Rare Presentation of Large Cell Lymphoma

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ABSTRACT
Lymphoma is a common cancer of childhood. Its pathologic subtype of anaplastic large cell Non-Hodgkins Lymphoma (NHL) is rare and spread to the central nervous system (CNS) is even rarer. We present here such a case who presented to us with an acute history of fever and diplopia and co-existent polyarthritis since 8 years diagnosed as NHL with CNS involvement. CNS involvement is a rare presenting manifestation of NHL and is an important cause of morbidity and mortality in these patients. Chronic arthritis could be a risk factor or manifestation of immunodeficiency or immune dysregulation when associated with lymphoma. It is important to suspect NHL in children presenting with these symptoms for prompt evaluation and better clinical outcome.

Keywords: Pediatric lymphoma, Anaplastic large cell lymphoma, ALK-1.

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INTRODUCTION
Lymphoma is the third most common cancer among United States children.6 Of its two broad categories, Hodgkins Lymphoma (HL) and Non-Hodgkins Lymphoma (NHL), NHL is 1.5 times more common and affects boys three times as frequently as girls.

The clinical presentation of NHL depends upon the site, extent and pathologic subtype of the tumor. In the head and neck region it manifests as painless lymph gland enlargement; in the abdomen as mass or intestinal obstruction; in the Central Nervous System (CNS) as increased intracranial pressure. In the chest it usually arises in the anterior mediastinum leading to compression of the airways and superior vena cava.

The four major pathologic subtypes are Burkitt lymphoma (BL), lymphoblastic lymphoma (LL), diffuse large B cell lymphoma (DLBCL) and anaplastic large cell lymphoma (ALCL). About 70% of cases of ALCL are of T cell origin, 20% are of null cell origin and 10% of B cell origin. Patients with ALCL commonly have a t (2; 5) translocation (90%), which results in the formation of a fusion gene encoding the constitutively active NPM-Activin receptor like kinase 1 (ALK 1) tyrosine kinase.

ALCL manifests either as a primary cutaneous manifestation (10%) or as systemic disease (fever, weight loss) with dissemination to liver, spleen, lung, mediastinum or skin; spread to the bone marrow or CNS is rare.1,2 Secondary spread of primary nodal or systemic ALCL to the CNS is also unusual. Till date in literature only 15 cases of primary ALCL of CNS have been reported.1,2,4,5

CASE REPORT
A 16-year-old boy presented to us with intermittent low grade fever from 2 weeks, headache and double vision in left eye since 2 days and pain in the back and right leg since 1 day. Possible infective or inflammatory etiology with raised intracranial tension, e.g. viral encephalitis, vasculitis, DVT with embolization, trauma with fat embolism, thromboembolism was suspected. Our patient did not have symptoms of dyspnea, rashes, convulsions, vomiting and trauma. The child also had complaints of swelling, pain and restriction of movement in knees, ankles and multiple small joints of both lower limbs since the age of 6 years for which he had multiple orthopedic consultations and had received multiple medications but was never relieved. At the onset of the joint complaints child was diagnosed as a case of tuberculosis (TB) of left knee joint based on synovial fluid TB Polymerase Chain Reaction and had received anti-tuberculosis treatment for 6 months as per medical records.

Physical examination at presentation to us showed a well-grown child with a pulse rate of 96 per minute with normal rhythm, volume and character; respiratory rate of 22/min and BP of 120/72 mm Hg. He had no pallor, cyanosis, edema or significant lymphadenopathy at any of the lymph node areas and no calf tenderness. He had inflamed small joints of all 4 limbs as well as both ankles.

He was conscious, well behaved child, with intact higher functions. There was evidence of left lateral rectus palsy (6th cranial nerve); other cranial nerves were normal and no evidence of papilledema. Nutrition was normal. Power and tone were normal in all the joints and groups of
muscles. Deep tendon reflexes were brisk. Babinski’s sign was positive on both the sides. Cerebellar functions were normal and there were no signs of meningeal irritation. There were decreased breath sounds on right inframammary area without any adventitious sounds. There was no evidence of any organomegaly. With these findings, the initial provisional diagnostic possibilities considered were systemic onset juvenile rheumatoid arthritis, reactivation of tuberculosis with multi system involvement, histiocytosis and macrophage activating syndrome. The child had a normal hemoglobin, raised total leukocyte counts (21,830 per cu mm) with neutrophilic predominance (83%) and raised platelets (6,93,000 per cu mm), ESR of 28 mm at the end of 1 hour. Liver and kidney function tests were normal. There were decreased breath sounds in the right para hilar regions on chest X-ray. Contrast enhanced computed tomography (CECT) of chest showed mildly enhancing anterior mediastinal mass of 8.4 × 5.6 cm with a radiological differential diagnosis of thymic lesion or nodal mass, with sub centric nodes in pre and paratracheal region, subcarinal region with few subpleural subcentimetric opacities in bilateral lung fields (Fig. 1). On contrast enhanced scan of brain there were symmetrical areas of hyperintensity on T2 weighted imaging and FLAIR involving bilateral paramedian thalami with restricted diffusion on Diffusion weighted Imaging suggestive of encephalitis or infarcts (Fig. 2). Bone marrow aspirate was normocellular with increase in myeloblastic, megaloblastic, plasma cell numbers. Cerebrospinal fluid analysis was normal, lupus anticoagulant was absent, direct coombs test was negative, serum ferritin, plasma fibrinogen were in normal limits. The child was referred to pediatric oncology center for further management. CT guided biopsy of anterior mediastinal mass was carried out. Histopathology confirmed the diagnosis of ALCL. Immunohistochemistry showed T-cell immunophenotype with tumor cells immunopositive for CD 30, CD 3, ALK-1, Mic-2 and LCA and immunonegative to CD-34, CD-20, Pax-5 and CD-15. Positron Emission Tomography - CT whole body showed avid FDG uptake in the bilateral thalamic regions, pituitary fossa, in the spinal cord at the level of C1, in the prevascular, anterior mediastinal, right internal mammary, bilateral hilar and subcarinal nodes, right deep pectoral and left axillary adenopathy, nodular infiltrate in both lungs predominantly the lower lobes, perigastric, peripancreatic, periportal adenopathy, diffuse gastric wall thickening, pulmonary nodules suggestive of high grade lymphomatous involvement along with soft tissue deposits along the nerve roots exiting from the sacral foramina secondary to lymphomatous involvement. With the presence of generalized lymphadenopathy, a final diagnosis of secondary ALK-positive ALCL with CNS involvement was made. Patient was to be started on chemotherapy but before that child landed up in hypovolemic shock due to severe upper gastrointestinal bleeding and succumbed to the same. No postmortem was carried out and cause of death was given as hypovolemic shock due to upper gastrointestinal bleeding in a child with stage 4 non-Hodgkin’s lymphoma.

DISCUSSION

ALCL accounts for approximately 3% of adult and 10 to 15% of childhood non-Hodgkin’s lymphoma. It frequently involves both nodal and extranodal sites. Extranodal sites which are most commonly involved are skin, bone, soft tissue and liver. Primary CNS lymphomas are rare, mostly represented by diffuse large B cell lymphoma. Till date in literature only 15 cases of primary ALCL of CNS have been reported. CNS is rare site to be involved by systemic ALCL. Kaplinsky et al reported a 2-year-old boy with generalized lymphadenopathy, skin involvement, hepatosplenomegaly and pulmonary infiltrates along
with CNS involvement; our case did not have cutaneous manifestations. A case reported by Karikari et al was a primary ALK-1 positive ALCL who developed cervical lymphadenopathy 3 weeks after the diagnosis of primary CNS lymphoma. In their report, they have discussed the possibility of a primary nodal lymphoma with metastasis to the brain.

ALK-1 positive ALCL is a clinically aggressive lymphoma. However, overall survival and longer disease free survival is observed after treatment with aggressive chemotherapy. Patients affected by ALK-1 positive ALCL have a significant better overall survival than ALK-1 negative ALCL patients (5-year overall survival: 70 to 80 vs 33-49%). It is still controversially discussed if this observation can be explained by the biological role of the ALK-1 fusion proteins or by the younger age of ALK-1 positive ALCL patients. Another unexplained manifestation in our case was the long standing history of polyarthritis which had been unresponsive to the antituberculous treatment that the child was given at the outset and the presence of arthritis at presentation to us. The PET CT did not show any joint or bone uptake. So it is unlikely that the arthritis was because of lymphomatous etiology. Systemic onset juvenile idiopathic arthritis is known to get complicated with macrophage activating syndrome and hemophagocytic lymphohistiocytosis. Autoimmune conditions like arthritis and lymphomas are found in primary immunodeficiency disorders like hyper IgM syndromes, autoimmune lymphoproliferative syndrome. But there were no other autoimmune manifestations other than arthritis in favor in our patient. Immunological workup for immunodeficiency was not done for this child.

Gastrointestinal bleeding is a known complication of non-Hodgkin’s lymphoma. The PET scan in our patient showed diffuse gastric wall thickening. The platelet count at this stage was normal. Local pathology bleeding profusely into the GI tract with resultant hypovolemia caused death of the child. This exceptionally unusual case widens the differential diagnosis of mediastinal mass in childhood and emphasizes that thorough workup and clinical examination are the most important for early diagnosis and treatment.

REFERENCES