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Case Report

Paediatric cutaneous mastocytosis-A rare case report and approach to diagnosis

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Abstract

Mastocytoses are described as a heterogeneous group of disorders characterized by clonal proliferation and accumulation of phenotypically atypical mast cells in one or more organs.Mastocytoses are categorized into two broad categories: cutaneous mastocytosis (CM) and systemic mastocytosis (SM).Paediatric mastocytosis usually presents before 2 years of age in 90% and in a few at birth.Approximately 15% of cases are congenital. Mastocytoses affect all races with gender predilection; however, few of the studies indicated a slight male predominance.CM is most common in the paediatric age group, representing 90% of the cases involving only skin in the absence of systemic presentation. SM is associated with haematological malignancy, commonly seen in adult-onset mastocytosis.In 2019, WHO issued the latest classification of mastocytosis. Literature testifies to the rarity of data of CM from India. We present a case report in a 3-year-old child from the Garhwal region of North India. The aim of our case report is to illuminate the diagnostic approach in paediatric mastocytosis as per current WHO guidelines.

Keywords: Cutaneous mastocytosis, Giemsa Stain, Maculopapular Rashes, WHO diagnostic criteria, Kit sequencing

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1. Introduction

Mastocytoses are described as a heterogeneous group of disorders characterized by clonal proliferation and accumulation of phenotypically atypical mast cells in one or more organs.[1] The most common organs involved are the bone marrow, skin, spleen, liver, lymph node, and gastrointestinal tract.[2] The disease can involve all age groups, including infants.[2] Mastocytoses are categorized into two broad categories: cutaneous mastocytosis (CM) and systemic mastocytosis (SM).

Paediatric mastocytosis usually presents before 2 years of age in 90% and in a few at birth,.[3] with the majority of them occurring in the first 6 months of life.[4] 15% of cases are congenital. Mastocytoses affect all races with gender predilection; however, few of the studies indicated a slight male predominance.[3] Cases in twins and triplets and also familial disease has also been documented in the archive.[5]

Adult mastocytosis develops between 20s and mid-30s, and there is documented association with *c-KIT* mutations in exon 17.[6] The *KIT* D816V mutation is the most common genetic defect known for SM,[7,8,9] being present in >95% of adults with indolent SM and aggressive form SM.[10]

Paediatric mastocytosis can be associated with activating mutations in *c-KIT* involving exons 8, 9, or 11 along with exon 17.[6,11]

CM is most common in the paediatric age group, representing 90% of the cases involving only skin in the absence of systemic presentation.[6] SM is associated with haematological malignancy, commonly seen in adult-onset mastocytosis and commonly seen with acute myeloid leukemia.[12]

The exact prevalence of paediatric mastocytosis is not known, but it is slightly more or has almost equal prevalence in adults, approximately 10–13 per lakh population according

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to epidemiological studies.[13] The annual incidence is around 5–10 new cases per million population.[4]

Despite available archives from various parts of the world, literature testifies to the rarity of data from India. We present a case report in a 3-year-old child from the Garhwal region of North India. The aim of our case report is to illuminate the diagnostic approach in paediatric mastocytosis as per current guidelines.

2. Case Report

A 3-year-old female child, firstborn, came to the Dermatology OPD with complaints of dark brown maculopapular lesions since 3 months of age whose size varies from 1 cm to 0.2 cm, hives after itching present all over the body, more on the ventral surface, and sparing palms and soles. These lesions were very tiny and began as red-brown patches, gradually progressing in size and count.**[Figure 1]** The parents gave a history of frequent low-grade fever and facial flushing off and on. There was no documentation of any previous illness, nor was fever recorded by thermometer. The birth of the child was via normal vaginal delivery, which was uneventful. The vaccination status was up-to-date, and no history of post-vaccination illness was present. The parents had no history of prolonged sickness or any genetic disease. The child has no siblings.

On examination, Darier's sign was first performed, resulting in the appearance of hives after stroking the skin on the forearm. The child had protein-energy malnutrition with frizzy cotton woolly hair and brittle nails. Pallor was present and icterus absent. The oral cavity and nasal speculum examination were within normal limits. The milestones were fair. There was no difficulty in micturition or passage of stool. No lymph nodes, liver, or spleen palpable.

The skin biopsy was performed under aseptic precautions from the left thigh and right cheek and submitted to the histopathology laboratory for histopathological examination. A few investigations were ordered, i.e., complete blood count (CBC), C-reactive protein (CRP), serum tryptase level, ultrasound abdomen for organomegaly, and X-ray to rule out skeletal involvement. Other investigations include liver function tests, kidney function tests, urine routine and microscopy, stool for microscopy and occult blood, typhidot test, etc were also performed.

2.1. Histopathology findings

The gross examination shows two skin-covered tissue bits measuring 0.3x0.2x0.2 cm each. The base is inked, and the tissue is processed as a whole. No remnants were kept. Serial H&E-stained sections taken from both the bits examined under the microscope revealed similar histomorphological features. The skin biopsy studied is covered with epidermis and exhibits basket weave orthokeratosis and increased pigmentation in the basal layer along with focal basal vacuolations. Pandermis is almost completely replaced by an infiltrating monomorphic population of mast cells along with intermixed eosinophils, focally sparing papillary dermis. These cells are dispersed singly and have a round to oval-shaped nucleus with an abundant amount of eosinophilic cytoplasm. The interspersed collagen fibers are separated by proliferating thin caliber blood vessels. Areas show absence of adnexal structures, however noted at uninvolved margin. The cellular infiltration is reaching up to the base **[Figure 2, Figure 3,** Figure **4].**

To conclude the diagnosis, Giemsa stain was performed to confirm mast cells and highlight its cytoplasmic granules. The Ramanowsky-stained section shows intense metachromatic violet-red cytoplasmic granule positivity in mast cells sparing eosinophils **[Figure 5A, B]**. Hence, a diagnosis of "Cutaneous Mastocytosis" was awarded.

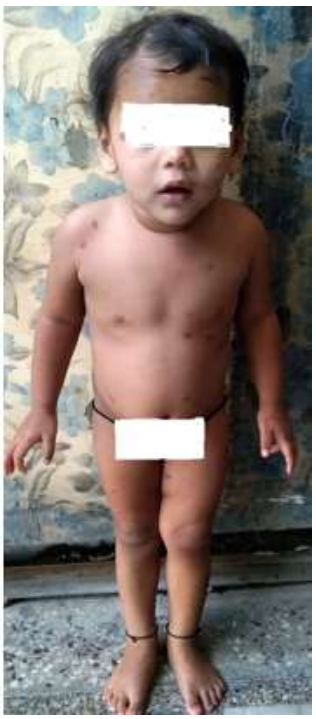

Figure 1: Clinical picture of the patient showing brown black colored maculo-papular lesions of various shapes and sizes distributed throughout the body.

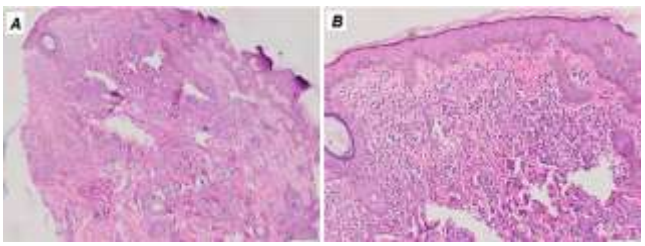

Figure 2: A,B: Diffuse dense infiltration of mast cells onto the dermis replacing normal parenchyma of whole dermis reaching to the base [H&E, 40X&400X]

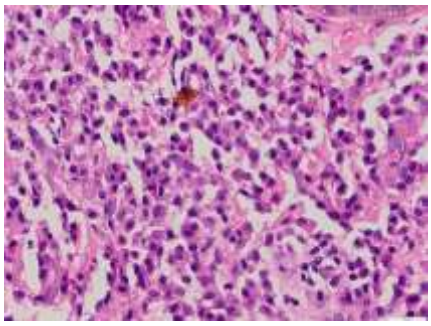

Figure 3: These (mast cells) have round to oval shaped nucleus with abundant amount of dense amphiphilic cytoplasm [H&E, oil immersion]

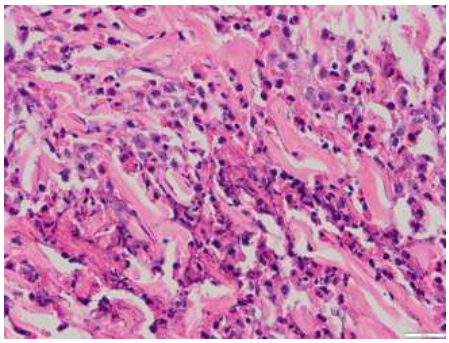

Figure 4: Aggregates of eosinophils are also noted interspersed with mast cells along with intervening collagen fibres and congested arterioles[H&E, oil immersion]

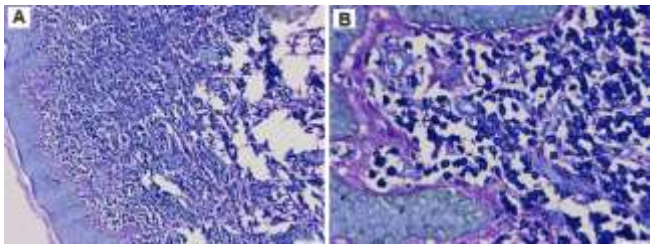

Figure 5: A,B: Special stain, Giemsa highlight the granules of infiltrating mast cells in pandermis. [Giemsa, 400X &oil immersion]

The Complete blood count (CBC) showed a moderate degree of microcytic hypochromic anaemia and mild thrombocytopenia. The serum tryptase levels were increased (21 ng/mL). Qualitative CRP test came out positive, Typhidot was negative, and liver function test, kidney function test, urine, and stool showed no significant findings.

3. Discussion

Being an extremely rare entity and very interesting to know, this particular case is a diagnosis of histopathological examination with assistance of a special stain. The special stain, i.e., Giemsa, used is a cheap, easily available stain and it is less time-consuming, and is specific to label mast cells [**Figure 5B**]. The patient was prescribed with a topical steroid cream for rashes and anti-histaminics for 1 month. The patient did not appear for follow up.

Satiskumaret al.[14] conducted an 11-year retrospective study in South India on a paediatric age group (<= 16 years) with clinically suspected mastocytosis (n = 110). A total of 66 cases were histologically confirmed, out of 85 consented for skin biopsy. Rest 19 came out with different diagnoses as follows: insect bite reactions, non-specific causes, lichen planus, histiocytosis, and juvenile xanthogranuloma.[14] Serum tryptase levels were performed in 33 cases and showed high levels >24 ng/mL in 9 cases (5 cases of mastocytoma and 4 cases of maculopapular CM). Amongst them, 4 had extensive involvement, and one had diarrhea. Rest 12 cases showed normal tryptase levels; 1 had systemic symptoms (recurrent abdominal pain).[14]This states that a lower level of S.tryptase cannot rule out mastocytoses. However, higher levels were found to be correlated with paediatric CM.

In 1955, Degos and a few modifications later, WHO in 2001, and a working conference on mastocytosis (2005) revised the classification of mastocytosis. In 2019, WHO issued the latest classification of mastocytosis.[2,14]

1. Cutaneous mastocytosis
2. Indolent systemic mastocytosis: not associated with haematological malignancy
3. Systemic mastocytosis: associated with haematological malignancy
4. Smoldering systemic mastocytosis
5. Systemic mastocytosis (aggressive form): not associated with mast cell leukaemia
6. Mast cell sarcoma: presented with localized destructive growth pattern with no association with SM
7. Mast cell leukaemia: an extremely rare form of SM <1% of all cases of mastocytosis. To make a diagnosis, dense diffuse infiltration of >20% atypical mast cells in bone marrow aspirate/biopsy and peripheral blood smear show>10% of mast cells.[1,16,17] The treatment usually fails with a median survival of <6 months duration.[2]

Cutaneous mastocytosis is described as the following types:[2,16]

1. Maculopapularmastocytosis (includes urticariapigmentosa): most common type, presented commonly before 6 months of age. The variability of rashes is more common in paediatric CM, has a good prognosis, and regresses spontaneously in the majority of cases by puberty. However, the same size rashes occur more in adults. The children with monomorphic rashes, the prognosis is bad and progresses to puberty[2]
2. Mastocytoma: 10–30% of paediatric CM[2]
3. Diffuse cutaneous mastocytosis: rare and most severe form constitutes 1–13% of paediatric CM[2]
4. Telangiectasia macula riseruptivaperstans: extremely rare in children[2]
5. Other rare variants: giant suprapubic and inguinal masses, anetoderma,[19] bullous, and blaschkoid[2]

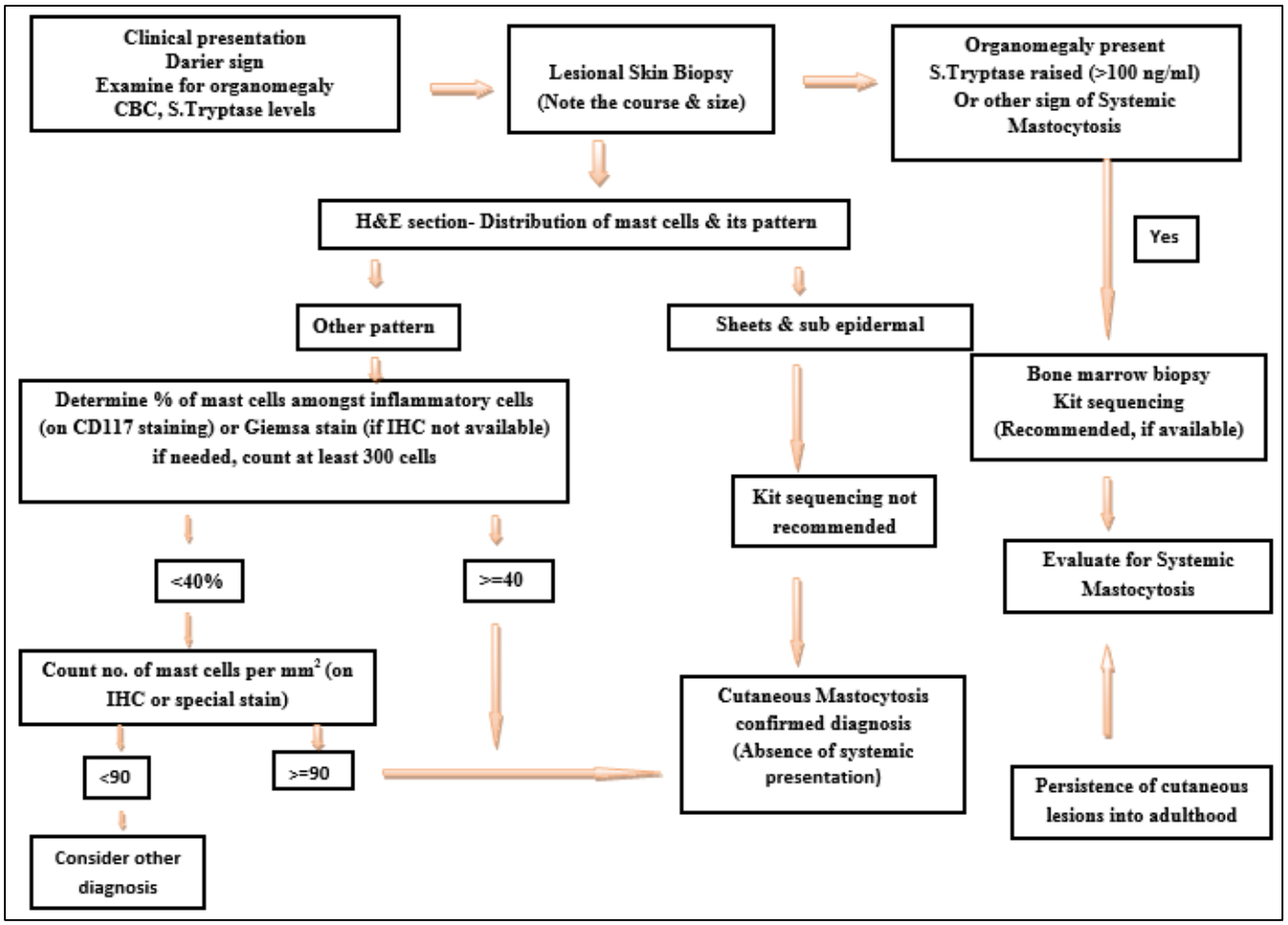

Chart 1: Our step wise diagnostic approach of a case of paediatric mastocytosis (IHC-Imunohistochemistry, CBC-complete blood count)

Amongst paediatric mastocytoses, >90% cases have skin involvement only. The criteria are based on the EU/US consensus group as follows: [2,6,20]

1. Absence of signs and criteria of SM
2. Major criterion—Typical CM lesions associated with positive Darier's sign
3. Minor criteria—lesional skin biopsy sample shows (one or both of the criteria)
   a. Increased mast cell count
   b. c-KIT mutation

On the basis of intense research and experience across the world along with our personal experience of the case reported, our approach for the diagnosis of paediatric CM has been described in (**Chart 1**).

4. Conclusion

Mastocytoses is a broad term for clonal proliferation of mast cells, may have systemic involvement or can only involve skin. The approach of paediatric mastocytosis is quite different from adult onset mastocytosis and systemic mastocytosis. The onset in paediatric CM is very early in life and, in most of the cases, regresses up to puberty when presented with polymorphic rashes and carries a good prognosis. Maculopapular variant is the commonest form. The skin biopsy is required to make the diagnosis, and confirmation with a simple basic stain like giemsa is of great help. Necessary precautions must be taken while taking skin biopsies in order to prevent mast cell degranulation and procedure artifacts. The c-KIT mutation is easy to confirm with CD117 immunohistochemistry when the molecular testing is not available, like in developing countries. CD117 IHC, or molecular testing, plays a pivotal role for the proper utilization of precision medicine in the form of targeted therapy. Overall, a good prognosis in paediatric CM is a matter of great relief; however, proper long-term follow-up needs to be done for evaluation of progression to SM, especially when the disease persists till adulthood.

5. Abbreviations

CBC- Complete Blood Count, CM- Cutaneous Mastocytosis, CRP- C-Reactive Protein, IHC- Immunohistochemistry, SM-Systemic Mastocytosis, USG- Ultrasonography, WHO-World Health organisation.

6. Sources of funding

None.

7. Conflict of Interest

None.

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