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CASE REPORT

Mastocytosis and diffuse large B-cell lymphoma, an unlikely combination

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ABSTRACT

Systemic mastocytosis may be accompanied by a second haematological malignancy, usually of myeloid origin. However, a number of case reports describe systemic mastocytosis coexisting with a second haematological malignancy of lymphoid origin. Here, we report a case of a 74-year-old man with systemic mastocytosis who developed a diffuse large B-cell lymphoma. A short overview of the literature concerning mastocytosis accompanied by a second haematological malignancy is presented.

Keywords: B-cell lymphoma, SM-AHNMD, systemic mastocytosis

INTRODUCTION

The term systemic mastocytosis (SM) encompasses a group of disorders defined by the accumulation and abnormal growth of mast cells. The physiological role of mast cells is mainly in type I immune responses. Clinical findings in SM are categorised into 1) constitutional symptoms, 2) skin manifestations, 3) mediator-related systemic events, and 4) musculoskeletal complaints.

Systemic mastocytosis is defined by the World Health Organisation according to major and minor criteria, which are explained in *table 1*.[1] SM is further divided into: indolent systemic mastocytosis (ISM) in which maculopapular skin lesions are usually present, aggressive systemic mastocytosis (ASM) defined by pathological mast cells infiltrating bone marrow, liver, spleen, gastrointestinal tract and the skeletal system, and mast cell leukaemia (MCL), characterised by pathological mast cells in high percentages (>20%) in bone marrow and peripheral blood, resulting in multi-organ failure and a fatal outcome.

Another subgroup is SM with an associated clonal haematological non-mast cell lineage disease (SM-AHNMD), in which the nature of the associated haematological dictates treatment and prognosis. Most often a myeloid neoplasm is diagnosed but lymphoproliferative neoplasms have also been described. In this case report, we describe a patient with systemic mastocytosis who developed a diffuse large B-cell lymphoma.

CASE REPORT

A 74-year-old male patient who had suffered from urticaria pigmentosa for years presented at our outpatient clinic with a history of attacks of bilateral abdominal pain and some weight loss during the past three months. His medical history was significant for biopsy proven urticaria pigmentosa for six years. He was taking levocetirizine on occasions. On physical examination he had skin lesions in accordance with urticaria pigmentosa. The spleen could not be palpated and there was no lymphadenopathy. A computed tomography (CT) scan of the neck, thorax and abdomen confirmed splenomegaly (16.2 x 5.6 cm) which was previously seen during ultrasound examination of the abdomen, and some borderline lymphomas. A 24-hour collection of urine showed elevated metabolites of histamine, the N-methylhistamine was 298 µmol/mol creatinine (<150) and the N-methyl-imidazole acetic acid 4.6 mmol/mol creatinine (0.90 to 1.9). Serum tryptase was 74.5 µg/l (reference values <11.4 g/l). The combination of biopsy proven urticaria pigmentosa, elevated histamine excretion and serum tryptase levels and splenomegaly led to the diagnosis of systemic mastocytosis, although a bone marrow biopsy was needed to meet the WHO criteria (*table 1*). A bone marrow biopsy was initially not performed, because his systemic complaints resolved spontaneously. No treatment was initiated at that time.

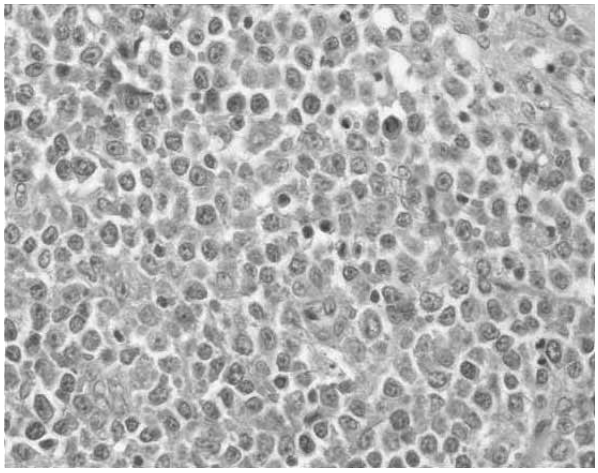
Table 1. *WHO classification of systemic mastocytosis (from WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Swerdlow et al. 2008[11])*

The diagnosis systemic mastocytosis can be made when the major criterion and one minor criterion or at least three minor criteria are present.

Major criterion:
Multifocal, dense infiltrates of mast cells (≥15 mast cells in aggregates) detected in sections of bone marrow and/or other extracutaneous organ(s).

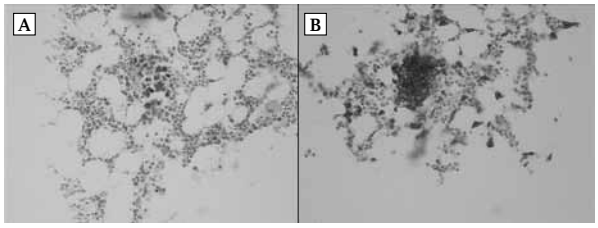
Minor criteria:
1. In biopsy sections of bone marrow or other extracutaneous organs, >25% of the mast cells in the infiltrate are spindle-shaped or have atypical morphology or, of all mast cells in bone marrow aspirate smears, >25% are immature or atypical.
2. Detection of an activating point mutation at codon 816 of *KIT* in bone marrow, blood or another extracutaneous organ.
3. Mast cells in bone marrow, blood or other extracutaneous organs express CD2 and/or CD25 in addition to normal mast cell markers.
4. Serum total tryptase persistently exceeds 20 ng/ml (unless there is an associated clonal myeloid disorder, in which case this parameter is not valid).

Figure 1. *Lymph node resection*



H&E staining. Histopathology of diffuse large B-cell lymphoma occuring in the lymph node. A diffuse lymphocytic infiltrate with blasts replaces the normal architecture.

Figure 2. *Bone marrow biopsy*



Abnormal amounts of both solitary and clustered mastocytes in the bone marrow. The typical metochromatic granules in mastocytes are stained in purple in the Toluidine blue stain (a). Immunohistochemistry shows mastocytes immunoreactive for CD 117 (b).

Seven months later, he was admitted to our department with a history of progressive lower back pain, radiating towards the groin. On physical examination, axillar lymphadenopathy was found. On the MRI scan of the vertebrae, there was a decreased T2-weighted signal on multiple levels. A new CT scan of the neck, thorax and abdomen showed widespread enlarged lymph nodes, mostly in the right axilla, alongside the aorta and the left iliac artery. Microscopic evaluation of a resected axillary lymph node showed blasts positive on CD20, CD79a and PAX5 staining, consistent with a diffuse large B-cell lymphoma (*figure 1*). CD117/KIT staining was negative. No mastocytosis was found in this lymph node. Bone marrow biopsy showed aggregates of spindle-shaped mast cells with reduced granulation, fitting the diagnosis systemic mastocytosis (*figure 2*). These cells were positive on CD117/KIT staining and negative on CD20, CD23 and PAX5 staining. A malignant lymphoma could not be found in this specimen. Based on these results stage III diffuse large B-cell lymphoma (DLBCL) coexisting with systemic mastocytosis was diagnosed (SM-AHNMD).

A treatment regimen of rituximab, cyclophosphamide, doxorubicin and prednisolone was started. Vincristine was not added because of his vulnerable clinical condition. The patient developed an allergic reaction to rituximab, which resolved after cessation of this therapy. Shortly hereafter, the patient developed leucopenic fever accompanied by a rise in lactate dehydrogenase up to 356 U/l after an initial drop in response to chemotherapy. He subsequently developed a persistent ileus and pneumonia. Further treatment was refused and shortly thereafter he died, probably due to progressive disease. Consent for post-mortem was not obtained.

DISCUSSION

It is well known that some patients with systemic mastocytosis develop a second haematological malignancy, called systemic mastocytosis associated clonal haematological non-mast cell lineage disease (SM-AHNMD).[1,2] SM-AHNMD encompasses systemic mastocytosis coexisting with myeloid as well as lymphoid malignancies, although the vast majority of these malignancies are of myeloid origin. Of the lymphoid malignancies occurring as SM-AHNMD, mostly B-cell malignancies are reported.[3,4]

A few cases of lymphoid neoplasms coexisting with systemic mastocytosis have been published. Sanz *et al.* presented a patient with systemic mastocytosis who developed chronic lymphocytic leukaemia (CLL).[5] Horny *et al.* described a case of a synchronous manifestation of systemic mastocytosis and CLL, in which a distinct clonal origin could be demonstrated by detecting an activating c-kit point mutation in mast cells from the bone marrow biopsy and wild-type c-kit in the microdissected

CD23-positive B lymphocytes.[6] Kim *et al.* described a patient with systemic mastocytosis coexisting with low-grade B-cell non-Hodgkin's lymphoma. Distinct clonal origins of the neoplastic mast cells and lymphoma cells were also demonstrated by presence of an activating c-kit mutation in the microdissected mast cells with absence of this mutation in the neoplastic B lymphocytes.[7] Focal accumulation of lymphocytes surrounding infiltrates of mast cells in patients with systemic mastocytosis is usually reactive, but it should be differentiated from clonal lymphoid disorders.

In our case, a distinct clonal origin of the neoplastic mast cells and lymphocytes could not be confirmed without post-mortem. However, immunohistochemical investigations clearly defined two distinct haematological conditions on two different anatomical sites, fitting the classification SM-AHNMD.[8] Due to the low prevalence, this combination of SM and diffuse large B-cell lymphoma can be accidental.[9] However, as mentioned in the article by Sperr *et al.,* in cases of lymphoproliferative malignancies mostly B cell malignancies may develop in SM.[10] This case is therefore important to report in addition to previous cases and as a learning point to always take into account the possibility of development of a second malignancy in a patient with SM.

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