Case Presentation 18- Cutaneous Mastocytosis with Features of Telangiectasia Macularis Eruptiva Perstans

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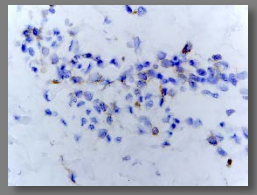
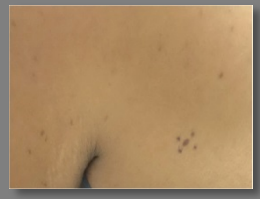
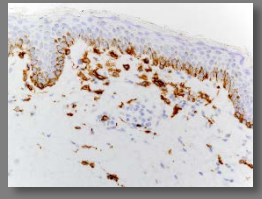
Weill Cornell Medicine Dermatopathology







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Clinical History

A 42-year-old female with a past medical history of multiple sclerosis for which she was receiving rituximab twice a year presented with scattered 2-4mm brown macules and papules over her trunk and bilateral upper and lower extremities (Figure 1). Though these lesions had been present for two years, the patient was otherwise asymptomatic. A biopsy of one of the lesions located on her upper back was performed.

Histologic Findings

The biopsy revealed a superficial perivascular and interstitial spindle cell infiltrate with a moderate amount of amphophilic granular cytoplasm, specifically in the context of spindled mast cells. There was also an admixture of perivenular lymphocytes and scattered eosinophils (Figure 2a-b). The Giemsa stain along with CD117 preparation highlighted many of the mast cells (Figure 3). The mast cell density was quite significant superficially and in certain fields was at least 5 times the upper limit of normal. A subset of the mast cells stained positively for CD25 (Figure 4). The reactive T-cells were highlighted by CD3. The findings were characteristic for cutaneous mastocytosis with classic morphologic features of telangiectasia macularis eruptiva perstans.

Discussion

The diagnosis in this case is telangiectasia macularis eruptive perstans, one of the classic clonal mast cell dyscrasias. To fully understand cutaneous mastocytosis one must revisit its ontogeny, addressing its benign counterpart, namely the reactive mast cell. From a morphologic perspective, mast cells are round to oval in shape, measure 8–15 µm in diameter with a central nucleus and basophilic cytoplasmic granules. The granules stain metachromatically with the toluidine blue and Giemsa stains. There are approximately 7000 mast cells/mm skin and are found mostly in the superficial vascular plexus of the dermis and around appendages. Mast cells express tryptase, leukocyte common antigen (CD45), CD43, CD68 and CD117. CD117 is also known as the KIT proto-oncogene and encodes a tyrosine kinase transmembrane receptor, being expressed on many cells including mast cells, hemopoietic stem cells, and melanocytes. The KIT mutations have been found in sporadic adult mastocytosis and in children at risk for extensive or persistent disease, but not in typical self resolving pediatric mastocytosis. [1]

Mastocytosis represents a clonal proliferation of mast cells in one or more organs. It usually occurs as a sporadic disease that is often transient in children while in adults it is a more ominous condition, characteristically being progressive. There may be symptoms, such as pruritus, dermographism, and flushing. Classification of variants of mastocytosis in the World Health Organization (WHO) is mainly based on the hematological manifestations [2, 3], however, there is a more traditional classification regarding cutaneous mastocytosis, as follows:

Cutaneous mastocytosis (CM)
Solitary mastocytoma
Diffuse cutaneous mastocytosis
Urticaria pigmentosa
Telangiectasia macularis eruptiva perstans (TMEP)

Systemic mastocytosis
With cutaneous lesions
With extracutaneous lesions only

Malignant mast cell disease
Malignant mastocytosis
Mast cell leukemia.

Most patients with cutaneous mastocytosis (CM) will have an indolent clinical course with the disease limited to the skin. There are several different forms of cutaneous mastocytosis. These include solitary mastocytoma, diffuse CM and maculopapular cutaneous mastocytosis (MPCM), which can present as urticaria pigmentosa (UP) or as telangiectasia macularis eruptiva perstans (TMEP). [1]

TMEP is a rare adult form of cutaneous mastocytosis whereby subsequent investigations typically disclose a significant incidenc of systemic involvement.[4] Familial series with childhood onset have been also reported. [5] There is a rare association with multiple myeloma[6] and it has been suggested that KIT mutation may explain the abnormal proliferation of both lineages. [7, 8, 9]

Clinically, the lesions of TMEP are small erythematous telangiectatic macules (2-4mm in size) on the trunk and proximal parts of the extremities. The lesions are usually non-pruritic and only exhibit a Darier's sign if vigorously rubbed. [1, 10, 11]

The histological pattern of mastocytosis is similar regardless of the clinical type. The infiltrate is predominantly in the upper third of the dermis. There might be a small number of eosinophils as well as superficial edema in lesions that are rubbed prior to removal. Basal hyperpigmentation is a usually present. In solitary mastocytoma there are dense aggregates of mast cells in the dermis, sometimes extending into its deeper levels and even into the subcutis. In TMEP there may be only subtle alterations; the cells are mostly arranged around the dilated vessels of the superficial plexus. In diffuse cutaneous mastocytosis, however, mast cells are loosely arranged throughout the dermis. Fibrosis is sometimes present. The number of mast cells in the cutaneous mastocytosis varies from 2 to 160 times that in the adjacent normal skin. Normal skin may contain up to 20 mast cells per high-power field. In TMEP it is often useful to have normal skin for comparison with lesional skin. Qualitatively, the mast cells in mastocytosis are quite distinctive, characteristically exhibiting a large more elongate and spindled morphology compared to a reactive mast cell. They can be highlighted with toluidine blue, Giemsa, chloroacetate esterase and tryptase. Immunohistochemistry for CD117 and CD68 has been used. The baseline criteria for rendering a histologic diagnosis of mastocytosis is one of clusters of mast cells comprising 15 or more mast cells versus 20 or more mast cells per high power field and or the demonstration of a C KIT mutation on condon 86d0 procured from RNA extracted from a skin biopsy.

In 1998, Tebbe et. al. studied 14 adult patients diagnosed with varying forms of CM. In these cases, all 14 patients developed extracutaneous manifestations. The interval between the diagnosis of cutaneous mastocytosis and extracutaneous

Continued

involvement ranged from months to years. Also, the intensity of clinical symptoms was highly variable between patients.
The most common manifestations included gastro-intestinal symptoms, bone marrow involvement, hepatosplenomegaly, anemia, thrombocytopenia, headaches, flushing and orthostatic hypotension. The progression of disease was rather slow among the patients followed and malignant transformation was not seen. [12]
In a very recent study by Severino and co-workers, in a large cohort of 243 patients 14% had TMEP[13]. The median age at diagnosis was 42 years and most patients were diagnosed within 2 years of initial commencement of symptoms. 47% of patients developed signs of systemic mastocytosis and 9% had severe organ impairment including bone fractures and malabsorption. Features of systemic involvement include elevated tryptase and symptoms of generalized mast cell activation such as flushing, diarrhea, abdominal pain, fatigue and headache. An important practical issue is whether there is any way of predicting which patients with CM who will progress to systemic involvement and who among these patients will have an indolent vs. severe course. In one study, it was found that the extent and density of cutaneous involvement in adults with CM is directly related to the likelihood of developing systemic disease. Patients with more widespread skin lesions were found to have more pruritus, flushing, musculoskeletal pain, hepatomegaly, splenomegaly and lymphadenopathy. The histologic pattern of mast [14]
However the phenotypic profile may be of some value. CD25 expression in adult patients with any form of cutaneous mastocytosis including TMEP might be predictive of extracutaneous organ involvement . [1]

It has been proposed that routine procedure should include a bone marrow biopsy and aspirate for all adult patients diagnosed with CM for baseline staging. Bone scans may also be helpful to identify diffuse mineralization, osteosclerosis, and fractures that may result in skeletal disease. Finally, endoscopy may be helpful to evaluate for gastrointestinal involvement.
Though there is no cure for mastocytosis and no evidence that any therapy will influence the course of disease, patients can be managed symptomatically. Avoidance of known stimulants such as extremes in temperature and certain ingestants may help. Patients have also been managed with histamine receptor antagonists and mast cell stabilizers. Even with systemic disease, the prognosis is fair as the disease is usually indolent and life-threatening complications are rarely seen.

Figure Legend

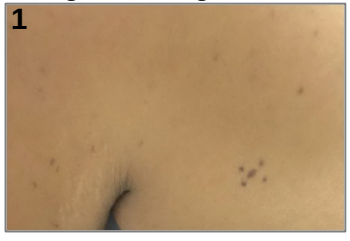
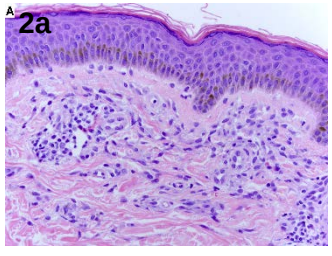


***Figure 1**: Clinical photograph showing 2-4mm red-brown macules scattered over the patient's back.*



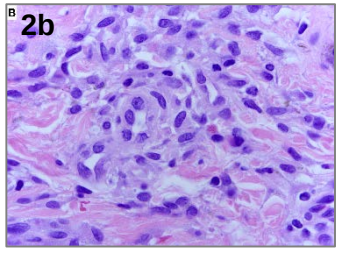


***Figure 2a-b**: Histologic examination revealed telangiectasia macular eruptiva perstans. There is epidermal basal layer hyperpigmentation. Telangiectasias are seen along with a spindled mast cell infiltrate in the superficial dermis. Perivascular lymphocytes aND eosinophils are also seen. Hematoxylin and eosin 40X (a), 100X (b).*

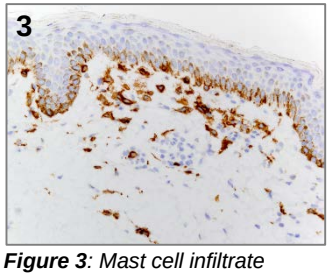


***Figure 3**: Mast cell infiltrate highlighted with CD117 (a)*

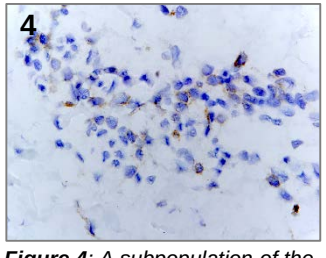


***Figure 4**: A subpopulation of the mast cells are positive for CD25.*

Case References

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Under the direction of Dr. Cynthia M. Magro, the Weill Cornell Comprehensive Dermatopathology Service is a leading edge consultation service and CAP-accredited laboratory for dermatologists, plastic and general surgeons and other dermatopathologists. Dr. Magro is an internationally renowned dermatopathologist, educator and author. She is a Professor of Pathology and Laboratory Medicine at the Weill Cornell Medical College in Manhattan, and is board certified in anatomic pathology, dermatopathology and cytopathology. Dr. Magro is an expert in the diagnosis of complex inflammatory skin diseases. Her areas of expertise include cutaneous manifestations of auto-immune disease, systemic viral disease and vasculitis, atypical drug reactions, benign, atypical and overtly malignant lymphocytic infiltrates of the skin, and diagnostically difficult melanocytic proliferations.The award-winning author of *The Melanocytic Proliferation: A Comprehensive Textbook of Pigmented Lesions*, Dr. Magro has recently completed her second book, *The Cutaneous Lymphoid Proliferation, a comprehensive textbook on benign and malignant lymphocytic infiltrates*. She has co-authored over 300 peer reviewed papers and several textbook chapters. Dr. Magro frequently presents courses on inflammatory skin pathology and difficult melanocytic proliferations to the American Academy of Dermatology, the United States and Canadian Academy of Pathology, and the American Society of Clinical Pathology. Dr Magro has consistently been recognized in Who's Who in America®, Castle Connolly's renowned America's Top Doctors – New York Metro Area® edition and in the Super Doctors® list published in The New York Times Magazine.

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