Case Reports

Subcutaneous panniculitic T cell lymphoma mimicking histiocytic cytophagic panniculitis in a child

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ABSTRACT

Subcutaneous panniculitc T-cell lymphoma is a very rare malignancy in the pediatric age group, its association with hemophagocytic syndrome had been described but the association with the skin lesions mimicking histiocytic cytophagic panniculitis which is characteristic of hemophagocytic syndrome has not, to our knowledge, been described in children. We report a child with panniculitic T-cell lymphoma associated with bone marrow hemophagocytosis and subcutaneous histiocytic infiltration with active phagocytosis simulating histiocytic cytophagic. We stress the importance of searching for T-cell lymphoma in patients with panniculitis and hemophagocytic syndrome.

Keywords: Hemophagocytic syndrome, cytophagic panniculitis, T cell-lymphoma.

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The hemophagocytic syndrome is a clinico-pathological entity in which macrophages phagocytose blood elements in bone marrow and other reticuloendothelial tissues. Clinically, it is characterized by fever, hepatosplenomegaly, pancytopenia, lymphadenopathy, coagulation disturbance, hypertriglyceridemia and low ferritin with varying degrees of severity. It is generally classified into primary familial type with autosomal ressesive inheritance and acquired (reactive) type which is associated with infectious (viruses, tuberculosis etc.) or malignant aetiology, particularly T-cell lymphoma.[1-4] Histiocytic cytophagic panniculitis (HCP) is the skin manifestation characteristic of hemophagocytic syndrome. The hallmark of cytophagic panniculitis (CP) is infiltration of subcutaneous fat with histiocytes with active phagocytosis.[3,4] Clinically, these patients present with fever, skin nodules, hepatomegaly and increased liver enzymes, neutropenia and they may progress to develop the full-blown picture of HPS with coagulopathy, hypertriglyceridemia and pancytopenia.[4] Although the triggering agent can be either benign or malignant the terminal event of HPS can be fatal.[4,5] Search for subcutaneous T-cell lymphoma is mandatory as the histopathological appearance of such lymphomas can be very similar to HCP.[4,6] Some investigators suggest that HCP is an early stage of lymphoma by finding clonal T-cell proliferation[6] and some histopathologists had used the terms HCP and panniculitic T-cell lymphoma (PTCL) interchangeably indicating the difficulty in differentiating one from the other.[7] In other reports infectious etiology (Herpes simplex virus, Ebestein-Bar virus) rather than lymphoma was documented.[3-5,8,9]

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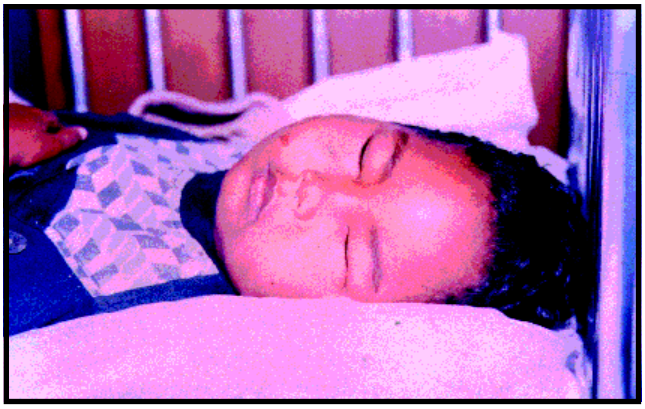

Figure 1 - Picture showing massive swelling of the cheeks extending to periorbital region.

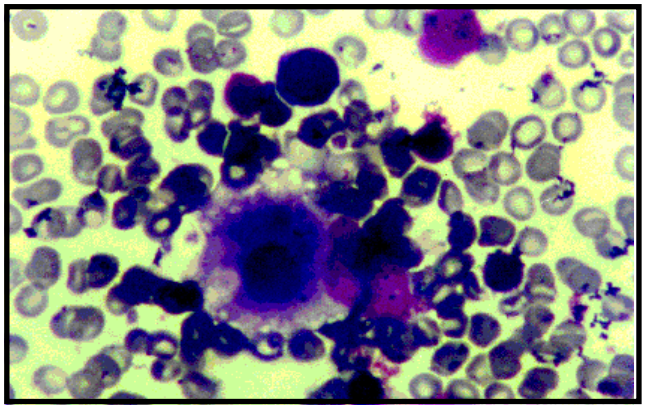

Figure 2 - Bone marrow showing a macrophage with red blood cell and lymphocyte in its cytoplasm (hemophagocyte).

Case Report. A 4-year-old Sudanese boy presented with subcutaneous swelling at the left inguinolumbar region associated with marked loss of weight for 6 weeks. Initial examination revealed a relatively well looking child of 15-kg weight, afebrile with no lymphadenopathy. The swelling was 3x4 cm firm, nontender, attached to subcutaneous tissue with some hyperpigmentation. The liver was 3 cm below costal margin, firm and there was no splenomegaly. Initial CBC: WBC 4000 with normal differential, Hb12 g/dl & platelet 200,000, ESR 5mm/hr; Mantoux test was negative. The child was admitted for skin biopsy, on admission he developed high swinging fever of 39-40°C. that continued for 14 days. At same time he developed bilateral cheek swelling which progressively increased over a few days to become massive involving the whole face with eyes almost buried (Figure 1). The swelling was firm and not tender, liver still enlarged but no splenomegaly or lymphadenopathy throughout his illness, there was a 1x1 cm red firm nodule on the left chest wall which appeared after admission. CNS and musculoskeletal systems were normal but later on he started to have diffuse bony tenderness. White blood cell count decreased progressively from 4 to 3, 2 then 0.9 thousand and neutrophil from 40% to 30% then 20%. Liver enzymes showed three fold increase throughout his illness, ESR increased from 5 to 14.PT and APTT were normal, triglyceride level 1.6 (0.34-2.3), lactate dehydrogenase (LDH) 1147 (100-190), urine VMA spot test was negative and antinuclear factor (ANA) was negative. Infectious causes were ruled out by negative cultures (blood, urine and surgical wound swab). Typhoid and brucella titters, gastric aspirate for alcohol acid fast bacilli (three times), malaria smear, HIV and leshmania serology and Ebestein bar virus IgM were all negative. Bone marrow aspiration revealed

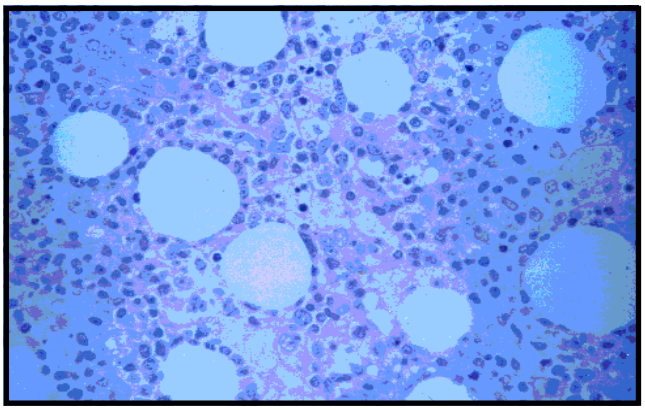

Figure 3 - Neoplastic cells infiltrate the subcutaneous tissue with rimming of fat cells. The infiltrate consists of small and large lymphoid cells admixed with hitiocytes, containing karyorrhectic bodies (H & E x 200).

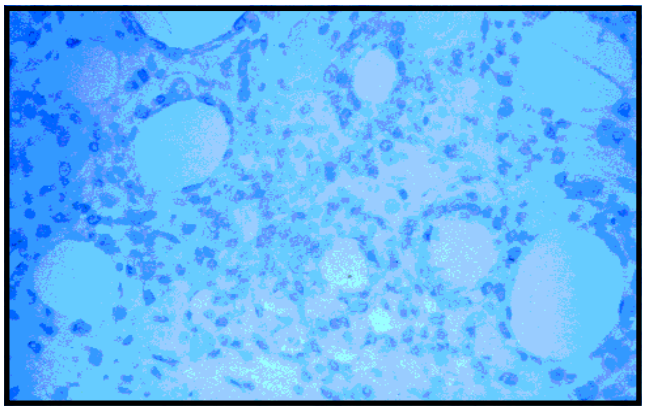

Figure 4 - CD8 - Positive lymphoid cells rimming fat cells (Immuno-peroxidase technique, x 200).

moderate reduction in overall cellularity with conspicuous increase in hemophagocytosis, (Figure 2), no leukemia or lymphoma identified and no malaria or leshmania parasites were seen.

Radiological investigations. Chest X-ray and X-ray of jaw and mandible were normal; ultrasound abdomen showed hepatomegaly, no splenomegaly or renal masses. CT scan of the chest showed no lymph node or mediastinal masses, CT abdomen revealed conspicuous increase in subcutaneous tissue of the left abdominal wall with increase in density of subcutaneous fat. At this stage we considered the diagnosis of HCP and considered the treatment options, he was already receiving different antibiotics (cefuroxime then pipracillin/gentamicin then ceftriaxone/amikacin) without improvement so we opted to treat him with high dose intravenous immunoglobulin (1 gm/Kg/dose for three doses) plus steroids (prednisone 2mg/Kg/day) as there was administrative difficulties in transferring him to a specialized center. He showed good response within three days with decrease in temperature and modest decrease in facial swelling. His white blood cell count improved from 0.9 to 4000, hemoglobin remained the same and platelet showed modest decrease to 140,000. Skin biopsy was first reported as cellulitis but it was sent for a second opinion and reported as: atypical lymphoid cells infiltrating subcutaneous tissue. The cells rimmed individual fat cells in a lace-like pattern. The infiltrate comprised of small and large lymphoid cell with round to irregular nuclei and occasional prominent nulleoli. (Figure 3).

Numerous karyorrhectic bodies were seen both inside and outside the histiocytes. Many mitoses were seen. Cells infiltrate blood vessels and extend into deep dermis. Immunophenotyping of paraffin-embedded tissue showed T phenotype. The cells were positive for CD3 and CD8. (Figure 4). The cells didn't express CD30, CD56 and CD57. In-situ hybridization for Ebestein-Barr virus was negative.

TCR gene rearrangement was detected by TCR-PCR performed on the paraffin-embedded tissue. These findings are consistent with the diagnosis of panniculitic T-cell lymphoma and the patient was referred to an oncology center for chemotherapy.

Discussion. This case represents the rare association of PTCL and features of histiocyte infiltration of subcutaneous tissue with active phagocytosis suggestive of HCP together with bone marrow hemophagocytosis. In literature, at least 3 cases of PTCL were reported in children, in one of these, HPS was present, and this child was treated with chemotherapy but did not respond and died 14 months after diagnosis.[10] The second case was a 5 year old girl with idiopathic myelofibrosis. She was treated with high dose steroids but succumbed later with recurrent sepsis.[11] In the third case there was no bone marrow involvement and the patient responded to prednisone and remained well 3 years after diagnosis.[10] Another case of cutaneous T-cell lymphma without panniculitis but with histiocytic infiltration of the skin in an 11 year old boy did not respond to steroids.[12] On the other hand, HCP had been described in at least 3 pediatric patients and all of them responded to cyclosporine, none of them were associated with T-cell lymphoma.[13,14] In adults, however, the association of PTCL with HPS and HCP is well documented.[3-5,8] In one series 50% of the cases of HCP were associated with viral infections in patients with altered immunity including immunodeficiency, autoimmune diseases and rarely following bone marrow transplantation.[4,15] Other associations with tuberculosis and mycoplasma infections has been reported.[16] The pathophysiology is thought to be the abnormal cytokine production like interferon gamma and granulocyte/macrophage colony stimulating factor produced by reactive or neoplastic T lymphocytes.[1,4,17] In a large series of 16 adults with PTCL intense positivity for cytotoxic granular proteins indicated an origin from cytotoxic T lymphocytes.[18] Differentiating PTCL and HCP can be extremely difficult and it is mandatory to send biopsy specimens of HCP or panniculitis with HPS to centers with experience in immunohistochemistry and tumor markers to be fully evaluated for possibility of PTCL. Different modalities of treatment for HCP with or without PTCL had been tried including high dose steroids, high dose immunoglobulin with or without steroids, immunomodulators, different chemotherapeutic agents and peripheral stem cell transplant with conflicting results.[4,7,13,14] In this patient, we were able to exclude the most important infectious causes particularly common in tropical areas (the child being from Sudan), especially malaria, leshmania and tuberculosis which are known to be associated with HPS. Epestien-Bar virus was ruled out but other viruses (herpes, CMV) and mycoplasma were not investigated. We conclude that the presence of panniculitis in children especially when associated with systemic manifestations should alert the physician and the pathologist to investigate for presence of HPS with or without HCP. Moreover, a search for PTCL is mandatory and immunohistochemistry should be carried out for the skin biopsy specimens. As experience with treating these patients is very limited, more case reports are warranted so that protocols can be agreed upon hoping to improve the guarded and unpredictable prognosis.

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