CLINICAL VIGNETTE

Long-Standing Rash: A Case of Indolent Systemic Mastocytosis

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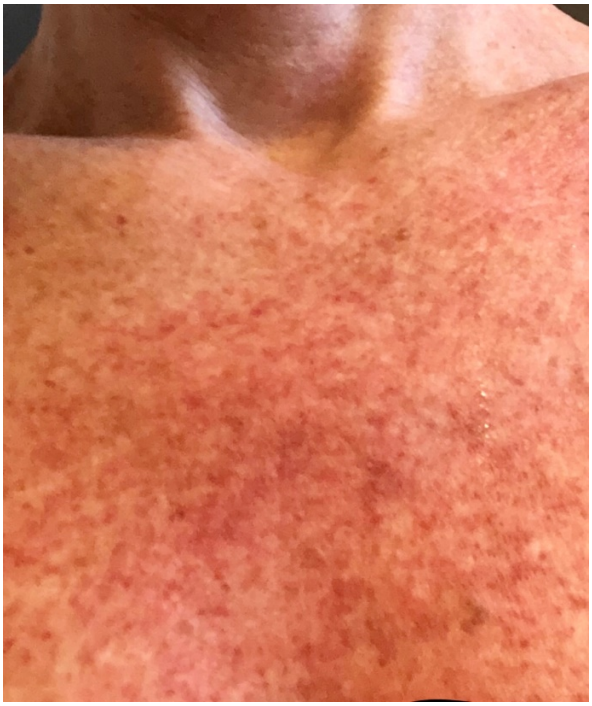
Case Presentation

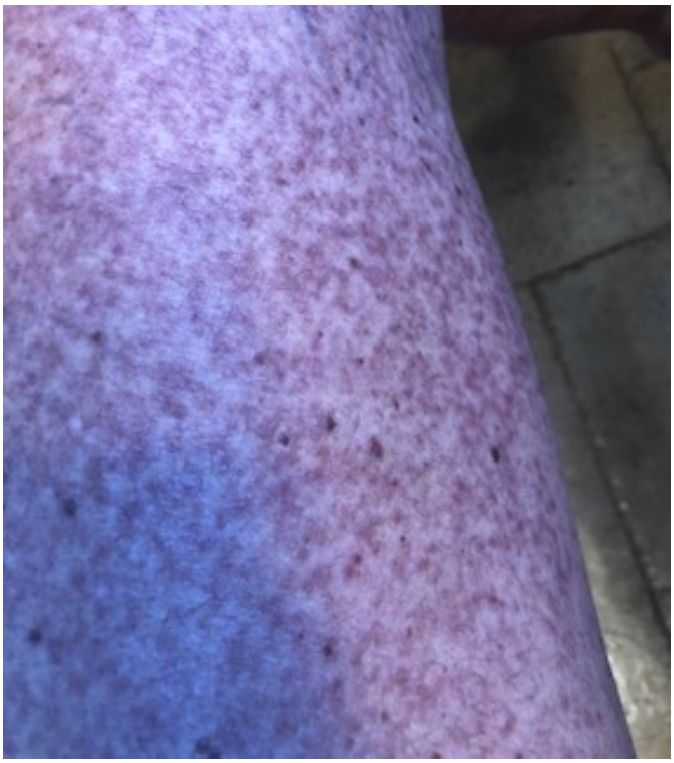
A 57-year-old woman initially presented with rash 25 years ago. The rash was described as small "spots" appearing on feet and extending up to her thighs in ensuing years. The rash was not itchy unless exposed to heat. Over time, she consulted a few dermatologists and underwent biopsy on the thigh, reportedly showed nonspecific vasculitis. She also consulted with rheumatologists, and was evaluated for autoimmune diseases. In her late 30s, she developed intermittent abdominal distension and pain and reported decreased concentration. In her 40s, the rash worsened extending further up to her hips and torso and became pruritic. The rash was exacerbated by psychological stresses (family death, relationship difficulties). Two years ago she took ibuprofen for headache, which exacerbated the rash. She was also evaluated in the ER after turning "beet red", with flushing palpitations, dyspnea, and near syncope. She eventually underwent another skin biopsy at UCLA, which demonstrated cutaneous mastocytosis. She was referred to hematology service for further evaluation. Bone marrow biopsy confirmed systemic mastocytosis. Her marrow was hypercellular and displayed several paratrabecular and interstitial spindled mast cells in compact and loose aggregate (~15% of marrow cells). Immunohistochemistry studies revealed mast cells positive for CD117, mast cell tryptase, and CD25. The characteristic *KIT* D816V mutation was also detected. Serum tryptase level was elevated up to 90 and mild splenomegaly was noted on imaging.

Mastocytosis

Mast cells are derived from myeloid stem cells and play a role in allergy and anaphylaxis. Mastocytosis is characterized by local or systemic proliferation and infiltration of mast cells in skin or extracuteneous organs such as bone marrow, spleen, and lymph node.[1] Mastocytosis is a rare disease with reported prevalence of approximately 0.5-1 per 10,000.[1,2] Mastocytosis is classified into cutaneous mastocytosis and systemic mastocytosis based on the extent of mast cell infiltration.[2] Cutaneous mastocytosis commonly affects children and can have spontaneous remission in adolescents.[1] Systemic mastocytosis commonly affects adults and may be associated with mast cell infiltration to internal organs with or without skin involvement.[1,2] Systemic mastocytosis is further subdivided into indolent systemic mastocytosis, smoldering systemic mastocytosis, systemic mastocytosis with associated clonal hematological non-mast cell lineage disease, aggressive systemic mastocytosis, and mast cell leukemia.[3]

Mastocytosis can have variable clinical manifestations through a number of mediators including histamine, leukotrienes, prostaglandins, and cytokines. This can make diagnosis difficult or delayed. The clinical manifestations of systemic mastocytosis are diverse, including skin symptoms such as pruritus to gastrointestinal disturbance, osteoporosis, hypotension, anaphylaxis, and neuropsychiatric symptoms.[2] Patients with advanced mastocytosis may develop hepatomegaly, splenomegaly, lymphadenopathy, and cytopenias.[3] The pathophysiologic hall mark of mastocytosis is a mutation of KIT(CD117), a receptor in mast cells as well as a proto-oncogene.[1,3] With somatic "gain-of-function" mutation in KIT, most commonly affecting codon 816 (D816V), KIT is constitutively activated via autophosphorylation to drive autonomous mast-cell differentiation and survival.[2]





Diagnosis

According to the WHO criteria, systemic mastocytosis is diagnosed by presence of one major criterion along with more than one minor criteria, or greater than three minor criteria.[1,2] The major criterion is multifocal, dense infiltrates of mast cells (≥15 mast cells in aggregates) detected in sections of bone marrow and/or another extracutaneous organs and confirmed by tryptase immunohistochemistry or other special stains.[4] Minor criteria include abnormal morphologic features of mast cells in bone marrow or other extracutaneous organs (e.g., atypical or spindle shapes morphology), the presence of the KIT D816V mutation, expression of CD2, CD25, or both on mast cells, and an increased basal serum tryptase level (> 20 ng/ml).[2] In addition to thorough history and physical examination, the finding of increased serum tryptase levels can be a clue for the consideration of mastocytosis.[3] Once mastocytosis is histologically confirmed in skin lesion, it should be differentiated from systemic mastocytosis by means of bone marrow biopsy.[2] The screening for D816V KIT mutation in peripheral blood can aid the diagnosis of systemic mastocytosis. For confirmation of diagnosis of systemic mastocytosis, multifocal clusters of mast cells with the expression of CD2 or CD25, or KIT mutation should be demonstrated on bone marrow biopsy specimen.[4]

Management

This condition is generally incurable and is managed with supportive care alleviating the symptoms.[4] Patients need to avoid the "triggers", namely the substances and environments that may provoke mast-cell activation. H1 antihistamines are commonly used for management of symptoms associated with histamine release. H2 antihistamines are preferred for patients with gastrointestinal symptoms.[2] When used in combination with antihistamines, antileukotrienes may be beneficial.[5] Additionally, cromolyn sodium may be useful to relieve gastrointestinal manifestations.[5] Self-injectable epinephrine (EpiPen) is recommended for all patients with mastocytosis in the event of anaphylaxis.[5] Anti-IgE monoclonal antibody omalizumab may be beneficial to prevent recurrent anaphylactic episodes.[6] Patients with advanced systemic mastocytosis may be treated with cytoreductive therapy to reduce mast cell burden.[5] In patients with KIT D816V mutation, midostaurin may be beneficial as initial treatment.[7] Imatinib is an alternative option in the absence of KIT D816V mutation.[3] Allogenic stem cell transplantation may be potentially curative in select patients with advanced forms of systemic mastocytosis.[7]

Prognosis

The prognosis for systemic mastocytosis varies greatly. Indolent systemic mastocytosis has good prognosis with near normal life expectancy with very rare transformation to aggressive systemic mastocytosis (as low as 3%).[8] Patients with smoldering systemic mastocytosis have a significantly shorter survival (median 10 years).[8] The prognosis for systemic mastocytosis with associated clonal hematological non-mast cell lineage disease depends on prognosis of the associated hematologic malignancy.[8] Aggressive systemic mastocytosis and mast cell leukemia have poor prognoses with overall median survival of 41 months and less than a year, respectively.[7]

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