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Review

Cutaneous mastocytosis

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Abstract

Review on cutaneous mastocytosis, with data on clinics, pathology, and involved genes.

Keywords
cutaneous mastocytosis, diffuse cutaneous mastocytosis, maculopapular cutaneous mastocytosis, mastocytoma, mastocytosis, urticaria pigmentosa

Identity

Other names
Diffuse cutaneous mastocytosis, maculopapular cutaneous mastocytosis, mastocytoma, urticaria pigmentosa

Clinics and pathology

Disease

Cutaneous mastocytosis is characterized as a proliferation of mast cells in the skin. Three main forms of cutaneous mastocytosis are recognized: urticaria pigmentosa/maculopapular cutaneous mastocytosis (MPCM), mastocytoma, and diffuse cutaneous mastocytosis (DCM) (Hartmann et al, 2016). MPCM is subdivided into 2 variants: a monomorphic variant and a polymorphic variant (Hartmann et al, 2016). Of note, systemic mastocytosis can also have cutaneous involvement.

Phenotype/cell stem origin

The cells of origin are mast cells.

Epidemiology

Cutaneous mastocytosis is predominantly a disease of childhood. In a literature review involving 1747 cases, 23% of cases had congenital mastocytosis and 90% of cases had disease onset before the 2 years of age (Méni et al, 2015). In a series of 101 children with mastocytosis, 73% of cases presented within the first 6 months of life and 97% of cases presented by 2 years of age (Lange et al, 2013) Urticaria pigmentosa/maculopapular cutaneous mastocytosis (MPCM) has the highest incidence rate of 74.8-84.7%, followed by mastocytoma at 6.9-19.5%, and lastly diffuse cutaneous mastocytosis at 5.2-9% (Bodemer et al, 2010; Lange et al, 2013; Kiszewski et al, 2004; Méni et al, 2015; Wiechers et al, 2015). Polymorphic MPCM is more prevalent in children with an earlier onset (< 7 months of age) and shorter duration of disease (Wiechers et al, 2015). Monomorphic MPCM usually has a later onset of disease (58% of children have onset of disease after 24 months of age) and increased disease duration with persistence into adulthood (Wiechers et al, 2015). In this respect, monomorphic MPCM has been postulated to represent an early presentation of systemic mastocytosis. Approximately 4-8% of patients with cutaneous mastocytosis have familial disease (Bodemer et al, 2010; Méni et al, 2015). Adults usually present with either MCPM or DCM, not cutaneous mastocytomas (Hartmann et al, 2016).

Clinics

In any of the subtypes of cutaneous mastocytosis, blistering and/or bullae may occur. Between 40-100% of cases demonstrate Darier's sign, in which a wheal and flare is elicited after slight scratching (Le et al, 2017). However, it is recommended not to perform Darier sign in cases of DCM and large mastocytomas as it could lead to massive mast cell degranulation with severe symptoms (Matito et al, 2018; Klaiber et al, 2017). Other skin manifestations

include pruritus and flushing. Most of the symptoms including the gastrointestinal complaints, such as pain and vomiting, are due to release of mediators from the mast cells. Symptoms appear to be more frequent in patients with DCM (Méni et al, 2015).
Maculopapular cutaneous mastocytosis (MPCM) lesions have variable appearances, including reddish-brown macules, papules, plaques, or small nodules. Those with monomorphic maculopapular lesions usually have lesions measuring
Cutaneous mastocytoma usually presents as a single elevated red-brown or orange-yellow nodule measuring >1 cm in diameter. The term mastocytoma can also be used when there are up to three lesions as long as they are morphologically different than typical MPCM (Hartmann et al, 2016). Mastocytomas are predominantly on the extremities but also can occur on the head and trunk (Hartmann et al, 2016). These lesions usually blister.
Diffuse cutaneous mastocytosis (DCM) usually presents as diffusely erythematous and thickened skin (pachydermia), sometimes with a peau d'orange (orange peel) or leathery appearance. However, papules may also be present. These children often demonstrate dermographism, in which a wheal and flare response occurs after scratching in surrounding normal skin. Blistering is also very common. Cases of DCM usually present prior to 7 months of age.
While they can have elevated serum tryptase levels, this elevation is believed to be more related to the marked mast cell infiltrate of the skin and not due to systemic involvement (Carter et al, 2015; Wiechers et al, 2015).

Pathology

In all three types of cutaneous mastocytosis, mast cells infiltrate the dermis, sparing the epidermis. These mast cells are often spherical or spindled in shape with round to oval nuclei, clumped chromatin, inconspicuous nucleoli, and plentiful cytoplasm filled with tiny granules.
Mast cells should be increased at least 4-8 fold compared to normal skin for a diagnosis. In urticaria pigmentosa/maculopapular cutaneous mastocytosis, the mast cells are prominent in the papillary dermis and extend into the reticular dermis in a periadnexal and perivascular distribution. Admixed eosinophils may be present. The overlying epidermis may be hyperpigmented. In mastocytoma, the skin shows sheets of mast cells in the full thickness dermis, sometimes infiltrating into the subcutaneous adipose tissue. In diffuse cutaneous mastocytosis, the skin has a band-like mast cell infiltrate in the papillary and superficial reticular dermis; the overlying epidermis may be hyperpigmented.

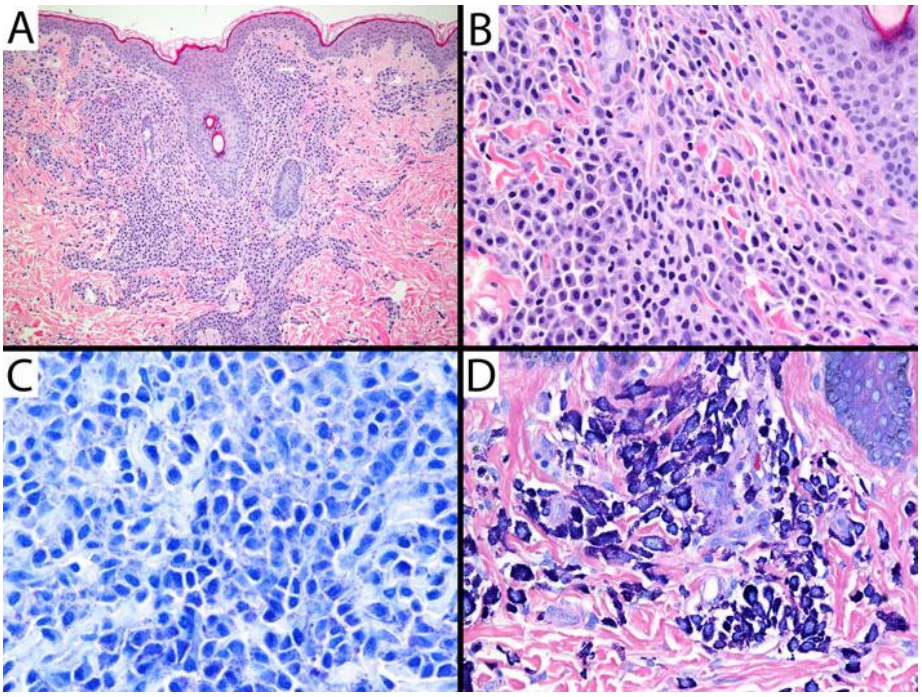

Figure 1: Urticaria pigmentosa/maculopapular cutaneous mastocytosis. A) Hematoxylin and eosin (HE, 100X) demonstrating a proliferation of mast cells surrounding vessels and adnexa within the dermis. B) Higher power (HE, 400X) shows mast cells with round to elongate nuclear contours, and moderate amounts of lightly basophilic cytoplasm. C) Toluidine blue stain highlights the mast cell granules in a blue/purple color (400X). D) Giemsa staining highlights the mast cell granules in purple (400X).

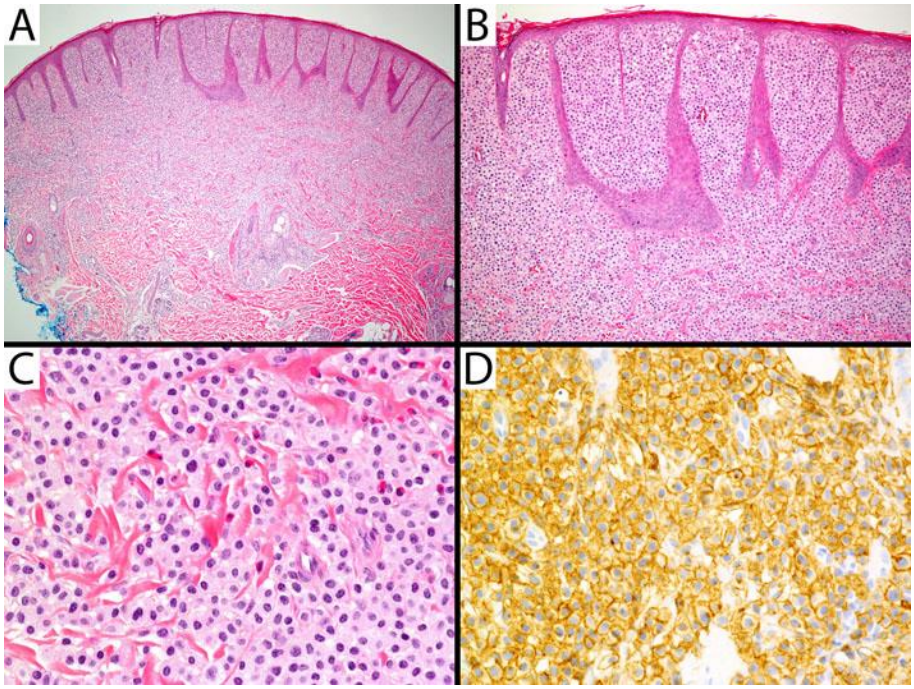

Figure 2: Cutaneous mastocytoma. A) Hematoxylin and eosin (HE, 40X) demonstrating a diffuse proliferation of mast cells spanning the dermis. B) Higher power (HE, 100X) shows the proliferation of mast cells in the papillary dermis between rete pegs. C) High power (HE, 400X) demonstrating the mast cells with round nuclear contours and moderate to ample amounts of amphophilic cytoplasm. Scattered eosinophils are present. D) CD117 immunohistochemical stain (400X) highlights the mast cells.

Genes

In pediatric cutaneous mastocytosis, somatic mutations in KIT are identified in up to 86% of cases of skin biopsies (Bodemer et al, 2010). Most commonly (in approximately 34-42% of cases), these mutations involve the kinase domain, in exon 17, and specifically at amino acid 816 (Bodemer et al, 2010; Méni et al, 2015). This mutation is usually p.D816V, but also rarely p.D816Y and p.D816I. Another 44% of mutations are identified in exons 8 and 9, involving the fifth Ig loop of the extracellular domain, as well as exon 11 (Bodemer et al, 2010). Mutations in these other exons are mutually exclusive of mutations at codon 816. No specific genotype-phenotype correlations have been identified (Bodemer et al, 2010). The mutations cause constitutive ligand-independent activation of KIT (Bodemer et al, 2010). KIT D817V mutations are usually not identified in peripheral blood in those with only cutaneous disease, but can be found in those with systemic disease (Carter et al, 2018). There is no identified association between clinical subtype and the identified KIT mutation (Meni et al, 2018).

Treatment

Therapies for cutaneous mastocytosis are usually based upon symptoms. Most commonly antihistamines are used, especially in urticarial pigmentosa. However, the efficiency of antihistamines varies from complete resolution to no resolution of symptoms such as pruritus (Le et al, 2017). Topical corticosteroids can be used in cutaneous mastocytoma cases, usually resulting in complete resolution and plaque regression (Le et al, 2017). Oral corticosteroids can lead to rapid regression and remission of blistering in bullous cutaneous lesions of diffuse cutaneous mastocytosis (Le et al, 2017). Phototherapy can also be used to decrease refractory pruritus in urticarial pigmentosa and decrease dermographism and leathery skin thickening in diffuse cutaneous mastocytosis (Le et al, 2017). Imatinib and omalizumab can be used in cutaneous mastocytoses, with the former decreasing pruritus and bullous lesions, and the latter preventing bronchospasm and anaphylaxis (Le et al, 2017).

Evolution

Many cases of mastocytosis resolve over a period years, usually puberty. These lesions may start as nodules during infancy, transform into plaques in mid childhood, and then into macules after 10 years of age, before regressing during puberty (Hartmann et al, 2016). In some that don't regress completely, the lesions may flatten with time (Hartmann et al, 2016). Blistering usually lessens within 3-4 years of lesion identification (Hartmann et al, 2016). In a large literature review with outcome data on 621 cases with a median follow-up of 6 years, complete regression was observed in 29% of cases, partial regression in 39% of cases, and stabilization in 27% of cases (Méni et al, 2015). In another large

literature review, mastocytomas had a complete resolution rate of 10% per year and urticarial pigmentosa had a resolution rate of 1.9% per year; diffuse cutaneous mastocytosis did not show evidence of complete resolution (Le et al, 2017). Of note, in children with monomorphic MPCM, the lesions may persist into adulthood and represent systemic mastocytosis (Hartmann et al, 2016; Wiechers et al, 2015). There is no identified association between evolution of the skin lesions and the identified KIT mutation (Meni et al, 2018).

Prognosis

In children, the prognosis is favorable, with most patients showing some degree of spontaneous regression by puberty (Hartmann et al, 2016). Of note, cutaneous mastocytosis in children is usually not a systemic disease and routine bone marrow evaluations are not recommended, unless signs of systemic mastocytosis are present such as hepatosplenomegaly (Carter et al, 2015). However, in adults, cutaneous mastocytosis more commonly is associated with systemic mastocytosis.

Genes involved and proteins

KIT (KIT proto-oncogene, receptor tyrosine kinase)

Location 4q12

Note

Mutations cause constitutive ligand-independent activation of KIT, with the highest phosphorylation status for exon 17 mutations.

DNA/RNA 21 exons

Protein

This protein is a transmembrane receptor for mast cell growth factor (also known as stem cell factor) which has tyrosine kinase activity.

Somatic mutations

34-42% of cases have mutations at D816 in exon 17 (usually p.D816V, but also rarely p.D816Y and p.D816I (Bodemer et al, 2010)). Other mutations occur in the fifth Ig loop of the extracellular domain encoded by exon 8 (InsFF419, Δ 419, Δ 417-419insY, Δ 418-419insS, C443Y), exon 9 (S476I, ITD501-502, ITD502-503, Δ 503-504insSY ITD505-508, Δ Δ508-509insYFAF, K509I), and exon 11 (Δ 564-576, D572A) (Bodemer et al, 2010, Meni et al, 2018).

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