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Mastocytosis: an uncommon cause of collapse

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ABSTRACT A 59-year-old man was referred to the authors' medical clinic with a history of four episodes of collapse over five years. The patient had a history of urticaria pigmentosa diagnosed 12 months previously. The recognition of his skin condition and the history of recurrent, albeit infrequent, collapses accompanied by hypotension and pruritis led to the suspicion of mastocytosis. He had persistent elevation of serum tryptase consistent with mast cell disease, but the analysis of a bone marrow biopsy failed to confirm systemic disease. Mastocytosis can lead to numerous symptoms directly related to the degranulation of mast cells by certain physical and pharmacological stimuli, and can present with recurrent anaphylactic attacks. Provision of an EpiPen can be life-saving in affected individuals.

The association of urticaria pigmentosa and mastocytosis is of vital importance to physicians who are frequently faced by patients presenting with collapse without cause.

KEYWORDS Mastocytosis, tryptase, urticaria pigmentosa

LIST OF ABBREVIATIONS Cluster of differentiation (CD), CD2 (also called E rosette receptor; anti-CD2 antibodies inhibit formation of rosettes with sheep erythrocytes), CD25 (also called IL-2 receptor alpha chain), computerized tomography (CT), cutaneous mastocytosis (CM), 5 hydroxy indole acetic acid (5HIAA), full blood count (FBC), Glasgow coma scale (GCS), mast cells (MC), systemic mastocytosis (SM), World Health Organisation (WHO)

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CASE REPORT

A 59-year-old man presented to the general medical outpatient clinic with a history of four episodes of collapse. The first one was five years earlier (2002). He had been suffering with flu-like symptoms and took Lemsip (one tablet contains 650 mg paracetamol and 10 mg phenylephrine). Minutes later he developed pruritus and the urge to defecate, and passed out in the bathroom. He was found to have low blood pressure by the ambulance crew, but recovered rapidly. The second episode occurred six months later. Again he developed flu-like symptoms and, following intake of Lemsip, developed generalised itching and felt faint. He recovered spontaneously two hours later. The third episode occurred four years later when he lost consciousness. Once more, flu-like symptoms, generalised pruritis and on this occasion a 'hive-like eruption' on his arms preceded the collapse. His blood pressure was noted to be 60/40 mmHg and his GCS 3 when the paramedics attended. He was discharged from the emergency department without any intervention or follow-up. Two weeks later he re-attended A&E with breathlessness and chest and abdominal pain, following consumption of a prawn sandwich. He did not require any treatment and was later discharged.

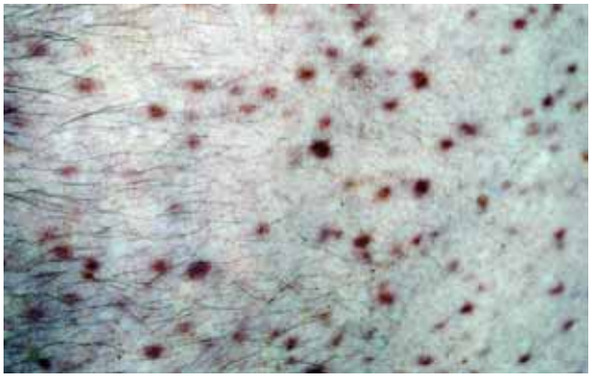

FIGURE 1 Skin lesions of urticaria pigmentosa on the trunk.

The patient had a history of a basal cell carcinoma and urticaria pigmentosa diagnosed on skin biopsy one year earlier. He was a non-smoker and drank alcohol only occasionally.

On examination he had a plethoric face and a diffuse non-blanching rash over his trunk and extremities. His pulse was 80 beats per minute and blood pressure 148/70 mmHg. Respiratory, cardiovascular and neurological examinations were unremarkable. He had no evident hepatosplenomegaly or lymphadenopathy.

The patient underwent several investigations from the clinic. His urine test was negative for 5 HIAA, as was his 24-hour urinary catecholamine level. His FBC was normal with no eosinophilia. His serum tryptase level was 20·7 (normal: 2–14 ug/l).

The patient was referred to haematology with a working diagnosis of mastocytosis. A CT scan of the thorax, abdomen and pelvis with contrast revealed no hepatosplenomegaly or lymphadenopathy. His tryptase continued to be high, with levels of 24·0 and 24·4 checked two and seven months later.

Bone marrow biopsy showed a small amount of normal cellular marrow that exhibited normal trilineage haemopoiesis. Scattered mast cells were present (particularly seen in the mast cell tryptase preparation), but they did not form aggregates and were not associated with eosinophils or fibrosis. The bone marrow sample was also examined at another centre. The sample was negative for the activating C KIT D816V mutation using standard pyrosequencing assay, but positive using a more sensitive allele-specific competitive blocker assay. The antibodies to CD2 and CD25 were not available to check co-expression of these markers. A skeletal survey was also normal.

Thus, our patient fulfilled two of the three minor WHO criteria necessary for the diagnosis of systemic mastocytosis (see discussion). We therefore knew that he had cutaneous mast cell disease with recurrent anaphylaxis, but could not exclude systemic disease. He was referred to a tertiary haematology unit, where it was felt that, as the patient was clinically stable, repeat bone marrow biopsy was not indicated and annual monitoring of symptoms and blood parameters alone was required.

The patient was warned to avoid potential triggers for vascular collapse, including extremes of heat as well as seafood. He was issued with an adrenaline auto injector (EpiPen) for self treatment during any future episodes, and a Medic Alert bracelet.

DISCUSSION

The term mastocytosis denotes a heterogeneous group of disorders characterised by abnormal growth and accumulation of MC in one or more organ systems.

Mastocytosis can be divided into cutaneous and systemic forms.[1] Both forms may be associated with episodic collapse. The diagnosis of CM is based on typical clinical and histological skin lesions and the absence of definitive signs (criteria) of systemic involvement. Most patients with CM are children, and present with maculopapular cutaneous mastocytosis (urticaria pigmentosa). Other less frequent forms of CM are diffuse cutaneous mastocytosis (DCM) and mastocytoma of the skin.[2] The characteristic rash of urticaria pigmentosa is present in most adults with the cutaneous form and many with the systemic variety. The lesions of urticaria pigmentosa are pruritic tan-coloured macules, which generally involve the trunk but can spread to the limbs while sparing the hands and feet. The rash is persistent and may exhibit Darier's sign (whereby rubbing of the lesion leads to localised urticaria).

Systemic mastocytosis occurs more commonly in adults. It is subdivided into the following categories: indolent systemic mastocytosis (ISM), SM with an associated clonal haematologic non-mast cell lineage disease (AHNMD), aggressive systemic mastocytosis (ASM) and mast cell leukemia (MCL).[2] World Health Organisation staging includes two more varieties: mast cell sarcoma and extracutaneous mastocytoma.[3]

Systemic mastocytosis is diagnosed if the patient meets one major and one minor, or three minor, WHO criteria.[4] The major criterion is dense bone marrow involvement by mast cells (>15 mast cells aggregating), while the minor criteria include:

(a) abnormal mast cells in the bone marrow
(b) codon 816 C Kit mutation in extracutaneous organs
(c) mast cells in the bone marrow expressing cell markers CD2, CD25 or both
(d) serum tryptase >20 ng/ml (>20 ug/l)

Our patient met criteria (b) and (d) and also had urticaria pigmentosa.

He therefore had two out of three minor criteria for SM. The fact that CD2 and CD25 markers were not sought means that we could not confirm SM. If either marker were present our patient would have indolent systemic mastocytosis, which usually presents with urticaria pigmentosa, recurrent anaphylactoid reactions and a raised tryptase.[5] This form of SM has a good prognosis.[2] It is for this reason that a repeat bone marrow biopsy was not performed as management of our patient would not have been altered by its outcome.

Mastocytosis can present in a variety of ways, from a pruritic rash or unexplained hepatosplenomegaly to an unexplained collapse or sudden death. Systemic disease most commonly affects the bone marrow, the gastro-intestinal tract, bone or the central nervous system, but other organs may be involved. When this disease is considered a possibility by the physician, diagnosis can be hindered by the technical requirements necessary for biopsy. This is best done in a specialist centre.

Symptoms of mastocytosis occur when pharmacologic or physical stimuli cause mast cell degranulation and the release of histamine, leukotrienes, prostaglandins, tryptase

and other chemical mediators. The concentration of the mediators varies from site to site, as does the stimulus required for their release.[6] Many drugs, toxins and physical stimuli can activate mast cells and cause vasodilatation, hypotension, bronchospasm and anaphylaxis.[7]

It should be noted that serum tryptase levels rise transiently 30–180 minutes after any systemic anaphylactic reaction but remain chronically elevated in mastocytosis. Diagnosis of the condition cannot therefore be made at the time of anaphylaxis.

In all cases, avoidance of triggers for mast cell degranulation and provision of an EpiPen remain the cornerstones of therapy.

Other symptoms may also require treatment[8] with H1 receptor blockers, psoralen ultraviolet therapy or leukotriene antagonists for pruritis; H2 receptor blockers and proton pump inhibitors for peptic ulcer disease; mast cell stabilisers (ketotifen) or glucocorticoids for anaphylaxis; sodium cromolyn for diarrhoea and headaches; and bisphosphonates for osteoporosis. For aggressive systemic disease or recurrent or persistent mediator-related symptoms, cytoreductive therapy with alpha-interferon[9] or cladiribine[10] may be warranted. Allogenic bone marrow transplantation is considered experimental and under trial in the US at the National Institutes of Health. The tyrosine kinase inhibitor imatinib mesylate (Gleevec) is useful[11] in a subtype of systemic mastocytosis that carries the FIP1L1-PDGFRA rearrangement but not in subtypes that have mutations of the codon 816 on the C-Kit gene, and hence not in our patient.

CONCLUSION

In a patient with a history of recurrent syncope and urticaria pigmentosa, or in patients in whom pruritis accompanies episodic collapse, the diagnosis of mastocytosis should not be forgotten. An elevated serum tryptase level measured outside the setting of an acute attack is the best screening test for the condition.

Patient consent The patient has given his permission for the writing-up of his case report with inclusion of the photographs of skin lesions.

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