A solitary nodule on the leg

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CLINICAL FINDINGS

An 18-month-old child presented with asymptomatic skin lesion since 5 months. The lesion showed gradual onset and slowly progressive course. It started as a pigmented flat lesion then grew up to a large nodule. The condition was treated initially with topical corticosteroid but without significant improvement. There was no history of previous trauma at the same site. The parents had noticed the presence of erythematous changes on the lesion at some occasions. On examination, there was a solitary slightly pigmented nodule on the anterior aspect of the right leg (Fig. 1). The lesion measured about 1.1x0.6 cm and it was slightly firm with smooth surface (Fig. 2). The borders of the lesion were well defined while the margin was skin-colored. General examination was irrelevant while routine investigations showed no significant abnormalities.

What is your clinical differential diagnosis?

Juvenile xanthogranuloma, Mastocytoma, Dermatofibroma, Reticulohistiocytoma, Neurofibroma and Pilomatricoma.

Pathological findings

An elliptical biopsy was performed from the edge of the lesion. Histological examination showed dense dermal infiltrate that was more localized to the upper dermis and extended into the papillary dermis (Fig. 3). The infiltrate was composed mainly of large sized cuboidal monomorphic cells with large rounded central nucleus and abundant granular cytoplasm (Fig. 4). The cytoplasmic granules showed strong

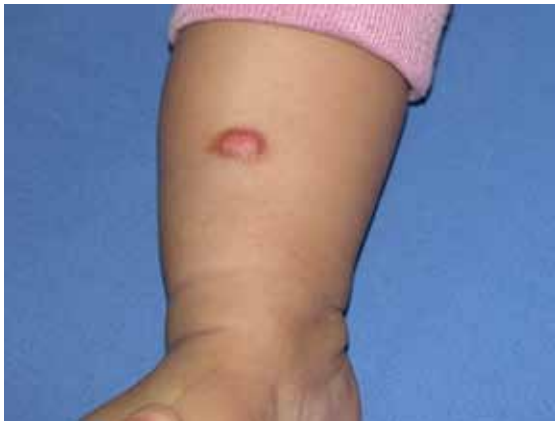

Fig 1 A solitary slightly pigmented nodule on the anterior aspect of the right leg.

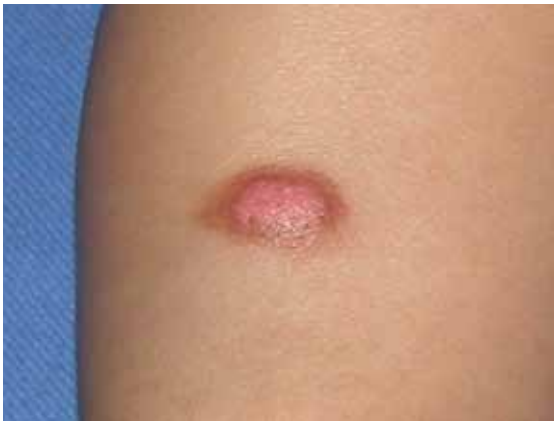

Fig 2 The lesion measured about 1.1 x 0.6 cm and it was slightly firm with smooth surface.

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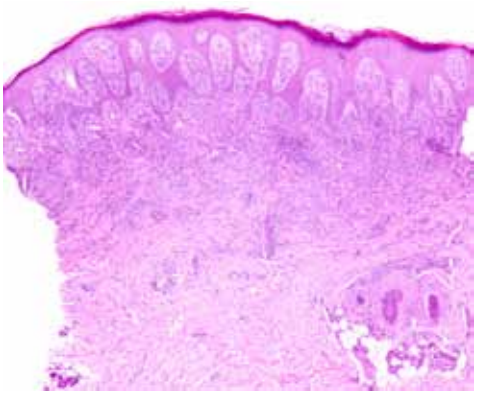

Fig 3 A dense dermal infiltrate that was more localized to the upper dermis and extended into the papillary dermis (H&E x40).

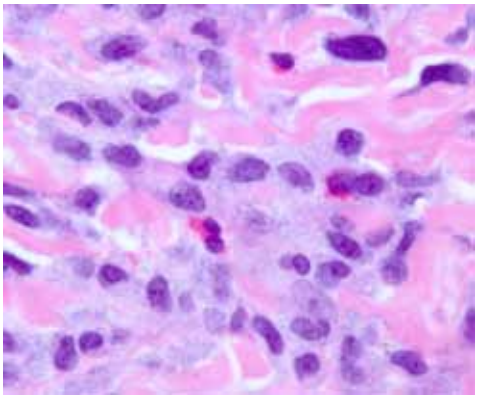

Fig 4 The infiltrate was composed mainly of large sized cuboidal monomorphic cells with large rounded central nucleus and abundant granular cytoplasm (H&E x1000).

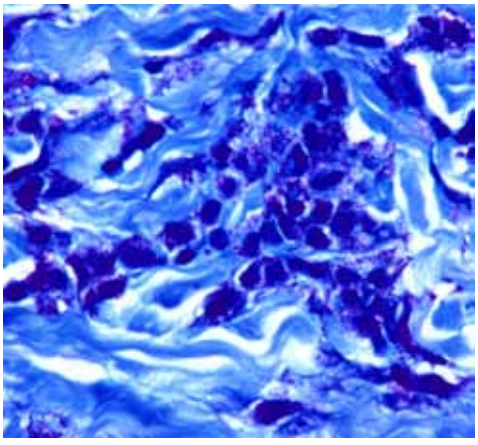

Fig 5 The cytoplasmic granules showed strong purple positive staining with Giemsa stain.

purple positive staining with Giemsa stain (Fig. 5) and the infiltrating cells were strongly positive for CD117 (Fig. 6) which is characteristic for mast cells. There were scattered eosinophils within the infiltrate. The epidermis showed mild elongation of rete ridges.

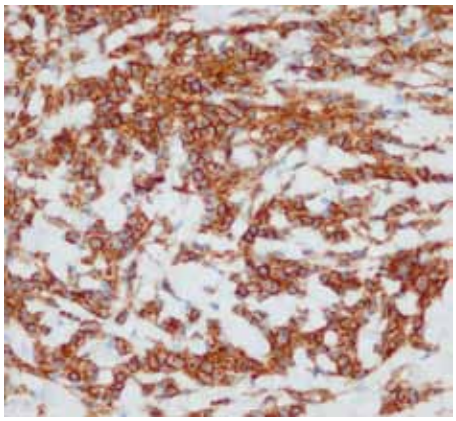

Fig 6 The infiltrating cells were strongly positive for CD117.

Diagnosis

Cutaneous Solitary Mastocytoma

COMMENT

Mastocytosis are group of disorders characterized by abnormal proliferation and accumulation of mast cells, involving the skin only (cutaneous mastocytosis) or the bone marrow and other extracutaneous organs (systemic mastocytosis). In children, skin is the most commonly involved organ.[1] Solitary mastocytoma, the second most common type of cutaneous mastocytosis, accounts for 10-15% of cutaneous mastocytosis. Nearly half of solitary mastocytomas present within the first 3 months of life and the remaining half during the first year. Solitary mastocytoma presenting in adults has also been noted. The most common locations of mastocytomas are on the trunk, neck, and arms.[2]

The pathogenesis of cutaneous mastocytosis is not well understood. A transient dysregulation of stem cell factor, a growth factor necessary for mast cell differentiation and growth, has been implicated as the underlying defect in cutaneous mastocytosis.[3] Mast cell degranulation within solitary mastocytomas may be triggered by a variety of factors, including physical stimuli (heat, cold, friction, and pressure), emotional

factors, certain medications (non-steroidal anti-inflammatory drugs, opioids, dextromethorphan, vancomycin, and general anesthetics), and radiocontrast media.[4]

Most solitary mastocytomas are about 1-5 cm in diameter and are seen as skin areas that are yellow to brown in color, and present as minimally elevated plaques with a smooth shiny surface having a soft to rubbery consistency. The lesion usually turns edematous and itchy on rubbing or trauma to the lesion. Mild tenderness and the formation of vesicles or bulla can also occur. These features can sometimes be so mild that they may not come to the attention of parents.[5]

The diagnosis of a solitary mastocytoma is suspected by the presence of a characteristic skin lesion, and confirmed by presence of mast cell clusters in biopsy and/or toluidine blue, Giemsa staining and specific mast cell marker c-kit/CD-117 staining.[6]

Diagnosis is confirmed by skin biopsy that reveals a dense monomorphic inflammatory infiltrate consisting of round to oval mast cells containing a clear cytoplasm and centrally located nuclei in the dermis. Confirmation of diagnosis is usually by special staining with toluidine blue that reveals the metachromatic staining of the monomorphic mast cells.[7] Laboratory evaluation is rarely needed unless lesions fail to regress overtime or systemic symptoms are present. The initial laboratory evaluation includes a complete blood count with differential, comprehensive metabolic profile and a serum tryptase level in symptomatic cases and ultrasonography of the abdomen for any systemic involvement. A bone marrow biopsy is not necessary in infants and children, unless extracutaneous organ involvement is suspected.[8]

The course of solitary mastocytomas is benign and the disease is self-limited. The goal of management of a symptomatic solitary mastocytoma is to prevent the release of mast cell mediators and alleviate symptoms associated with mediator release, particularly pruritus. However, no intervention is required if the lesion is asymptomatic.[9] Fortunately, the vast majority of children with solitary mastocytomas have a good prognosis with reduction or complete resolution of symptoms by puberty.[10] Due to spontaneous involution, solitary mastocytomas rarely remain symptomatic in older children, and only 10-15% of children have symptoms that persist into adulthood.[11]

The mainstay of therapy involves avoidance of potential triggers. In symptomatic patients, oral H1 and H2 antihistamines are commonly used. Other therapeutic options include topical steroids with or without occlusion, intralesional steroids, oral sodium cromoglycate, oral ketotifen and surgical excision are other treatment options. Though topical steroids have shown good results, their topical and systemic side effects are a matter of concern, especially when treating infants.[12] Tacrolimus and pimecrolimus are topical immunomodulators, the first in a new class of topical calcineurin inhibitors. These drugs act as immunosuppressants by binding to a cytosolic ligand in the cytoplasm of T cells called FK506-binding protein (FKBP) and inhibit the cytoplasmic enzyme calcineurin, thus inhibiting the activation and maturation of T cells and blocking transcriptional activation of several cytokine genes - interleukin (IL)-2 [mainly], IL-4, IL-10, interferon-γ, tumor necrosis factor-α, and granulocyte-macrophage colony-stimulating factor.[13]

The Clinicopathological challenges of Cutaneous solitary mastocytoma.

Diagnosis	Clinical	Pathological
Juvenile xanthogranuloma	• Predominant in infants and young children • Arise on any site of the body, but more frequent on the trunk and upper extremities • The lesions are smooth and pink bumps, but later develop a yellowish appearance • Usually less than 0.5 cm in diameter (papules), but giant nodules may be as large as 2 cm • May involve subcutis, skeletal muscle, eye, peripheral nerve and testis	• Usually poorly circumscribed, thin epidermis with elongated rete ridges, preservation of adnexae, prominent vasculature • Dense lymphohistiocytic proliferation in dermis • Foamy and Touton giant cells • Short fascicles of spindle cells, fibrohistiocytic cells and fibrosis • May have mild nuclear atypia, scattered mitotic figures, lymphocytes and eosinophils
Dermatofibroma	• Presents as slowly, slightly pigmented, solitary nodule • Frequently develops on the extremities (mostly the lower legs) • Usually asymptomatic but may be pruritic, tender or painful • Can occur in patients of any age but more common in adults	• A poorly defined proliferation of "fibrohistiocytic" cells within the dermis • The overlying epidermis may be acanthotic with increased basal layer pigmentation • The infiltrate is separated from the overlying epidermis by clear 'Grenz' zone • At the periphery of the lesion there is entrapment of collagen
Reticulohistiocytoma (Solitary epithelioid histiocytoma)	• A superficial, circumscribed, mildly elevated, solitary lesion • Size ranged from 1.5-11 mm (median 4mm) • Located mostly on the trunk, lower extremity, head and neck and upper extremity	• Typically involves upper and mid-dermis • Composed of large epithelioid histiocytes with a varying number of lymphocytes and neutrophils • The histiocytes have abundant, typically densely eosinophilic, cytoplasm • Multinucleated cells could also be present
Neurofibroma (Solitary cutaneous neurofibroma)	• Usually occurs between the ages of 20 and 30 • Presents as papular, nodular or pedunculated lesions and greyish white in colour • It is usually painless, slow growing and soft in consistency	• The lesion is non encapsulated and circumscribed • A grenz zone separates the lesion from the epidermis • The tumor is composed of interlacing bundles of elongated cells with wavy nuclei • Mast cells are present • The stroma is mostly fibromyxoid
Pilomatricoma (Pilomatrixoma)	• More common in children and young adults • Most reported in white persons and slightly preponderant in females • More located on the head and neck, upper and lower extremities • Presents as a single, firm, stony, hard nodule • Usually skin colored but may be reddish-purple • Positive "Tent sign"	• A well-circumscribed nodulocystic tumor • Predominantly seen within the lower dermis • Comprised of a basaloid proliferation resembling the hair matrix cells, which mature into structure-less eosinophilic cells lacking nuclei called shadow cells • Frequently there are areas of calcification • A histiocytic infiltrate with multinucleated cells forms at sites of rupture

Other immunomodulatory effects of tacrolimus include the inhibition of mast cell adhesion and the inhibition of the release of mediators from mast cells and basophils, which might explain its efficacy in the improvement of the lesion and alleviation of the symptoms in cutaneous mastocytosis.[14] These immunomodulators offer advantages over corticosteroids in terms of a more selective action, no associated systemic side-effects, and the absence of associated skin atrophy, depigmentation and telangiectasia.[15] Surgical excision can be curative if unresponsive to other therapies. In addition, families should be educated on the natural history of solitary mastocytoma.[16]

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