

# Urticaria Pigmentosa: A Case Report and Review of Current Standards in the Diagnosis of Systemic Mastocytosis

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## Abstract

*Mastocytosis is a group of diseases that is characterized by mast-cell infiltration of the skin. The cutaneous forms of the disease are most identifiable, yet it is important to recognize the progression to systemic disease due to the effect on morbidity and mortality. We Our goal is to describe a case of cutaneous mastocytosis as well as review the current standards in diagnosis and management of systemic mastocytosis.*

## Introduction

Mast-cell disease is a rare disorder, primarily of childhood, that is usually self-resolving. Approximately two-thirds of cases are limited to the skin. The most common forms of cutaneous mastocytosis include: mastocytoma, urticaria pigmentosa, telangiectasia macularis eruptiva perstans, maculopapular cutaneous mastocytosis, and diffuse cutaneous mastocytosis.<sup>1</sup> Our case report presents a patient with a history of urticaria pigmentosa (UP) that had not resolved as expected. Furthermore, she started to develop symptoms that raised concern for possible systemic mastocytosis (SM). Based upon our literature search, systemic mastocytosis is an extremely rare diagnosis, but a potentially life-threatening one. This paper will help Uth dermatologists become more familiar with worrisome signs/symptoms, diagnostic criteria, and treatments for systemic disease.

## Case Report

A 20-year-old Caucasian female with a history of urticaria pigmentosa since childhood presented to our office for initial evaluation of worsening symptoms involving multiple organ systems. She complained of bone pain often localized to the bilateral knees. In addition, the

patient had several bouts of loose stools. This was accompanied by bloating and indigestion, which occurred 30 minutes after a meal. A colonoscopy was performed one year prior at an outside facility, and it was within normal limits. However, no biopsies were performed to look for mast-cell infiltration of the digestive tract. Our patient also had sharp, intermittent, left upper quadrant abdominal pain that radiated to the left chest and shoulder. Remaining review of systems was negative except for occasional mild headaches and lightheadedness. She admitted to mild generalized pruritus for which she took hydroxyzine and cimetidine as needed. In addition, she experienced easy flushing, which was more pronounced while exercising and drinking alcohol.

The patient had a past medical history of mild asthma and attention deficit hyperactivity disorder. Social history included rare alcohol use, smoking one pack of cigarettes per day, and no illicit drugs. She was also exposed to different cleaning solvents daily as a carpet cleaner. Family history was non-contributory.

The physical examination revealed a subtle but diffuse, reddish-purple, mottled, reticular, macular discoloration involving the bilateral upper and lower extremities, chest, abdomen, and back

and spleen did not reveal any organomegaly. Muscle strength and tone appeared to be within normal limits. There were no palpable lymph nodes in the neck, axillae or groin regions.

Our differential diagnosis included systemic mastocytosis as well as carcinoid syndrome, pheochromocytoma, inflammatory bowel disease, urticaria, and myeloproliferative disorder.

Through a collaborative effort between dermatology and hematology/oncology, an extensive workup to rule out SM was performed. Initially, punch biopsies of the right shin and left dorsal forearm revealed cutaneous mast-cell disease. Stains were positive for mast-cell tryptase and CD117 (**Figure 5, p. 56**). Complete blood count with differential, comprehensive metabolic profile, lactate dehydrogenase, fractionated catecholamines, IgE level, and uric acid were all within normal limits. Serum tryptase level was 14.8. Additionally, she underwent imaging studies including a CT scan of the chest, abdomen, and pelvis, abdominal ultrasound, and skeletal survey, which were all unremarkable. A bone-marrow biopsy was performed and that showed at least 15 clusters of dense mast-cell aggregates (**Figure 6, p. 56**). However, flow cytometry did not reveal expression of CD2 or CD25 on CD117+ mast cells. Additionally, only about 10% of the mast cells were spindle-shaped within the bone marrow smear as opposed to greater than 25%. Furthermore, our patient tested negative for KIT D816V mutation.

Taking into account the clinical presentation, positive histopathology, and laboratory and bone-marrow findings, our patient did not meet the full criteria for the diagnosis of SM. For UP,



(**Figure 1-4, p. 55/56**). The head and neck were uninvolved. Upon stroking lesions on the bilateral forearms, the areas became swollen, itchy, and red, eliciting a positive Darier's sign. Examination of the liver





Figure 3



Figure 4

the patient was started on histamine H<sub>2</sub>-receptor antagonists, ranitidine 150 mg by mouth twice daily and famotidine 20 mg by mouth daily, as well as a mast-cell stabilizer, cromolyn 200 mg by mouth three times daily to control mast-cell activation. Additionally, she was given an epinephrine autoinjector in case of anaphylactic reactions. We suggested she also minimize exposure to cleaning solvents as this may be a potential aggravating factor. On follow-up, our patient's symptoms had improved. Cetirizine, a histamine H<sub>1</sub>-receptor antagonist, was also added to the regimen. In addition, we are considering phototherapy as an adjuvant treatment.

The patient continues to be closely monitored by both dermatology and oncology for potential risk of full-blown SM in the future. There is a likelihood that her disease will continue to progress. As a result, the patient was advised to follow up every four to six months for repeat labs. There is also a possibility that the patient may exhibit a wild-type KIT mutation other than D816V, and it may be prudent to include the full KIT mutation-panel testing at a future visit.

## Discussion

Mastocytosis is a group of diseases that is characterized by mast-cell infiltration of the skin.<sup>1</sup> Mast cells originate from CD34- antigen-positive, pluripotent progenitor cells in the bone marrow. From within their granules, they release from within their granules mediators such as histamine, heparin, chymase, tryptase, leukotrienes B<sub>4</sub>, C<sub>4</sub>, E<sub>4</sub>, platelet-activating factor, and prostaglandin D<sub>2</sub>.<sup>2</sup>

Mastocytosis was first discovered in 1869 by Nettleship and Tay, who recognized the classic cutaneous form of disease now known as urticaria pigmentosa. It was not until 1949 that Ellis discovered mast cells within a patient's liver, spleen, lymph nodes, and bone marrow, suggesting that it may also be a systemic disease.<sup>3</sup>

Mastocytosis is more common in children than adults. Over 50% of children are diagnosed prior to two years of age, and disease is usually limited to the skin. Most children will spontaneously resolve by adolescence. In contrast, initial diagnosis of cutaneous mastocytosis as an adult increases the likelihood of developing systemic disease. The median age at diagnosis of SM in adults is 55 years, with a slight male predominance. The incidence of systemic disease is extremely rare.<sup>4</sup> Neither cutaneous nor systemic forms of mastocytosis appear to be inherited.

Mutations of KIT have been implicated in the pathogenesis of both cutaneous and systemic mastocytosis. Mast cells express c-kit tyrosine kinase receptor on their surface, which serves as a site for attachment of stem-cell factor (SCF). SCF is a growth factor needed for the normal development and expansion of mast cells. In mastocytosis, there is a pathologic activation of the c-kit receptor, leading to unregulated clonal expansion and activation of mast cells. The most common mutation in systemic mastocytosis is on codon 816 replacing aspartic acid for valine. This is seen in up to 93% percent of patients with systemic mastocytosis.<sup>5</sup> Recently, additional mutations have been identified.

Initial workup for SM involves a thorough history and physical examination looking for clinical clues to indicate an excess release of mast-

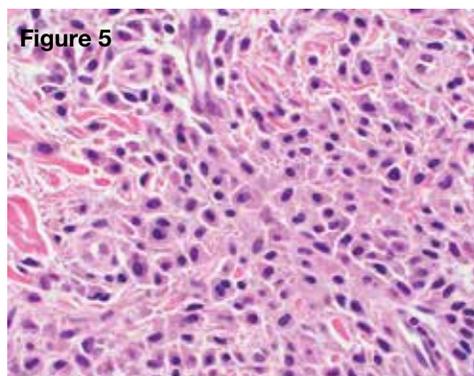


Figure 5

cell mediators in cutaneous and extracutaneous tissues. Symptoms that may raise suspicion include rhinitis, vomiting, abdominal pain, bloating, diarrhea, flushing, pruritus, bone pain, fever, chills, weight loss, tachycardia, headaches, syncope, difficulty concentrating, anxiety, and depression. Physical assessment may reveal organomegaly, predominately involving the liver or spleen, lymphadenopathy, gastroduodenal ulcerations, and signs of end-organ liver disease such as elevated transaminases, ascites, and portal hypertension in advanced disease forms.<sup>6</sup> In addition, one should investigate for skin findings consistent with reddish-brown, maculopapular, plaque-like, bullous or nodular lesions, diffuse skin involvement, solitary mastocytoma, telangiectasias, and positive Darier's sign. These findings may indicate a new or prior diagnosis of cutaneous mastocytosis and will help with the workup for systemic disease.<sup>7</sup>

The next step involves obtaining a skin biopsy. Special stains including Wright-Giemsa, Toluidine blue, tryptase, and CD117 should be ordered.<sup>8</sup> In addition, laboratory investigation should include complete blood count with differential. The peripheral blood picture can show anemia, thrombocytopenia, and leukocytosis. Some patients with SM may also present with elevated eosinophils, basophils, and/or platelets. Myeloproliferative or myelodysplastic changes can also be seen.

Occasionally, it may be feasible to obtain imaging studies in order to identify the extent or stage of disease. For example, computed tomography scan, endoscopy/colonoscopy, or abdominal ultrasound may be considered in patients who present with primarily gastrointestinal complaints. Skeletal surveys and dual-energy X-ray absorptiometry scans may be helpful in patients with suspected bone involvement such as osteoporosis, osteolysis, and evaluation for pathological fractures.<sup>8</sup> However, it is not necessary to evaluate extramedullary tissues for the presence of mast cells to make the diagnosis of SM if the bone marrow is being examined.<sup>6</sup>

Bone-marrow analysis is of crucial importance in the diagnosis of SM. The presence of multiple aggregates of mast cells in bone-marrow aspirate is the major diagnostic criterion for SM as determined by the World Health Organization (WHO). Each aggregate should contain greater than 15 mast cells. The cells are usually located paratrabecularly, but they can also be

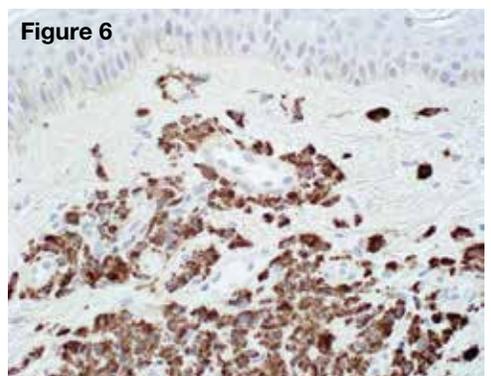


Figure 6

seen around vessels and adnexal structures.<sup>6</sup> In addition, there are several bone-marrow findings in the WHO minor criteria for SM, which include the following: 1) more than 25% of mast-cell infiltrates demonstrating an abnormal spindle-shape; 2) flow cytometry of bone-marrow preparation demonstrating mast cells that express CD2 and/or CD25; and 3) polymerase-chain-reaction evaluation of bone-marrow cells detecting a positive mutation of KIT D816V.<sup>6,8</sup> This mutation can also be evaluated via a blood test. Along with a serum tryptase level greater than 20 ng/mL, these four findings account for the WHO minor criteria for SM.<sup>9</sup> In order to make a diagnosis of SM, an individual must present with one minor and one major criterion or three minor criteria.

The treatment of mast-cell disease is multifaceted. First and foremost, patients should avoid triggers such as excess heat, intense exercise, insect and snake bites, medications like aspirin and non-steroidal anti-inflammatory drugs, and alcohol.<sup>6</sup> In addition, some muscle relaxants and inducing agents used during surgery for general anesthesia may cause mast-cell mediator release and potentially cause anaphylactic reaction. Radiocontrast media may cause a similar reaction.<sup>10</sup>

H1 histamine-receptor antagonists (H1) such as loratadine and hydroxyzine are the first-line treatments for symptoms caused by mast-cell mediator release. These help control urticaria and pruritus. Psoralen plus ultraviolet A (PUVA) therapy can also improve pruritus by reducing histamine release. Gastrointestinal symptoms respond better to H2 histamine-receptor antagonists (H2) like cimetidine and ranitidine.<sup>11</sup> Cromolyn sodium helps decrease diarrhea, malabsorption, and bloating.<sup>6</sup>

Individuals who demonstrate signs of osteoporosis benefit from calcium and vitamin D supplementation and may need bisphosphonates depending on the severity of disease. In addition, all patients should be given an epinephrine autoinjector and instructed on its use in case of anaphylaxis. Patients with more aggressive subvariants of SM may qualify for cytoreductive therapies such as imatinib mesylate, interferon alpha, and cladribine.<sup>6</sup> These treatments are not curative but are intended to improve symptoms and quality of life.

## Conclusion

This case highlights the important role that dermatologists play in the recognition of cutaneous mastocytosis progressing to systemic disease. It is imperative to perform a thorough history, physical, and review of systems in all patients with cutaneous mastocytosis to help initiate a comprehensive work up. Systemic disease can be quite aggressive and potentially life-threatening. Timely diagnosis and early treatment can decrease morbidity and mortality.

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