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Case Report

Anaplastic large cell lymphoma: a rare cause of extreme neutrophilia in a child

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ABSTRACT

Anaplastic large cell lymphoma (ALCL) in children can present with a broad spectrum of clinical manifestations which apart from nodal and extra nodal disease include paraneoplastic phenomena that can mimic an infection or inflammatory illness leading to delayed diagnosis. The following case report describes a child with prolonged fever, hepatosplenomegaly, polyserositis and extreme neutrophilia masquerading as an infection or inflammatory disorder for long before the definitive diagnosis of ALCL was made. This case highlights the rare paraneoplastic phenomena in ALCL and the heightened need to suspect this disorder when the search for underlying infections and connective tissue disorders are not conclusive.

Keywords: Anaplastic large cell lymphoma, Neutrophilia

CASE REPORT

A three year old boy was admitted to our hospital with history of high grade continuous fever of three weeks duration with no associated symptoms. He had been admitted in two other hospitals prior and had been administered multiple intravenous antibiotics. There was no significant past history. Examination revealed an ill looking child with pallor, icterus, presence of small cervical and axillary lymphadenopathy (1x1 cm), hepatosplenomegaly with polyserositis manifesting as moderate ascites and bilateral pleural effusion. There was no rash or arthritis. Initial investigations included haemoglobin 90 grams/L with positive direct coombs test, white blood cell (WBC) counts 20.7 x 10^9/cu.mm with 80% polymorphs and platelet count 5 lakhs/cu.mm. The liver function tests (LFT) showed total bilirubin of 4 mg/dl with indirect fraction 2 mg/dl, normal enzymes and albumin 25 gram/L. The renal functions were normal. He had erythrocyte sedimentation rate (ESR) of 70 mm/hour and C-reactive protein of 80 mg/L. There was no organism isolated in blood culture and work up for common infections like enteric fever, malaria; leptospirosis and scrub typhus were negative. Broad spectrum antibiotics were started. Antinuclear antibody test was negative. Skiagram of the chest showed bilateral

mild pleural effusion. Sonography of the abdomen showed hepatosplenomegaly with normal echogenicity, numerous slightly enlarged nodes at the portahepatis, celiac, mesenteric group, diffuse patchy thickening of omentum and moderate free fluid abdomen. This prompted a work up for tuberculosis which was negative. Serology for human immunodeficiency virus (HIV) and Epstein Barr virus (EBV) was also negative. Immunoglobulin profile was normal. Ascitic tap revealed WBC count 5600/cu.mm with 95% neutrophils. While on antibiotics he continued to be febrile, had increasing icterus, ascites with steadily rising WBC counts upto 110 x 10^9/cu.mm. The range of WBC counts during hospital stay is shown in Figure 1. Due to poor response to antibiotics, other alternative diagnosis was considered and a lymph node biopsy and bone marrow aspiration were done.

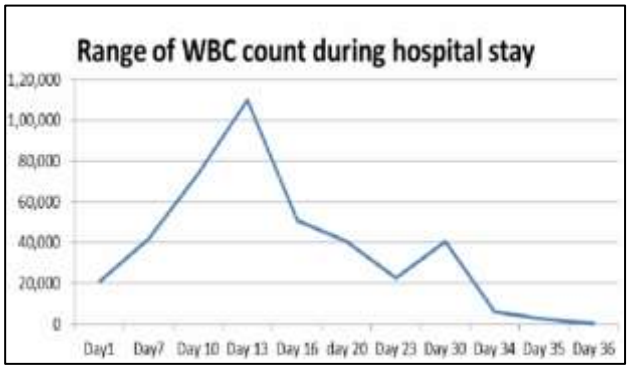

Figure 1: The trend of WBC counts in the child.

The lymph node histopathology showed diffuse effacement of architecture replaced by monomorphous intermediate to large cells with eosinophilic cytoplasm with vesicular nucleus with nucleoli. Few lymphocytes and plasma cells were seen. Immunohistochemistry (IHC) showed tumour cells positive for CD43, leucocyte common antigen, CD30, Anaplastic lymphoma kinase-1 (Alk-1), CD4 and negative for CD3, CD20, CD79a, CD15, and latent membrane protein. Ki67index was 30-40%. The findings were diagnostic of Anaplastic Large Cell Lymphoma.

Bone marrow morphology showed no involvement by ALCL. On Day 10 of admission he developed shock with acute kidney injury and coagulopathy. Work up for sepsis was again negative. While the criteria of HLH were met, the extreme neutrophilia and polyserositis could not be explained. Cerebrospinal fluid analysis needed for staging the disease was not done due to coagulopathy.

The child was treated with multiagent chemotherapy as per ALCL 99 protocol for high risk disease which included a prephase of dexamethasone and cyclophosphamide followed by Course A consisting of Ifosfamide, Cytarabine and Etoposide. Methotrexate was omitted due to renal failure and serositis. Though fever subsided after starting steroids, the child showed deterioration with progressive cholestasis, renal failure, areas of extensive skin necrosis and gastrointestinal bleed. He developed profound neutropenia post chemotherapy and died of multiorgan dysfunction during the week 8 of illness.

DISCUSSION

Anaplastic large cell lymphoma (ALCL) is a peripheral T cell lymphoma that comprises about 15-20% of Non-Hodgkin Lymphoma (NHL) in children.[1] They are characterized histopathologically by a variable number of anaplastic "hallmark" tumour cells or small cell type and lymphohistiocytic type variants and an immunohistochemistry profile of CD30 and Alk-1 positivity. They have a broad range of clinical manifestations which include nodal disease, isolated or extensive extra nodal involvement which includes skin, bone, lung, liver and spleen. They are also associated with many atypical presentations which include fever of unknown origin (FUO) mimicking sepsis, arthritis, autoimmune haemolytic anaemia, hemophagocytosis and leukemic presentation.[2-5] While the classic presentation with lymphadenopathy and hepatosplenomegaly can be diagnosed early, the many atypical presentations lead to a delay in diagnosis. These paraneoplastic manifestations are attributable at least in part to the abundant release of cytokines by the tumour cells. Apart from the risk stratification of ALCL based on organ of involvement, these unusual manifestations represent an aggressive tumour subtype portending a poor outcome.[2,6]

In a retrospective study of twenty three cases of ALCL by Mosunjac et al which included adults, five cases who did not have a premortem diagnosis were those who presented as fever of unknown origin (FUO) with disseminated intravascular coagulation (DIC) prompting a work up for sepsis which was negative.[2] Post mortem biopsy histopathology showed intravascular spread of the tumour and immunohistochemistry showed strong membrane positivity for CD25 (soluble interleukin-2 receptor), further lending credence to the role of cytokines in the aggressive course of disease. Our child had also presented as FUO with sepsis like picture and DIC.

ALCL cells express many cytokines including Interleukin-1 (IL-1), IL-5, IL-6, IL-8, IL-9, tumour necrosis factor – alpha (TNF-alpha) as well as a variety of cytokine receptors.[3] These are known to produce symptoms like fever, rash, anaemia even without bone marrow involvement and abnormal laboratory parameters like raised ESR and low serum albumin.[6] Cytokine expression is postulated to lead to an aggressive disease course and contribute to treatment resistance.[7]

Extreme leucocytosis has been rarely described in ALCL.[7,8] In a case report by Sueki et al, high levels of Interleukin-17 were found in an adult with ALCL who had presented with extreme leucocytosis and died due to

multiorgan dysfunction.[7] To the best of our knowledge there is only one case report in a child with ALCL who presented with a leukemoid reaction and had a fatal course.[9] In a case series by Chang et al, a study of five adults with ALCL presenting with leucocytosis found a significantly higher G-CSF and TNF-alpha expression and a rapidly fatal course in them compared to cases without leucocytosis.[10] Due to financial constraints we could not measure the cytokine levels in this patient.

CONCLUSION

In conclusion, ALCL should be suspected in cases of FUO with neutrophilic leucocytosis where no infection or inflammatory disease is diagnosed. ALCL in children can present with various paraneoplastic phenomena that can create a diagnostic confusion with infections or inflammatory disorders. Biopsy of even slightly enlarged lymph nodes can clinch the diagnosis. These cases represent an aggressive subtype of ALCL with manifestations due to hypercytokininemia. Though measurement of cytokine levels at present may not be in the reach of all, they could serve as a prognostic marker in the future.

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