95% reduction in CA-125 levels is associated with improved proliferation free survival (PFS), but not overall survival (OS). Pre-operative Ca-125 levels (after NACT) of less than 100 U/ml is associated with improved PFS as well as OS. Our data showed that >95% percent reduction in CA-125 and an absolute preoperative CA-125 value of less than 100U/ml can be used to predict the extent of IDS and survival

outcome in patients with advanced ovarian cancer who received NACT. These data are important in patient counseling and treatment plans.

04. A Case Report on "End of Life Care: A Beginning"

Joshi Geeta
Palliative Department

Summary

05. Association between circulatory 25(OH) D and Matrix metalloproteinases in breast cancer

Patel Shruti
Biochemistry Research Division

Summary

The aim was to study the clinical Significance of 25(OH) D levels, MMP-2 and MMP-9 expression in breast cancer. One hundred and forty breast cancer patients and 157 controls were enrolled for the study. Circulating 25(OH) D concentrations were measured by HPLC from serum samples. Expression of MMP-2 and MMP-9 were measured by Gelatin zymography from plasma samples. The results indicated that the prevalence of sever 25(OH) D deficiency and moderate 25(OH) D deficiency was 14.18% and 18.4% respectively in breast cancer patients. Thus, the prevalence of sever and moderate 25(OH) D deficiency was higher in breast cancer patients as compared to the controls. The mean levels of total 25(OH) D, mild 25(OH) D, moderate 25(OH) D, sever 25(OH) D and combined 25(OH) D were significantly lower (p=0.08, p=0.07, p=0.003, p=0.005 and p=0.001) in breast cancer patients as compared to the controls. Odds ratio was significantly higher in sever 25(OH) D deficient and combined 25(OH) D deficient patients (p=0.003 and 0.0013 respectively). All form of MMP-9 (pro, Active, total and activation ratio of MMP-9) were higher in breast cancer patients as compared to the controls. Similarly, all form of MMP-2 [Pro (p=0.04), active (p=0.001), total (p=0.002), activation ratio of MMP-2 (P=0.07)] were significantly higher in breast cancer patients as compared to the controls. There was inverse correlation between 25(OH) D was observed with proMMP-2 (r= -0.108), Pro MMP-9 (r=-0.044) and active MMP-9 (r=-0.033). ROC curve analysis revealed that, sever, moderate, combined 25(OH) D deficiency and active MMP-2 could significantly discriminate between breast cancer patients and controls (p=0.00, p=0.00, p=0.00 and p=0.003 respectively). Thus, low levels of serum 25(OH) D are associated with breast cancer risk. Hence, Vitamin D and its derivatives can evidently influence invasive processes.

Wherever the art of medicine is loved, there is also a love of humanity.
Hippocrates

Journal Club/Guest Lecture/ Review Lecture Presentations

(July 2015 to December 2015)

Sr. No.	Date	Presenter/ Department	Topic	Authors	Citation
1.	11.07.15	Rajvik Kruti Immunohisto chemistry & FlowCytometry Division	Serial enumeration of circulating tumor cells predicts treatment response and prognosis in metastatic breast cancer: a prospective study in 393 patients	Wallwiener M, Riethdorf S, Hartkopf AD, Modugno C, Nees J, Madhavan D, Sprick MR, et al	BMC Cancer. 2014 Jul 11;14(1):1.
2.	11.07.15	Gaadhe Ravindra IVTC	Management of patients with Hepatitis-B who require immunosuppressive therapy	Hwang JP, Lok AS.	Nature Reviews Gastroenterology and Hepatology. 2014 Apr 1;11(4):209-19.
3.	25.07.15	Varlekar Tapan Radiology	Bladder Malignancies on CT: The Underrated Role of CT in Diagnosis	Raman SP, Fishman EK.	American Journal of Roentgenolog. 2014 Aug;203(2):347-54.
4.	08.08.15	Patel Hiral Cell Biology Division	Diversity of breakpoints of variant Philadelphia chromosomes in chronic myeloid leukemia in Brazilian patients	Chauffaille MD, Bandeira AC, Silva AS.	Brazilian Journal of Hematology and Hemotherapy 2015 Jan-Feb; 37(1):17-20.
5.	22.08.15	Lunagaria Rahul Microbiology	Vancomycin MIC creep in methicillin-resistant Staphylococcus aureus (MRSA) isolates from 2006 to 2010 in a hospital in China	Chang W, Ma X, Gao P, Lv X, Lu H, Chen F.	Indian Journal of Medical Microbiology. 2015 Apr 1;33(2):262.
6.	12.09.15	Varshney Prateek Surgical Unit III	Prognosis of metastatic breast cancer: are there differences between patients with de novo and recurrent metastatic breast cancer?	Lobbezoo DJ, van Kampen RJ, Voogd AC, Dercksen MW, van den Berkmortel F, Smilde TJ, et al	British Journal of Cancer. 2015 Apr 28;112(9):1445-51.
7.	26.09.15	Gupta Sunnia Radiotherapy	Preoperative Intensity Modulated Radiation Therapy and Chemotherapy for Locally Advanced Vulvar Carcinoma	Beriwal S, Shukla G, Shinde A, Heron DE, Kelley JL, Edwards RP, et al	International Journal of Radiation Oncology Biology Physics. 2013 Apr1;85(5):1269-74.
8.	10.10.15	Mody Paresh Neuro Oncology	Management of low grade glioma	Pouratian N, Schiff D	Current Neurology Neuroscience Reports, 2010:10:224-231

Sr. No.	Date	Presenter/ Department	Topic	Authors	Citation
9.	12.12.15	Gupta Nayan Surgical Unit-II	Elective versus Therapeutic Neck Dissection in Node-Negative Oral Cancer	D'Cruz AK, Vaish R, Kapre N, Dandekar M, Gupta S, Hawaldar R, et al	New England Journal of Medicine. 2015 Aug 6;373(6):521-529.
10.	26.12.15	Shah Kinna Anasthesia	Difficult intubation in obese patients: incidence, risk factors and complications in the operating theatre and in intensive care units	De Jong A, Molinari N, Pouzeratte Y, Verzilli D, Chanques G, Jung B, et al	British Journal of Anaesthesia 2015; 114 (2): 297–306

Presentations at the Clinical Meetings

(July 2015 to December 2015)

Sr. No.	Date	Speaker/Department	Title
1.	25.07.2015	Bakshi Saaishta Pathology	Salivary Gland Neoplasms - An Overview of Cases at GCRI
2.	22.08.2015	Khoja Jasmin Physiotherapy	Management of knee pain
3.	26.09.2015	Gupta Monisha Gynec Oncology Unit-I	Correlation of percent reduction in CA-125 levels with extent of interval cytoreduction and survival outcome after Neo-adjuvant chemotherapy in patients with advanced stage ovarian cancer.
4.	24.10. 2015	Joshi Geeta Palliative Department	A Case Report on "End of Life Care: A Beginning"
5.	26.12.2015	Patel Shruti Biochemistry Research Division	Association between circulatory 25(OH) D and Matrix metalloproteinases in breast cancer

Case Presentations for Morbidity, Mortality at Clinical Meetings

(July 2015 to December 2015)

Sr. No.	Date	Presenter/Department	Case Discussion
1	25.07.2015	Shah Nishita Anesthesiology	Mortality and Morbidity Data presentation of Surgical and Medical Departments
2	25.07.2015	Patel Dipen Surgical Oncology	New Adjuvant Chemotherapy in Advanced Carcinoma of Gall Bladder: A Retrospective Study
3	22.08.2015	Pol Dhiraj Anesthesiology	Mortality and Morbidity Data presentation of Surgical and Medical Departments
4	22.08.2015	Tadiya Mahavir Surgical Oncology	Life Saving CPR in a case of Ca Oesophagus
5	26.09.2015	Roy Cherian Anesthesiology	Mortality and Morbidity Data presentation of Surgical and Medical Departments
6	26.09.2015	Khatwan Itesh Medical Oncology	Managing APML with Multiorgan Dysfunction: A Real Challenge
7	24.10.2015	Shaboo Surekha Anesthesiology	Mortality and Morbidity Data presentation of Surgical and Medical Departments
8	24.10.2015	Mahajan Abhinav Surgical Oncology	VAP/Septicemia/DIC in P/O Surgical Patient
9	21.11.2015	Shaboo Surekha Anesthesiology	Mortality and Morbidity Data presentation of Surgical and Medical Departments
10	21.11.2015	Galande Ashok Surgical Oncology	Wound Care and Management in case of Radical Cystectomy/ Major Surgery
11	26.12.2015	Shaboo Surekha Anesthesiology	Mortality and Morbidity Data presentation of Surgical and Medical Departments
12	26.12.2015	Tadel Avinash Medical Oncology	Morbidity and Mortality in Neutropenic Patient of Acute Myeloid Leukemia

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Milligram	mg	Hours	h
Micrometer	mm	Minutes	min
Molar	mol/L	Mililitre	ml
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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: Up To Date Cardiovascular Medicine [online] Available at: www.UpToDateInc.com/card. Accessed February 22, 2000.

In press

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Department of Orthopedic Oncology

Department of Orthopedic Oncology, a specialized branch in oncology, is the first kind in India managing and operating complex bone and soft tissue tumors. It is one of the foremost department to start modern orthopedic oncosurgery in Gujarat and also proud for performing Megaprostheisis, extracorporeal radiation therapy (ECRT) Surgery, Pelvic tumors surgery and Rotationplasty in the state. The orthopedic oncology work is backed by excellent team of surgical, medical and radiation oncology to provide patient care under one roof.

Foundation / Formation:

Advance Ortho Oncology Department was established since 1981 with tremendous efforts by senior orthopedic surgeon Dr. M T Mehta; he was the pioneer in bone tumor registry. The legacy was continued by senior orthopedic surgeon Dr. Jyotindra Pandit and Dr. Dilip Patel and the department started mega prosthesis surgery and limb salvage treatment and today it has reached new heights. Initially, supported by Dr. Dimple Parikh and Dr. Deepak Rathod, thereafter from 2008 to 2014, Dr. Mandip Shah, contribution enabled the department to start with rotationplasty and pelvic tumor surgery. Currently the department is functioning under the umbrella of Dr. Jyotindra Pandit with Dr. Jaymin Shah and Dr. Abhijeet Ashok Salunke. At present, they have started ECRT surgery for limb salvage. New research work and projects are under consideration for the improvement of bone cancer management. It is a separate department at room number 13 OPD building at first floor. At 2nd and 3rd floor, are orthopedic oncology wards comprising of male ward, female ward, pediatric ward, isolation ward, special rooms and nursing station. On 2nd floor, is the ICU and post-operative care unit with two Isolation beds. ICU with 4 dragger ventilators, multipara monitoring system. Exclusive Orthopedic Oncosurgery operation theatre no.6 with stann OT tables, laminar air flow system, synthes high speed drill, C-Arm.

Services:

The department runs OPD on Monday and Thursday every week where new and old cases are examined, and follow-up patients are regularly attended in the OPD. Furthermore, we attend and encourage patients any time of the day and also admit patients in emergency on Sundays and holidays. In each OPD they have average 50-60 patients (average 450-500 patients/month).The indoor references are regularly attended. Besides, services are offered to all the poor and needy patients for bone and soft tissue tumors.

Surgeries:

The department is performing average 2 to 3 Supra major (Joint replacement Mega prosthesis), 2 to 3 major surgeries (wide excision and reconstruction) every week (average 25-30 per month).Majority are wide excision and joint replacement (Mega prosthesis) for malignant and benign bone tumors. They are performing Complex pelvic tumor excision surgery with image intensifier guidance. Extra corporeal radiotherapy (ECRT) is performed in which tumor is excised, irradiated with 60 Gy radiation and re-implanted and fixed with native bone. Curettage for benign bone tumors. Fracture fixation for metastatic bone tumors with pathologic fractures of extremity. Wide excision of soft tissue tumors is performed. Last year we performed around 300 bone and soft tissue tumor surgeries.

Our Team:

There are 01 visiting orthopedic oncosurgeon: Dr. Jyotindra Pandit, 02 fulltime orthopedic oncosurgeon: Dr. Jaymin Shah and Dr. Abhijeet Ashok Salunke in the department. Backup by Ortho OT staffs, ICU staffs and ward staffs.

Training Education and Academic Activities:

1) All orthopedic surgeons are regularly attending and participating in conferences and workshops to remain updated in orthopedic oncology. They have presented their work which has been recognised.

2) Publications: The faculties have published the research work at esteemed Pub med indexed journals

Future Plan and Scope:

1) Proposal for purchase of computer navigation system. This armaments will help as in precise removal of tumors in pelvis and joint preservation surgery with decreased morbidity and mortality and ultimately benefit patients quality of life.

2) Plan to start NB (National board of Examinations) Fellowship.

3) Good scope for orthopedic surgeons interested in Ortho oncology with clinical and research fellowship.

4) To arrange a national conference on orthopedic oncosurgery

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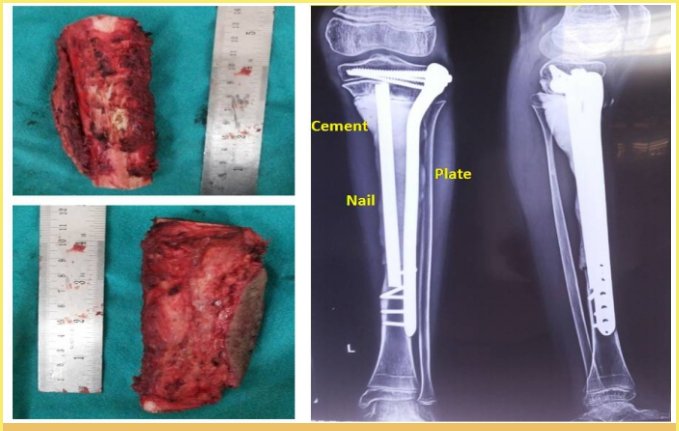
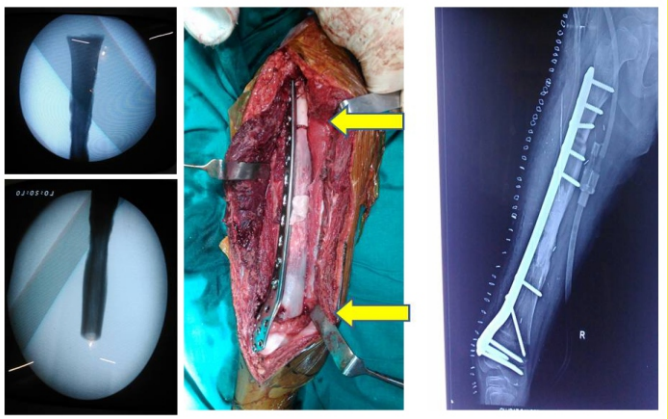
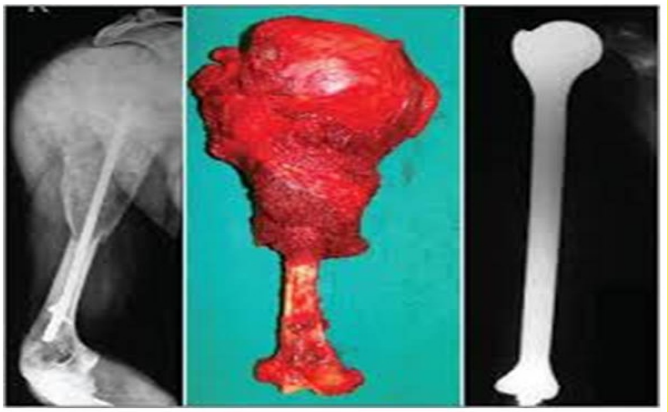


Wide Resection of Tumour and
Custom Made Plate Cement Spacer



Extra Corporiate Radiation Therapy (ECRT)
Surgery for Limb Salvage

Rotationplasty
Converts Above Knee to Below Knee Amputation



Total Humerus Replacement and Megaprosthesis