Sea Blue Histiocytosis with Thrombocytopenia – A Review

Iffat Jamal[1], Ravi Bhushan Raman[2], Vijayanand Choudhary[3]

[1, 2, 3] Department of Haematology, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India.

ABSTRACT

Sea blue histiocytosis is generally seen where the turnover of cells is high like in certain haematological malignancies like myelodysplastic syndromes, chronic myeloproliferative neoplasms, immune thrombocytopenias and lipid storage disorders etc. Most commonly involved organs are bone marrow, spleen and liver. We report a case of 32 year old male who was Hepatitis B positive and presented with thrombocytopenia. Bone marrow examination revealed presence of numerous sea blue histiocytes. Extensive haematological and biochemical investigations failed to find out the cause of thrombocytopenia with presence of sea blue histiocytes in bone marrow, that makes our case worth reporting. This present case highlights the necessity of good communication between clinicians and pathologists for the identification of this uncommon disorder. A PubMed search of literature review was done from 1972 to 2019 in order to find out the overall incidence of this rare entity and the various other differential diagnoses were discussed.

KEYWORDS

Sea Blue, Histiocytosis, Thrombocytopenia, Haematological, Malignancies, PubMed.

Corresponding Author:
Dr. Iffat Jamal,
Flat No – D / 2, Phase – 1,
Sapna Apartment, Nayatola,
Patna – 800004, Bihar, India.
E-mail: iffatjamal11@gmail.com

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Sea blue histiocytosis in bone marrow is a morphological abnormality observed in conditions of high rates of intramedullary death due to various causes like lipid storage disorders, haematological disorders like myelodysplastic syndromes, chronic myeloproliferative neoplasms, lymphomas, immune thrombocytopenia and Sea-Blue Histiocyte Syndrome (SBHS).[1-3] SBHS is an uncommon systemic histiocytosis which was first coined by Silverstein in 1970. It is characterized by organomegaly most commonly with hepatosplenomegaly along presence of numerous histiocytes in the bone marrow. These histiocytes contain numerous cytoplasmic granules that stain deep blue with May-Grunwald Games stain.[4] SBHS is generally observed with lipid storage diseases and in various haematological conditions, but the exact pathogenesis of the syndrome is still not well established.[5,6]

Review of Literature

A detailed PubMed based literature search was done from 1972 to 2019 with keywords sea blue, histiocytes, thrombocytopenia, myeloproliferative, neoplasms and haematological. Out of 45 articles 22 articles were studied by all authors and relevant findings were noted. References from these 22 articles were also tracked and studied in details.[7-9]

They are large macrophages with size varying from 20 - 60 µm in diameter with single eccentric nucleus with bluish green granules in the cytoplasm when stained with Wright-Giemsa stains. Sea blue histiocytes are associated with variety of metabolic and haematological disorders.[10-15] They may be seen occasionally in the bone marrow in absence of any overt disorder. Haematological disorders associated with marrow sea blue histiocytes are Chronic myeloid leukemia, chronic immune thrombocytopenic purport, sickle cell anaemia, thalassemia, myelodysplastic syndromes and polycythaemia vera.

It has been hypothesized that these macrophages are associated with excessive turn-over of haematopoietic cells.[16,17] In these haematological conditions, macrophages are unable to completely metabolize lipids of phagocytosed blood cells that leads to its accumulation. Apart from bone marrow, they are found located in liver and spleen and less frequently in lymph nodes, lungs etc. It has a milder course when it affects spleen or bone marrow and its most fatal when it affects central nervous system.[18,19,20]

Sea blue histiocytes are frequently observed in bone marrow and spleen where haematopoietic cells are phagocytosed. Links et al. demonstrated presence of Pseudo-Gaucher cells in pulmonary infiltrates in a case of pulmonary tuberculosis.

Various previous reports indicate that SBHS is seen associated with metabolic and haematological disorders. Most cases of non-idiopathic SBHS are usually secondary to lipid metabolic and ceroid storage diseases, like Niemann-Pick Disease, lecithin cholesterol acyltransferase deficiency, Fabry Disease, Gaucher Disease etc. Niemann-Pick Disease type F subgroup, which is seen in adults, has also been termed sometimes as "Sea-Blue Histiocytosis".

Another group of diseases that may be associated with SBHS are due to increased cell turn over, hyperproliferative states and intramedullary cell death as seen in chronic myeloid leukemia, immune thrombocytopenic purpura and other haematological conditions such as thalassemia, sickle-cell anaemia, multiple myeloma and Hodgkin's disease. An another group of diseases have also been associated with the syndrome includes Batten's disease, neuroaxonal dystrophy, Takayasu's arteritis and posterior column dysfunction.[21,22]

A summary of various aetiologies of SBHS described here are listed in Table 1. There are various conditions in which no aetiology has been identified even after extensive investigations and then its grouped as primary SBHS.[23] We have also included our case in this review article as well**.** A 32 year old male presented with weakness for 6 months and chest pain for 15 days. On clinical examination moderate splenomegaly was present. His complete haemogram revealed haemoglobin of 15.7 gm / dL, RBC count - 5.71 million / cumm, haematocrit - 49.5 %, WBC count - 5740 / cumm and with differential counts within normal limits. Platelet count was 70000 / cumm. He was positive for HBsAg on serology (by ELISA). His Hepatitis B viral DNA load was 6309 IU / mL. HIV and HCV was negative. Liver and renal function tests were within normal limits. USG revealed massive splenomegaly with spleen size of 17 cm with a focal mass lesion. Lipid profile was normal except for low LDL-cholesterol which was 46 mg / dL. Fibro-scanning of liver was also done to assess degree of liver fibrosis and median stiffness was found out to be 710 kPa.

Bone marrow aspirate was performed that showed normocellular marrow with trilineage haematopoiesis. Numerous macrophages were seen, majority of them morphologically resembled sea blue histiocytes having coarse blue granules in their cytoplasm. Occasional macrophages have abundant, pale and vacuolated cytoplasm. (Figure 2 & 3)

Special stain PAS and PAS-D revealed cytoplasmic positivity that was diastase resistant (Figure 4). Sudan black B revealed brown colored granules in cytoplasm (Figure 5). Perl's stain was negative in these histiocytes.

In a study done by Mounira et al., a 57-year-old female was referred to Gastrology department for further examination of anaemia.[24] Complete blood count revealed pancytopenia with total WBC count of 2910 / cumm, Hb-8.7 g / dL and platelets - 54,000 / µ. Electrophoresis of serum protein showed a M spike of 20.1 g / L. with immunofixation electrophoresis revealing IgG kappa monoclonality. β2 microglobulin was markedly raised (10,830 µg / L). A clinical diagnosis of multiple myeloma was rendered and bone marrow aspiration was advised which failed to show an increase in plasma cells, rather histiocytes were predominantly seen. Bone marrow biopsy also showed sheets of histiocytes with abundant vacuolated cytoplasm which were PAS and Giemsa stain positive and negative for Perls stain, confirming the diagnosis Sea blue histiocytosis.

In another case reported by Caetano, patient was admitted with symptoms of prolonged fever, vomiting and frontal headaches for 3 weeks. Physical examination revealed presence of icterus.[25] Her laboratory examination

revealed Haemoglobin levels of 5.4 g / dL, white blood cell count 3900 / cumm and platelet count 1.2 lacs / cumm. Bone marrow aspirate was performed and revealed increased granulocytic and megakaryocyte precursors along with lymphocytes. Bone marrow biopsy showed diffuse infiltration by histiocytes having abundant cytoplasm and fine granules that stained deep blue with Giemsa stain and were PAS positive and negative for Ziehl-Neelsen stain Reticulin stain revealed mild focal fibrosis. The overall findings were consistent with SBHS.

Krehbiel et al. in an another case study described a 32 year old female presented with left-sided abdominal pain with absence of other systemic manifestations like fever, chills, night sweats and weight loss.[26]

Abdominal computed tomography (CT) showed splenomegaly with hepatic steatosis. Laboratory investigations included a lipid profile in which total cholesterol was 218 mg / dL, triglycerides - 1790 mg / dL, and HDL of 10 mg / dL. Her CBC, peripheral blood smear, coagulation profile, renal and liver function tests were normal.[25,26]

Histopathological sections of splenic biopsy revealed presence of abundant foamy histiocytes within the cords of the red pulp of spleen. These histiocytes had foamy cytoplasm with fine homogenous appearance and lacking the characteristic "wrinkled tissue paper" appearance classically seen in Niemann-Pick and Gaucher disease.

These foamy histiocytes were found to be CD68 positive and S - 100 negative. Many of the histiocytes demonstrated staining with PAS with and without diastase and also stained with brilliant azure staining by Giemsa. The characteristic staining with special stains confirmed these histiocytes to be sea blue histiocytes only.

In an another study by Betul, a 5 month old boy was admitted in the hospital with severe neutropenia where he was diagnosed with Primary pulmonary hypertension (PPH) and atrial septal defects (ASD) on echocardiography.

Even after thorough investigations for finding out the cause of neutropenia, no conclusion was drawn (Table 2). Hence bone marrow aspiration was advised and bone marrow aspirate showed normocellular marrow with reduction in mature neutrophils.

Immunophenotypic findings of bone marrow and peripheral blood smear findings were normal. A homozygous mutation of G6PC3 confirmed the diagnosis of glucose - 6 - phosphatase catalytic subunit 3 (G6PC3) deficiency. GSF treatment was started and subsequently bone marrow aspiration revealed presence of numerous sea blue histiocytosis along with trilineage haematopoiesis. A triad of sea-blue histiocytes, hepatosplenomegaly and thrombocytopenia were defined as 'Sea blue histiocytosis'.

SBH is a rare entity and has multifactorial aetiopathogenesis. That's why it is essential for pathologists to know this rare entity and include it in the differential diagnoses.

SBH in the spleen is most commonly associated with one of the genetically based dyslipidaemias (Fig. 1). It could be due to Niemann-Pick type C disease and lipoprotein lipase (LpL) deficiency either due to a primary defect in the enzyme itself or due to mutation in apolipoprotein C-II (apoC-II) which is the obligatory activator of LpL.

The hallmark of insufficient LpL activity is hypertriglyceridemia. However, triglyceride concentration is seen elevated in patients with dyslipidaemias, a level exceeding 1000 mg / dL is rare and strongly favours LpL deficiency. The main differential diagnosis of SBH in patients associated with hyperlipidaemia are Tangier disease and chylomicronaemia. There is reduction of HDL and elevated triglyceride along with accumulation of cholesterol in tissues.

1. Primary Sea Blue Histiocytosis	No definite cause identified after thorough investigations
2. Secondary Sea Blue Histiocytosis	**A. Haematological causes**: CML ITP Other hyperproliferative disorders of bone marrow **B. Lipid metabolic disorders:** Niemann Pick disease Gaucher's disease Fabry's disease **C. Others :** Neuroaxonal dystrophy Posterior column defect

Table 1. Various Aetiologies of Sea Blue Histiocytosis

Authors Name	Year of Study	Number of Cases	Median Age / Sex	Clinical Presentation
Rainier Pope	1972	01	24 / M	Mild splenomegaly
Cecion A, DC Rosa L et al.	1975	01	37 / F	Hepatosplenomegaly
AC Parker, AD Ban et al.	1976	01	32 / Male	Perianal abscess and firm splenomegaly
M. Dewhurst et al.	1979	01	7 / Female	Abdominal pain and listlessness
Etcheverry R et al.	1991	01	56 / M	
Viana MB, Leite VH et al.	1992	04	NA	Hepatomegaly, low weight for age and diffuse interstitial pulmonary infiltration
Kesteven & Howard et al.	1993	55	48 - 88	35 cases - MDS 20 cases - CML
Suzuchi Abe et al.	2007	01	28 / F	Lipid metabolic disease
Mounira El. Euch et al.	2011	01	57 / F	Pancytopenia with mild splenomegaly

Table 2. Comparison of Various Studies on Sea Blue Histiocytosis

The most consistent and important clinical finding of the primary sea blue histiocytosis syndrome is splenomegaly and hepatomegaly observed approximately 60 % of the cases and haemorrhagic diathesis due to thrombocytopenia. Bleeding manifestations like ecchymoses, purpura, epistaxis etc may be other frequent presentations of the disease.

Pathophysiology of Sea blue histiocytosis:

Various hypothesis for development of sea blue histiocytosis have been given but no definite mechanism is yet known.

1. Due to abnormal lipid metabolism by histiocytes.
2. Due to excessive turnover of haematopoietic cells leading to increased phagocytic activity engulfing cell debris, oxidation products and lipids.
3. A decrease in various lipid metabolizing enzymes like sphingomyelinase that catalyses degradation of glycosphingolipids.

Biochemically these are unsaturated oxidized lipids, ceroid, lipofuscin or glycophospholipids that appear as large and coarse granules of 1 - 3 μ size and turn blue with May Grunwald staining, orange reddish with PAS and black with Sudan III stains.[25-28]

Mimics of sea blue histiocytosis are found in:

1. Gaucher's Disease: An inherited disorder in which glucocerebrosides accumulate in macrophages in liver, spleen and bone marrow. These macrophages are called "Gaucher cells" characterized by large, round to oval cells with eccentric nucleus and voluminous basophilic cytoplasm having wrinkled fibrillary appearance due to elongation of lysosomes. These stain positive with Sudan Black B and PAS. Non-specific esterase and TRAP may or may not be positive.
2. Niemann-Pick Disease: An inherited condition caused by reduced sphingomyelinase activity. It is characterized by presence of foamy lipid containing histiocytes in bone marrow and other tissues.
3. Crystal containing histiocytosis: Macrophages contain immunoglobulin crystals in lysosomes and such macrophages are found in Lymphoplasmacytic lymphoma, multiple myeloma and various conditions associated with presence of paraprotein.
   A strong association with kappa light chain is seen frequently.
4. Fabry's Disease: Macrophages have small globular inclusions which are PAS and Sudan Black B positive.
5. Conditions in which there is presence of foam cells that mimic sea blue histiocytosis as in trauma, fat necrosis, bone marrow infarction, infection, panniculitis etc.
6. Other acquired causes that are associated with an increase of foamy macrophages include Langerhans cell histiocytosis, bone marrow metastasis, sickle cell anemia etc.
7. Macrophages containing cholesterol crystals are found in various hyperlipidemic conditions which can be congenital or acquired. Such conditions include α-lipoprotein deficiency, hyperbetalipoproteinemia, poorly controlled Diabetes mellitus and hypothyroidism. They appear as needle like clefts within the macrophages.
8. Cystinosis: bone marrow macrophages are packed with colorless refractile crystals of various shapes. They are best visualized under polarized light and they are birefringent.
9. Hyperoxaluria: It is a metabolic disorder in which oxalates are deposited in various tissues like bone, bone marrow, liver, spleen ad kidneys. Bone marrow shows presence of needle like crystals arranged in radial pattern with many multinucleated macrophages.
10. Mucopolysaccharidoses: Inherited diseases characterized by storage of various mucopolysaccharides due to deficiency in lysosomal enzymes. Bone marrow shows macrophages containing abnormal metachromatic granules
11. Glycogen Storage Disease: PAS positive inclusions are seen in macrophages, sometimes mimicking sea blue histiocytes.

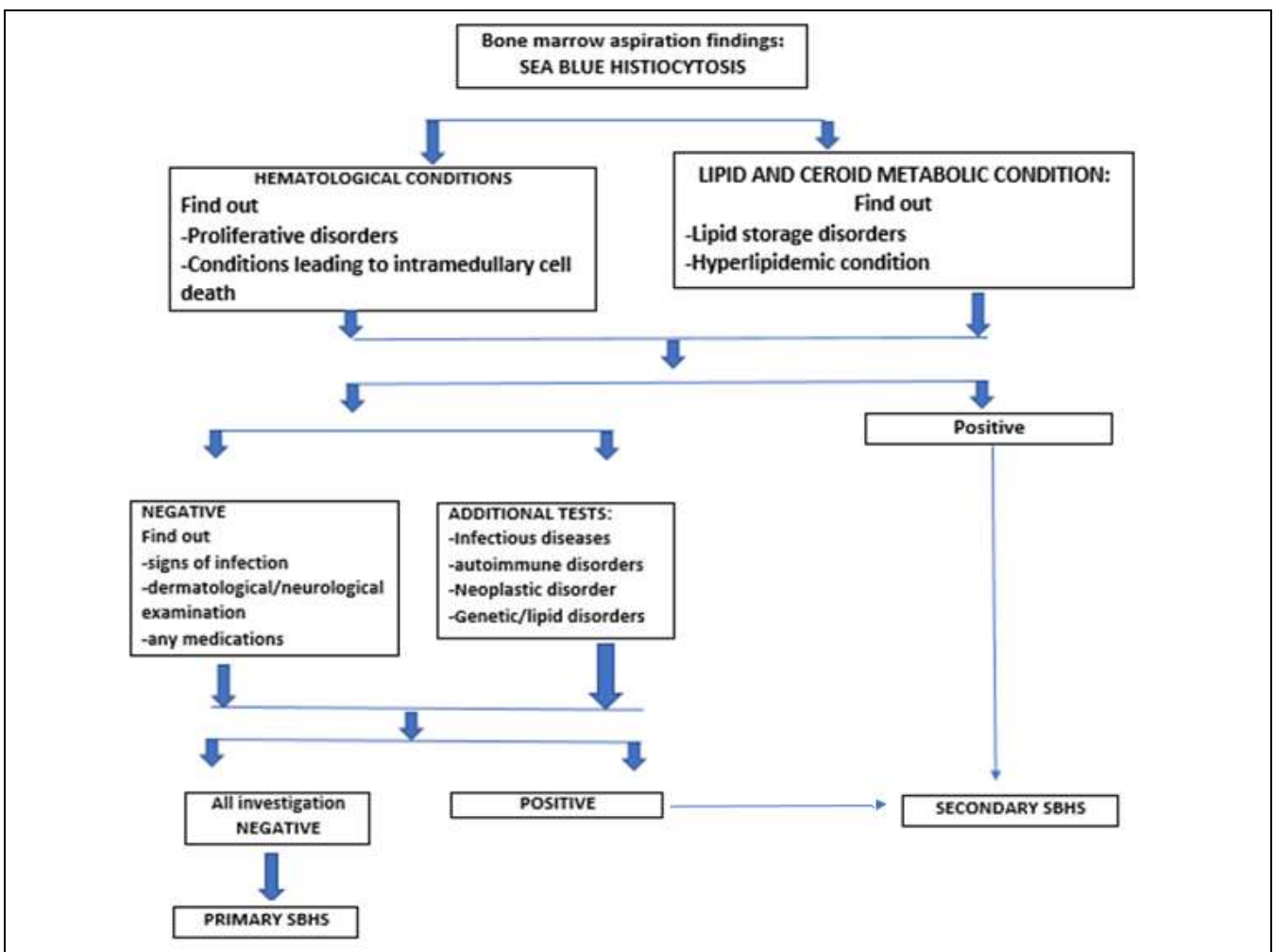

Figure 1. How to approach a Case of Sea Blue Histiocytosis

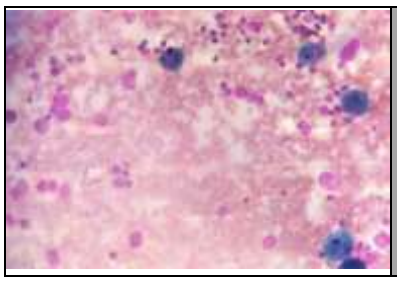

Figure 2. Microphotograph of Bone Marrow Aspirate Showing Sea Blue Histiocytes with Coarse Blue Granules in Cytoplasm and Eccentrically Placed Nuclei. (Leishman Stain; 400X)

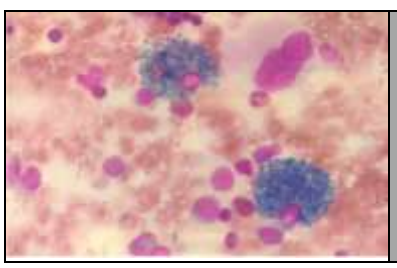

Figure 3. Microphotograph Showing Characteristic Sea Blue Histiocytes in Higher Magnification (Leishman Stain; 1000X)

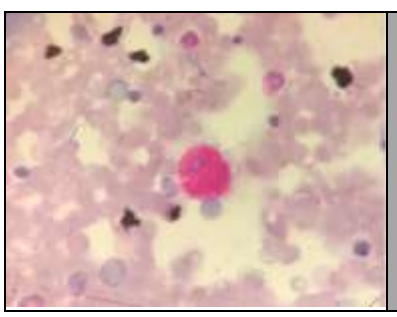

Figure 4. Microphotograph Showing PAS Positive Cytoplasmic Granules Which Were Diastase Resistant. (PAS Stain; 1000X)

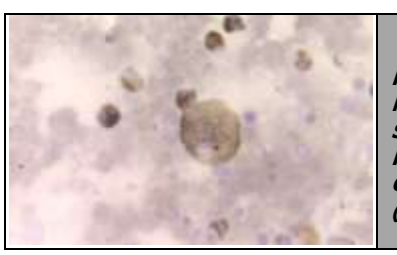

Figure 5. Microphotograph Showing Sudan Black B Positive Brown Cytoplasmic Granules (SBB; 1000X)

CONCLUSIONS

This review article highlights the importance of this rare entity and its broad differential diagnosis. A good communication between pathologists and clinicians is of utmost importance to ensure that patients receive correct and prompt treatment. It is also essential to rule out non-genetic acquired sources of hyperlipidaemia, prior to initiating a genetic work-up. In our case serum triglyceride concentrations were normal and patient had presented with thrombocytopenia with no obvious increase in megakaryocyte number in bone marrow aspirate. Such patients of primary disorder stay well without any specific treatment.

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