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Address for correspondence:

The Editors,
Gujarat Cancer Society Research Journal
GCS Journal Office, Research Wing,
The Gujarat Cancer and Research Institute
Asarwa, Ahmedabad 380016
Gujarat, India
gcsjournal2012@gmail.com
gcsjournal2012@gcriindia.org

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The Role of Pathology in the Era of Personalized (Precision) Medicine: Shifting Sands of Time

Trivedi Priti[1], Paul Thayakaran Immanuel[2]
Practicing Professor & Head of Department, Resident[2]
Department of Oncopathology,
The Gujarat Cancer & Research Institute, Asarwa, Ahmedabad, Gujarat
Corresponding author: priti.trivedi@gcriindia.org
https://orcid.org/0000-0003-1895-389X

Introduction

Diagnostic pathology in the early 19th century was restricted to postmortem assessment wherein the effects of disease and its sequelae were looked out for, described, and documented and thereby helping the medical personnel in identifying the disease in the clinic. However with the advent of light microscopy in the latter half of the 19th century, thanks to Rudolf Virchow (1821-1902) who was aptly named as "Father of modern pathology" there was a paradigm shift in the field of pathology where the pathologic diagnosis became an intrinsic component in patient management dictating what intervention would the patient need.

Detailed morphologic assessment and evaluation of a tumor under a light microscope led to the characterization of diverse types and morphology of a tumor setting in motion for the microscopic classification systems for several diseases. The classification especially of neoplastic tumors not only helped the pathologists to have a unified nomenclature but also created a better understanding of the diagnosis amongst the treating clinicians.

Just when the widespread knowledge of neoplastic pathology with well-defined classifications were doing round there was a major transpose in the field of pathology in the latter half of 20th century with the advent of immunohistochemistry which was of immense help especially in diagnosing the poorly differentiated neoplasms and more importantly immunohistochemistry served as a cornerstone in the sub classification of lymphoma which previously was solely dependent on morphology alone.

Twentieth century witnessed a major medical field awakening with many dramatic discoveries in cellular and molecular pathways. The knowledge accrued was extrapolated to improve disease diagnostics and prognostics. Many immunomarkers came into the fore which helped both in diagnosis and therapeutics. New genetic and molecular alterations were discovered which conferred differential prognosis for a single morphological disease entity highlighting the need and paving the way for the dawn of molecular classification of tumors.

The shifting sands of time in the field of pathology has propelled the pathologist out of a laboratory and commissioned the pathologist to the patient's bedside making pathology an integral part in the multidisciplinary/ tumor board meetings providing pertinent diagnostic, therapeutic and prognostic information where decisions are made for optimal management on a case-to-case basis paving the way for personalized (precision) medicine. (Figure 1)

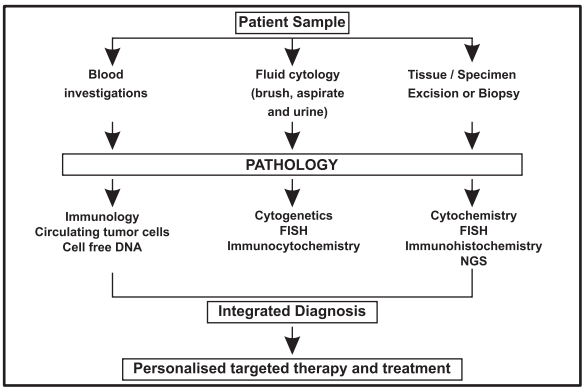

Figure 1: A proposed algorithm for the pathology role in personalized (precision) medicine.

Precision Medicine and Pathology

Gone is the idea of one-size –fits-all approach because history and studies have proven that there are innumerable variables predicting the patient's response to therapy and it markedly differs from one person to person. Personalized (precision) medicine is currently the standard of care in all cancers. Precision medicine is an innovative approach of tailoring disease treatment considering an individual's genetic make-up, environment and lifestyle. Precision medicine takes help of massive parallel sequencing, high throughput technologies to enable detection of minute changes at different molecular levels (DNA, RNA, protein). DNA/RNA sequencing, tissue

microarray technology, mass spectrophotometry, comparative genomic hybridization and digital polymerase chain reaction are the platforms used in arriving at the best plan of treatment.

When a tissue or specimen arrives to pathology lab for tissue diagnosis it is triaged based on the preliminary diagnosis and is segregated into different forms of preservation for appropriate downstream applications. The pathologist examines the tissue and a histologic diagnosis made keeping in mind at the same to assess the tissue for tumor quantity and tumor adequacy for further molecular tests. The pathologist interprets the findings in concert with molecular biologist and reports the relevant details.

The clinician accordingly plans the management of the patient based on the integrated pathology report which now includes morphological, immunohistochemical and molecular report. Integrated pathology report is now routinely practiced in many subspecialties in pathology including neuropathology, thoracic pathology and soft tissue pathology to name a few.

Role of Pathology in Patient Clinic

Tumor board meets or multidisciplinary meeting is an integral component of oncologic patient management where the pathologist, radiologist, medical and surgical oncologist come in concert and discuss the diagnosis and plan the management of the patient which aids in optimal treatment decisions.

From an oncologic perspective, preliminary patient management is based on the small tissue biopsy. The surgical management and the neoadjuvant chemotherapy are based on the type and the grade of tumor coupled with informative immunohistochemical markers and molecular tests wherever pertinent. Hormonal receptor status and HER2 amplification status in breast cancer remains a major cornerstone of treatment decision and selection of therapy. Identification of alterations in EGFR, ALK, ROS gene mutations in lung cancer aids the clinician in selecting the targeted drugs for initial management. Few patients have progressive disease which might indicate underlying resistance to the targeted drugs where a repeat biopsy from the involved site can identify concomitantly the tumor and the resistant mutation it has accrued, for example identification of T790M mutation in patients with EGFR mutated lung cancer helps the clinician to escalate the therapy to Osimertinib which is effective in these patients.

Recently predictive biomarkers which identify whether a patient will respond to a particular therapy have become a norm for certain tumors like HER2 receptor status in breast cancer which is a prototype. Some aggressive or poorly differentiated cancers where the patient is not responding to conventional treatment modalities, additional molecular markers or mutations are actively hunted for in a tumor sample which can aid in the addition of drugs which can prolong patient survival. Immune checkpoint inhibitors can be utilized in the therapy by performing immunohistochemistry and looking at the PD1 receptor status in the tumor infiltrating lymphocytes and the PDL1 receptor status in the tumor cells.

The time has come for most of the tumors which were previously classified based solely on morphology to transit into the era of molecular medicine where most of the tumor classification systems currently are on the road to adapting molecular classifications. A classic example would be the lymphoma and leukemia classification which initially was based on morphology alone (Rappaport classification, 1966) followed by addition of immunohistochemistry (Kiel classification, 1975), addition of molecular and clinical profile (Revised European America Lymphoma – REAL classification, 1994) to the current WHO classification which has undergone subsequent editions.

Molecular classification of breast cancer has been well established in the past decade with recent consolidation of molecular classification of endometrial cancer and urothelial cancer. Molecular classification of sinonasal cancers are still in the pipeline. It is now well known that the molecular subgroups have divergent disease biology which might dictate diverse treatment algorithms. The pathologist in the clinic is expected to give not only an integrated report but also provide a holistic report based on the current advances in oncological practice.

Role of Pathology in Research

The field of oncopathology witnesses new tumor entities by the day, thanks to the advent of molecular diagnostics. A new tumor/entity is birthed when a pathologist comes across a tumor which does not follow the book. When a cluster of similar cases are identified in the archives or subsequently, the tissue is subjected to molecular studies whichever platform is feasible. When those cases cluster in commonality with respect to genetic rearrangements which translates to clinically divergent prognosis, justifies the cause for those subsets to morph into a new entity. The trigger for identification of new entities is both from the pathologist and the treating physician. When a treating physician perceives the patient is not responding to the time-tested classic therapy of particular tumor or when a pathologist is not able to categorize a tumor into one basket, the communication of information and the transference of perspective amongst each other goes a long way in tailoring the therapy for the particular patient. This asynchrony of the morphology and the patient's

response to therapy gives an essential thrust for research.

An interesting and well-known example is CIC-DUX4 rearranged sarcoma which was previously clumped under Ewing sarcoma because they resembled in morphology and immunophenotype to an extent. Now CIC-DUX4 rearranged sarcoma is pathologically and clinically a distinct entity with divergent treatment and prognosis.

The ever-expanding study of molecular aberrations in different tumor subtypes have led to the discovery of many drugs. The so called 'druggable tumor specific molecular aberrations' are validated in clinical trial and then approved by FDA. These druggable molecular aberrations are initially validated across several available testing platforms and the most appropriate type is chosen as a routine diagnostic/prognostic test.

A classic example would be the discovery of NTRK (Neurotropic tyrosine receptor kinase) rearrangements in many tumors. Other than the classical infantile fibrosarcoma, NTRK rearrangements can be seen in a variety of tumors including secretory carcinoma, subset of pediatric gliomas, colorectal carcinoma, melanoma, and cholangiocarcinoma with NTRK rearranged sarcoma joining the list recently. US FDA approved Entrectinib and Larotrectinib, NTRK inhibitors got accelerated drug approval in 2019. Larotrectinib showed age agnostic and histology agnostic responses making it a breakthrough drug.

The Next Generation Pathologist

Pathology is not the same anymore limited to a histologic diagnosis. It is the integration of histologic, molecular, cytogenetic, genomic and epigenetic information into clinically relevant document which conveys the diagnostic, predictive and prognostic information. It is easier said than done. The pathologist must judiciously triage the tissue or specimen which comes to the laboratory for diagnosis anticipating the imminent tests which will be required across different platforms.

Many of the predictive markers can be assessed by immunohistochemistry whereas certain molecular classifications may require the use of cytogenetic and molecular tests ranging from regular PCR (Polymerase Chain Reaction) based assays to next generation sequencing. Appropriate tissue handling, preservation and storage is a critical part of this complex process because all downstream results are dependent on the tissue fidelity.

The future pathologist should be well versed not only with morphology but also molecular pathology which is a subspecialty in itself. A sound knowledge of morphology with an adequate connaissance of molecular pathology sets the apt platform for the genesis of a next generation pathologist which is the need of the hour.

There is a global trend towards sub specializing in pathology akin to surgical oncology where subspecializing is becoming the norm. This molecular era beckons for the realignment of pathology as a specialty where both the educational and the practical aspects of molecular pathology "has" to be intricately woven into the training residency programs with further organ or system based subspecialties. Because gone are the shackles that chained the pathologist to a laboratory, now the role of the pathologist has transcended beyond diagnostics into therapeutics and prognostication aiding the clinician in optimal patient management.

Conclusion

The so-called molecular revolution has ushered in a new era catapulting the pathologist to a different dimension where a banal morphologic diagnosis is not the norm. It calls for the judicious use and application of predictive biomarkers coupled with assessment of tumor mutations using next generation sequencing or other platforms with a tiny piece of tumor tissue at hand. It might not suffice to say that the pathologist transforms this tiny tissue which enters the laboratory into a giant leap of information aiding in optimal patient management and continuous medical knowledge.

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Shri Madanmohan Ramanlal GCRI Luminary Oration Award - 2022

Dr. Shakuntala V. Shah
MBBS, MS

Former Professor & Chief,
Department of Surgical Oncology,
The Gujarat Cancer & Research Institute, Ahmedabad

My Journey through Onco Domains and Journey of Breast Cancer - Paths Well Tread

When as 1st year resident in general surgery, dealing with lumps and bumps in abdomen, fantabulous appendix, hernia, trauma care, ear repairs, impossible passage of bladder necks at mid nights and early dawns, dressing of burns for hours at length----------and then 2nd year residency in GCRI, and hell let loose. Had to face dismal depressive atmosphere and had to work tireless. Oncosurgery was not my choice in male dominated field- but carried on and it became passion.

Those were late 70s where oncology did not see changes in treatment that frequently as today and now there is tremendous progress with newer treatment modalities. Those were the days in oncology which was same world over and now these are the days we have metamorphosed to passionate surgical oncologists, whatever were the challenges always feeling proud of GCRI to have groomed us. That is my journey.

I have witnessed
- most radical ablations to organ preservation
- cobalt, caesium, thorastrone radiotherapy sources to proton beam units
- preventive oncology
- personalised medicines

But as a surgeon, the most captivating changes is in breast oncology.

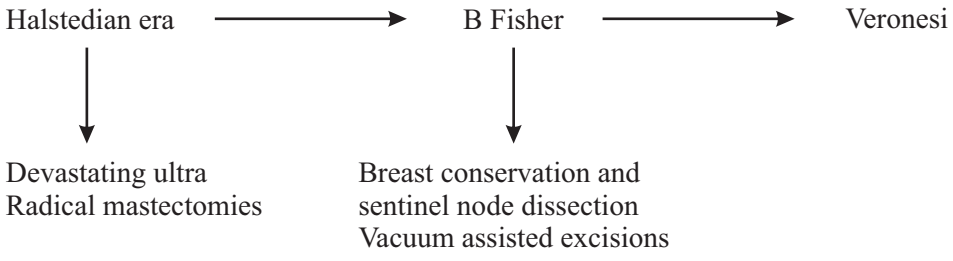
Breast screening has given mortality benefits as shown by Swedish 2 country trial in 1980 where reduction in mortality is by 25-40%.

The salient features of breast screening are:
1. Optimising organisation of screening which has to be quality oriented and cost effective
2. Setting targets for quality management
3. Optimising interpretation of mammography
4. Setting optimal screening intervals to pick up early interval cases

The advancement in mammography has come up from digital mammography to **D**igital **B**reast **T**omography (DBT), **C**ontrast **E**nhanced **S**pectral **M**ammography (CESM) and breast MRI. Recommendations come through need for individual patient.

Hence breast cancer detection and treatment has seen vast rapid changes from 1980 onwards.

My journey continues.



Dr. Shilin N. Shukla Medical Oncology Oration Award - 2022

Dr Sandip A Shah
MBBS, MD

Part time Associate Professor and Incharge BMT unit,
The Gujarat Cancer & Research Institute, Asarwa, Ahmedabad
Email : sandip60@yahoo.com

Evolution of Haematopoetic Stem Cell Transplantation in Gujarat - A Personal Journey through Three Decades

Haematopoetic Stem Cell Transplantation (HSCT) involves the intravenous infusion of hematopoietic stem cells in order to re-establish blood cell production in patients whose bone marrow or immune system is damaged or defective. This helps to augment bone marrow function and depending on the disease being treated, leads to either destruction of malignant tumor cells or to generation of functional cells that can replace the dysfunctional ones, as is the case of immune-deficiency syndromes, hemoglobinopathies, and other diseases. Since it was first used successfully in 1986, HSCT has become one of the most promising treatments for a number of serious illnesses. Over the past half century, this technique has been increasingly used to treat numerous malignant and nonmalignant diseases. The success of HSCT is influenced by a number of factors, including age of patient, general physical conditions, primary diagnosis, status of disease at the time of HSCT and type of donor, etc.

Stem cells

Cells for HSCT may be obtained from the patient himself or herself (autologous transplant) or from another person, such as a sibling or unrelated donor (allogeneic transplant) or an identical twin (syngeneic transplant). Cell sources include bone marrow; peripheral blood; umbilical cord blood; or, rarely, fetal liver.

Conditioning regimen

During the "count down" period, usually five to 10 days before the stem cell infusion, conditioning regimen is administered. The chemotherapeutic agents and/or radiotherapy that are used vary with the underlying disease. The overall goals of the conditioning regimen are to destroy any residual cancer cells in case of autologous transplant. In allogenic transplant it additionally suppress the immune system so that the patient do not reject the new stem cells and make room in the bone marrow for the donor stem cells to grow.

Autologous bone marrow transplantation

The bone marrow products are collected from the patient and are reinfused after giving high dose chemotherapy to the patient. The advantages include no graft versus host disease (GVHD). The disadvantage is that the bone marrow products may contain abnormal cells that can cause relapse in the case of malignancy. Hence theoretically, this method cannot be used in all cases of abnormal bone marrow diseases. It is performed for stem cell rescue after high-dose chemotherapy in patients of multiple myeloma, Hodgkin disease, neuroblastoma, plasma cell disorders, etc.

Syngeneic bone marrow transplantation

The donor and the recipient are identical twins. The advantages include no GVHD and no graft failure. However, only a tiny number of transplant patients will have the ability to have an identical twin for transplantation.

Allogenic transplantation

The donor is an HLA matched family member, unrelated matched donor or mismatched family donors (haploidentical). It is performed in conditions where replenishment of deficient or dysfunctional cells is required as in Thalassemia, Mucopolysaccharidosis, Aplastic anemia, Gauchers disease or to treat malignant conditions like acute leukemia, non-Hodgkin lymphoma.

Cord blood transplantation

The source of stem cells is umbilical cord blood. This procedure has not been in much use in India as its storage requirement are not cost effective for developing countries. Moreover, the present storage conditions and availability in India do not provide adequate yield of stem cells for successful transplant. Also improved outcome of haploidentical transplant has outweighed the requirement of cord blood transplantation.

HSCT at GCRI

GCRI began its glorious journey of HSCT under the guidance of Dr Sandeep Shah by performing first autologous transplant in the year 1999 in a patient of multiple myeloma.

The bone marrow transplant centre is a five bedded transplant centre. The institute takes pride in having performed more than 530 transplants over its journey of 23 years in transplant, of which 228 are autologous , 230 allogenic (including 48 haploidentical, and 7 matched unrelated donor transplant), and 17 cord blood transplant uptil now.

GCRI holds to its credit, performing nations first umblical stem cell transplantation in a child with thalassemia. Presently umblical cord blood cell transplantation has fallen out of favour as it exhibits poor outcome in developing countries like India due to poor storage conditions and infrastructure. Additionally, the improving survival outcome of haploidentical autologous HSCT makes it more feasible and cost effective.

Strength / workload

Approximately 50 HSCT transplants a year and hematology OPD twice weekly for complex haematological disorders.

Area of Activity

GCRI excells in conducting HSCT. The centre gets patients from various states of India for autologous and allogeneic transplant for various benign and malignant conditions. Number of haploidentical transplants have increased over recent years for patients who don't have matched sibling donor and are not able to undergo matched unrelated donor transplant.

Bone marrow transplant unit at GCRI has a very high success rate and transplant related mortality (TRM) is comparable to any other institute in the world.

Diagnostic Value of Neutrophil Leukocyte Ratio and Platelet Lymphocyte Ratio to Differentiate Adnexal Masses as Benign or Malignant in the Preoperative Period

Hantodkar Rujuta[1], Patel Bijal[2], Dave Pariseema[3], Parekh Chetana[4], Kar Bijoy[5]
Resident[1], Professor[2], Professor & Chief of Unit-II[3], Associate professor[4], Lecturer[5]
Department of Gynaecological Oncology
The Gujarat Cancer & Research Institute, Asarwa, Ahmedabad, Gujarat.
Corresponding Author: pariseema.dave@gcriindia.org
[2]https://orcid.org/0000-0002-5446-1959
[3]https://orcid.org/0000-0003-3300-4414
[4]https://orcid.org/0000-0003-4811-5889
[5]https://orcid.org/0000-0001-6176-8687

Summary
Aims and Objectives: To assess the diagnostic accuracy of neutrophil leukocyte ratio (NLR), platelet lymphocyte ratio (PLR) and CA125 individually and in combination with each other to help differentiate between malignant and benign adnexal masses preoperatively.
Material and Methods: This is a retrospective analytical study with a sample size of 166 conducted from January 2018 to February 2021 at the Regional Cancer Centre. The records of all women presenting to our institute were screened based on the inclusion criteria and consecutive cases of 166 women with adnexal masses with a complete blood count (CBC) and CA125 done preoperatively were included. NLR and PLR were calculated and their cut-offs were measured using the receiver operating characteristic (ROC) curve. The diagnostic efficacy of these markers was measured by using the statistical results of specificity, sensitivity, negative predictive value and positive predictive value.
Results: As per our study, CA125 was the most sensitive (67.57%) in distinguishing malignant from benign adnexal masses. The best positive predictive value is indicated by PLR and CA125≥35 together (62.75%) whereas the best negative predictive value is seen with NLR and CA125<35 (78.95). As per the statistics, the diagnostic accuracy of NLR and CA125<35 is better (63.01%) than the other parameters.
Conclusion: Although in our study NLR and CA125<35 had the best negative predictive value, specificity and diagnostic accuracy out of all the parameters considered, these values are only fairly significant and their clinical significance needs to be studied further.

Introduction

Adnexal masses can be functional or neoplastic. Neoplastic tumors can be benign or malignant. During the reproductive years, the ovarian masses are most commonly benign but the possibility of malignancy must be considered.[1]

Out of all the gynaecologic malignancies, ovarian cancer has the highest mortality rate because more than two-thirds of patients have advanced disease at presentation.[2]

Adnexal masses are frequently detected on imaging exams such as transvaginal ultrasonography. The nature of these masses is diagnostically challenging. The diagnostic accuracy of serum biomarkers like cancer antigen 125 (CA125) alone has been evaluated and established. Different approaches incorporating other factors like imaging, menopausal status and other biomarkers are available, such as the risk of malignancy index (RMI), the risk of ovarian malignancy algorithm (ROMA), and OVA1. In spite of these, there is a dearth of simpler and more accessible tools which can be widely used in a population with adnexal masses.[3]

Infiltrating cancers can provoke an extensive chronic inflammatory reaction. Inflammatory cells also modify the tumor cells and the local microenvironment. This enables many of the hallmarks of cancer either by direct interactions between inflammatory and tumor cells or through indirect effects on other stromal cells, particularly cancer-associated fibroblasts and endothelial cells.[4]

Systemic inflammatory response (SIR) mediators compromise immune function, which increases the concentrations of the white blood cells, polymorphonuclear leucocytes, and thrombocytes. As a result, preoperative inflammatory markers, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been suggested to be useful for distinguishing benign from malignant ovarian tumors. NLR and PLR are non-invasive and can be measured by a simple CBC which is an easily available and cost-effective investigation.[5]

This study was performed to establish NLR and PLR with CA125 as a diagnostic marker to preoperatively distinguish adnexal masses as benign or malignant.

Materials and Method

The present retrospective study was conducted at the Gynaecological Oncology Department of the Gujarat Cancer and Research Institute, Ahmedabad. The sample size was 166 cases evaluated from January 2018 to February 2021.

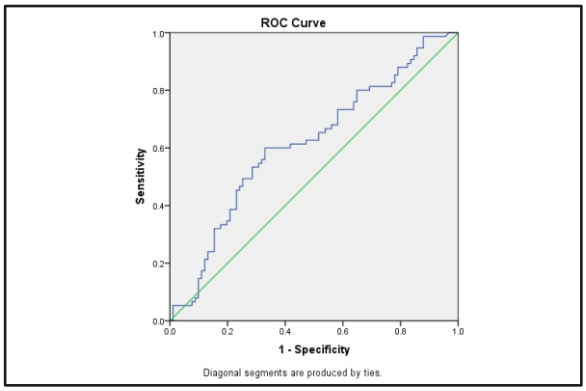


Figure1: ROC curve for NLR [For NLR, the best cut off based on the receiver operating characteristic (ROC) analysis was 3.09 [Area under curve=0.615 (0.529 to 0.702), p value=0.012]

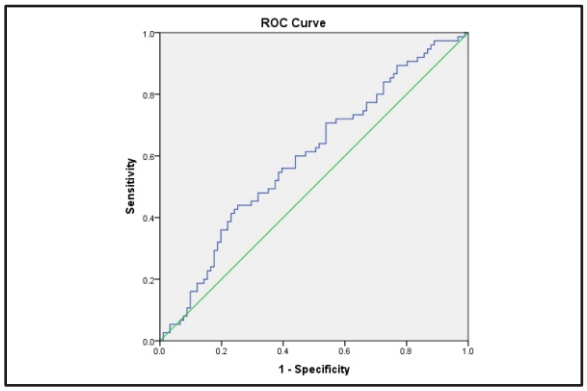


Figure 2: ROC curve for PLR [For PLR, the best cut off based on the above receiver operating characteristic (ROC) analysis was 203.68 [Area under curve=0.595 (0.509 to 0.682), p value=0.044].

Table 1: Sensitivity, specificity, negative predictive value, positive predictive value and diagnostic accuracy measured of NLR, PLR, CA125 and combination of these parameters

Parameter	Sensitivity (lower and upper 95% confidence interval)	Specificity (lower and upper 95% confidence interval)	Positive predictive value (lower and upper 95% confidence interval)	Negative predictive value (lower and upper 95% confidence interval)	Diagnostic accuracy
NLR≥3.09	61.33 (50.02 - 71.54)	58.24 (47.98 - 67.84)	54.76 (44.14– 64.96)	64.63 (53.84– 74.11)	59.64 (52.04 – 66.8)
PLR≥203.68	60.00 (48.69 - 70.34)	53.85 (43.66 - 63.72)	51.72 (41.37– 61.93)	62.03 (51 – 71.93)	56.63 (49.02 – 63.93)
CA125 (cut-off 35 U/mL)	67.57 (56.27 - 77.14)	53.85 (43.66 - 63.72)	54.35 (44.2 – 64.15)	67.12 (55.73 – 76.81)	60 (52.38 – 67.17)
NLR and CA125<35	66.67 (46.71 - 82.03)	61.22 (47.25 - 73.57)	45.71 (30.47– 61.81)	78.95 (63.65 – 88.93)	63.01 (51.55 – 73.18)
NLR and CA125≥35	58 (44.23 - 70.63)	54.76 (39.95 - 68.78)	60.42 (46.31– 72.98)	52.27 (37.94 – 66.25)	56.22 (46.33 – 66.19)
PLR and CA125<35	50 (31.43 - 68.57)	53.06 (39.38 - 66.30)	34.29 (20.83– 50.85)	68.42 (52.54 – 80.92)	52.05 (40.78 – 63.12)
PLR and CA125≥35	66.30 (50.14 - 75.86)	54.76 (39.95 - 68.78)	62.75 (49.02– 74.68)	56.10 (41.04 – 70.11)	59.78 (49.57 – 69.22)

All the women who had preoperative ultrasonography showing adnexal masses, CA125 and a CBC within one month of surgery and whose final histopathology showed ovarian pathology were included in the study. Those cases who were already operated outside or had received preoperative chemotherapy were excluded from the study. Fungal and tubercular infections causing adnexal masses were also excluded to remove bias as they also cause an increase in leucocytes and would distort the outcome of the study. On retrospective examination of the histopathological results, out of 166 cases studied, 91 were benign and 75 were either borderline or malignant. All borderline and malignant cases were considered together as a single category.

The CBC, CA125 reports and the final histopathological reports were reviewed retrospectively. The data of neutrophils, lymphocytes, absolute neutrophil count, absolute lymphocyte count and thrombocyte count were collected from CBC reports. NLR and PLR were calculated from these values.

Data collection, compilation and analysis was done by EPI info (version 7.2). The qualitative variables were expressed as percentages. The quantitative variables were categorized and expressed as percentages or terms of mean and standard deviations. The chi-square test was used to interpret the difference between the two proportions. The student t-test was used to evaluate the difference between the two means. The diagnostic performance of the data was measured in terms of sensitivity, specificity, positive predictive value, negative value and diagnostic accuracy. We used receiver operating characteristic (ROC) curves to determine the best cut-off. The analysis was 2-tailed. The significance level was set at 0.05. Based on Youden's index the best cut-off for NLR was 3.09 [Area under curve=0.615 (0.529 to 0.702), p value=0.012] and for PLR was 203.68 [Area under curve=0.595 (0.509 to 0.682), p value=0.044](Figure 1 and Figure 2). The cut-off for CA125 is 35 U/mL.

Result

A total of 166 women with ultrasound showing adnexal masses were enrolled. The patient distribution as per their final histopathological reports showed that 91 cases (54.82%) were benign whereas 75 cases (45.18%) were either borderline or malignant. All borderline and malignant cases were considered together as a single category.

The sensitivity of CA125 (67.57%) is better than NLR (61.33%) or PLR (60%) whereas the specificity was better when NLR was considered with CA125<35 (61.22%). This indicates that CA125 is a better marker than NLR or PLR alone or even if considered together with CA125, to distinguish malignant from benign ovarian masses preoperatively. But if CA125 is less than 35 IU/ml and NLR < 3.09, then the chances of the ovarian mass being benign are more. The best positive predictive value is indicated by PLR and CA125≥35 together (62.75%) whereas the best negative predictive value is seen with NLR and CA125<35 (78.95%). Therefore, if CA125 is more than 35 and PLR ≥ 203.68, the ovarian mass is likely to be malignant. If NLR<3.09 and CA125<35, the ovarian mass is more likely to be benign. As per the statistics, the diagnostic accuracy of NLR and CA125<35 is better (63.01%) than the other parameters (Table-1).

Discussion

The carcinogenesis of different types of tumors, including ovarian cancer (OC), has been associated with chronic inflammation. There are multiple mechanisms involving inhibition of apoptosis, angiogenesis, non-repair or deliberate DNA damage, and overexpression of cytokines and inflammatory mediators which advance this process. In addition, SIR mediators weaken the immune system. This causes an increase in the concentrations of leukocytes, neutrophils, platelets, C-reactive protein (CRP) and fibrinogen, and decreased levels of albumin and lymphocytes.[3] The majority of adnexal masses are benign and only ~20% are malignant. Hence the identification of novel markers in the preoperative period to determine the nature of the suspected adnexal masses has become essential.[7]

In the present study, we evaluated and compared CBC parameters alone and in combination with the CA125 levels and their diagnostic accuracy in 166 women with various types of ovarian tumors. We showed that the NLR, the PLR or their association with CA125 could not present a superior performance in the prediction of malignancy in the preoperative setting which was also proved by Yoshida et al,[3] but opposed to Khatib et al and Cramer et al, whose studies prove the contrary to be true.[5,6] Although in our study NLR and CA125<35 had the best negative predictive value, specificity and diagnostic accuracy out of all the parameters considered, these values are only fairly significant. This parameter may be useful to distinguish benign from malignant ovarian masses, but its clinical significance needs to be studied further.

NLR and PLR in our study show better sensitivity than specificity as compared to the study by Yoshida et al whose results had better specificity than sensitivity.[3] According to present study, NLR and PLR alone are only fairly significant to indicate preoperatively whether the adnexal mass is malignant.

Conclusion

Given the discrepancies in the results of various studies and the non-uniformity in the cut-off values for NLR and PLR, more studies need to be conducted to determine the cut-offs and also their clinical significance. Our study showed better statistical significance of NLR in combination with CA125 rather than with NLR alone. Hence, the significance of NLR and PLR with other sociodemographic factors as well as other biomarkers needs to be studied to further evaluate their significance to distinguish adnexal masses preoperatively to help make suitable therapeutic decisions.

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It's Better to Be Alive While Dying than Dead While Living

Trivedi Maharshi
Assistant Professor
Department of Medical and Pediatric Oncology,
The Gujarat Cancer & Research Institute, Asarwa, Ahmedabad, Gujarat
Corresponding Author: dr.maharshi@yahoo.com
https://orcid.org/0000-0002-4872-7159

Human beings these days are more engrossed in negativity and hopelessness. The spirit of liveliness for life has become a rare quality. As a consequence, we often encounter depressed souls lamenting over life and its hustles, rather than lively people who celebrate and enjoy every moment of life.

I fondly remember one of my young patient who made me think of being courageous in life and continue working without worrying about results. A three-year-old boy was diagnosed to have neuroblastoma, a life threatening cancer. On investigations he was found to have very aggressive tumour and required to undergo intensive treatment with chemotherapy and bone marrow transplant. He received intensive chemotherapy without any tantrums and was admitted for the bone marrow transplant. He was aware that during the course of transplant he will be confined to a room for almost two weeks and will not be allowed to go out till he recovers completely. The little champ entered the room without any fuss and we did not encounter any resistance while preparing him for the daily treatment doses. As a habit while getting ready for my daily morning rounds, I used to watch him from outside the room through a glass window. He would deligently blow a balloon given to him for lung exercises. While on rounds, he engaged us all in energetic chit-chats about his friends, family, favourite chores and would give me an energetic hi- five to bid bye. To our plight during the course of BMT, he developed severe oral ulcers, causing him throat pain along with fever. It became difficult for him to swallow meals or water without severe pain. While prepping up for my morning rounds, I assumed he must be sleeping or crying because of pain and must be asking to go home. But to my surprise when I looked at him from the glass window, he was blowing the balloon as usual. Although he couldn't speak because of throat pain, he happily allowed me to examine him completely and gave me the usual warm hi-five. He did not ask about his discharge even once in his fifteen days stay inside the room. This incident surprised me as I often encounter adult patients becoming cranky when they develop similar complications, they stop doing their daily activities and start whining often asking to go out to meet people.

In this fast paced world seeking instant gratification most of us have forgotten the art of living. People find it difficult to live in the present moment, while they keep contemplating for the future. In this conundrum they miss out living life for what it offers and taking up challenges as part of life. Most of us are busy finding faults in the system, blaming fate, cursing others for incompetency, and become unhappy seeing other people happy. We try to find excuses to run away from the daily discipline and would find reasons to not work hard and fret about not getting the desired results. This child did not refuse or find excuses to run away from treatment. He was doing his daily routine happily and did not bother about what was going to happen next. We adults forget to adopt the basic life tools of discipline, patience and perseverance, which makes us anxious and sad.

I remember another young soul, a 15 years old girl, who was diagnosed with a bone tumor called Ewing's sarcoma. She underwent surgery to remove the tumor and received chemotherapy for almost a year. Unfortunately, her tumor progressed at the end of treatment and spread to lungs and other bones. Her condition worsened rapidly and she developed breathlessness requiring oxygen support, and was not able to speak or eat because of the distress. Her worsening health condition saddened her parents. They started avoiding conversation about the disease condition with their daughter and pretended to be happy when with her, as they felt this would further demotivate her from receiving the palliative care. The girl however had understood that the tumor has spread everywhere and she was not going to make it. What caught my attention was her understanding for her parents' mental state and agony. I was surprised to see her acceptance for her unfortunate fate. On my visit to her, she would request me to comfort her parents to not worry and give them hope by telling them that she will be fine after one dose of medication. She would often request me to give her some medications which could

reduce her breathing difficulty so that she can talk with her parents and eat well and not make them anxious. While doing so she did not become depressed thinking that she is not going get cured. She understood the limitations of treatment strategies and never demanded that she should be cured by any means. Never did she expressed the desire to run away from the hospital where so far she received only pricks and pain without any benefit. She did not exhibit any tantrums, which we expect from older children or adolescents.

This girl was brave and happy even at the end of her life. She lived the time that she had in hand with her. We many times burden ourselves with lot of expectations from life. In the run of life, we forget to live and keep chasing the unending trail of targets set by us. We ascribe life with terms and conditions while missing out on cherishing that it has to offer. People undermine the importance of spending quality time with family and people around us, and seldom connect with nature. While coping with the self-created overwhelming stress for life, we often start acting on spinal level and operating like robots. These are the root reasons that make people unhappy, predisposing them to anxiety and depression. There is a need to slow our pace while running from posts to pillar chasing happiness and targets which are actually pseudo destinations set by us. We should remember to savor small moments in this journey of life while cherishing the present.

We need to learn to be alive even at our deathbed like this girl instead of living life like a lifeless person.

Living one day at a time,
Enjoying one moment at a time,
Accepting hardship as a pathway to peace,
Taking, as He did,
This sinful world as it is,
Not as I would have it,
Trusting that He will make all things right,
If I surrender to His will,
That I may be reasonably happy in this life,
And supremely happy with Him forever in the next.

Amen

Squamous Cell Carcinoma of External Auditory Canal Metastasis to CSF: A Diagnostic Conundrum

BR Nagarjun[1], Patel Trupti[2], Shah Majal[3], Dhandapani Kartik[1]
Resident[1], Associate Professor[2], Assistant Professor[3]
Department of Oncopathology,
The Gujarat Cancer & Research Institute, Asarwa, Ahmedabad, Gujarat
Corresponding Author: trupti.patel@gcriindia.org
[1]https://orcid.org/0000-0002-5158-9236
[2]https://orcid.org/0000-0002-5887-2042

Summary

Squamous cell carcinoma (SCC) metastatizing to leptomeninges is rare. We report a case of immunocytochemistry proven cerebrospinal fluid (CSF) involvement in a diagnosed case of SCC of external auditory canal (EAC). This report discusses the diagnostic challenges in cyto-morphological diagnosis, major differential diagnosis and underscores the need to look for leptomeningeal involvement at the earliest due to its prognostic importance despite remote clinical possibility.

Keywords: Squamous cell carcinoma, external auditory canal, CSF

Introduction

CSF cytology is a routinely practised test due to its simplicity, diagnostic ability and prognostic significance. In oncology practise, CSF examination is commonly performed to rule out Central Nervous System (CNS) infection in view of chronic immunosuppression, in dwelling vascular catheter, head and neck surgeries and CNS metastasis which affects the therapeutic management and clinical outcome.[1, 2] Presence of tumor cells in leptomeninges or CSF away from primary tumor is defined as leptomeningeal metastasis (LM).

Around 5-15% of haematological malignancies and 5-8% of solid tumors involve leptomeninges as late complication.[3,4]

Metastatic carcinomas from lung, breast, gastrointestinal tract are commonly reported.[3] SCC involving CSF is extremely rare with few case reports mentioning different sites of head and neck region as primaries.[4] Incidence of SCC of EAC is rare with a reported incidence of between 1 to 6 cases per million population per year and metastasis to CSF is unreported.[5]

Case Detail

A 40-year male patient presented to emergency department (ED) with complains of left sided facial weakness and hoarseness of voice. MRI brain revealed peripherally enhancing hypo intense lesion with absence of perilesional edema measuring 15x8mm in left temporal lobe suggesting possibility of brain abscess. (Figure 1) Patient was diagnosed case of SCC of left EAC a year back and on chemotherapy with regular follow up showing signs of improvement. Tumor did not show any direct extension into the brain parenchyma (Figure 1).

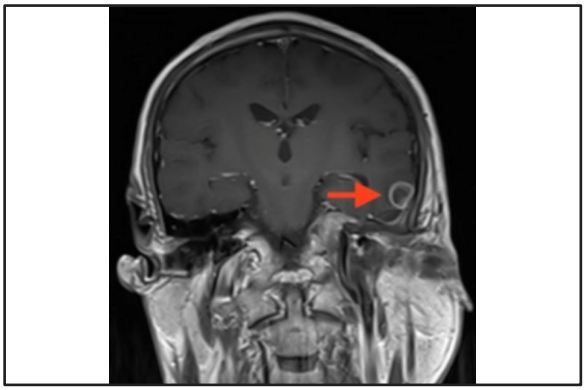

Figure 1: MRI Coronal view shows ring enhancing lesion and absence of perilesional edema suggestive of brain abscess

Presently patient had no complains of fever and on examination signs of meningitis were not elicited. Microbial etiology was suspected as the patient had already completed 5 cycles of carboplatin and paclitaxel, lumbar puncture was performed and CSF tapped was subjected for biochemical, microbiological and cytological examination.

CSF Examination

CSF sample collected by lumbar puncture was around 6ml and clear in appearance. Biochemical examination revealed hypoglycorrhachia (15.34 mg/dl), raised protein (176.11 mg/dl), chloride of 121.6 mmol/dl. Wet mount preparation suggested hyaline round structures similar to size of RBCs and considered a possibility of cryptococcal infection. However, CSF culture was sterile after 14 days of incubation.

CSF Cytology

Cytoprep and papanicolaou stained smears

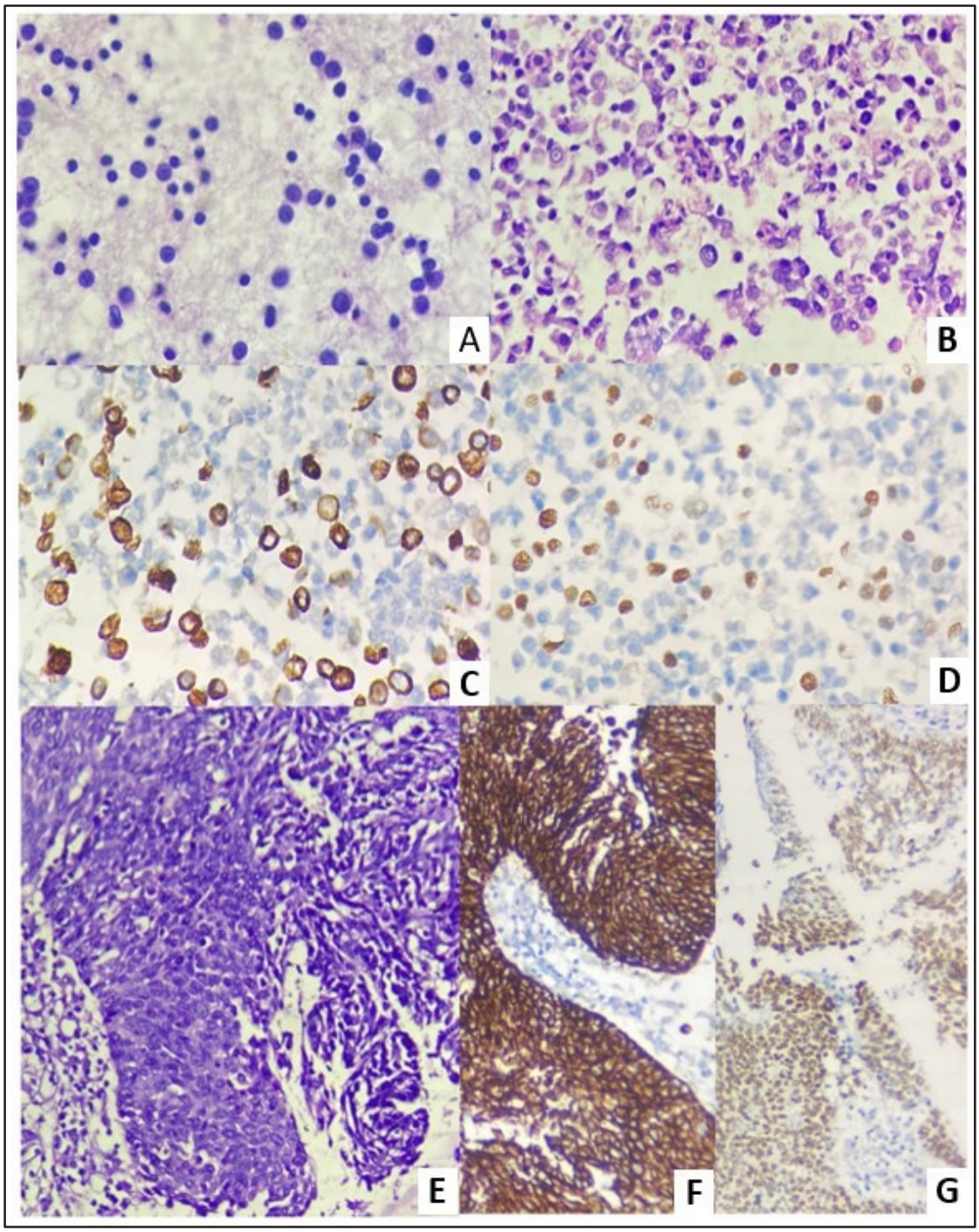

Figure 2: Pap stained cytospin smear shows tumor cells in loose aggregates and scattered singly with uniform round to oval hyperchromatic nuclear and minimal to moderate amount of cytoplasm with scattered lymphocytes in background (A) x20. H&E stained cellblock section is cellular and shows tumor cells with hyperchromatic and vesicular nuclei and moderate amount of cytoplasm (B) x20. H&E stained biopsy from EAC show tumor cell in cord like fashion with basaloid morphology and intercellular bridges are appreciated (E) x20. AE1/AE3 shows membranous staining pattern and p63 shows nuclear staining in (C) and (D) respectively which corresponds to the staining pattern on the biopsy slide from EAC in (F) and (G) respectively.

examined were highly cellular with malignant tumor cells arranged in clusters and scattered singly. Tumor cells had variable nuclear size, regular nuclear contour, round to oval nuclei, fine chromatin and mild to moderate amount of cytoplasm. (Figure 2A) Tumor giant cells and few bizzare cells were noted amidst scattered lymphocytes and macrophages. Structures resembling microorganisms was not identified. Cell

block prepared by fixed sediment method and stained by hematoxylin and eosin revealed pleomorphic cells having fine to vesicular nuclei and moderate amount of cytoplasm with plenty of artifactual cytoplasmic vacoulations. (Figure 2B)

Discussion

Carcinomas metastatizing to CSF is a complication in the natural course of disease and is seen in 5-8% of solid tumors.[3] LM spread from SCC is exceedingly rare with case reports from various sites of head and neck (lip, oropharynx, larynnx, nasopharynx), lung, genitourinary and skin. Occurance of SCC in EAC is quite uncommon and metastasis to CSF is unreported based on Pubmed search.

In this case, clinical and radiologic findings had a very minimal suspicion of metastasis to CSF. Cyto-morphologically also the tumor cell sin CSF failed to show any squamous features such as thick, dense cytoplasm with well-defined cell borders or keratin pearls. The common primaries such as of adenocarcinoma from lung or GIT was considered but glandular morphology of tumor cells and supporting radiological findings were absent. No evidence of moulding was seen to suspect small cell carcinoma lung. Possibility of melanoma was ruled out due to absence of large cells with macronucleoli or melanin pigment.

Since the tumor morphology at the primary site was predominantly basaloid (Figure 2E), the metastatic spread was confirmed by the same immunopanel applied on the biopsy. AE1/AE3 and p63 confirmed the squamous nature of the tumor and reinforced the fact that primary was from EAC. (Figure 2C-D, 2F-G). Generally, identification of malignant squamous cells in CSF is limited and require repeated tapping in addition it is uncommon to encounter the characteristic cytology which adds to the diagnostic difficulty.[3] Despite immunocytochemistry aids in diagnostic accuracy, is limited if the cellularity is low.

Several mechanisms of CSF involvement have been postulated with perineural mode commonly described in SCC metastasis.[2] The mode of CSF involvement in our case has occurred as direct extension through temporal bone.

The incidence of leptomeningeal involvement is increasing as a price paid for longer survival in cancer patients and improvised neuroimaging studies has led to increased detection frequency.[3] LM of SCC carries dismayed outcome and is generally less sampled due to its varied clinical presentation and delayed clinical suspicion. Nevertheless, diagnosis at the earliest warrants a palliative care which carries a benefit of prolonged survival.[6]

Even in the era of remarkable advances in diagnostic field with MRI, DNA amplification, flow cytometry, mere cytological examination of CSF continues to remain gold standard for its simplicity and diagnostic ability.[7] In our case, simple and cost effective CSF examination with immunocytochemistry led to the diagnosis of this exceedingly unusual and probably the first reported work of basaloid SCC of EAC metastasizing to CSF.

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Primary Pleomorphic Liposarcoma of Bone: A Rare Tumor in Unusual Location with Review of Literature

Vanik Sangeeta A[1], Gami Amisha[1], Kaur Kanwalpreet[1], Trivedi Priti[2]
Assistant Professor[1], Professor[2]
Department of Oncopathology,
The Gujarat Cancer & Research Institute, Asarwa, Ahmedabad, Gujarat
Corresponding Author: priti.trivedi@gcriindia.org
https://orcid.org/0000-0002-6821-6129

Summary

Primary liposarcoma of bone is an extremely rare tumor and accounts for only 0.03% of all primary bone tumors. Herein we report two rare cases of primary pleomorphic liposarcoma of long bone. Both cases presented with localised swelling and pain. Imaging study revealed that origin of tumor was primarily of bone. J needle biopsy in both cases showed highly pleomorphic cells with no malignant osteoid. Diagnosis of high-grade sarcoma was given. Histomorphology of post-chemotherapy resected specimens showed many pleomorphic lipoblasts with large areas of necrosis and no malignant osteoid. After ruling out the various differentials, final diagnosis of primary pleomorphic liposarcoma of bone were given in both cases. Hence, biopsy material alone is very challenging for the diagnosis. Careful histopathological examination with keeping in mind of a rare diagnosis along with a clinicoradiological correlation as well as immunohistochemistry play a useful role in confirmation of the diagnosis.

Keywords: Malignant bone tumor, Pleomorphic liposarcoma, Liposarcoma of bone, Rare primary bone tumor

Introduction

Primary liposarcoma of bone is an extremely rare tumor, with prevalence of only 0.03% among all bone tumors.[1] In 1955, Dawson reported the first convincing case of primary liposarcoma of bone. Subsequently over the years other authors also reported this rare entity. But in 1982, Addison and Payne reviewed all and found only 6 convincing cases.[2] Among all malignant adipocytic tumors, Pleomorphic Lipo Sarcoma (PLS) was least common.[1] We report two cases of primary PLS of bone with the aim to enrich the existing literature and a focus on potential pitfalls in diagnosis.

Case Details

Twenty-six and 16-year-old young males presented with pain and swelling in their left knee joint for 2 past months. Magnetic resonance imaging (MRI) revealed ill-defined tumor involving epi-meta-diaphysis of distal femur and proximal tibia, respectively. Both the cases showed altered marrow signal intensity which appeared hypointense on T1W and heterogeneously hyperintense on STIR with associated periosteal reaction, periosteal thickening and soft tissue component. Possibility of primary malignant bone tumor? Osteosarcoma was suggested in both the cases.

J needle biopsy of both the cases showed clusters of atypical cells having highly pleomorphic, hyperchromatic nuclei, irregular nuclear membrane and vacuolated cytoplasm. Malignant osteoid were not identified in both the cases (Figure 1a). Correlation of histopathology with clinicoradiological findings, diagnosis of high-grade sarcoma with possibilities of osteosarcoma with clear cell component, pleomorphic liposarcoma and metastatic carcinoma were given.

Both the cases received chemotherapy followed by surgery. Gross feature of case 1 showed, a 17x17x6 cm tumor involving the epi-meta-diaphysis of left distal femur. Cut surface was mainly necrotic (≥ 90%) and bony area was solid, greyish white to tan. (Figure 1b). Case 2 showed, a 17x8x6 cm tumor involving epi-metaphysis of left proximal tibia. Cut section of tumor was solid, greyish yellow to white, soft to firm, also areas of necrosis were evident. Both showed soft tissue extension and case 2 also showed overlying skin ulceration. Microscopic examination of both the cases showed many uni- and multi-vacuolated pleomorphic lipoblasts with extreme pleomorphism, brisk mitotic activity and areas of necrosis. Malignant osteoid were not identified. (Figure 1c, 2a, b).

Differential diagnosis include metastatic pleomorphic liposarcoma, primary pleomorphic liposarcoma, high grade osteosarcoma, dedifferentiated liposarcoma and undifferentiated pleomorphic sarcoma. Both patients were screened by positron emission tomography and computed tomography PET-CT scan which suggested primary bone tumor with no distant metastasis at time of diagnosis. Absence of malignant osteoid and no well differentiated liposarcomatous area ruled out osteosarcoma and dedifferentiated liposarcoma respectively. Presence of typical pleomorphic lipoblasts ruled out the undifferentiated pleomorphic sarcoma.

IHC was done to rule out the various differentials. Tumour cells were immunoreactive for vimentin, focally for S100 protein and negative for SATB2. (Figure 1d, e, f, Figure 2c, d).

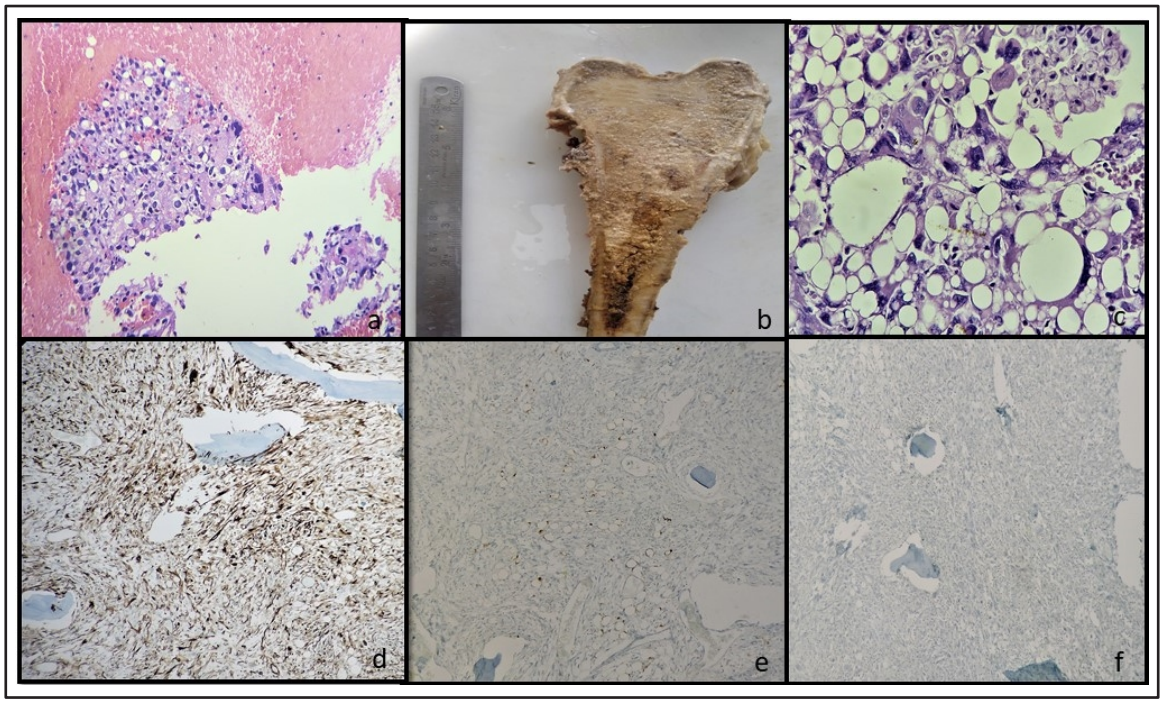

Figure 1: Case 1/ (a) H and E staining from J needle biopsy showed many atypical cells with hyperchromatic nuclei and vacuolated cytoplasm 20x (b) Gross photograph of post chemotherapy specimen (c) Many pleomorphic lipoblasts in resection specimen 40x (d to f) Immunohistochemical stains 20x (d) vimentin(cytoplasmic) positive (e) S100 protein (nuclear and cytoplasmic) focal positive (f) Negative SATB2.

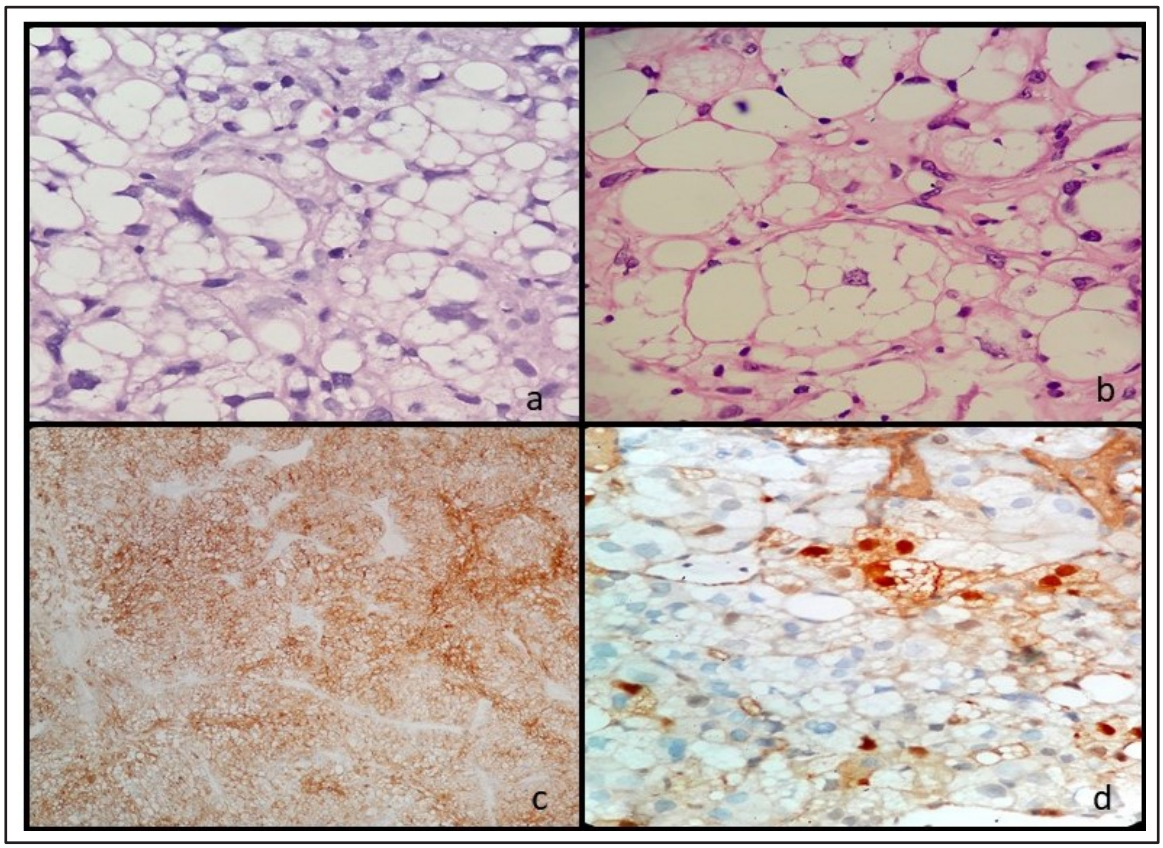

Figure 2: Case 2(a, b) Histomorphology of resected specimen shows many pleomorphic lipoblasts 40x (c,d) Immunohistochemical stain (c) vimentin (cytoplasmic) positive (d) S100 protein (nuclear and cytoplasm) focal positive.

Table 1: Previously reported cases of pleomorphic liposarcoma of bone

Study	Age/sex	Site	Metastasis	Treatment received	Follow up
Torok et al[2]	34/M	Femur	Lung	Wide resection, radiation, chemotherapy	Died, 16 months
Hamlat et al[3]	45/F	Thoracic spine	Lung and rib	Laminectomy T7-T8 and radiotherapy	Alive,19 months
Torigoe et al[4]	38/F	Humerus	Liver	Wide resection, Initial high-dose ifosfamide followed by cisplatin and doxorubicin	Died, 8 months
Lmejjati et al[5]	35/M	Lumber spine	Locally invasive	Emergency decompression at L4/L5 and radiotherapy	Died, 3 months
Rasalkar[6]	13/M	Femur	Lung	Neoadjuvant chemotherapy (methotrexate, cisplatin), Surgery, Adjuvant chemotherapy (ifosfamide/etoposide and adriamycin/cisplatin)	Alive, 13 months
Tiemeier GL et al[7]	18/M	Tibia	Femur and lung	Chemotherapy (methotrexate, doxorubicin and cisplatin), wide resection	Alive,12 months
Fajolu O et al[8]	19/M	Femur	Lung, liver,vertebra, scapula	Chemotherapy (etoposide,ifosfamide) and wide resection	Died, 8 months
Our study	16/M	Tibia	Contralateral Femur	Chemotherapy and wide resection	Lost follow up after 7 months
	26/M	Femur	-	Chemotherapy (Doxorubicin, cisplatin), wide resection	Died, 6 months

After excluding all differentials final diagnosis of primary pleomorphic liposarcoma of bone were given in both the cases. Case 2 also showed metastasis to the contralateral side of distal femur after 2 months of initial diagnosis.

Both cases were followed up. Case 1 died after 6 months of initial symptoms, while we lost follow up of case 2 after 7 months of initial symptoms.

Discussion

Malignant adipocytic tumor accounts for 10-35% of all soft-tissue sarcomas,[1] and PLS is the least common subtype, with prevalence of only 5- 15% of all liposarcomatous lesions. Liposarcoma arising from the bone is a rare entity and very few confirmed cases of primary PLS of bone have been reported in literature.[1] Total of 1008 primary malignant bone tumors were reported between 2018 to 2020 in our hospital. Most common primary malignant bone tumor was osteosarcoma (57.83%) followed by Ewing sarcoma (26.58%) and chondrosarcoma (15.37%), and only two cases of primary liposarcoma of bone were reported. Till date only 7 cases of primary PLS of bone have been reported in literature (Table 1).[2-8] Diagnosis of primary liposarcoma of bone can be considered only if it arises from the bone and have characteristic gross and histological features.[1]

Primary PLS of bone affect a wide age range from 15-53 years and equally affects both genders.[1] Long bones of lower extremities and upper extremity most frequently affected while rarely it can affect scapula, maxilla and mandible.[1]

Radiology of primary liposarcoma of bone shows non-specific features such as large osteolytic lesion with cortical destruction. PLS contain less adipocytic component as compared to other subtypes and this makes imaging diagnosis difficult.[1] MRI study shows intermediate signal intensity with T1 weighting and intermediate to high signal intensity with T2W.[1] These findings were concordant with our cases.

Histomorphology of PLS includes a lipogenic area with variable number of pleomorphic lipoblasts and non-lipogenic area with high grade sarcoma features. Both our cases had similar histomorphology with lipogenic areas showing many pleomorphic lipoblasts and non-lipogenic areas having high grade sarcomatous features.

Immunohistochemistry and molecular analysis have very limited diagnostic role. Murine Double Minute 2 (MDM2) amplification is negative in PLS while osteosarcoma, low grade and parosteal and those that dedifferentiate into high grade osteosarcoma show positive staining.[9] Gebhard et al,[10] observed that S-100 protein immunoreactivity was seen in up to 48% of lipogenic areas which were concordant with our cases.

Primary osseous liposarcoma is an aggressive malignancy with mean survival rate of two years only.[1] Wide surgical resection is the mainstay of

treatment of primary osseous liposarcoma, with radiation therapy used for palliation or following excision to prevent local recurrence.[1] Both our cases received chemotherapy prior to surgery. One patient succumbed to death post operatively while another showed osseous metastasis in contralateral long bone. However, we lost follow up of the patient after this.

Conclusion

Primary pleomorphic liposarcoma of bone is an extremely rare tumor. Diagnosis alone on biopsy material is very challenging. Due to rarity of tumor, despite of the presence of lipoblasts, one may still miss the diagnosis if not aware of the entity.

Conflict of interest

No conflict of interest.

Acknowledgements

None

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Recurrence Developing 21 Years After Treatment of Breast Cancer

Vagashiya Vidhi[1], Mehta Maitrik[2], Parikh Ankita[2], Shah Sonal[3], Suryanarayan U[2]
Resident[1], Professor[2], Associate professor[3]
Department of Radiation Oncology,
The Gujarat Cancer & Research Institute, Asarwa, Ahmedabad, Gujarat
Corresponding Author: maitrik.mehta@gcriindia.org
https://orcid.org/0000-0001-6503-9182

Summary
Background: Breast cancer is a very common cancer among females. In which most recurrences (around 75%) occur within the initial 5 years after diagnosis, especially within 3 years. Recurrence after 20 years is very less reported in the last few decades.
Case Information: We present the case of a 67-year-old woman who presented with pleural based nodules suggestive of lung metastasis followed by brain metastasis. After reviewing history, we came to know that the patient was a previously treated case of breast carcinoma treated 22 years back with mastectomy.
Conclusion: We report late recurrence of breast cancer occurring 21 years after mastectomy suggesting that possibility of recurrence in carcinoma breast with a 21-years latency period although rare should be taken into consideration when making decisions regarding patients who may need long term follow up.
Keywords: late recurrence, breast cancer

Introduction

Understanding the risk of recurrence more than 10 years after primary diagnosis helps distinguish patients who may be candidates for long-term follow-up.[1] After diagnosis of 1847 patients who underwent breast-conserving surgery between 1989 and 1999 in a Danish study showed a cumulative incidence of 15% for local recurrence and 21% for distant metastases after 20 years post diagnosis.[2]

Case Report

A 67-year-old postmenopausal female presented with chief complaints of right limb weakness, headache with constipation for 6 days in August 2021. There was no associated complaint of fever, seizures, or loss of consciousness. On taking detailed history, she was a known case of carcinoma of the left breast. Estrogen and progesterone receptor negative and HER2/neu positive diagnosed and treated 22 years before. She had undergone modified radical mastectomy + 5 cycle CMF (5-FU, methotrexate and endoxan) chemotherapy treatment for the same. Patient did not receive any adjuvant radiotherapy. The patient was started on tablet tamoxifen and continued the same till 5 years. Patient was then lost to follow up for two years and presented back to our institute in August 2008 after which the patient was kept under observation.

Patient then presented with a complaint of right sided chest pain in August 2020. CT scan of September 2020 showed recurrent lesion involving left anterior chest wall, precarinal node, upper para aortic node with bilateral lung and bone metastases.

Immunohistochemistry (IHC) of CT guided lung biopsy was suggestive of metastatic ductal carcinoma (GATA - 3 +ve) with ER +ve, PR -ve and Her2/neu negative.

CT guided lung biopsy showed poorly differentiated carcinoma with IHC showing metastatic ductal carcinoma. Patient received 3 cycles of paclitaxel. Patient was kept on letrozole for one year. Patient presented to us with right upper limb weakness. On examination, the patient was semiconscious and disoriented with power 1 out of 5 in all limbs except 4 out of 5 in the left upper limb with decreased sensation and constipation for 6 days.

Routine blood investigations were normal. NCCT of the brain was suggestive of 24x13 mm left occipital metastasis. CT scan showed residual lesion and D9 vertebrae metastasis with lesion involving left high parietal region, left occipital region.

Patient was referred to the department of radiation oncology for palliative whole brain radiation therapy (WBRT). The patient was planned for palliative WBRT of a dose schedule of 3000 cGy in 10 fractions at 3 Gy in each fraction daily to be completed in 2 weeks through two parallel opposed fields. However, the patient took discharge against medical advice without starting WBRT.

Discussion

Breast cancer is seen as more of a chornic disease where survival curves start to parallel that of the general population after 10 to 25 years. In breast cancer we cannot define a period after which a patient can be considered cured as it is seen with curable acute malignancies.[3,4] In breast carcinoma, late relapses are observed frequently.[5] Statistical cure is considered if the patient's survival curve parallels that of the general population.[2,3,4] The high-risk breast cancer group achieve statistical cure earlier than low-risk group

(respectively 10–15 vs 20–25 years after diagnosis). As seen from the survival curves, it's starting to match the survival curve for the general population earlier than early stage breast cancer.

According to a study by Rikke Nongaard Pedersen et al, recurrences have been reported in literature as occuring even up to 32 years after diagnosis of the primary.[1] Women with large tumor size, higher lymph node burden and ER-Positive tumors show higher late recurrence risk.[1]

Even though the statistics of these patients of carcinoma breast shows that long term disease free survival can be achieved with adequate treatment in early stages, it remains a question that - after how many years of disease free survival we can guarantee that the patient will have 0% chances of relapse .

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Presentations at the Clinical Meetings (January 2022 to June 2022)

Sr No.	Date	Speaker / Department	Title
1	13.01.2022	Patel Vivek Medical Oncology	Pre-operative Neoadjuvant Chemotherapy Cycles and Survival in Newly Diagnosed Ovarian Cancer: What is the Optimal Number? A Memorial Sloan Kettering Cancer Centre Team Ovary Study
		Tarun B Surgical Oncology	Short-course Radiotherapy Followed by Chemotherapy Before Total Mesorectal Excision (TME) Versus Preoperative Chemoradiotherapy, TME, and Optional Adjuvant Chemotherapy in Locally Advanced Rectal Cancer (RAPIDO): A Randomised, Open-label, Phase 3 Trial
2	27.01.2022	Verma Naveen Surgical Oncology	Postoperative Concurrent Radiotherapy and Chemotherapy for High Risk SCC in Head and Neck Malignancy (RTOG9501)
		Baranda Sheetal Anaesthesiology	Anatomic Accuracy of Airway Training Manikins Compared with Humans
3	10.02.2022	Shukla Shivang Surgical Oncology	Minimally Invasive Lung Surgeries (Uniportal VATS) – GCRI Experience
		Rachh Swati Nuclear Medicine	Comparison of 68Ga-FAPI and 18F-FDG Uptake in Gastric, Duodenal and Colorectal Cancers
4	22.02.2022	Kapoor Shilpa Oncopathology	CIMPACT – Now Updates and their Significance to Current Neurooncology Practice
		Abhilash V Gynaecological Oncology	The Systemic Therapy of Recurrent Ovarian Cancer Revisited from Annals of Oncology
5	10.03.2022	Patel Nupur Immunohematology	Exosomal miRNA Profiles of Triple Negative Breast in Neoadjuvant Treatment
		Chandra Minu Medical Oncology	Aromatase Inhibitors Versus Tamoxifen in Premenopausal Women with Oestrogen Receptor-positive Early-stage Breast Cancer Treated with Ovarian Suppression: A Patient-level Meta-analysis of 7030 Women from Four Randomised Trials
6	24.03.2022	Shah Veer Surgical Oncology	Perioperative Chemotherapy with Fluorouracil Plus Leucovorin, Oxaliplatin, and Docetaxel Versus Fluorouracil or Capecetabine Plus Cisplatin and Epirubicin for Locally Advanced, Resectable Gastric or Gastro-oesophageal Junction Adenocarcinoma (FLOT4): A Randomised, Phase 2/3 Trial
		Shah Anand Community Oncology	Determinants of Compliance for Breast and Cervical Cancers Screening among Female Police Personnel of Mumbai, India – A Cross Sectional Study
7	25.04.2022	Yadav Varun Palliative Medicine	End-Of-Life Care Policy: An Integrated Care Plan for The Dying
		Gajjar Kinjal Molecular Diagnostics & Research Lab I	Association of Expression of Inflammatory Response Genes and DNA Repair Genes in Colorectal Cancer
8	12.05.2022	Prasad Reecha Radiodiagnosis	MR Enterography and its Role in Evaluation of Small Bowel Pathologies
		Shah Vrashesh Neuro Oncology	Endoscopic Pituitary Surgery: Study of 250 Cases Per Operative Variant, Approach, and Local Changes by Pathology
9	26.05.2022	Chakravarty Sutanuka Radiation Oncology	A Rare Vulval Benign Tumor (Buschke Lowenstein Tumor) Treated with Radical Radiotherapy
		Bhalala Neha Molecular Diagnostics & Research Lab II	Droplet Digital PCR Assay for Detecting TERT Promoter Mutations in Patients with Glioma

About the Journal and Instructions to Authors

About the Journal

Gujarat Cancer Society Research Journal is a biannually (April and October) peer-reviewed journal published by the Gujarat Cancer Society (formerly published as GCS Research Bulletin). The journal's full text is available online at http://www.cancerindia.org

Scope of the Journal

The Journal intents to cover basic, clinical, clinico-basic research and medical education carried out by the staff of the Gujarat Cancer Society and Gujarat Cancer and Research Institute related to human well being including ethical and social issues in the field of Oncology. The Journal gives preferences to original scientific papers, case reports, anecdotal reports and minireviews. It may comprise invited review articles, publish oration speeches and work presented in the clinical meetings and the journal clubs. Hence it will continue to serve as an academic-research bridge between the basic sciences and the applied sciences, viz. various disciplines of medicine within and outside GCS-GCRI.

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Chapter in a Book
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Detection of Genetic Alterations in Cancer by fully automated Next Generation Sequencer at Cancer Biology Department, GCRI

Mandalia Toral[1], Vora Hemangini[2]
Research Assistant[1], Professor & Head[2]
Cancer Biology Department, The Gujarat Cancer & Research Institute, Asarwa, Ahmedabad, Gujarat, India
Corresponding Author: hemangini.vora@gcriindia.org
[1]https://orcid.org/0000-0002-3495-1600
[2]https://orcid.org/0000-0003-3893-9999

Cancer is now considered as Genetic Disease meaning that cancer is caused by certain changes to genes that control the cells function, especially how they grow and divide. Certain gene changes can cause cells to evade normal growth controls and transform into cancer. Some cancer-causing gene changes increase production of a protein that makes cells grow. The genetic changes are of two types, germline changes and somatic changes. Genetic changes that promote cancer can be inherited from parents to offspring called germline changes. Cancer-causing genetic changes can also be acquired during one's lifetime, as the result of errors that occur as cells divide or from exposure to carcinogenic substances that damage DNA, such as certain chemicals in tobacco smoke and chewing tobacco, and radiation, such as ultraviolet rays from the sun. Genetic changes that occur after conception are called somatic (or acquired) changes.

These gene mutations can be identified in DNA and RNA of an individual by Next Generation Sequencing (NGS). DNA or RNA sequencing tests can "read" DNA or RNA, respectively. By comparing the sequence of DNA or RNA in cancer cells with that in normal cells, identify genetic changes in cancer cells that may be driving the growth of an individual's cancer. This information will help to predict which therapies might work best against a particular tumor.

Currently, cancer treatment decisions are increasingly made on the basis of genomic information, and there are currently large numbers of genomic tests available to oncologists. Genomic tests designed to facilitate decisions about treatment management include those that identify alterations in single genes and multimarker tumor panels. Multigene panels include targeted gene-expression profiling tests that are used to estimate prognosis and/or the likelihood of recurrence. Multimarker panels also include DNA and RNA analysis through NGS technologies, including custom panels that profile multiple actionable driver genes, fusion genes and tumor characteristics that may guide the selection of targeted therapies.

Hence, NGS is of utmost requirement for identification of gene mutations in various cancers as well as in hereditary cancers for identification of family members at risk of cancer.

There are disease specific Multigene-Cancer Panels available that analyze number of genes associated with hereditary and sporadic cancers across major organ systems, including:

- breast and gynecologic (breast, ovarian, uterine)
- gastrointestinal (colorectal, gastric, pancreatic)
- endocrine (thyroid, paraganglioma/ pheochromocytoma, parathyroid, pituitary)
- genitourinary (renal/urinary tract, prostate)
- skin (melanoma, basal cell carcinoma)
- brain/nervous system
- sarcoma
- hematologic(myelodysplastic syndrome/ leukemia)

The Multigene-Cancer Panel is designed to maximize diagnostic yield for individuals with a personal or family history of mixed cancers affecting multiple organ systems.

Genetic testing of these genes may confirm a diagnosis and help guide treatment and management decisions. Identification of a disease-causing variant would also guide testing and diagnosis of at-risk relatives.

Recently, Next Generation Sequencing (NGS) facility: The IontorrentTM Genexus Integrated Sequencer and Ion GeneStudio S5 system (ThermoFisher Scientific) is established at the Cancer Biology Department, GCRI.

The **Genexus Integrated Sequencer - Ion Torrent** is the first turnkey next-generation sequencing (NGS) solution that automates all steps of the targeted NGS workflow starting from Nucleic Acid to results. The Nucleic Acid to Result workflow starts from purified and quantified nucleic acid

samples. Purified nucleic acid samples are pipet into a 96-well sample input plate and then loaded into the Genexus™ Integrated Sequencer for library preparation, templating, and sequencing. With a single touchpoint and five minutes of hands-on time, the Genexus sequencer automates NGS library preparation (including cDNA synthesis), template preparation, sequencing, primary data analysis, and variant reporting for DNA, RNA, and cfDNA applications. Sequencing on the Genexus sequencer is done on a four-lane semiconductor chip: the Ion Torrent GX5 Chip. Each of the four lanes of the GX5 Chip supports the output of 12–15 million reads, and they can be used individually or all at once depending on throughput needs. Ion Torrent Genexus Software streamlines the NGS workflow by integrating the setup-to-report workflow within a single software ecosystem.

The **Ion GeneStudio S5 system** is designed to enable a broad range of targeted next-generation sequencing (NGS) applications with speed and scalability. Five Ion S5 chips (Ion 550 chip, Ion 540 chip, Ion 530 chip, Ion 520 chip and Ion 510 chip) enable a sequencing throughput range of 2M to 130M reads per run.

During standardization on NGS, eight samples of each DNA and RNA of AML patients were sequenced using the Ion Torrent Oncomine Myeloid Assay GX v2 by Molecular Diagnostics & Research Lab-2 (MDRL-2). Moreover, DNA and RNA samples of four lung carcinoma and four brain tumor patients were sequenced and analyzed using the Oncomine Precision Assay (OPA) by MDRL-3 and MDRL-1 of Cancer Biology Department, respectively.

Ion Torrent Oncomine Myeloid Assay GX v2

The Ion Torrent Oncomine Myeloid Assay GX v2 is a comprehensive targeted next-generation sequencing (NGS) assay designed for sensitive detection of myeloid disorder-associated DNA mutations and RNA fusion transcripts in blood and bone marrow samples. This assay is compatible with the Genexus Integrated Sequencer, which performs library preparation, sequencing, analysis, and reporting in an automated sample-to-result workflow. Depending on the workflow, results can be obtained in as little as a single day.

Oncomine Myeloid Assay GX v2 features include:

- Comprehensive coverage of key DNA mutations and >700 fusion transcripts associated with myeloid disorders
- Automated sample-to-report workflow on the Genexus sequencer in less than a day
- Sequencing of up to eight samples (DNA & RNA) per lane on a GX5 Chip in a single run
- Less than 15 minutes hands-on time
- Detection of somatic variants down to 5% allele frequency

With the Oncomine Myeloid Assay GX v2, 45 DNA target genes and 35 RNA fusion driver genes can be interrogated simultaneously, covering the most relevant targets associated with major myeloid disorders, including acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), myeloproliferative neoplasms (MPN), chronic myeloid leukemia (CML), chronic myelomonocytic leukemia (CMML) and juvenile myelomonocytic leukemia (JMML) (Table 1).

Table 1: Gene content of the Oncomine Myeloid Assay GX v2 panel

Hotspot genes (28)		**Full genes (17)**		**Fusion driver genes (35)**			**Expression genes (5)**	**Expression control genes (5)**
ANKRD2 6 ABL1	KRAS MPL	ASXL1 BCOR	PRPF8 RB1	ABL1 ABL2	HMGA2 JAK2	NUP214 NUP98	BAALC MECOM	EIF2B1 FBXW2
BRAF	MYD88	CALR	RUNX1	BCL2	KAT6A	PAX5	MYC	PSMB2
CBL	NPM1	CEBPA	SH2B3	BRAF	(MOZ)	PDGFR	SMC1A	PUM1
CSF3R	NRAS	ETV6	STAG2	CCND1	KAT6B	PDGFRB	Wt1	TRIM27
DDX41	PPM1D	EZH2	TET2	CREBBP	KMT2A	RARA		
DNMT3 A FLT3	PTPN11	IKZF1	TP53	EGFR	KMT2A-	RUNX1		
(ITD +	SMC1A	NF1	ZRSR2	ETV6	PTDs	TCF3		
TKD)	SMC3	PHF6		FGFR1	MECOM	TFE3		
GATA2	SETBP1			FGFR2	MET	ZNF384		
HRAS	SF3B1			FUS	MLLT10			
IDH1	SRSF2				MRTFA			
IDH2	U2AF1				(MKL1)			
JAK2	Wt1				MYBL1			
KIT					MYH11			
					NTRK2			
					NTRK3			

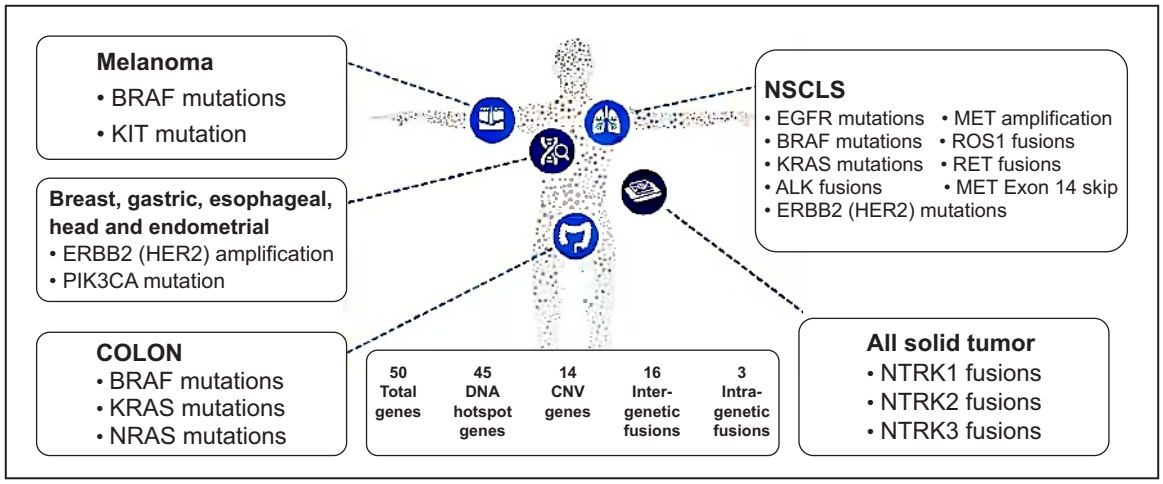

Figure 1: Oncomine Precision Assay content

Table 2: Results of Oncomine Myeloid assay GX v2

Patients	RNA		DNA	
	CNV	Fusion	SNV / Indels	
			Gene	Type of mutation
Patient 1	-	-	WT1	Truncating- Loss of function
Patient 2	-	-	DNMT3A	Hotspot- Loss of function
			PTPN11	Hotspot- Gain of function
Patient 3	-	-	FLT3	Hotspot- Gain of function
			NPM1	Truncating- Loss of function
			WT1	Truncating- Loss of function
Patient 4	-	PML(6)-RARA(3)	DNMT3A	Hotspot- Loss of function
			NPM1	Truncating- Loss of function
Patient 5	-	-	-	-
Patient 6	-	PML(6)- RARA(3)	-	-
Patient 7	-	BCR(13)-ABL1(2)	IDH2	Hotspot- Gain of function
			NPM1	Truncating- Loss of function
Patient 8		BCR(13)-ABL1(2)	IDH2	Hotspot- Gain of function
			NPM1	Truncating- Loss of function

This multiplex primer design leverages Ion AmpliSeq technology to generate results from multiple samples in a single run. Sequencing results are automatically analyzed by Genexus software using an optimized assay-specific analysis workflow.

Oncomine Precision Assay

The Oncomine Precision Assay enables simultaneous detection of biomarkers across 50 genes, including key targets within EGFR, BRAF, KRAS, ALK, ROS1, NTRK, RET, and others, from both solid tissue and liquid biopsy samples. (Figure 1) The kit provides a targeted pan-cancer panel and library reagents sufficient to perform up to 32 sequencing reactions on the Ion Torrent Genexus Integrated Sequencer using the Ion Torrent GX5 Chip.

When used with the Oncomine Precision Assay, the Genexus Integrated Sequencer performs library preparation, sequencing, analysis, and reporting in an automated sample-to-result workflow that delivers results in as little as a single day. Moreover, the Oncomine Precision Assay, based on Ion Torrent™ AmpliSeq™ HD technology, requires only 10 ng of DNA or RNA, resulting in more than 95% of samples producing sequencing results. Minimum sample input and maximum sample success rate Key benefits of the Oncomine Precision Assay on the integrated Genexus System all operated by one Ion

Table 3: Results of Oncomine Precision Assay (OPA)

Patients	Cancer site	DNA			RNA
		CNV	SNV / Indels		Fusion genes
			Gene	Type of mutation	
Patient 1	Brain	-	TP53	Hotspot- Loss of function	-
			FLT3	Hotspot- Gain of function	
			IDH1	Hotspot- Gain of function	
Patient 2	Brain	-	IDH1	Hotspot- Gain of function	ALAS1, ANKRD17, AR, EIF2B1, FGFR3 G6PD, HMBS, MET, TBP
Patient 3	Brain	AR	FLT3	Hotspot- Gain of function	ESR1-CCDC170, BAG4-FGFR1.B1F2,
			IDH2	Hotspot- Gain of function	
			NTRK1	Hotspot- Gain of function	
Patient 4	Brain	EGFR	FLT3	Hotspot- Gain of function	
			IDH1	Hotspot- Gain of function	
Patient 5	Lung	-	EGFR	Hotspot- Gain of function	
Patient 6	Lung	-	HRAS	Hotspot- Gain of function	
			TP53	Hotspot- Loss of function	
Patient 7	Lung	-	EGFR	Hotspot- Gain of function	AR, EGFR, EIF2B1, G6PD, HMBS, MET, TBP, TRIM27
Patient 8	Lung	AR	EGFR	Exon 9 deletion- Gain of Function	
			Tp53	Hotspot- Gain of function	

Table 4: Oncomine Assays and Panels compatible with Genexus Integrated Sequencer and Ion GeneStudio S5 system

Genexus	S5 Sequencer
	Oncomine Precision Assay Plus – 500 genes panel includes TMB, MSI
Oncomine Precision Assay – 50 genes panel	Oncomine Precision Assay – 50 genes panel
	Oncomine Focus Assay – 52 genes panel
Oncomine Comprehensive Assay v3 – 161 genes panel	Oncomine Comprehensive Assay v3 – 161 genes panel
	15-30 genes panel
	Oncomine Bladder Panel
Oncomine BRCA Panel	Oncomine BRCA Extended Panel
	Oncomine CRC and Pancreatic Panel
	Oncomine Gastric & Esophageal Panel
	Oncomine Gynecological Panel
	Oncomine Kidney Panel
	Oncomine Liver Panel
	Oncomine Lymphoma Panel
	Oncomine Melanoma Panel
	Oncomine Prostate Panel
Oncomine Myeloid Assay	Oncomine Myeloid Assay
Oncomine cfDNA Assay	Oncomine cfDNA Assay
	Oncomine Tumor Mutation Load Assay
	HLA Sequencing

Torrent™ Genexus™ software solution.

Oncomine Precision Assay key features include:

- Mutation, CNV, and fusion variant types across 50 key genes such as EGFR, ALK, BRAF, ROS1, RET, KRAS, PIK3CA, and ERBB2, among others
- One-day, hands-free workflow with only two touch points and 10 minutes of hands-on time
- Only 10 ng of DNA/RNA required, allowing for more samples to be tested
- Compatible with FFPE tissue as well as liquid biopsy samples

The Oncomine Precision Assay analyzes 78 variants, including mutations (45), CNVs (14), and fusion variants (19), across 50 key genes. Included are tumor suppressor genes such as TP53, cancer drivers, and resistance mutations. Content has been carefully curated to include all potentially relevant targets of emerging importance for fast genomic profiling in clinical cancer research.

The results of Ion Torrent Oncomine Myeloid Assay GX v2 and the Oncomine Precision Assay (OPA) are shown in Table 2 and Table 3, respectively.

Apart from these, there are multimarker panels for different malignancies that are compatible with Genexus Integrated Sequencer and Ion GeneStudio S5 system (Table 4).

The NGS facility is installed with the help of Corporate Social Responsibility (CSR) of Gujarat Government.

Figure 2 and 3 show the representative images of results for Oncomine Precision Assay (OPA) and Oncomine Myeloid assay GX v2, respectively by Ion Torrent Genexus Software.

Variant Report

Oncomine Precision - GX5 - Solid Tumor - DNA and Fusions - w3.2.0

Cancer Type: **Glioblastoma** Date: 22 Sep 2022

Sample Details		Sample Details	
Sample Name:	**Brain-3**	Collection Date:	**20 SEP 2022**
Application Category:	**Solid Tumor**	Gender:	**Unknown**
Sample Type:	**DNA & RNA**	%Cellularity:	**50**
Cancer Type:	**Glioblastoma**	%Necrosis:	
Cancer Stage:	**Unknown**		

Results for Sequence Variations Detected

SNVs/Indels

Gene	Variant ID	Oncomine Variant Class	Oncomine Gene Class	AA Change	Call	Allele Frequency
FLT3	COSM785	Hotspot	Gain-of-Function	p.D835H	PRESENT (HETEROZYGOUS)	0.311
IDH2	COSM33733	Hotspot	Gain-of-Function	p.R172K	PRESENT (HETEROZYGOUS)	0.423
NTRK1	BT104	Hotspot	Gain-of-Function	p.V573M	PRESENT (HETEROZYGOUS)	0.041

Fusions

Oncomine Driver Gene	Variant ID	Oncomine Variant Class	Oncomine Gene Class	Type	Call	Read Counts
ESR1	ESR1-CCDC170.E2C8.1	Fusion	Gain-of-Function	Fusion	PRESENT	41
FGFR1	BAG4-FGFR1.B1F2	Fusion	Gain-of-Function	Fusion	PRESENT	26

CNVs

Gene	Oncomine Variant Class	Oncomine Gene Class	Call	Copy Number
AR			PRESENT (LOSS)	0.08

Figure 2: Ion Torrent Genexus Software results for Oncomine Precision Assay (OPA)

Variant Report
Oncomine Myeloid v2 - GX5 - DNA and Fusions - w4.2.2

Cancer Type: **Myoepithelial Carcinoma** Date: 17 Sep 2022

Sample Details		Sample Details	
Sample Name:	**AML-10**	Collection Date:	**13 SEP 2022**
Application Category:	**Hematologic Cancer**	Gender:	**Female**
Sample Type:	**DNA & RNA**	%Cellularity:	
Cancer Type:	**Myoepithelial Carcinoma**	%Necrosis:	
Cancer Stage:	**Unknown**		

Results for Sequence Variations Detected

SNVs/Indels

Gene	Variant ID	Oncomine Variant Class	Oncomine Gene Class	AA Change	Call	Allele Frequency
FLT3	.	FLT3ITD	Gain-of-Function	p.Asp586_Arg595dup	PRESENT (HETEROZYGOUS)	0.002
FLT3	.	FLT3ITD	Gain-of-Function	p.Val592_Asp593insAlaMetThrGlySerSerAspAsnGluTyrPheTyrVal	PRESENT (HETEROZYGOUS)	0.035
FLT3	.	FLT3ITD	Gain-of-Function	p.Glu598_Tyr599insSerTyrValAspPheArgGluTyrGlu	PRESENT (HETEROZYGOUS)	0.003
FLT3	.	FLT3ITD	Gain-of-Function	p.Tyr597_Glu598insAspArgValGlnValThrSerSerSerAspAsnGluTyrPheTyrValAspPheArgGluTyr	PRESENT (HETEROZYGOUS)	0.211
FLT3	.	FLT3ITD	Gain-of-Function	p.Glu596_Tyr597insAspProAspPheArgGlu	PRESENT (HETEROZYGOUS)	0.003
FLT3	.	FLT3ITD	Gain-of-Function	p.Glu596_Tyr597insAspProAspPheArgGlu	PRESENT (HETEROZYGOUS)	0.077
FLT3	.	FLT3ITD	Gain-of-Function	p.Glu596_Tyr597insAspProAspPheArgGlu	PRESENT (HETEROZYGOUS)	0.074
FLT3	.	FLT3ITD	Gain-of-Function	p.Leu601_Lys602insGlySerGlnLeuGlnMetValGlnValThrGlySerSerAspAsnGluTyrPheTyrValAspPheArgGluTyrGluTyrAspLeu	PRESENT (HETEROZYGOUS)	0.002
FLT3	.	FLT3ITD	Gain-of-Function	p.Tyr597_Glu598insAspArgValGlnValThrGlySerSerAspAsnGluTyrPheTyrValAspPheArgGluTyr	PRESENT (HETEROZYGOUS)	0.204
FLT3	.	FLT3ITD	Gain-of-Function	p.Arg595_Glu596insLysGluAsnAsnGluTyrPheTyrValAspPheArg	PRESENT (HETEROZYGOUS)	0.009
WT1	.	Truncating	Loss-of-Function	p.Leu383CysfsTer11	PRESENT (HETEROZYGOUS)	0.095
WT1	.	Truncating	Loss-of-Function	p.Arg375AspfsTer8	PRESENT (HETEROZYGOUS)	0.353
WT1	COSM27309	Truncating	Loss-of-Function	p.Ser386LeufsTer71	PRESENT (HETEROZYGOUS)	0.477

Fusions

None Detected

CNVs

None Detected

Figure 3: Ion Torrent Genexus Software results for Oncomine Myeloid assay GX v2

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