Case report

Evaluation for systemic mastocytosis in adults with cutaneous mastocytosis

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Abstract In adults with cutaneous mastocytosis there is a high probability of systemic involvement, which can lead to anaphylaxis. Consequently, when cutaneous mastocytosis is diagnosed in adults, it is important to also check for systemic involvement. A 30-year-old Singaporean man presented with generalized asymptomatic monomorphic brownish macules and papules. The lesions were aggravated by consumption of alcohol. Light microscopic study and immunohistochemistry staining results were consistent with cutaneous monomorphic maculopapular mastocytosis. Symptomatic treatment with antihistamine was prescribed and he was advised to avoid alcohol. The patient indicated he would seek further evaluation in Singapore. **Chiang Mai Medical Journal 2017;56(1):43-48.**

Keywords: adult-onset cutaneous mastocytosis, systemic mastocytosis

Background

Mastocytosis is a rare group of disorder characterized by an abnormal proliferation of mast cells accumulating in one or more organs. Skin involvement is the first clinical manifestation in the majority of cases (1). Adult-onset cutaneous mastocytosis frequently includes systemic involvement. Occasionally, it can lead to a life-threatening anaphylactic reaction (2). Diagnosis of cutaneous mastocytosis is based on clinical findings, the presence of cutaneous lesions and a positive Darier's sign together with pathologic findings from a skin biopsy.

Cutaneous mastocytosis can mimic skin disorders such as eruptive xanthogranuloma, generalized eruptive histiocytoma and Langerhans cell histiocytosis which may hinder diagnosis. Increased awareness of the possibility of cutaneous mastocytosis in adults presenting with chronic asymptomatic cutaneous lesions could lead to more accurate diagnosis and early investigation which would benefit patients.

Case presentation

A healthy Singaporean man in his 30s presented with a 4-year history of slowly progressive, asymptomatic skin lesions on the trunk and extremities. The lesions seemed more erythemic after consuming alcohol. The patient denied previous flushing or urticarial-like lesions and stated that no family members had similar cutaneous symptoms.

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Physical examination revealed asymptomatic generalized brownish macules and papules, predominantly on the trunk (Figure 1A). The face was spared. Rubbing the lesions revealed itchy wheals (Figure 1B). The lesions were biopsied and sent for histopathology and immunochemistry studies (Figures 2A, 2B).

Microscopic biopsy examination of a sample from a lesion on the trunk showed an increased number of the granule-rich mononuclear cells in the upper dermis (Figure 2A). Immunohistochemistry staining showed that these cells were positive for anti-KIT (CD117) (Figure 2B). Correlation of the clinical presentation and pathologic findings established the diagnosis of adult-onset maculopapular cutaneous mastocytosis.

We discussed with the patient the option of conducting extensive evaluation to identify any systemic involvement , but he decided to return to Singapore for further workup.

Discussion

Mastocytosis is a rare neoplastic disease of bone marrow origin that is characterized by abnormal growth and/or accumulation of clonal mast cells in at least one organ; its exact prevalence is unknown. The skin and bone marrow are the most common organs involved (3). The disease is divided into two major categories: cutaneous mastocytosis (CM) and systemic mastocytosis (SM).

Cutaneous mastocytosis usually develops in young adults between 20 and 35 years old (4). Currently, CM is divided into three subtypes: (1) maculopapular cutaneous mastocytosis (MPCM), also known as urticaria pigmentosa; (2) diffuse cutaneous mastocytosis (DCM); and (3) mastocytoma (4). MPCM is further sub-divided into two variants: (1) a monomorphic variant with small round, brown or red maculopapular lesions, usually seen in adult patients, and (2) a polymorphic variant with larger lesions and lesions with varying morphology, characteristics typical of lesions found in children (4).

Cutaneous mastocytosis is diagnosed based on the presence of typical skin lesions associated with a positive Darier's sign, the major criterion. Lesions vary from fewer than ten to almost universal coverage. It often involves the trunk and extremities, but spares the face. Darier's sign is elicited by stroking a CM lesion about five times with a tongue spatula using moderate pressure. An urticarial rash will develop within a few minutes. A clearly positive Darier's sign is an important diagnostic finding in patients with mastocytosis. The minor criteria for diagnosing CM are: (i) increased numbers of mast cells in biopsy sections of lesional skin and (ii) (Activating)

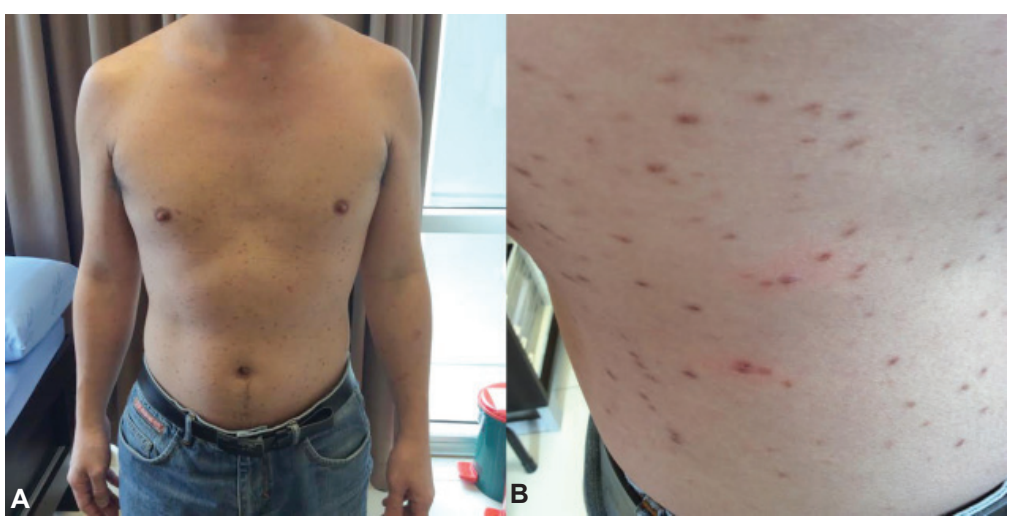

Figure 1. A) Generalized monomorphic brownish maculopapular lesions, predominantly on the trunk, **B)** After rubbing the lesions, itchy wheals developed.

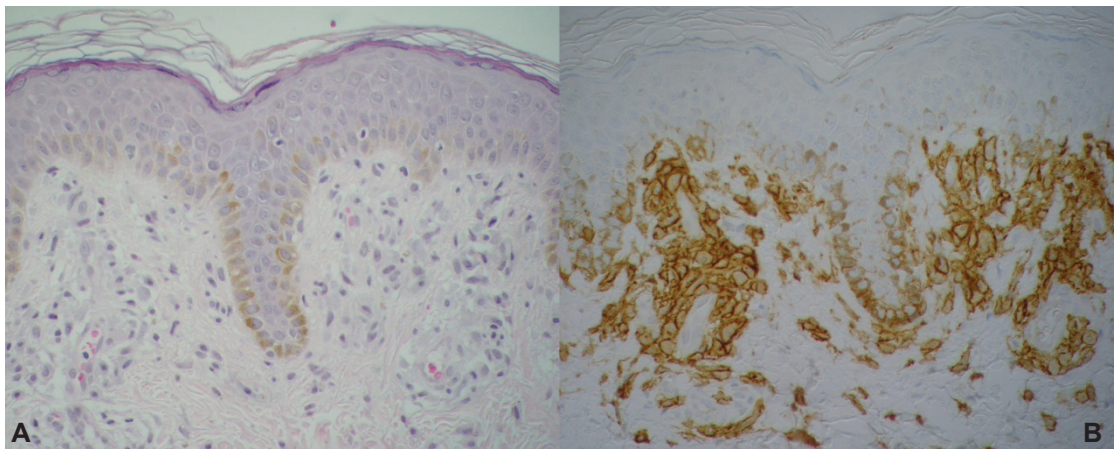

Figure 2. A) Microscopic examination of a biopsy section showed an increased number of granule-rich mononuclear cells in the upper dermis (hematoxylin and eosin X40), **B)** Immunohistochemistry staining; the granule-rich mononuclear cells were positive for anti-KIT (CD117) (Immunohistochemistry for CD117 X40).

Table 1. Clinical manifestation differences between adult-onset and childhood-onset cutaneous mastocytosis

Clinical manifestation	Adult-onset CM	Childhood-onset CM
Most frequent type of cutaneous lesions	Maculopapular	Maculopapular
Typical morphology of maculopapular lesions	Monomorphic	Polymorphic
Typical size of maculopapular lesions	Small	Large
Typical distribution of maculopapular lesions	Thigh, trunk	Trunk, head, extremities
Most frequent category of mastocytosis	ISM	Cutaneous mastocytosis
Typical course of the disease	Chronic	Temporary

CM; cutaneous mastocytosis, ISM; indolent systemic mastocytosis

KIT mutation in lesional skin tissue (4). Important differences between adult-onset and childhood-onset cutaneous mastocytosis are summarized in Table 1 (4).

Our patient presented with generalized monomorphic brownish macules and papules with positive Darier's sign. The pathologic and immunohistochemistry examinations confirmed the diagnosis of cutaneous mastocytosis. The final diagnosis was the monomorphic variant of MPCM, which is more commonly found in adults than children.

The level of systemic involvement in adult patients with cutaneous mastocytosis reported in previous studies has ranged from 41-73% (5). However, a recent study by Berezowska et al. found that nearly all adult patients (97%) with cutaneous mastocytosis had systemic involvement (5).

Serum tryptase can predict systemic involvement in patients with cutaneous mastocytosis. Serum tryptase levels usually range from 0-15 ng/mL in healthy individuals. The levels are slightly elevated in CM patients with systemic involvement and in patients with isolated bone marrow involvement. Higher tryptase levels are observed in SM patients with multi-organ involvement (6).

Bone marrow biopsy studies, including histology, immunophenotyping and KIT D816V mutation screening, should be done in all adults who present with cutaneous mastocytosis irrespective of the clinical course, symptoms and serum tryptase level (1).

Systemic mastocytosis is diagnosed based on WHO criteria (Table 2) (1). Patients with SM may present with mast cell mediator-related symptoms such as flushing, itching,

Table 2. WHO diagnostic criteria for systemic mastocytosis*

Major criterion
Multifocal, compact infiltrates of mast cells >15 mast cells in aggregates detected in sections of bone marrow and/or other extracutaneous organs
Minor criteria
1. More than 25% spindle-shaped mast cells in bone marrow smears 2. Aberrant expression of CD25 and/or CD2 by bone marrow mast cells 3. Detection of D816V KIT mutation in bone marrow 4. Serum tryptase levels >20 ng/mL (not a criterion in patients with clonal haematological non-mast cell lineage disease)

*Diagnosis of systemic mastocytosis requires either the major plus 1 minor or 3 minor criteria.

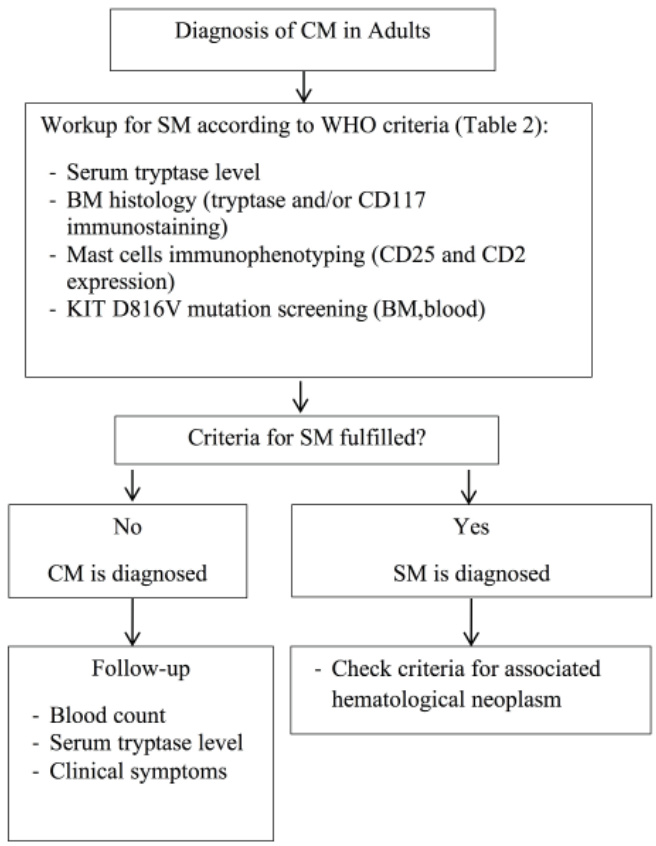

Figure 3. Diagnostic algorithm for systemic mastocytosis in adults with cutaneous mastocytosis. [Adapted from Ref.(1)]. BM, bone marrow; CM, cutaneous mastocytosis; SM, systemic mastocytosis.

blistering, diarrhoea, abdominal cramping and pain, vomiting, peptic symptoms, hypotensive episodes with vascular collapse, anaphylaxis, headache and bone pain (1). With a cumulative incidence of anaphylaxis as high as 49% in SM patients, it is recommended that they carry an emergency set of epinephrine injections (2). Major trigger factors are hymenoptera stings, particular foods, physical stimuli, alcohol and some medications such as NSAIDs, anesthetics, dextran, and contrast media (7). Individuals with systemic mastocytosis have higher basal tryptase levels. Serum tryptase levels can be used to predict the risk of anaphylaxis (2). In patients with advanced stage SM, mast cells infiltration in particular organs may result

in lymphadenopathies, liver failure, ascites, malabsorption, cytopaenias, osteopaenia, osteoporosis and osteolysis (1).

Cutaneous mastocytosis is managed by symptomatic treatments, e.g., antihistamine for the pruritic lesions and avoidance of precipitating factors. We prescribed antihistamine for our patient and advised him to avoid all triggering factors, including alcohol.

As in the case of this patient, the rarity and nonspecific symptoms of cutaneous mastocytosis in individuals who present with asymptomatic generalized brownish macules and papules may delay or hinder diagnosis of MPCM. Consequently, when patients present with generalized monomorphic maculopapules, with or without allergic reactions, cutaneous mastocytosis should be considered as one of the differential diagnoses. As this condition is frequently associated with systemic involvement that can lead to a life-threatening anaphylactoid reaction, all adults with cutaneous mastocytosis should undergo further investigation to exclude systemic mastocytosis. (The diagnostic algorithm for systemic mastocytosis in adults is shown in Figure 3.)

Conflict of Interest Disclosures: The authors have no conflicts of interest to report.

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การประเมินโรคแมสโตไซโตซิสในระบบอื่น ๆ ในผู้ใหญ่ที่ได้รับการวินิจฉัยเป็นโรคผิวหนังแมสโตไซโตซิส

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โรคแมสโตไซโตซิสบริเวณผิวหนังในผู้ใหญ่ มักพบร่วมกับโรคแมสโตไซโตซิสในระบบอื่น ๆ ด้วย ซึ่งอาจก่อให้เกิดภาวะที่อันตรายถึงแก่ชีวิตเช่น โรคภูมิแพ้ชนิดรุนแรงแอแนฟิแลกซิสได้ เพราะฉะนั้นเมื่อแพทย์วินิจฉัยโรคผิวหนังแมสโตไซโตซิสในผู้ใหญ่ ผู้ป่วยทุกคนควรได้รับการ ตรวจเลือดและไขกระดูกเพิ่มเติมเพื่อหาความผิดปกติในระบบอื่น ๆ ร่วมด้วย รายงานผู้ป่วยฉบับนี้ นำเสนอ ผู้ป่วยชายชาวสิงคโปร์อายุ 38 ปี ที่มาด้วยผื่นนูนและผื่นราบสีน้ำตาลขนาดเล็กทั่วร่างกาย ผื่นเพิ่มจำนวนขึ้นอย่างช้า ๆ ในช่วงเวลา 4 ปี โดยไม่มีอาการคันหรือเจ็บ ผื่นจะเด่นชัดขึ้นเมื่อดื่มเครื่องดื่มที่มีแอลกอฮอล์ การตรวจชิ้นเนื้อผิวหนังด้วยกล้องจุลทรรศน์และ อิมมูโนพยาธิวิทยาพบว่าเข้าได้กับโรคผิวหนังแมสโตไซโตซิส ผู้ป่วยได้รับการรักษาด้วย ยาแอนไทฮิสทะมีน และได้รับคำแนะนำให้หลีกเลี่ยงแอลกอฮอล์ แพทย์ผู้รักษาได้แนะนำให้ผู้ป่วย รับการตรวจเพิ่มเติม แต่ผู้ป่วยประสงค์จะไปรักษาต่อที่ประเทศสิงคโปร์ **เชียงใหม่เวชสาร 2560;56(1):43-48.**

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