NEWSLETTER

PEDIATRIC HEMATOLOGY/ONCOLOGY & BONE MARROW TRANSPLANT

VOL 1, NOV 2015

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GUEST EDITORIAL

Childhood malignancies are a distinct entity with a better prognosis than in adults.

The challenge is to identify these children early , investigate correctly, and treat appropriately with a multi disciplinary approach , keeping in mind long term risks of treatment , and the future growth of the child survivor .

The department of Pediatric Oncology at HCG has made rapid strides in a short span of time , and has many plans for academic and professional activities in the future.

This newsletter seeks to share these activities with Pediatricians, Oncologists and Pediatric Oncologists .

Dr. B.S. Ajai Kumar,
Chairman, HCG

ABOUT THE NEWSLETTER

Pediatric oncology as a specialty is in its infancy in India. A dedicated newsletter would help educate and raise awareness about this specialty and how it improves care for pediatric cancer patients. We aim to disseminate up-to-date and authoritative information to encourage quality and outcomes based pediatric cancer care.

We will share information on treatment protocols, diagnostic strategies, multidisciplinary approaches to challenging cases and aid in implementation of best practice guidelines.

Our aim is that all pediatric cancer in India should be treated by a dedicated team led by well trained pediatric oncologists in line with global standards. The Pediatric Oncology Department of HCG strives to attain outcomes comparable to the best hospitals in the world. Feedback on this newsletter is welcome and may be sent to **rasmipalassery@gmail.com.**

The newsletter will be widely circulated across the country and read by oncologists and general pediatricians.

NEWSLETTER PEDIATRIC HEMATOLOGY/ONCOLOGY & BONE MARROW TRANSPLANT
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CASE SERIES

UNUSUAL PRESENTATIONS OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

Acute Lymphoblastic Leukemia (ALL) is the most common cancer in children. Peak incidence is between 2 - 5 years. Once diagnosed and treated with standard of care chemotherapy, pediatric ALL has an excellent survival rate of about 80%. Children with leukemia usually present with signs and symptoms that reflect bone marrow infiltration with or without extramedullary disease. The most common presentations include fever, bone pains, fatigue, bleeding, anemia, thrombocytopenia, neutropenia, lymphadenopathy, hepatosplenomegaly, and rarely extramedullary masses. Here we present two cases with significant extramedullary involvement that created a dilemma in the initial diagnosis.

Case 1: An 8 year old boy presented with right sided neck swelling for 2 weeks. FNAC of the lymph node showed possibility of lymphoma. Excision biopsy of the node confirmed pre-B Lymphoblastic lymphoma. PET-CT showed focal hypermetabolism in the left

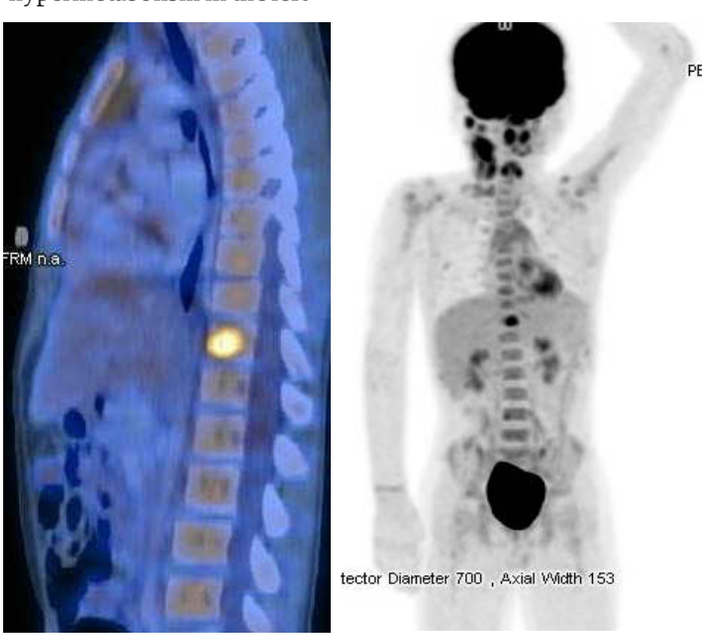

Fig. 1: PET scan of the case. 1 at diagnosis

anterior body of D11 vertebra (SUV 4.6) along with involvement of right cervical and supraclavicular lymph nodes, mild tonsillar and adenoid hyperplasia.CSF was negative and bone marrow aspirate and biospy revealed lymphomatous involvement of marrow with 27% lymphoid blasts. BCR-ABL and MLL were negative.

The patient was diagnosed with pre-B ALL with extramedullary lesions and started on chemotherapy for ALL (per UK ALL Reg B). The D11 vertebra remained PET active after induction and hence it was decided to give him local radiation to the vertebral body between the delayed intensification and maintenance stages of chemotherapy.

Case 2: A 1.5 years old girl who presented to an outside center with fever and prolonged bleeding for 1.5 months was found to have on examination, hepatosplenomegaly. CBC revealed lymphocytosis. CT Abdomen done showed a 5.7 *3cms pelvic mass, bilateral kidney masses and retroperitoneal lymph nodes. She underwent left adnexal mass excision with left salpingo-oophorectomy. Biopsy of the mass showed malignant round cells. Bone marrow aspiration and biopsy revealed lymphoid blasts. With the provincial diagnosis of lymphoma vs. leukemia, she received chemotherapy with intrathecal methotrexate and IV dexamethasone.

She was then transferred to our center where we noted persistent cervical lymphadenopathy, hepatosplenomegaly and an ill-defined left-sided lower abdominal mass on exam. She was anemic and thrombocytopenic with normal WBC counts. However, bone marrow biopsy did not show any malignant cells; possibly due to steroid therapy given earlier. A review of the bone marrow and abdominal mass biopsy slides and block at our center suggested pre-B cell ALL.

Due to non-medical reasons, there was an interruption in her inpatient stay at our center. In her 2nd presentation, her WBC count was 52,540/mm^3.

A whole body PET CT scan showed hepatosplenomegaly, bilateral cervical and pelvic lymphadenopathy, parenchymal soft tissue deposit in the liver, bilateral renal parenchymal deposits and retroperitoneal lesions. Bone marrow had > 70% lymphoid blasts. She was diagnosed with pre-B Cell ALL. Genetic testing showed MLL positive and hence she was started on treatment as per the BFM -ALL 90 Protocol (High risk group).

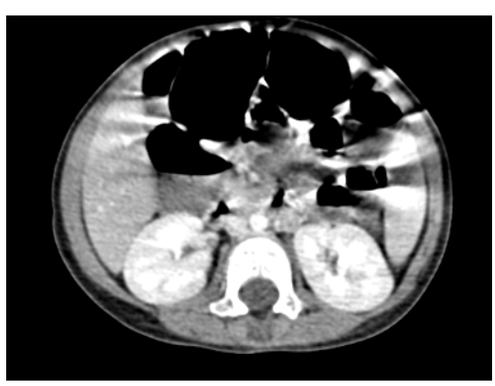

Fig. 2: CT scan abdomen of case. 2 at diagnosis

Discussion

Since Sternberg et al. first published the literature on relation between nodal and leukemic presentations of pre-B cell neoplasms in 1905, there have been multiple case reports and series on bizarre presentations of ALL in both pediatric and adult age group with extra-medullary involvement. About 80% of immature B-cell/pre-B-cell neoplasms present as BM involvement alone with no extra-medullary lesions. Isolated extra-medullary disease/ B-cell lymphoblastic lymphoma (B-LBL) incidence is about 10% and mixed B-ALL/B-LBL is also about 10%. While majority of the extra-medullary leukemia/lymphomas are T-cell in origin, B-LBL amount to about 10-15% of lymphoblastic leukemia/lymphomas.

Frequently, extra-medullary presentations often have bone marrow involvement as well at diagnosis. However, the peripheral blood counts may be normal at diagnosis and the BM involvement patchy, which can complicate the diagnosis. The definitive diagnosis depends on sophisticated testing including

comprehensive pathologic review, flowcytometry, immunohistochemistry, cytogenetics and molecular analysis to ensure diagnostic accuracy.

According to the 2008 WHO criteria, B-ALL and B-LBL are both classified under a spectrum disorder, with B-LBL defined by the presence of extra-medullary lesions with < 25% marrow blasts. The commonest sites of involvement of B-LBL are lymph nodes and extra-nodal sites including skin, bone and soft tissue. Other areas of involvement include head and neck (parotid gland, Waldeyer ring), retroperitoneum, mediastinum, pleura, breast, ovary, GI tract, kidneys, brain and soft tissue. Mediastinal masses are less common. B-ALL rarely present with skin involvement.

In pediatric patients, presence of extra-medullary disease has prognostic implications in pre-B ALL. Extra-medullary involvement in the form of either CNS or testicular involvement adversely affects prognosis. Other extra-medullary lesions do not necessarily have a prognostic significance; however can be a treatment challenge especially as in the case of our initial patient who had an isolated bone lesion. B-LBL with or without BM involvement is also treated with ALL like chemotherapy.

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TARGETED THERAPY

THE NEW FUTURE OF PEDIATRIC ONCOLOGY CARE

Cancers in pediatric population are fortunately infrequent and has overall, good cure rates. The crux of pediatric oncology care so far has been the administration of dose intensive cytotoxic chemotherapy and radiotherapy. With almost 75% overall survival rate for childhood cancer in developed countries, the current focus has shifted towards minimizing therapy related toxicities and addressing the cancers that are less sensitive to conventional treatment strategies. Targeted therapies have emerged as a strong candidate in this scenario where they aim to improve efficacy and decrease toxicity by specifically affecting malignant cells or their supporting stroma. With an advanced understanding of cancer genomics, we are now shifting more towards a personalized approach to treating cancer where we go away from the 'one-size-fits-all' chemotherapy protocols to searching for specific abnormalities that are present in different types of cancers and targeting those weaknesses.

Targeted therapies are a product of 'rational drug design' where a molecule integral to carcinogenesis or tumor growth is identified and then specifically manipulated. One of the earliest developed such drug was Imatinib mesylate for treatment of Chronic Myelogenous Leukemia (CML). In CML, t(9;11) Philadelphia chromosome leads to a fusion protein bcr-abl, which is a constitutively active tyrosine kinase (TK). Imatinib is a TK inhibitor and consequently decreases bcr-abl activity. The drug was developed in the early 1990s in USA and first went in to patient trial in 1998. It received FDA approval in 2001. Since its conception, Imatinib has contributed to the improvement of survival rates in CML from 31% in 1993 to 59% for those diagnosed between 2003 and 2009.

Targeted therapies can be broadly classified as follows:

- Hormone therapy – inhibits tumor growth/survival by manipulation of the endocrine system through exogenous administration of specific hormones or drugs that inhibit the production/activity of such hormones (Eg: Tamoxifen, DES, Flutamide, Octreotide).
- Signal transduction inhibitors - targets signaling pathways (TKI, mTOR, Braf etc.) with key roles in cancer cell survival and proliferation (Eg: Imatinib, Geftinib, Bortezomib, Temsirolimus).
- Gene expression modulator – modulates the endogenous transcription by specifically targeting those genes at the gDNA level, there by correcting the misregulated genes involved in oncogenesis.
- Apoptosis inducer – induces the otherwise 'immortal' cancer cell to undergo apoptosis (Eg: OGX-011, Hsp90 inhibitors).
- Angiogenesis inhibitor – Actively dividing tumors undergo an 'angiogenic switch on' that leads to tumor expression of pro-angiogenic factors thereby increasing tumor vascularization. Inhibitors of angiogenesis reduce the production of pro-angiogenic factors, prevent them binding to their receptors or block their actions (Eg: Bevacizumab/Avastin).
- Immunotherapies – Enhances the host's own immune response towards destroying the cancer cells. The various modalities used in cancer immunosuppressive therapy include dendritic cell therapy, adoptive T-cell transfer, genetically engineered T cells (CAR-T cells) and monoclonal antibodies (Eg: Rituximab, Alemtuzumab, Pembrolizumab)
- Small molecule/Antibody-drug conjugates – An antibody or a small molecule that specifically targets a tumor marker or receptor is linked to a biologically active cytotoxic agent via a stable, chemical, linker with labile bonds (Eg: Vintafolide, Gemtuzumab-ozogamicin, brentuximab-vedotin).

Targeted therapies differ from the standard chemotherapies in that they are deliberately chosen or designed to interact with their target, whereas many standard chemotherapies were identified because they kill dividing cells. The targeted therapies are often cytostatic whereas standard chemotherapy agents are cytotoxic.

Hence the typical side effects seen with the standard chemotherapy drugs may not be there with the targeted agents. The common side effect profile of targeted therapies are but not limited to the following - Diarrhea, rare GIT perforation, liver dysfunction, skin problems (acneiform rash, dry skin, nail changes, hair de-pigmentation), abnormal coagulation profile, high blood pressure etc.

Targeted agents are commonly given in combination with other specific agents or with one or more traditional chemotherapy drugs (eg: Trastuzumab in combination with Docetaxel in metastatic breast cancer that over expresses HER2/neu).

Targeted therapies have a few limitations as well. One is the development of resistance either through the mutation of the target so that the targeted therapy no longer interacts well with it or through activation of other pathways that bypass the target. There is also the issue that certain target antagonists are difficult to develop in the lab due to the complexity of the protein structure or the cellular pathways.

TARGETED THERAPY

The Triesta Center of Cancer Genomics at HCG is a state of the art genomics center offering comprehensive genomics based diagnostics with the aim of establishing a new standard of cancer care. Massively parallel deep sequencing of genes by Next Generation Sequencing (NGS) to test multi-gene mutation profile of tumors at 'one go' can provide a comprehensive understanding of the processes that drive an individual's cancer. The Genomics Center at HCG has profiled 500+ patient tumors for a larger number of somatic/actionable/ germ line mutations using NGS. The genetic profile of these patients, when linked to the clinico-pathological parameters, provided a deep genomic insight of the tumor and helped in selecting targeted therapy and personalized treatment for improved outcome.

The application of this sophisticated technology at our center will break the cycle of 'trial and error' medicine and link the test to patient tailored action and evidence based therapy/treatment plan in cancer. Using genomic markers for response to chemotherapy may dramatically improve response rates impacting the risk–benefit ratio for these patients which will not only be more cost effective but also add value in terms of changing therapy regimen, stratifying responders vs. non responders.

Upfront targeted therapy in pediatric oncology in India has so far been mostly limited to the use of TKIs in CML. But current international pediatric trials have started using newer targeted agents for a variety of other pediatric malignancies at the initial diagnosis. Examples include Rituximab for mature B cell lymphomas, brentuximab-vedotin for advanced stage Hodgkin's disease and gemtuzumab-ozogamicin (Myelotarg) for high risk AML. With the help of our committed personnels in our genetics lab, we hope to extend this advanced care to more children in India.

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MULTI-DISCIPLINARY TEAM (MDT) CASE DISCUSSION

A multidisciplinary team approach is integral in addressing certain patients' unique care situation by a team of health care professionals consisting of oncologists, surgeons, radiation oncologists, pathologists and radiologists to provide the right advice and ensure the best outcome. The pathology slides and radiology films are reviewed by the team and each physician provides expert opinion regarding the treatment plan best suited for the patient. The following are two such vignettes where the patients had rare presentation/complications and they were addressed appropriately through the MDT and proper management instituted.

Case 1:

A 6 year old girl presented with a painful mass in the left wrist for the last 6 months. A highly enhancing soft tissue mass was shown in the MRI along the medial aspect of wrist joint abutting the ulnar styloid and extensor carpi ulnaris tendon suggestive of a vascular tumour. A partial excision of mass was done at an outside center. The histology showed synovial cell sarcoma. Patient subsequently was referred to us. A repeat MRI of the left wrist showed residual mass which was active in the FDG PET scan with no evidence of metastasis.

A detailed discussion with a multidisciplinary team comprising of pediatric oncologists, orthopaedic surgeon and radiation oncologists was done. Since the previous surgery was not a gross total resection (GTR), the team decided to do local control upfront which included local excision of residual tumour followed by external beam radiotherapy. In pediatric non-rhabdoid soft tissue (NRST) sarcomas, the gold standard for management is GTR of the primary disease and metastatic lesions upfront, whenever possible. The patient then received adjuvant chemotherapy with Ifosfamide and Doxorubicin and continues to be in remission for over a year.

Case 2:

A 2 month old female presented with swelling of left nose, had an excision biopsy done outside that showed alveolar rhabdomyosarcoma (RMS). Patient was referred to us for further management. PET scan showed a metabolically active small subcutaneous soft tissue thickening in the left nasal ala concerning for residual disease and left submandibular level I B cervical lymph node involvement. She was started on chemotherapy per EpSSG Protocol RMS 2005 with Ifosfamide,Vincristine and Actinomycin, omitting Doxorubicin due to the young age. Patient had Klebsiella bacteremia after the 1st cycle, frank sepsis, multi-organ dysfunction and development of malignant hypertension after the 2nd cycle and a 2nd episode of Klebsiella bacteremia after the 3rd cycle all of which caused some treatment delays as well. Unfortunately, scans post the 3rd cycle showed local progression with loco-regional metastasis. She was labeled as progressive refractory RMS.

A MDT discussion was conducted involving pediatric oncology, ENT surgery and radiation oncology. She posed the following therapeutic challenges – very young age, progression of disease while on upfront chemo agents and severe infectious complications with aggressive chemotherapy. Since the patient had finished 3 cycles of chemotherapy, the team felt that proceeding with local control (surgical resection) was the next step. Had the patient been older, consolidating the local control surgery with radiation therapy would have been ideal. However, due to her young age, radiation involving head and neck runs the risk of serious long term complications. Treating her with an alternate regimen of high dose aggressive chemotherapy (Ifosfamide, Vincristine, Dactinomycin alternating with Carboplatin, Epirubicin and Vincristine) will also not be ideal because of her history of prior complications. Hence the team decided to proceed with a combination regimen of Irinotecan and Vincristine (VI). The VI combination was used in the Children's Oncology Group (COG) trial ARST0431 for RMS as a window regimen and shown to be effective with good tolerance especially while given concurrently with radiation. Patient tolerated the first cycle well with no serious complications and we will be proceeding with further cycles.

JOURNAL SCAN

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   To determine whether male and female patients differ with regard to acute treatment-related toxicities, data collected on the Children's cancer group (CCG) high-risk acute lymphoblastic leukemia (ALL-HR) study (CCG-1961) and standard-risk ALL (ALL-SR) study (CCG-1991) was reviewed. The incidence of toxicity among male and female patients was compared. It was noted that among ALL-HR and ALL-SR patients, females had significantly more hospital days, delays in therapy, grade 3 or 4 toxicities (e.g., gastrointestinal, liver), and supportive care interventions (e.g., transfusions, intravenous antibiotics) than males. Females were significantly more likely to have died of treatment-related causes than males in the ALL-HR group.

Editorial comment

It is important to note that ALL treatment mortality and morbidity in the above data review is higher in females who actually receive a year less of therapy than males in the CCG protocols. Even though the etiology for this disparity is not clear at present, these results call for a review of the current treatment strategies and assess the need for individualized treatment regimens based on the sex of the patient.

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   This study was undertaken to determine the long-term risk of intestinal obstruction from surgery, chemotherapy, and radiotherapy in adult survivors of childhood cancer. The incidence of intestinal obstruction requiring surgery (IOS) occurring 5 or more years after diagnosis was evaluated in 12,316 five year survivors in the Childhood Cancer Survivor Study (2,002 with and 10,314 without abdomino-pelvic tumors) and 4,023 sibling participants and the cumulative incidence of IOS was calculated. The incidence of late IOS at 35 years was 5.8% among survivors with abdomino-pelvic tumors, 1.0% among those without abdomino-pelvic tumors, and 0.3% among siblings, with impact on mortality in the survisors. As expected, abdomino-pelvic tumor and abdominal/pelvic radiotherapy within 5 years of cancer diagnosis emerged as risk factors.

Editorial comment

As the survival rate of childhood cancer continues to improve, focus should shift towards addressing the long term side effects among the adult survivors of childhood cancer. This study highlights the importance of appropriate patient counseling, promoting awareness about various complications and follow-up in the survivor population.

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VOL 1, NOV 2015

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Title
Untitled

Media
Mixed Media on canvas

Size
72 x 36 inches

Year
2009

Courtesy

Swasti Art Gallery, HCG K.R.Road

Proceeds of the sale of this painting will be used for assisting poor patients.

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