

Case Report



Systemic Mastocytosis With Features of Chronic Liver Disease, Proptosis and Itchy Hyper-Pigmented Skin Lesion

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Abstract

Mastocytosis is a rare disorder of functionally defective mast cells. Infiltration of this functionally defective mast cells and CD34+ mast cell precursors in various organ leads to clinical manifestation. Skin is the most common affected organ. In systemic mastocytosis along with skin, internal organs such as the liver, spleen, bone marrow, small intestines and eye also involve. Diagnosis is done on the basis of WHO diagnostic criteria. Here we presenting this rare entity presented to us with features of chronic liver disease, proptosis and itchy hyper-pigmented skin lesion diagnosed as systemic mastocytosis.

Keywords: Mastocytosis, Mast cells, Proptosis, Chronic Liver Disease.

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Introduction

Mastocytosis is a rare disorder affecting both children and adults caused by the accumulation of functionally defective mast cells (also called mastocytes) and CD34+ mast cell precursors in skin and/or internal organs such as the liver, spleen, bone marrow, and small intestines.¹

Mastocytosis was first described by Nettleship and Tay in 1869 and later due to the appearance like urticaria, the term urticaria pigmentosa (UP) was coined by Sangster in 1878.^{2,3} Ellis in 1949 while doing an autopsy in a child with fatal UP documented the presence of mast cell (MC) infiltration in skin, liver, spleen, lymph nodes, and bone marrow.⁴

The World Health Organization (WHO) classification of mastocytosis includes the following:^{5,6}

a) Cutaneous mastocytosis UP maculopapular cutaneous diffuse cutaneous mastocytosis, mastocytoma of skin

- b) Indolent systemic mastocytosis
- c) Systemic mastocytosis with an associated (clonal) hematologic non-mast cell lineage disease
- d) Aggressive systemic mastocytosis
- e) Mast cell leukemia
- f) Mast cell sarcoma
- g) Extracutaneous mastocytoma

Children present with cutaneous or systemic mastocytosis (SM) or overlap of these 2 conditions.⁷ The most common form of pediatric presentation is cutaneous mastocytosis.⁸

Case Report

A 4 ½ year old boy, 2nd issue of non-consanguineous parents, presented with gradual abdominal distension from 1 year of age. He had history of red-colored skin lesions, 4-5 in numbers over the body which was noticed since 3 days of birth, progressing to multiple lesions over entire body (Figure-1)

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Within a month, the lesions healed with hyper-pigmentation and were associated with itching. The smaller lesions kept on appearing till 4 months of age and latter all lesions healed with hyper-pigmentation. Skin biopsy was done at 5 months of age and it showed non-specific changes. From 1 year of his age, he developed abdominal distension which was increasing day by day. He was diagnosed as a case of chronic liver disease due to Storage disease at 2 ½ years of age.

There was no history of hematemesis, melena, jaundice, decrease urine output, contact with TB patient, sib death and family history of liver disease or same type of illness. He had multiple episodes of paracentesis, in last 3 months almost once in three days with albumin infusion. The child also had anaemia, thrombocytopenia and was transfused with packed cells, platelets for several times.

On examination, Abdullah was mildly pale, anicteric, afebrile, no lymphadenopathy, frontal bossing, proptosis (bilateral) and clubbing was present. Vitals were normal (RR: 38br/min, 90/60 mm of Hg). Skin survey showed multiple ill defined hyper-pigmented macules with areas of erythema and telangiectasia over lower and upper extremities. Anthropometrically, he was severely stunted and had severe malnutrition (mid upper arm circumference 10cm). Bed side urine albumin was nil. On systemic examination, Abdomen was distended, flanks full, umbilicus everted, dilated viens present, hepato-splenomegaly present 10cm and 12cm respectively. Ascites present evidence by fluid thrill. On locomotor system, genu valgum present. Other systemic examination reveals no abnormality.

With these scenario he was evaluated in Christian Medical College, India. His investigations revealed Hb% decreased (10g/dl), TC of WBC: increased (12,700/cmm), platelets 235000/mm³, S.Albumin low (2.1 g/dl), other liver function test were normal (S.ALT: 8U/L, S.AST 33 U/L, S.bilirubin 0.3 mg/dl, prothrombine time 17 sec), renal function test was normal, lipid profile was normal, S. LDH: 455 U/L, USG of whole abdomen showed coarse hepatic echotexture with Ascites with normal Doppler study with hepatosplenomegaly with left renal calculi, endoscopy of upper GIT was normal. DTPA: No obstruction with normal function, echocardiography was normal. Ascitic fluid study: protein 2g/dl, ADA: 3.76 U/L, WBC: 30/cmm, N: 08%, L: 89%, ascitic fluid for malignant cell was negative, Gene- xpert was negative. Serum tissue transglutaminase IgA was negative, immunoglobulin panel was normal, bone marrow study (Trephine biopsy) reveals mildly hypercellular marrow with trilineage haematopoiesis. Femur x-ray showed generalized increased bone density with gross expansion of the medullary cavities and Erlenmayer flask deformity of bilateral femora, S.vit D (25 OH) showed mild deficiency (20.1ng/ml). Skin biopsy showed telangiectasia with moderate increase in mast cells, consistent with UP. Liver biopsy showed mild to moderate portal and sinusoidal increase in mast cell (CD117 +ve, CD 25+ ve) and with portal and periportal fibrosis.

Review of bone marrow with immunohistochemistry showed there are perivascular and paratrabecular small aggregates (about 6 aggregates, most of which have about 20-30 cells, one with about 50 cells) of oval to spindle shaped cells with eosinophilic cytoplasm which are highlighted on immunohistochemistry for CD25 and CD117. Mast cell tryptase <0.5.ng/ml. A codon 816 c-kit point mutation positive at peripheral blood.

We therefore diagnosed this case as Systemic Mastocytosis with Left Renal Calculi. He was treated with tab. imatinib and prednisolone along with supportive measurement. Plan to do allogeneic stem cell transplantation.



Figure-1: Our case with proptosis (B/L) with hugely distended abdomen due to ascites.

Discussion

Pediatric mastocytosis is generally a benign disease that is transient in nature, as there is generally a spontaneous regression of the condition by puberty.^{7,8} Symptoms of mastocytosis may start at any age; around 50% of the patients, these symptoms experience from birth to second year of life.^{9,10} In our case, cutaneous symptoms begin since birth.

Several organs involved in mastocytosis, more commonly skin. The clinical symptoms of mastocytosis on the skin are: telangiectasia macularis eruptiva perstans, mastocytoma, diffuse cutaneous mastocytosis and (UP).¹¹⁻¹⁴ In our case, he had hyper-pigmented macules with areas of erythema and telangiectasia. Skin biopsy for histopathology consistent with UP.

In systemic Mastocytosis, MC infiltrate several vital organ. Due to hepatic infiltration of MC patient may developed hepatomegaly, ascites, portal hypertension, which can evolve into portal fibrosis, and more rarely, cirrhosis.^{15,16} In our case, hepatomegaly, refractory ascites, stigmata of chronic liver disease (clubbing) was present. Histopathology of liver biopsy showed portal and periportal fibrosis.

Due to MC infiltration in digestive system (esophagus, stomach, intestine) malabsorption syndrome may developed.^{15,16} In our case, no features of malabsorption.

Mast cell infiltration may also affect the spleen resulting splenomegaly.^{15,16} Our case also had splenomegaly.

Mast cell proliferation in bone marrow can cause abnormalities in peripheral blood: anemia (the most common abnormality), cytopenias and pancytopenia.^{15,17} Our case had history of anaemia, thrombocytopenia and was transfused with packed cells, platelets for several times.

Regarding ocular manifestation, bilateral exophthalmos due systemic mastocytosis was reported.¹⁸ Our case had bilateral exophthalmos.

In Systemic Mastocytosis (SM), mast cells released the high levels of histamine leading to increase in gastric-acid secretions resulting in gastrointestinal bleeding and peptic ulcers disease.¹⁹ In our case, there was no history of gastrointestinal bleeding and esophago gastrod-udenoscopy was normal.

Bone marrow infiltration with mast cells may include bone disorders and musculoskeletal symptoms include bone pain, arthralgia. The lesions can be detected, in most cases, by radiography, through osteolysis, osteosclerosis or osteoporosis on medical imaging.^{15,17} Our case had genu valgum and Femur x-ray showed generalized increased bone density with gross expansion of the medullary cavities and Erlenmayer flask deformity of bilateral femora.

The diagnosis of mastocytosis is mainly clinical. The diagnostic work up in a child with mastocytosis is following- Baseline investigations (Skin biopsy, complete blood counts, serum tryptase levels, urine or plasma histamine levels, chest X ray, liver function test, ultrasound) with Bone densitometry if bone involvement, bone marrow biopsy, flow cytometry for bone marrow Mast cells for the presence of CD2 and CD25, determination of c kit mutation (D816V) for SM.^{7,8,15,17,20,21} In our case, haematological study and other investigation done to exclude differentials were non specific. Skin biopsy consistent with UP. Bonemarrow Study with immunohistochemistry showed there are perivascular and paratrabeular small aggregates of MC, highlighted on immunohistochemistry for CD25 and CD117. Liver biopsy showed mild to moderate portal and sinusoidal increase in mast cell (CD117 +ve, CD 25+ ve). A codon 816 c-kit point mutation positive at peripheral blood.

Diagnosis of SM done by WHO Diagnostic Criteria for SM. Diagnosis requires either 1 major and 1 minor criterion or 3 minor criteria. Major criterion: Multifocal, dense aggregates of mast cells (15 or more) detected in sections of extracutaneous tissues (commonly bone marrow) confirmed by tryptase immunohistochemistry and/or KIT immunohistochemistry. Minor criteria: a) in biopsy section, more than 25% of the mast cells in the infiltrate have atypical morphology, or, of all the

mast cells in the aspirate smear, more than 25% are immature or atypical, b) Mast cells coexpress CD117 with CD2 and/or CD25, c) Detection of KIT point mutation at codon 816 in bone marrow, blood, or other extracutaneous organs, d) Serum total tryptase persistently >20 ng/ml.²² In our case, major criteria was positive on basis of bone marrow immunohistochemistry and first 3 minor criteria was also positive. Mast cell tryptase level was <0.5ng/ml.

Treatment modalities SM include anti-mediator therapies, cytoreductive (IFN, Cladribine, cytarabine or fludarabine), targeted therapies (Antibody-Mediated Targeted Therapy targets Related to Signaling or Apoptosis), tyrosine kinase inhibitors (Imatinib, Dasatinib, Nilotinib), Corticosteroids, Allogeneic Hematopoietic Stem Cell Transplantation (AlloHSCT). AlloHSCT remains the only potentially curative treatment for patients with advanced SM.²³ Our patient was treated with tab. imatinib and prednisolone along with anti-mediator supportive measurement. Plan to do allogeneic stem cell transplantation.

Conclusion

Children with unexplained hepatosplenomegaly, ascites along with skin manifestation like itching, hyperpigmentation, UP should suspect for systemic mastocytosis. Other features like proptosis, haematological parameter and bone deformity should consider to support the diagnosis.

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