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CASE REPORT

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Urticaria pigmentosa and systemic mastocytosis

Jonathan Keow[1] | **Benjamin Chin-Yee**[2,3] | **Cyrus C. Hsia**[2] | **Kara Robertson**[4]

[1]DynaLIFE Medical Labs, Edmonton, Alberta, Canada

[2]Division of Hematology, Department of Medicine, University of Western Ontario, London, Ontario, Canada

[3]Department of History and Philosophy of Science, University of Cambridge, Cambridge, United Kingdom

[4]Division of Clinical Immunology and Allergy, Department of Medicine, University of Western Ontario, London, Ontario, Canada

Correspondence
Benjamin Chin-Yee, Division of Hematology, Department of Medicine, Schulich School of Medicine, University of Western Ontario, 800 Commissioners Rd E, Rm. E6-211, London, Ontario N6A 5W9, Canada.
Email: benjamin.chin-yee@lhsc.on.ca

Key Clinical Message

Additional investigations for systemic involvement should be initiated once the diagnosis of cutaneous mastocytosis has been established in an adult patient. A serum tryptase can serve as a screening test for systemic mastocytosis, and persistent elevations should prompt further investigations, such as bone marrow studies.

Abstract

Urticaria pigmentosa (UP) is the most common form of cutaneous mastocytosis, presenting as a wide variety of macroscopic appearances. Cutaneous mastocytosis in pediatric patients usually does not present with systemic involvement, but more than half of adult patients with cutaneous mastocytosis demonstrate systemic involvement. Currently, there is no guidance surrounding systemic testing in patients with UP. A 50-year-old Caucasian male was referred to the Clinical Immunology and Allergy clinic with a history of a rash. He initially presented to hospital 12 years prior with group A beta hemolytic streptococcus bacteremia treated with multiple different antibiotics. One week following discharge, he developed erythematous brown spots on his right leg which were flat, non-pruritic, and not painful. The rash later expanded to his trunk and extremities. A skin biopsy performed 2 years prior to referral to our clinic demonstrated urticaria pigmentosa. The CD117 immunohistochemical stain showed increased perivascular and interstitial mast cells in the superficial dermis. Darier's sign was negative on physical examination, and venom testing was also negative. Although he had no symptoms of systemic involvement, his serum tryptase was elevated at 47.6 ng/mL in the context of normal kidney and liver function. A skeletal survey was normal, and an abdominal ultrasound ruled out splenomegaly. Bone marrow biopsy demonstrated a mild increase in paratrabecular and perivascular atypical mast cells, in keeping with systemic mastocytosis. Adult patients with cutaneous mastocytosis have a high likelihood of having an underlying systemic mast cell disorder. Therefore, any patient presenting with characteristic skin findings should be investigated as having a cutaneous manifestation of systemic mastocytosis. This case demonstrates the utility of serum tryptase and its role in triggering additional investigations and guiding appropriate therapy.

KEYWORDS
cutaneous mastocytosis, systemic mastocytosis, urticaria pigmentosa

1 | BACKGROUND

Mastocytosis is a disease characterized by an abnormal infiltrate of neoplastic (clonal) mast cells in one or more organs.[1] This disorder is characterized by its heterogenous presentation and is classified by its distribution of disease. The two major variants of mastocytosis are cutaneous mastocytosis, where the neoplastic mast cell infiltrate is confined to the skin, and systemic mastocytosis, where at least one extracutaneous organ is involved.[2]

Urticaria pigmentosa (UP) is the most common form of cutaneous mastocytosis.[3] The pathogenesis of mastocytosis often involves an activating mutation in the *KIT* gene in a mature mast cell to produce a neoplastic population of clonal mast cells. UP usually presents as localized, monomorphic, tan-brown maculopapular lesion that can urticate when mechanically agitated. However, UP may take on a variety of clinical appearances,[4] sometimes presenting as ill-defined reddish brown macules with associated telangiectasias (termed 'telangiectasia macularis eruptiva perstans'), caused by the perivascular infiltration of atypical neoplastic mast cells around dermal capillaries.[5] These atypical presentations can often be misdiagnosed as telangiectatic disorders, such as scleroderma, hereditary hemorrhagic telangiectasia or telangiectasias secondary to cirrhosis, but their clinical outcome is indistinguishable from classical UP, despite the difference in macroscopic appearance. In all cases of cutaneous mastocytosis, Darier's sign may be positive, where an urticarial wheal appears following iatrogenic excoriation because of mechanical degranulation from the excess cutaneous neoplastic mast cells.

Although cutaneous mastocytosis in pediatric patients rarely presents with systemic involvement,[6] up to half of all adult UP cases will have an associated systemic mastocytosis.[7] However, there are no established consensus guidelines surrounding testing for systemic involvement in patients with UP.

The prognosis and treatment options for patients with mastocytosis are markedly different, depending on extent of clinical manifestations and distribution of disease. Complete resolution of the disease occurs more frequently in patients with limited cutaneous mastocytosis than in patients with systemic mastocytosis.[8] In addition, these patients also have a higher rate of Hymenoptera venom allergy than the general population.[9] However, treatment options are limited to symptom management, with steroid therapy, antihistamines, tyrosine kinase inhibitors (imatinib and midostaurin), and omalizumab as possible therapeutic agents depending on disease extent.[10]

Here we described the clinical course, associated findings, and work-up in a patient with UP, and the diagnostic uncertainty preceding identification of systemic involvement.

2 | CASE PRESENTATION

A 50-year-old male was referred to the Clinical Immunology and Allergy clinic with a history of a rash suspected to be secondary to a drug reaction. He had initially developed erythematous brown macules on his right leg following treatment with multiple different antibiotics for group A beta hemolytic Streptococcus bacteremia 12 years prior. These lesions were flat, non-pruritic, and not painful, and later expanded to involve his trunk and extremities. A skin biopsy performed immediately prior to referral to our clinic demonstrated an increase in perivascular and interstitial mast cells in the superficial dermis, consistent with urticaria pigmentosa (Figure 1A). The *KIT* (CD117) immunohistochemical stain showed an increased number of perivascular spindled mast cells (Figure 1B), in keeping with a cutaneous manifestation of mastocytosis.

The patient was otherwise healthy and did not have any symptoms that would have been suggestive of systemic involvement, such as flushing, abdominal pain, fevers, drenching night sweats, weight loss, respiratory symptoms, or musculoskeletal symptoms. The macules were present across the trunk and extremities at time of physical examination, and Darier's sign was negative. There was no lymphadenopathy or hepatosplenomegaly. Despite having no symptoms of systemic involvement, a serum tryptase was drawn, given the association between UP and systemic involvement. Testing for honeybee, yellow jacket, white-faced hornet, yellow hornet, and wasp venoms (intradermal and serum-specific IgE) was negative.

His serum tryptase was elevated at 47.6 ng/mL (normal 3.8–11.4 mg/mL) in the context of normal kidney and liver function. Bloodwork demonstrated leukocytes at 5.4×10^9/L, hemoglobin 148 g/L, platelets 251×10^9/L, neutrophils 2.2×10^9/L, lymphocytes 2.7×10^9/L, and eosinophils 0.1×10^9/L. Lactose dehydrogenase and coagulation assays (INR, PTT) were normal. Bone scintigraphy did not identify any osseous lesions, and an abdominal ultrasound ruled out ascites and hepatosplenomegaly.

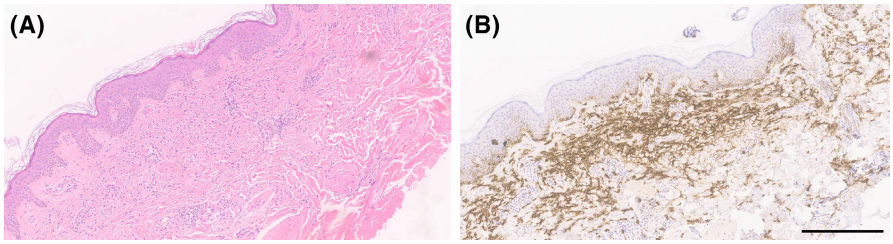

FIGURE 1 Skin punch biopsy showing an increase in perivascular and interstitial mast cells within the dermis, with associated lymphocytes, histiocytes and eosinophils (A). These mast cells are positive by immunohistochemistry (diaminobenzidine stain, brown) for CD117 (KIT) overexpression (B), supporting the diagnosis of urticaria pigmentosa. Scale bar = 0.3 mm.

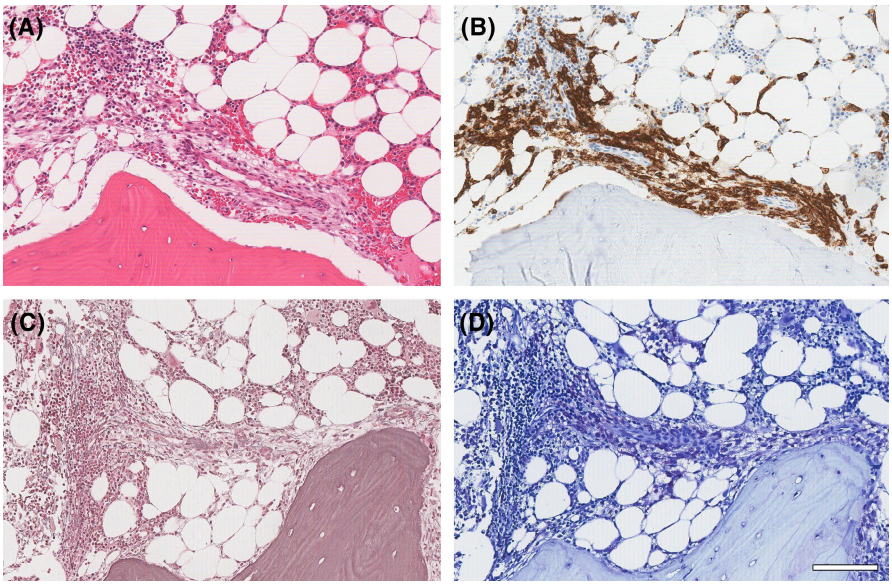

FIGURE 2 Bone marrow biopsy shows a mild increase in paratrabecular and perivascular atypical mast cells (A) that are positive by immunohistochemistry (diaminobenzidine stain, brown) for CD117 (KIT) overexpression (B). A reticulin stain (C) shows patchy mild reticulin fibrosis, corresponding to foci of mast cell aggregation. A toluidine blue stain (D) shows patchy small aggregates of mast cells with metachromatic granules (purple), particularly in paratrabecular and perivascular areas. Scale bar = 0.1 mm.

Based on the elevation in serum tryptase, the patent was referred to hematology, and a bone marrow biopsy from the right posterior superior iliac spine demonstrated a mild increase in paratrabecular and perivascular atypical mast cells (Figure 2A) that were positive by immunohistochemistry for CD117 (KIT) overexpression (Figure 2B). A reticulin stain (Figure 2C) demonstrated patchy mild reticulin fibrosis, corresponding to foci of mast cell aggregation, and a toluidine blue stain (Figure 2D) highlighted the metachromatic granules within these small aggregates of mast cells. Overall, these findings were in keeping with systemic mastocytosis. His cytogenetics demonstrated a normal karyotype; however, next-generation sequencing revealed no point mutation at codon 816 of *KIT*.

He was ultimately diagnosed with indolent systemic mastocytosis, with skin lesions and low mast cell burden. There was an absence of B ('burden of disease') and C ('cytoreduction-requiring') findings that are seen with the more aggressive variants of systemic mastocytosis. Given this diagnosis, no systemic therapies were initiated at the current time.

3 | DISCUSSION AND CONCLUSIONS

Mastocytosis is a clinically heterogeneous condition with indolent to aggressive disease presentations. There are several variants of systemic mastocytosis, including indolent systemic mastocytosis (the most common), aggressive systemic mastocytosis, and mast cell leukemia.[2]

Systemic mastocytosis is associated with systemic symptoms due to inappropriate release of mast cell mediators and the possible development of splenomegaly, lymphadenopathy, and hepatomegaly. However, these findings are uncommon in the indolent variants and more often present with advanced or aggressive disease.[1] Severe systemic symptoms such as anaphylaxis may occur in aggressive disease because of ongoing neoplastic mast cell degranulation, and gastrointestinal manifestations such as diarrhea and peptic ulcers may also occur due to excess systemic histamine, eicosanoid, protease, and heparin release.[11] However, cutaneous symptoms may be present in up to 80% of patients with systemic mastocytosis.[12,13]

Although UP is generally well-recognized when presenting with its classical appearance, unusual macroscopic presentations of cutaneous mastocytosis are often misdiagnosed given the potential variability in clinical presentation and subtlety with establishing the histological diagnosis in the context of a low pre-test probability.[14] Adult patients with UP often have a high likelihood of an underlying systemic mast cell disorder.[15] One case series described systemic involvement in up to 47% of cases with cutaneous mastocytosis[16] with aggressive (non-indolent) systemic mastocytosis in up to 9% of those cases. Therefore, any patient presenting with characteristic skin findings should be investigated as having a cutaneous manifestation of systemic mastocytosis. However, there is often a delay in the identification of this association with one case series describing a mean interval of 2 years before the workup of systemic mastocytosis.[17]

Additional investigations for systemic involvement should be initiated once the diagnosis of cutaneous mastocytosis has been established in an adult patient.[18] A serum tryptase can serve as a screening test for systemic mastocytosis, since serum tryptase levels are normal or slightly elevated in mastocytosis patients limited to cutaneous involvement.[19,20] Persistent elevations above 20 ng/mL are suggestive for systemic mastocytosis and may prompt further investigations, such as bone scintigraphy and a bone marrow biopsy, as was done with this patient.

The elevation in serum tryptase served as an inciting event to trigger further investigations for systemic mast cell involvement. However, elevations in serum tryptase are nonspecific in isolation and can be falsely positive in the setting of a variety of different disorders.[21] Therefore, serum tryptase must be interpreted in settings with a high index of suspicion for systemic mastocytosis (e.g., skin findings, B findings, or C findings) with appropriate clinical correlation to trigger marrow-specific investigations.

Additionally, molecular studies for the presence of a pathogenic *KIT* D816V mutation in the peripheral blood or bone marrow may be helpful to identify a mast cell disorder.[22] In our case, no *KIT* mutation was detected, likely due to the patchy disease process and low mast cell frequency, but rather a suboptimal aspirate sample for molecular testing, suggesting a false negative result.

This case report adds to the growing literature, and demonstrates the utility of serum tryptase and its role in triggering additional investigations and guiding appropriate therapy.

AUTHOR CONTRIBUTIONS

Jonathan Keow: Data curation; writing – original draft; writing – review and editing. **Benjamin Chin-Yee:** Data curation; investigation; writing – original draft; writing – review and editing. **Cyrus C. Hsia:** Conceptualization; investigation; writing – original draft; writing – review and editing. **Kara Robertson:** Conceptualization; data curation; formal analysis; investigation; project administration; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

All data is stored and available in the patient's case files. A copy may be requested to see at any stage. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

Written and oral informed consent for publication has been obtained from the patient. A copy may be requested at any stage.

CONSENT

Written and oral informed consent for publication has been obtained from the patient. A copy may be requested at any stage.

ORCID

Jonathan Keow https://orcid.org/0000-0001-5985-4770

REFERENCES

1. Valent P, Akin C, Metcalfe DD. Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. *Blood*. 2017;129:1420-1427. doi:10.1182/BLOOD-2016-09-731893
2. Valent P, Akin C, Hartmann K, et al. Advances in the classification and treatment of Mastocytosis: current status and outlook toward the future. *Cancer Res*. 2017;77:1261-1270. doi:10.1158/0008-5472.CAN-16-2234
3. Di Raimondo C, Del Duca E, Silvaggio D, et al. Cutaneous mastocytosis: a dermatological perspective. *Australas J Dermatol*. 2021;62:e1-e7. doi:10.1111/AJD.13443
4. Sławińska M, Kaszuba A, Lange M, Nowicki RJ, Sobjanek M, Errichetti E. Dermoscopic features of different forms of cutaneous Mastocytosis: a systematic review. *J Clin Med*. 2022;11:11. doi:10.3390/jcm11164649
5. Watkins CE, Bokor WB, Leicht S, Youngberg G, Krishnaswamy G. Telangiectasia macularis eruptiva perstans: more than skin deep. *Dermatol Reports*. 2011;3:e12. doi:10.4081/DR.2011.E12

6. Nemat K, Abraham S. Cutaneous mastocytosis in childhood. *Allergol Select*. 2022;6:1-10. doi:10.5414/alx02304e
7. Damman J, Diercks GFH, van Doorn MB, Pasmans SG, Hermans MAW. Cutaneous lesions of Mastocytosis: mast cell count, morphology, and Immunomolecular phenotype. *Am J Dermatopathol*. 2023;45:1-7. doi:10.1097/dad.0000000000002474
8. Le M, Miedzybrodzki B, Olynych T, Chapdelaine H, Ben-Shoshan M. Natural history and treatment of cutaneous and systemic mastocytosis. *Postgrad Med*. 2017;129:896-901. doi:10.1080/00325481.2017.1364124
9. Schuler CF, Volertas S, Khokhar D, et al. Prevalence of mastocytosis and hymenoptera venom allergy in the United States. *J Allergy Clin Immunol*. 2021;148:1316-1323. doi:10.1016/j.jaci.2021.04.013
10. Scherber RM, Borate U. How we diagnose and treat systemic mastocytosis in adults. *Br J Haematol*. 2018;180:11-23. doi:10.1111/BJH.14967
11. Doyle LA, Sepehr GJ, Hamilton MJ, Akin C, Castells MC, Hornick JL. A clinicopathologic study of 24 cases of systemic mastocytosis involving the gastrointestinal tract and assessment of mucosal mast cell density in irritable bowel syndrome and asymptomatic patients. *Am J Surg Pathol*. 2014;38:832-843. doi:10.1097/PAS.0000000000000190
12. Hartmann K, Henz BM. Cutaneous mastocytosis – clinical heterogeneity. *Int Arch Allergy Immunol*. 2002;127:143-146. doi:10.1159/000048187
13. Pardanani A, Akin C, Valent P. Pathogenesis, clinical features, and treatment advances in mastocytosis. *Best Pract Res Clin Haematol*. 2006;19:595-615. doi:10.1016/j.beha.2005.07.010
14. Tumer G, Jow T, McElligott S, Schwartz RA, Clark LW. Telangiectasia macularis eruptiva perstans: report of three cases. *Skinmed*. 2017;15:171-174.
15. Cohn MS, Mahon MJ. Telangiectasia macularis eruptiva perstans. *J Am Osteopath Assoc*. 1994;94:246-248.
16. Severino M, Chandesris MO, Barete S, et al. Telangiectasia macularis eruptiva perstans (TMEP): a form of cutaneous mastocytosis with potential systemic involvement. *J Am Acad Dermatol*. 2016;74:885-891.e1. doi:10.1016/J.JAAD.2015.10.050
17. Michelerio A, Grassi S, Elena C, et al. Telangiectasia macularis eruptiva perstans: a neglected type of mastocytosis with exclusively cutaneous involvement? A Case Series. *Eur J Dermatol*. 2019;29:174-178. doi:10.1684/ejd.2019.3532
18. Greenberger PA, Metcalfe DD. Controversies in allergy: is a bone marrow biopsy optional or essential in the evaluation of the patient with a suspected mast cell disorder? *J Allergy Clin Immunol Pract*. 2019;7:1134-1138. doi:10.1016/J.JAIP.2018.11.019
19. Valent P, Horny HP, Escribano L, et al. Diagnostic criteria and classification of mastocytosis: a consensus proposal. *Leuk Res*. 2001;25:603-625. doi:10.1016/S0145-2126(01)00038-8
20. Schwartz LB, Sakai K, Bradford TR, et al. The α form of human tryptase is the predominant type present in blood at baseline in normal subjects and is elevated in those with systemic mastocytosis. *J Clin Invest*. 1995;96:2702-2710. doi:10.1172/JCI118337
21. Lee AYS. Elevated serum tryptase in non-anaphylaxis cases: a concise review. *Int Arch Allergy Immunol*. 2020;181:357-364. doi:10.1159/000506199
22. Kristensen T, Vestergaard H, Bindslev-Jensen C, et al. Prospective evaluation of the diagnostic value of sensitive KIT D816V mutation analysis of blood in adults with suspected systemic mastocytosis. *Allergy*. 2017;72:1737-1743. doi:10.1111/ALL.13187

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