Too many dangerous allergies

Stefania Scarlini,[1] Fabrizio Turrini,[1] Antonella Caronna,[1] Roberto Messora,[1] Luca Sarti,[1] Goretta Bonacorsi,[2] Marco Bondi[1]

[1]Medicina Interna ad indirizzo Cardiovascolare, Nuovo Ospedale Civile Sant'Agostino Estense di Modena; [2]Ematologia, Policlinico di Modena, Italy

ABSTRACT

Mastocytosis is a rare clonal disease characterized by an abnormal proliferation of mast cells, which accumulate in one or several organ systems such as skin, bone marrow, liver, spleen, lymph nodes and gastrointestinal tract. The heterogeneity of the clinical presentation is typically related to different disease burdens in various tissues and symptoms due to the release of mast cell mediators. The diagnosis is often difficult and delayed. Here we describe the case of a 70-year old patient with a past history of drug-induced anaphylactic shock whose clinical presentation was dramatic and required intensive support: the diagnosis of systemic mastocytosis was reached after the exclusion of diseases more commonly encountered in routine clinical practice (*e.g.* stroke, pulmonary embolism).

Case Report

A 70-year old Caucasian woman felt a drowning sensation and fell unconscious in front of her husband at home. The emergency services were called and the ambulance staff intubated her immediately. On arrival at hospital her Glasgow Coma Scale score was 3 out of 15. Her blood pressure was 120/60 mmHg and her heart rate was 81 beats per minute. An itchy erythema was found on her trunk and her face. Once in hospital she was mechanically ventilated and a nasogastric tube was placed.

Correspondence: Fabrizio Turrini, Medicina Cardiovascolare, Nuovo Ospedale Civile Sant'Agostino Estense di Modena, via Giardini 1355, 41126 Modena, Italy.
Tel.: +39.059.3961100.
E-mail: f.turrini@ausl.mo.it

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The woman had been complaining of progressive dyspnea over the preceding several weeks and was being investigated for an approximately 1-year history of chronic low back pain which it was thought might be due to Paget's disease although a definitive diagnosis had not been made. Bone scintigraphy showed diffuse 99mTc-HDP hyper fixation. The woman was known to have diabetes mellitus and hypertension. She also reported a past medical history of two episodes of anaphylactic shock following administration of amoxicillin and ibuprofen.

Her medications on admission were telmisartan, escitalopram, sulpiride and insulin.

Blood examinations showed raised levels of inflammatory markers (first day: white blood cell count 12,300/mm^3; C-reactive protein 0.8 mg/dL; third day: white blood cell count 14,200/mm^3; C-reactive protein 9.2 mg/dL; procalcitonin 0.8 ng/mL) and mildly elevated myocardial markers (creatine kinase-MB 8.6 ng/mL and troponin 1.19 ng/mL). Toxicological tests were all negative.

Blood gas analysis during ventilation showed metabolic acidosis (pH 7.32, pO_2 95 mmHg, pCO_2 48 mmHg, HCO_3 17 mmol/L). An electrocardiogram did not show any ST-T alterations and no abnormalities of wall motion were found on echocardiography. To rule out an acute cerebrovascular event, computed tomography (CT) of the brain with an angiographic study was done. No ischemic lesions or vascular stenosis were found, but a small subdural hematoma (of a few millimeters) was detected. Electroencephalography was unremarkable.

A chest CT was also done at admission; being the second CT scan in the same day and because of the presence of a skin reaction, it was performed without contrast agents: it showed multiple alveolar consoli-

dation consistent with bilateral pneumonia. Bronchoalveolar lavage was performed: microscopic examination of the lavage fluid revealed Gram-positive bacteria but cultures led to the growth of mixed flora.

Abdominal ultrasound revealed a small splenic lesion of unknown origin (traumatic? angioma?). Urine culture was positive for a multisensitive *Enterobacter aerogenes*.

Antibiotic therapy with teicoplanin and gentamicin was started; fluids and steroids were also given in order to correct the metabolic acidosis and control the erythema. After 2 days the patient was definitely better; she was extubated and moved to our medical ward.

Fluids were discontinued and steroid tapered. Her neurological status became normal again. Her blood examinations revealed that the markers of infection were decreasing. Immunoelectrophoresis showed a monoclonal component (IgGκ <0.5 g/dL). A mild eosinophilia was present (420/mm^3) and the concentration of alkaline phosphatase was slightly raised (187 U/L).

Thoracic and abdominal CT scan done on day 6 showed hilar hepatic and splenic lymphadenopathy. A bone marrow biopsy done the following day revealed bone remodeling with intense fibrosis; mast cells, most of which were atypical, were found in 30% of spaces. These findings were consistent with systemic mastocytosis (Figures 1 and 2). Serum tryptase was than measured and resulted 87 ng/mL.

Total body magnetic resonance imaging revealed diffuse bone infiltration without osteolytic lesions. The hematologist made a diagnosis of *smoldering systemic mastocytosis*. After a short course of oral steroids the patient was stable. It was suggested that she keeps an adrenaline pen in her bag and takes steroids only in the case of a skin reaction. Nevertheless, 2 months later she was admitted again for a cutaneous allergic reaction after taking aspirin.

Discussion

Systemic mastocytosis is a rare heterogeneous group of disorders characterized by proliferation and accumulation of abnormal mast cells in one or more extra-cutaneous organs. Its reported annual incidence in the general population is three new cases per 100,000 people. It is included in *myeloproliferative neoplasms* in the World Health Organization (WHO) classification.[1]

The clinical diagnosis can be quite elusive and is often missed because of the wide spectrum of symptoms, ranging from itching, flushing, abdominal cramping and diarrhea to severe anaphylaxis with vascular collapse.

The heterogeneity of the clinical presentation of mastocytosis is typically related to the mast cell burden in different tissues, symptoms due to the release of mast cell mediators, the patient's age at the onset and any associated hematological disorders. The correct diagnosis may be reached only after years.[2,3]

The clinical scenario varies from a relatively benign condition with isolated cutaneous lesions to a very aggressive systemic condition with a serious prognosis.[4] According to 2008 WHO classification it can be divided into: cutaneous mastocytosis which is confined to the skin and systemic mastocytosis (SM) which is a clonal and disseminated condition. The cutaneous form more often affects children and usually improves or resolves spontaneously before adulthood. Mastocytosis in adults instead tends to be systemic and to persist.[5]

The case we have described had very acute symptoms that required intensive treatment; this is due to

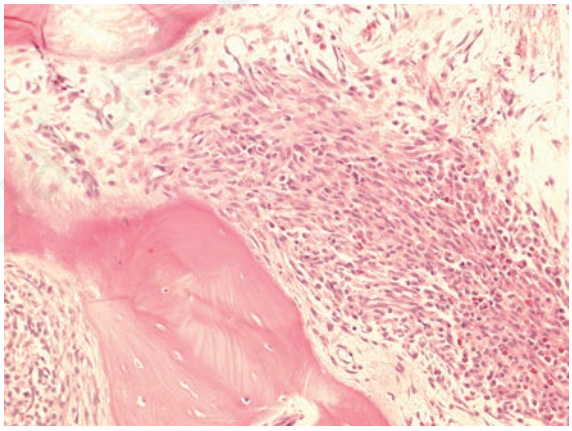

Figure 1. H&E staining shows the bone marrow occupied by a large aggregate of atypical mast cells, which are mainly spindle-shaped.

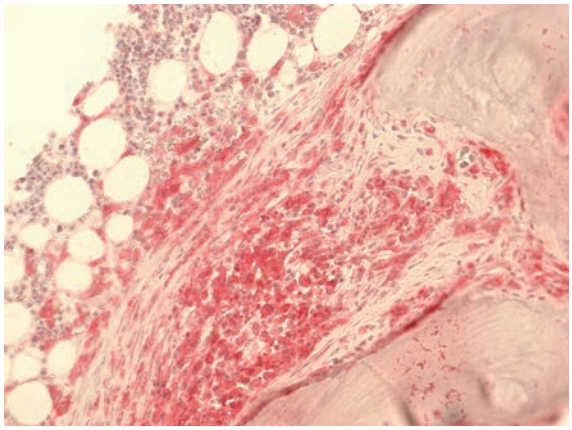

Figure 2. Mast cell aggregate detected by CD117 immunostaining.

release of mast cells mediators (mast cell-*release* symptoms). Mast cell mediators typically induce vasodilatation, hypotension, flushing, itching, syncope, abdominal discomfort, vomiting and diarrhea. The intensity of symptoms varies from mild allergic reactions to severe, life-threatening anaphylaxis. The symptoms can be triggered by a broad range of specific factors such as various drugs (narcotics, opioids, non-steroidal anti-inflammatory drugs, ionic contrast media, antibiotics and muscle relaxants used for anesthesia) acting through IgE, and also by non-specific factors such as hot baths, physical activity, surgical procedures, infection and emotional stress. Less frequently the condition results in more chronic symptoms, *e.g.* persistent gastrointestinal complaints.[6,7]

Although not seen in our case, other typical clinical features are **s**kin symptoms. *Urticaria pigmentosa* is the most common findings (almost 90% of patients with SM have skin symptoms) and consists of brown or reddish brown freckles predominantly on the trunk and limbs. Itching is the main complaint and can be triggered by changes in temperature, hot baths, physical activity, some foods, alcohol or drugs.[8]

There is also a broad spectrum of signs that are generally defined non-cutaneous manifestations, such as anemia, thrombocytopenia, malabsorption, hepatosplenomegaly, bone disease in the form of lytic lesions and pathological fractures. These manifestations are all results of organ infiltration with secondary organ dysfunction. In our case, low back pain was present many months before and can be considered very non-specific as a clue to the diagnosis.

As a general rule, a physical examination should include a search for skin lesions such as urticaria pigmentosa. Once urticaria pigmentosa is suspected, the examiner should lightly scratch a small area of the affected skin: the development of erythema over or around the lesion is called *Darier's sign* and is pathognomonic for the presence of mast cells within the lesion.

The laboratory findings included mild eosinophilia and raised alkaline phosphatase, which are quite characteristic for SM. In general, some liver function tests abnormalities are common; in our case we did not measure alkaline phosphatase fractions to determine the possible bone origin of this marker.

Serum tryptase measurement is the cornerstone of laboratory tests when SM is suspected; in our case it was performed once the diagnosis had been made because of the suspicion of a hematological disorder that clearly mandated bone marrow biopsy. Tryptase is a trypsin-like proteinase that is abundant in human mast cells and basophils. The main clinical utility of its measurement is to help to make the diagnosis of SM. Raised levels can be found in the first 3 h after an episode of anaphylactic shock. In SM the tryptase level is permanently elevated and is considered diagnostic for the condition if >20 ng/mL, even when measured during the acute phase.

A definite diagnosis of SM can be made only on the basis of the findings of bone marrow biopsy and aspiration. This diagnostic examination is especially recommended in all adult patients with: i) urticaria pigmentosa, even without other evident signs and symptoms of systemic disease, as the incidence of SM in this population is high; ii) unexplained flushing or anaphylaxis, particularly if associated with documented hypotensive episodes; iii) unexplained gastrointestinal abnormalities (*e.g.*, peptic ulcer, malabsorption, or diarrhea); iv) unexplained peripheral blood abnormalities; v) unexplained hepatomegaly, splenomegaly or lymphadenopathy; and vi) unexplained pathological bone fractures, osteopenia, osteoporosis or osteosclerosis.

A simple bone marrow biopsy with histological studies is less likely to be diagnostic of clonal mast cell disease in patients with serum tryptase levels <20 ng/mL. In the case of suspected mastocytosis, tryptase measurement is strongly recommended before bone marrow examination.

In our case and in the majority of cases, SM was recognized on the basis of careful histopathological examination of bone marrow even if other internal organs might also have been involved, in particular the liver, spleen, gastrointestinal tract and lymph nodes. The examination should include immunohistochemical staining for tryptase, CD117, CD25 and CD2 as a discrete mast cell infiltration can otherwise be overlooked.[9] The application of molecular criteria is very important for making the diagnosis in order to distinguish mastocytosis from reactive mast cells hyperplasia or myelomastocytic disorders.[10]

Using sensitive methods of analysis, it is possible to demonstrate a somatic mutation in the coding sequence of the *KIT* gene in 95% of adult cases of SM. The most common mutation is a substitution of aspartate by valine at position 816 in the kinase domain, which causes stimulating colony factor-independent auto-activation of CD117. Studies of mast cell lines and murine models have shown that this mutation alone is sufficient to cause SM.[11]

According to the WHO, SM is defined by major and minor criteria: the diagnosis can be made if at least one major and one minor or at least three minor criteria are fulfilled.[1] The major criterion is multifocal, dense infiltrates of mast cells (15 or more mast cells in aggregates) detected in sections of bone marrow and/or other extra-cutaneous organ(s), and confirmed by tryptase immunohistochemistry or other special stains. The minor criteria are: i) in biopsy sections of bone marrow or other extra-cutaneous organs, more than 25% of the mast cells in the infiltrate are spindle-shaped or have atypical morphology or, of all mast

Table 1. Treatment of principal manifestations of systemic mastocytosis.

Symptoms	Treatment options	Additional options	Special cases
Pruritus	H1 antihistamine	H2 antihistamine	Leukotriene antagonists
Flushing	H1 antihistamine	-	-
Anaphylaxis	H1 and H2 antihistamines Adrenaline auto-injector	Glucocorticoids	-
Diarrhea, nausea, vomiting, abdominal discomfort	H2 antihistamine	Sodium cromoglygate	Leukotriene antagonists and/or glucocorticoids
Malabsorption	Sodium cromoglycate	Glucocorticoids	-
Osteoporosis	Calcium supplements and vitamin D	Bisphosphonates	Interferon-α
Bone pain	Analgesics (non-NSAID)	NSAID under observation	Localized radiation to specific sites for pain relief

NSAID, non-steroidal anti-inflammatory drug.

cells in bone marrow aspirate smears, more than 25% are immature or atypical mast cells; ii) detection of a *KIT* point mutation at codon 816 in bone marrow, blood or other extra-cutaneous organ(s); iii) mast cells in bone marrow, blood or other extra-cutaneous organs that co-express CD117 with CD2 and/or CD25; iv) serum total tryptase persistently >20 ng/mL (unless there is an associated clonal myeloid disorder in which case this parameter is not valid).

Once the diagnosis is clear, the prognosis remains to be defined. The clinical features and findings of our patient were typical of an indolent form (or smoldering) and are called *B findings*. B findings include: bone marrow biopsy showing >30% infiltration by mast cells and/or serum total tryptase levels >200 ng/mL; signs of dysplasia or myeloproliferation in non-mast cell lineages but insufficient criteria for a definite diagnosis of a hematological neoplasm and hepatomegaly without impairment of liver function and/or palpable splenomegaly without hypersplenism.

A more aggressive disease is usually characterized by progression and clinical features such as cytopenia, hepatomegaly with impairment of liver function, ascites or portal hypertension, palpable splenomegaly with hypersplenism, osteolytic lesions or pathological fractures, and malabsorption with weight loss. These features are called *C findings.*

Indolent forms progress slowly or do not progress at all and most patients have a normal life expectancy. Only 1 to 5% will evolve into a more severe form. Patients with aggressive forms may also survive many years, although the appearance of new C findings or evolution into mast cell leukemia anticipates a rapid decline.

The indolent form of SM in our patient did not require any continuous treatment. In fact at present, there are only palliative therapies for SM, since aggressive up-front treatment does not guarantee patients a longer life expectancy. The purpose of treatment is, therefore, to relieve symptoms and increase quality of life. Knowledge of patient-specific factors that lead to degranulation may ensure that the patient avoids these factors and thereby prevent disturbing symptoms.[12]

As a general rule, patients should avoid triggers for mast cell degranulation. These include physical triggers, alcohol, certain medications, emotional stress and allergens to which the individual is sensitized. We suggest particular attention and surveillance when taking new medications as we saw our patient admitted to the hospital again after taking aspirin.

Pharmacological therapy, when required, is based on the use of anti-mediator drugs and can be tailored according to symptoms as shown in Table 1.

Conclusions

This case report underlines the importance of considering mastocytosis in patients with a long history of histamine-mediated symptoms: a large variety of clinical manifestations that usually remain unexplained for a long time.

Serum tryptase levels could be helpful as a screening test once the suspicion has been raised.

References

1. Horny H, Akin C, Metcalfe D. Mastocytosis. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Origin. Lyon: IARC; 2008. pp 54-63.
2. Valent P, Akin C, Escribano L, et al. Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria. Eur J Clin Invest 2007;37:435-53.
3. Pardanani A, Akin C, Valent P. Pathogenesis, clinical features, and treatment advances in mastocytosis. Best Pract Res Clin Haematol 2006;19:595-615.

4. Horny HP, Sotlar K, Valent P, Hartmann K. Mastocytosis a disease of the hematopoietic stem cell. Dtsch Arztebl Int 2008;105:686-92.
5. Hartmann K, Metcalfe DD. Pediatric mastocytosis. Hematol Oncol Clin North Am 2000;14:625-40.
6. Austen KF. Systemic mastocytosis. N Engl J Med 1992; 326:639-40.
7. Castells M, Austen KF. Mastocytosis: mediator-related signs and symptoms. Int Arch Allergy Immunol 2002;127:147-52.
8. Soter NA. Mastocytosis and the skin. Hematol Oncol Clin North Am 2000;14:537-55.
9. Lim KH, Pardanani A, Butterfield JH, et al. Cytoreductive therapy in 108 adults with systemic mastocytosis: outcome analysis and response prediction during treatment with interferon-alpha, hydroxyurea, imatinib mesylate or 2-chlorodeoxyadenosine. Am J Hematol 2009;84:790-4.
10. Pardanani A. Systemic mastocytosis in adults: 2011 update on diagnosis, risk stratification, and management. Am J Hematol 2011;86:362-71.
11. Orfao A, Garcia-Montero AC, Sanchez L, et al. Recent advances in the understanding of mastocytosis: the role of KIT mutations. Br J Haematol 2007;138:12-30.
12. Pardanani A. How I treat patients with indolent and smoldering mastocytosis (rare conditions but difficult to manage). Blood 2013;121:3085-94.