Clinical and molecular categorization of progressive, adult-onset cutaneous mastocytosis

Courtney Tate, BSc (Hons), MBBS, PhD,[a] Fiona Tang, BMedSc, MBBS, FRCPA,[a,b] Steven W. Lane, MBBS (Hons), PhD, FRACP, FRCPA,[b,c] and Louise Seymour, MBBS, BPharm (Hons), MPhil, FRCPA[a,b]
Herston and St. Lucia, Australia

Key words: mastocytosis; radiotherapy-induced telangiectasia; telangiectasia macularis eruptive perstans.

INTRODUCTION

Diagnosis of mastocytosis is frequently delayed given the variable clinical phenotypes at presentation. Here we present a case of a 64-year-old woman diagnosed with cutaneous mastocytosis (CM), specifically urticaria pigmentosa (UP), initially localized to an area treated with radiotherapy that subsequently progressed to indolent systemic mastocytosis (SM).

Abbreviations used:

BMAT:	bone marrow aspirate and trephine
CM:	cutaneous mastocytosis
CT:	computed tomography
UP:	urticaria pigmentosa
SM:	systemic mastocytosis
TMEP:	telangiectasia macularis eruptive perstans
WHO:	World Health Organization

CASE REPORT

A 64-year-old woman had an 18-month history of a maculopapular telangiectatic rash on her right breast (Fig 1). Darier sign was positive. She had no systemic symptoms and was otherwise well. The rash was first noticed 3 months after treatment for high-grade ductal carcinoma in situ with wide local excision, radiotherapy (50 Gy in 25 fractions), and anastrozole. A skin biopsy of the rash was performed and histopathologic findings were consistent with CM (Fig 2), and considering the predominant maculopapular nature of the rash with only minimal telangiectasia, the diagnosis of UP was favored.

SM was excluded after hematologic review of computed tomography (CT) scans of the patient's neck, chest, abdomen, and pelvis; bone marrow aspirate and trephine (BMAT); and bone densitometry, all of which showed no evidence of extracutaneous involvement. There was no hepatosplenomegaly or lymphadenopathy, and PCR for *c-KIT* D816V mutation of BMAT was negative. The patient had no malabsorptive symptoms, no drug or other allergies, and no history of anaphylaxis. She was counseled in a dermatology clinic to avoid provoking factors and use antihistamines as necessary.

Over the following 5 years, the patient's rash progressively spread to include most of her torso. She developed systemic symptoms consistent with mast cell mediator release including hot flushes and erythema after showering. Her basal serum tryptase increased (Fig 3). Repeat BMAT showed multifocal mast cell aggregates admixed with mature lymphocytes. More than 25% of her mast cells were spindle shaped with atypical morphology (Fig 4). There was no morphologic evidence of associated clonal hematologic non−mast cell disease. PCR for *c-KIT* D816V mutation of BMAT was positive.

Restaged CT scan and bone densitometry scan were normal. Given the absence of B or C findings[1] used to classify clinical variants of SM, and the absence of a clonal hematologic non−mast cell disease, the patient was diagnosed with indolent

From the Pathology Queensland, Royal Brisbane and Women's Hospital, Herston[a]; The University of Queensland, St. Lucia[b]; and Cancer Care Services, Royal Brisbane and Women's Hospital, Herston.[c]

Funding sources: None.
Conflicts of interest: None declared.

Correspondence to: Courtney Tate, BSc (Hons), MBBS, PhD, Pathology Queensland, Royal Brisbane and Women's Hospital, Herston, 4006 Australia. E-mail: courtmodra@hotmail.com.

JAAD Case Reports 2018;4:30-2.
2352-5126

https://doi.org/10.1016/j.jdcr.2017.09.038

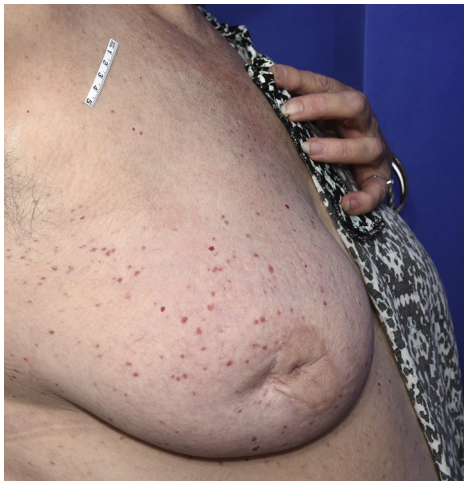

Fig 1. A maculopapular telangiectatic rash on the patient's right breast.

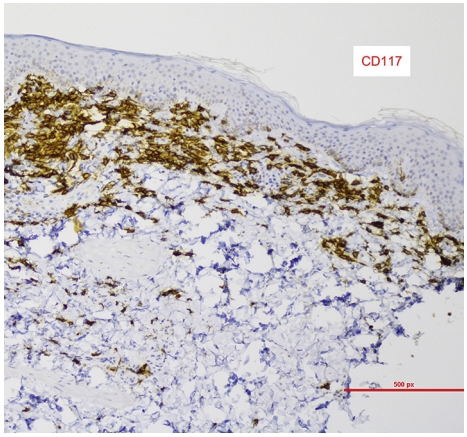

Fig 2. Skin biopsy at initial presentation of affected area on right breast shows mast cells highlighted by immunoperoxidase stain CD117 (c-kit).

SM. The patient continues to receive supportive care with antihistamines and avoidance of triggers.

DISCUSSION

Mastocytosis is a heterogeneous disease caused by accumulation of clonal mast cells within cutaneous and extracutaneous tissues. Patients have variable clinical phenotypes on the basis of mast cell skin infiltration patterns, mast cell–mediator release, and mast cell organ infiltration and often require multidisciplinary management from dermatologists, immunologists, and hematologists. Owing in part to its rarity and the variable clinical phenotypes at presentation, the diagnosis of mastocytosis is delayed on average by 9 years.[2]

Variants of mastocytosis are broadly classified by the World Health Organization (WHO) as either CM

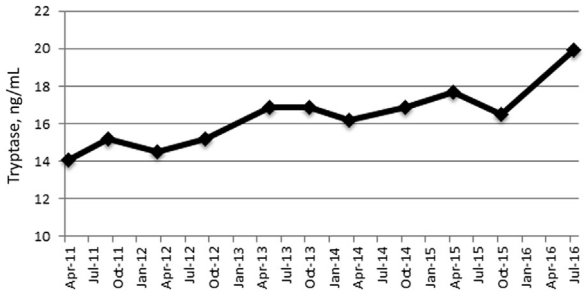

Fig 3. Basal serum tryptase increasing over time.

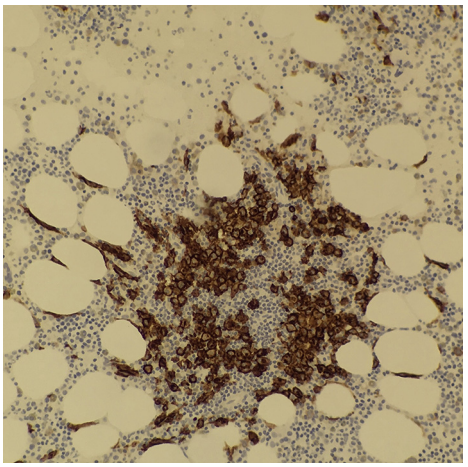

Fig 4. Bone marrow aspirate from patient after symptom progression has clot section with mast cell aggregate admixed with small mature lymphocytes highlighted by immunoperoxidase stain CD117 (c-kit). Some mast cells have atypical spindle-shaped morphology.

or, if extracutaneous tissue involvement exists, SM.[1] CM subclassification relies heavily on the clinical features of the rash, with the WHO recognizing 3 distinct CM entities. Some authors suggest a fourth subtype of CM, telangiectasia macularis eruptive perstans (TMEP), should be considered a distinct entity from UP.[3] In this case, in the context of recent radiotherapy to the biopsied area that could have increased both telangiectasia and reactive mast cell numbers, the differentials of UP, TMEP, and radiotherapy-induced telangiectasia were considered. Histopathologic stains showed a higher density of mast cells than what is typical for a subclassification of TMEP or radiotherapy-induced telangiectasia, and a diagnosis of UP was favored. Clinical features, in particular the predominant maculopapular nature of the rash with only minimal telangiectasia, were also in keeping with a diagnosis of UP.

Of interest was the close proximity of radiotherapy to the initial diagnosis of CM. CM localized to a radiation field has been reported twice

previously,[4,5] and in all cases followed breast cancer treatment. Whether radiotherapy has a direct role in pathogenesis, perhaps through acquisition of additional mutations in signaling pathways, epigenetic regulators, RNA splicing machinery, or transcription factors, is not clear. *c-KIT* D816V mutation burden does not correlate with clinical manifestations, mastocytosis subclassification, disease severity, or progression,[6] rather acquired mutations have been proposed to contribute to the variable symptomatology.[7]

Identification of patients with SM is crucial, allowing the relevant subspecialty to optimally manage variable symptoms. The literature reports that 85%-90% of adult-onset mastocytosis are diagnosed with SM. However, a recent study showed that in adult-onset, biopsy-proven mastocytosis of the skin, 97% fulfill the WHO criteria for diagnosis of SM when using a highly sensitive molecular method involving microdissection of mast cells from bone marrow biopsy for *c-KIT* D816V PCR analysis, a technique not routinely available to diagnostic laboratories. Even of the remaining 3% who failed to meet the diagnostic WHO criteria for SM, rare dissected marrow mast cells (at <1% of total marrow cellularity) were positive for *c-KIT* D816V, challenging the concept and diagnosis of adult-onset CM.[1]

Considering that most diagnostic laboratories perform *c-KIT* D816V PCR on whole genomic DNA extracted from formalin-fixed and paraffin-embedded bone marrow biopsies, a diagnosis of SM might be missed in 15% of cases that would have been met using microdissection of mast cells. Therefore, rather than our case representing evolution of CM to SM, it is likely that the patient had clonally aberrant mast cells present in the initial bone marrow biopsy with which routine *c-KIT* D816V testing was performed but not sensitive enough to detect.

Importantly, this case highlights the need to be aware of the high likelihood of a diagnosis of SM in adult-onset mastocytosis of the skin, for which the clinical implications are substantial. Patients diagnosed with SM by using standard molecular techniques have a higher (up to 49%) cumulative risk of anaphylaxis[8]; they are advised to carry an emergency adrenalin autoinjector (EpiPen, King Pharmaceuticals, Bristol, TN) and use precaution around operations and anesthetics, which can precipitate anaphylaxis. Furthermore, they require ongoing hematologic review to monitor for extracutaneous organ dysfunction, as well as for evolution to more aggressive forms of SM requiring systemic chemotherapy. Whether these increased risks pertain to SM with a low bone marrow burden of mast cell disease detected only using more sensitive molecular techniques remains to be determined.

REFERENCES

1. Valent P, Akin C, Metcalfe DD. Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. *Blood*. 2017;129(11):1420-1427.
2. Berezowska S, Flaig MJ, Ruëff F, et al. Adult-onset mastocytosis in the skin is highly suggestive of systemic mastocytosis. *Mod Pathol*. 2014;27(1):19-29.
3. 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(5):885-891.
4. Comte C, Bessis D, Dereure O, et al. Urticaria pigmentosa localized on radiation field. *Eur J Dermatol*. 2003;13(4):408-409.
5. Soilleux EJ, Brown VL, Bowling J. Cutaneous mastocytosis localized to a radiotherapy field. *Clin Exp Dermatol*. 2009;34(1):111-112.
6. Broesby-Olsen S, Kristensen T, Vestergaard H, et al. *KIT* D816V mutation burden does not correlate to clinical manifestations of indolent systemic mastocytosis. *J Allergy Clin Immunol*. 2013;132(3):723-728.
7. Molderings GJ. The genetic basis of mast cell activation disease — looking through a glass darkly. *Crit Rev Oncol Hematol*. 2015;93(2):75-89.
8. Brockow K, Jofer C, Behrendt H, et al. Anaphylaxis in patients with mastocytosis: a study on history, clinical features and risk factors in 120 patients. *Allergy*. 2008;63(2):226-232.