



INTERESTING LESIONS OF BONE MARROW

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ABSTRACT

Bone marrow provides a unique microenvironment for the orderly proliferation, differentiation and release of blood cells. Diseases that distort the marrow architecture such as granulomatous disease, storage disorders or metastatic disease disturb the normal function. We hereby present three cases, Hemophagocytic lymphohistiocytosis, Amyloid involving bone marrow and Neimann Pick disease, which are rare lesions in bone marrow,.

KEYWORD: Bone marrow, Hemophagocytic lymphohistiocytosis, Amyloid, Nimann Pick disease.

MATERIAL AND METHODS

All the three cases were investigated for routine biochemical examinations. Depending on the clinical diagnosis, relevant special tests were performed. Bone marrow aspiration and biopsy was done using Jamshidi bonemarrow needle and samples were processed accordingly.

INTERESTING LESIONS OF BONE MARROW

Bone marrow provides a unique microenvironment for the orderly proliferation, differentiation and release of blood cells. The normal marrow is organised anatomically in subtle but important ways. Diseases that distort the marrow architecture such as granulomatous disease, storage disorders or metastatic disease disturb the normal function.

We hereby present three cases, which showed rare, interesting pathological findings in bone marrow examination.

Case 1

A two month old male child was brought to paediatric OPD with complaints of cough, fever, vomiting and shortness of breath of 3 weeks duration. Fever was high grade, continuous which subsided with medication. Dyspnoea aggravated on feeding. 2 days before admission, he developed morbilliform rash, not associated with itching. Child was born of a consanguineous marriage, first in birth order. There was no significant antenatal or post natal history. On examination, baby was dyspnoeic, febrile and pale. Morbilliform rash was seen all over the body. No

Cyanosis/clubbing/icterus/oedema/lymphadenopathy was noted. Vital signs were normal.

SYSTEMIC EXAMINATION

General examination revealed mildly distended abdomen. Liver was palpable 3.5cm below the right costal margin. Spleen was palpable 3cms below the left costal margin, smooth surface and non tender. No shifting dullness noted. A differential diagnosis of? Bronchopneumonia with septicaemia?? Neonatal TORCH infection was considered.

Investigations done revealed a blood picture which showed Hb-5gm%, Total leucocyte count of 3000/cu.mm, and platelets- 1.3 lakhs/cu.mm, suggestive of pancytopenia. Reticulocyte count was 0.4%. Other routine biochemical parameters like LFT, RFT were within normal limits. C-reactive protein was increased - 35.9mg/dl (n=6mg/dl.). ESR was 28 & 64mm - 1st & 2nd hr respectively. Serum triglycerides (557 mg/dl) and serum ferritin (>16,500 ng/ml) and Serum LDH levels were increased (1544u/L). Serum fibrinogen (65 mg/dl) was decreased. TORCH profile was negative. Ultrasound abdomen revealed hepatosplenomegaly, minimal gallbladder wall thickening, and ascites. Chest X-ray was normal.

To identify the underlying cause, bone marrow aspiration was done from right anterior tibial tuberosity under aseptic conditions. Aspiration smears were showed hematopoietic cells and histiocytes. Most of the marrow histiocytes showed phagocytosis of red blood cells, platelets and lymphocytes also. Based on these findings,

a diagnosis of Hemophagocytic lymphohistiocytosis was made.

Case2

A 27 year old female presented with right knee joint pain and swelling since 1 week .Pain gradually increased by the end of the day. There were no associated complaints. Past history of abdominal pain 6 yrs ago, lasted for one month was noted. On USG examination, she was diagnosed as left ovarian hemorrhagic cyst. As she had history of recurrent joint pains involving small joints of hands and feet, and avascular necrosis of right tibia, immunological profile done revealed positivity for RA factor and ANA. As she was also found to have albuminuria, apart from relevant tests, renal biopsy was performed, which revealed amyloid deposits in renal parenchyma leading to nephrotic range proteinuria. During the course of illness, she developed generalised weakness. Peripheral smear examination revealed pancytopenia. Serum B12 and folic acid levels were within normal limits. As Bone marrow aspiration were hypocellular, bone marrow biopsy was done, which revealed bony trabeculae with reduced hemopoietic elements and focal deposition of eosinophilic, homogenous extracellular material. Special stain congo red showed majenta color positivity. Final diagnosis of amyloid deposition in the bone marrow was made.

CASE 3

A 13 yrs male child presented with fever, dyspnoea and jaundice since 10 days. History of malena +. Past history of jaundice, 5 episodes since the age of 10 yrs, for which he was treated with herbal medication. His elder sister died of same disease. On examination, hepatosplenomegaly was present. No lymphnodes were palpable.CBP done showed pancytopenia.Bone marrow aspiration done from iliac crest showed hypercellular marrow. E: M ratio 3:1 with megaloblastic erythropoiesis.Granulopoiesis showed all stages of maturation with increased eosinophilic precursors. Lymphocytes were slightly increased. Megakaryocytic series was normal. Reticuloendothelial cells series showed occasional large cell with abundant wispy cytoplasm and an eccentric bland nucleus, suggestive of storage disorder, morphologically favouring Neimann Pick disease. Patient was referred to higher centre for getting enzyme levels done.

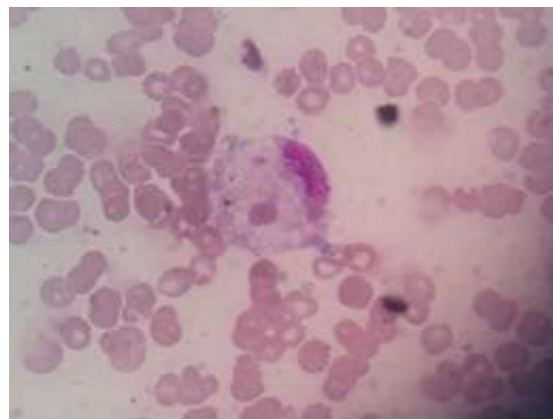


Figure 1: Bone marrow aspirate smears showing phagocytosis.(Leishman stain,10x)

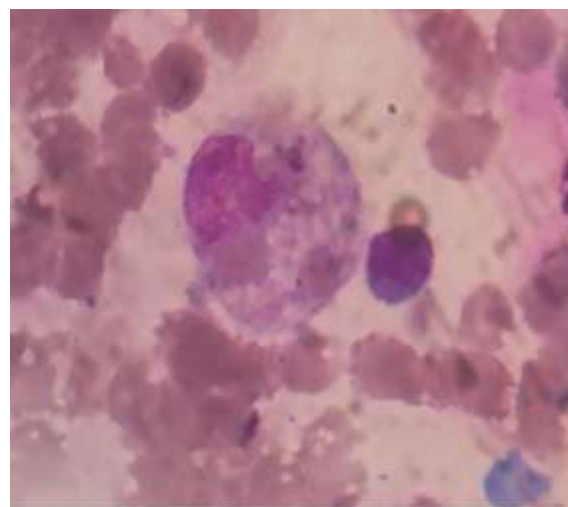


Figure 2: BMA smear showing phagocytosis of lymphocytes (Leishman stain x40x)

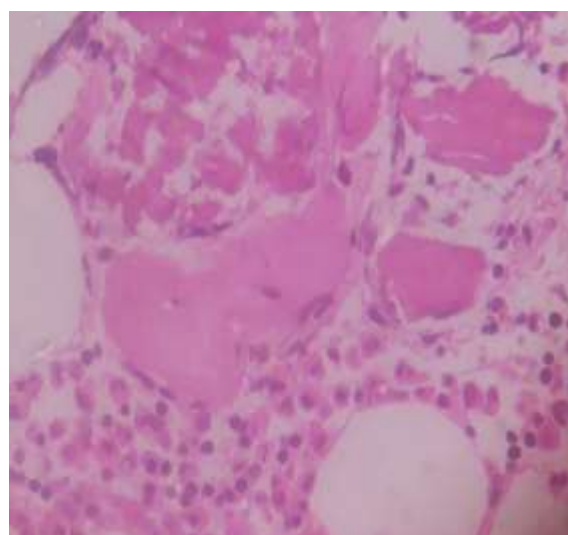


Figure 3: Bone marrow biopsy showing eosinophilic amyloid material. (Hx&E stain.40x)

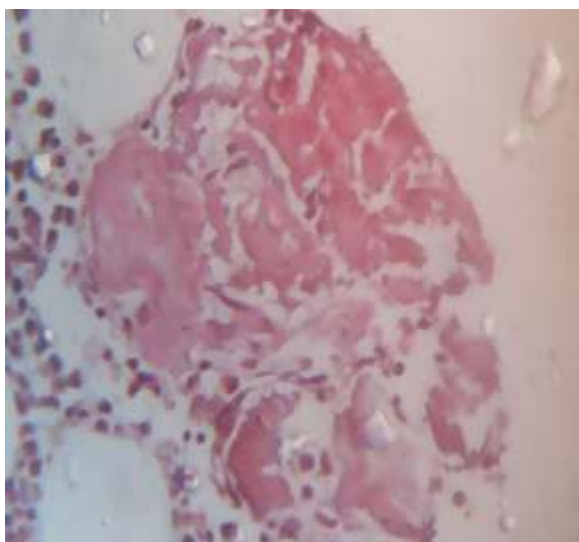


Figure 4: Bone marrow biopsy showing magenta colour positivity of amyloid material. (Congo red stain 40x)

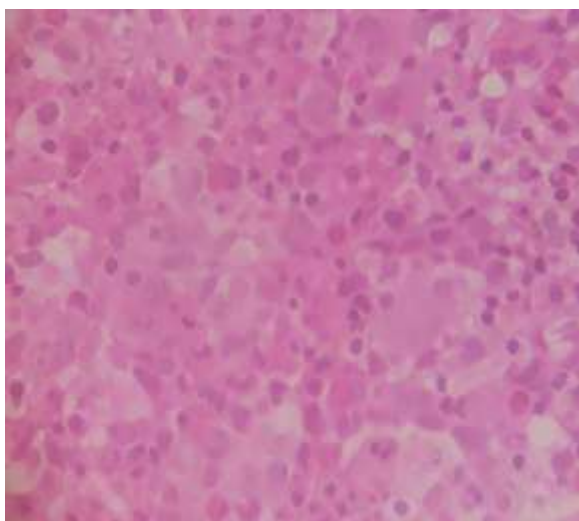


Figure 5: Bone marrow biopsy showing cells with abundant wispy cytoplasm and an eccentric bland nucleus. (Leishman stain.40x).

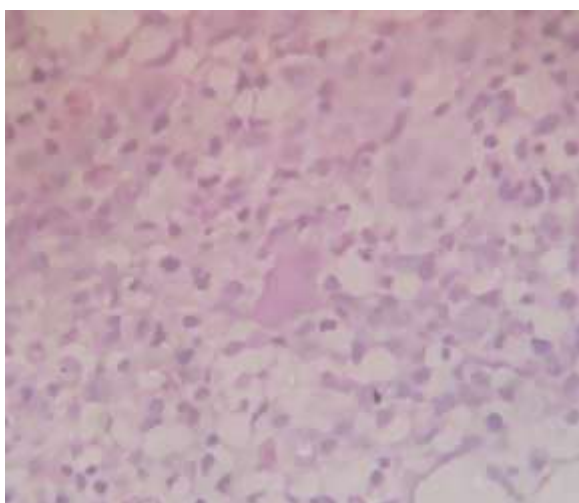


Figure 6: Bone marrow biopsy showing PAS stain positivity (PAS stain.40x).

DISCUSSION

The hemophagocytic syndromes are a group of disorders which show proliferation of phagocytic histiocytes that are present in all hematopoietic organs.

Familial HLH is an autosomal recessive disease that develops during infancy in most cases though it can affect all age groups from preterm neonates to elderly adults. Parental consanguinity is common and approximately two thirds of cases occur in siblings.^[1]

Reactive or secondary hemophagocytic syndrome is an uncommon disorder that is often associated with infection or lymphoma. Various infections have been associated with HLH and viral associated HLH is by far the most common form.^[2]

Herpes family virus including EBV and CMV are frequent causes of infection associated with secondary HLH.^[3] Systemic onset of juvenile idiopathic arthritis and systemic lupus erythematosus are the rheumatological conditions most commonly seen with macrophage activation syndrome.^[4] Among malignancies acute lymphoblastic leukemia and lymphoma have been reported in children with HLH.^[5]

Most patients with familial HLH have defects in lymphocyte cytotoxicity, leading to ineffective infection control and dysregulation resulting in massive activation and expansion of cytotoxic T lymphocytes and macrophages.^[6] The immune activation results in marked elevation of inflammatory cytokines and extreme hyper inflammatory state.^[7] Clinically patients with both primary and secondary or reactive HLH typically present with high grade fever, progressive cytopenias, liver dysfunction, coagulopathy and variable degree of neurological manifestations.^[8] A current accepted theory involves an inappropriate immune reaction caused by proliferating and activated T cells associated with macrophage activation and inadequate apoptosis of immunogenic cells. Although the precise mechanism remains unclear, many research teams propose convincing pictures for the role of perforin and natural killer (NK) cells in the hemophagocytic-lymphohistiocytosis subtypes. 30% of cases have mutations in perforin genes.^[9]

Amyloid deposits in the bone marrow are rare.^[10] In generalized vascular amyloidosis the vessels of the bone marrow are sometimes involved but parenchyma is rarely affected, in amyloidosis secondary to chronic diseases such as rheumatoid arthritis or osteomyelitis. Apart from its occurrence as in accompaniment vascular amyloidosis, 3 types of amyloidosis of the bone marrow amyloidosis: (a). Diffuse amyloidosis with or without coexisting local tumor like masses. (b). Amyloidosis associated with malignant tumor. (c). local tumor like accumulations of amyloid in the absence of generalised amyloidosis. General amyloidosis with the involvement of bone marrow in the absence of any demonstrable

primary disease seems to be first described by Garber^[12] Primary amyloidosis can no longer be regarded as extremely rare, but amyloid deposits in bone marrow are very common. Case with myeloma protein in the blood showed amyloid deposits in the bone marrow. There was evidence of chronic infection in this patient in the form of arthritis. When amyloidosis occurs in association with malignant disease it usually accompanies myelomatosis but sometimes occur with renal cancer or medullary thyroid cancer.^[11] Our patient had no other symptoms except long standing joint pains. Cases with local amyloidosis and Bence –Jones proteins in the urine without radiologically or histologically demonstrable myeloma have been described.^[13]

Amyloidosis are disorders of secondary structure in which a soluble protein secreted from a cell forms insoluble, fibrillar tissue deposit leading to organ dysfunction. The site and rate of deposition determines clinical presentation. Amyloid deposits contain a single fibrillar component and minor nonfibrillar component. Patients with MIDD-Monoclonal immunoglobulin deposition disease, without myeloma usually present with proteinuria or with full nephrotic syndrome with nodular glomerular sclerosis and slowly developing renal failure.^[14]

Approximately 40% of the patients have more than 10% plasma cells in the marrow. Light chain immunophenotyping of the marrow cells, even in the absence of increased number of plasma cells, usually reveal the distortion in the ratio of K or λ , reflecting the L –chain type of the amyloid precursors.^[15]

Our case also showed heavy proteinuria with amyloid deposits in kidney and also in bone marrow.

Niemann pick and Gaucher diseases are amongst the various lysosomal storage disorder which manifest with infiltration by macrophages in reticulo endothelial system and other organs of the body.^[16] Lysosomal storage disorders are rare inborn errors of metabolism with a combined incidence of 1 in 1500 to 7000 live births. These result from inherited deficiency of one or more of the many catabolic enzymes located in the lysosomes. These group of inborn errors of metabolism encompass >500 different disorders, each characterised by the accumulation of the specific substrate. Such accumulation of the substrate within the lysosomes of the cells is believed to contribute to the disease manifestation. These relatively rare disorders are seldom considered in the evaluation of sick children.^[17]

Gaucher disease and Niemann pick disease are the two lipid storage disorders that are most likely to be encountered by haematologist as both may cause splenomegaly and cytopenias.

Niemann, a Berlin paediatrician reported a case of infant who died at age of 18 months, because of deficiency of

sphingomyelinase enzyme activity and accumulation of phospholipid sphingomyelin.^[18] It is a heterogeneous group of disorder consisting of various subtypes. Type A & B are autosomal recessive disorders and are caused by mutations of the gene for sphingomyelinase required to cleave the bond between ceramide and phosphoryl choline. Type C is also autosomal recessive and is caused by mutation in either NPC 1 or NPC2.^[19]

Type A is associated with severe neurological deficit and patients die during first few years of life, while Type B is later onset and neurological deficit is generally absent. Type C is associated with neurological symptoms and hepatosplenomegaly. Currently, there is no treatment but patients have benefited from liver transplantation. Our case in 13 year male child who presented with hepatosplenomegaly and peripheral pancytopenia, diagnosed as Niemann pick disease.

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