Systemic mastocytosis (SM) and associated malignant bone marrow histiocytosis – a hitherto undescribed form of SM-AHNMD

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An elderly woman presented with anaemia, thrombocytopenia and multifocal lytic and sclerotic bone lesions. Trephine bone marrow biopsy demonstrated widespread involvement by systemic mastocytosis (SM). The neoplastic mast cells expressed mast cell tryptase, CD117, CD25 and CD9, and were accompanied by compact sheets of atypical large histiocytic cells, expressing CD68, CD4, S-100 protein and CD14, in keeping with a concomitant histiocytosis (SM-AHNMD). Mutation analysis revealed the activating point mutation D816V of the c-kit proto-oncogene in microdissected pooled bone marrow mast cells. Partial remission was achieved using interferon alpha. To the best of our knowledge this is the first reported case of SM-AHNMD with histiocytosis as the non-mast cell component.

Key words: systemic mastocytosis, histiocytosis, SM-AHNMD, bone marrow biopsy.

Systemic mastocytosis (SM) is a rare haematopoietic malignancy, typically presenting with bone marrow involvement and characterised by frequent activating mutations in the catalytic domain of the tyrosine kinase receptor C-KIT, usually D816V [1, 2]. A unique feature of SM is its frequent association with other haematopoietic non-mast cell lineage neoplastic disease (SM-AHNMD), found in approximately 30% of SM cases [3]. The AHNMD components described so far belong to a wide spectrum of haematopoietic neoplasia, including lymphomas, chronic myeloproliferative neoplasms, myelodysplastic syndromes and acute myeloid leukaemias; however, to the best of our knowledge, association of SM with histiocytic neoplasia has not been described. In contrast to acute leukaemias with monocytic/monoblastic differentiation, the neoplasms with features of mature histiocytes are probably even less frequent than SM,

accounting for much less than 0.5% of all haematopoietic malignancies [4]. Referred to as "histiocytoses" or "histiocytic sarcomas", they typically present as solid-organ tumours, but may also be primarily based in bone marrow [5]. We describe a first case of SM-AHNMD in which the non-mast cell component was a histiocytic sarcoma with features of reticulum/interdigitating cell origin.

An elderly female presented with several months history of fatigue, fever, weight loss and night sweats. There was no organomegaly, but chest X-ray revealed numerous, small, osteolytic and osteosclerotic lesions of T12, L1 and bilateral ribs. The patient was anaemic (haemoglobin 114 g/l, erythrocytes 2.9×10^9/l) and thrombocytopenic (platelets 90×10^9/l). White blood cell count (4×10^9/l) included 16% bands, 32% segmented neutrophils, 12% eosinophils, 36% lymphocytes and 4% monocytes. LDH was normal
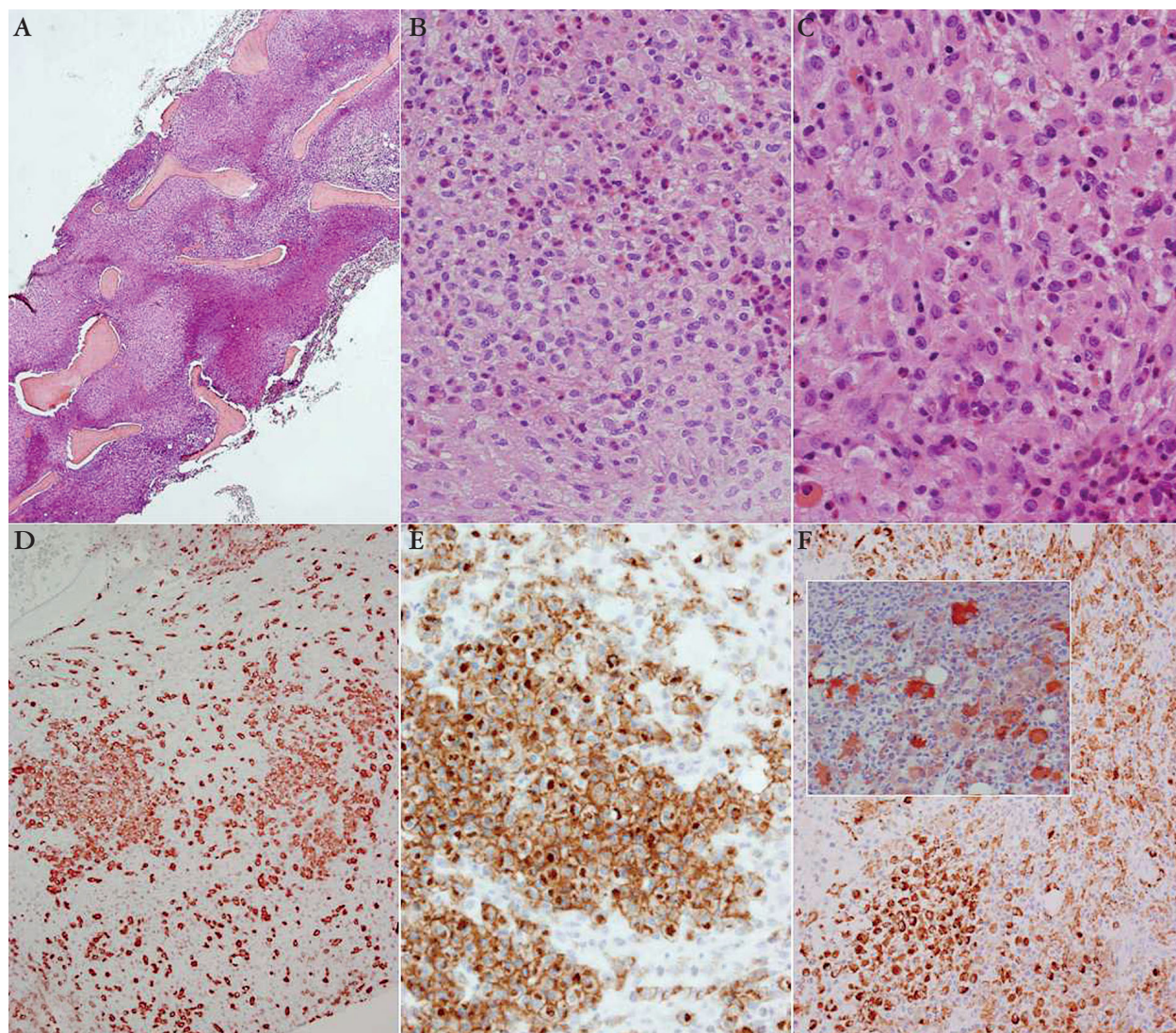
Fig 1. A-F. A – low-power view. Pale, frequently paratrabecular infiltrates, extensively involving the bone marrow. At this magnification (objective 4×) the mast cell clusters are not distinguishable from aggregates of histiocytes. B and C – comparison of morphology of mast cell and histiocyte infiltrates, respectively (same magnification for both panels, with a 60× objective). D – mast cell tryptase (20× objective). E – CD25 (60× objective). F – CD68 (60× objective), inset: S100.

(236 U/l). Serum mast cell tryptase was not measured at that time. The past medical history did not include any medical conditions or therapies known to increase the risk of haematopoietic neoplasia.

Trephine bone marrow biopsy revealed highly cellular fibrotic marrow. Haematoxylin/eosin and Giemsa stains, CD34 and CD117 failed to show excess of blasts. Three major haematopoietic lineages were not dysplastic, occupying 25-30% of intertrabecular spaces. Remaining areas contained patchy infiltrates, composed of two different types of atypical cells, forming distinct and non-overlapping clusters (Fig. 1 A-C). The first population comprised smaller, round, oval, and rarely spindle-shaped cells usually without obvious cytoplasmic granules, char-

acterised by expression of mast cell markers, including CD25, in keeping with their neoplastic nature (Fig. 1 D-E). The second atypical population consisted of markedly larger cells with occasional phagocytosis. These cells were negative for mast cell markers, expressing instead histiocytic antigens along with focal S100, CD10 and faint CD1a in single cells, indicating an aberrant immunoprofile, consistent with histiocytosis/histiocytic sarcoma, likely with interdigitating reticulum cell differentiation (Fig. 1 F). Complete immunoprofiles of both atypical populations are summarised in Table I.

In order to detect the D816V mutation of C-KIT, tryptase-positive mast cells were microdissected by laser pressure catapulting, pooled and used for nest-

Table I. Immunohistochemistry: antibodies and immunoprofiles of two distinct neoplastic populations

Antigen	Supplier	Titre	Antigen retrieval method	Mast cells	Histiocytes
Leukocyte Common Antigen (CD45)	DAKO	1 : 100	citrate, pH = 6.0, MW	(+)	(–)
CD68-PGM1	DAKO	1 : 50	citrate, pH = 6.0, MW	(–)	(+)
CD1a	DAKO	1 : 50	MW, decloaker	(–)	(–/+)
S100	DAKO	1 : 200	None	(–)	(+)
CD14	Novocastra	1 : 50	MW, decloaker	(–)	(+)
CD4	Sanova	1 : 25	MW, decloaker	(–)	(+)
CD10	Novocastra	1 : 50	EDTA, pH=8.0, MW	(–)	(+)
CD117	DAKO	1 : 25	EDTA, pH=8.0, MW	(+)	(–)
CD25	Novocastra	1 : 50	MW, decloaker	(+)	(–)
CD9	Novocastra	1 : 100	EDTA, MW, decloaker	(+)	(–)
mast cell tryptase	Novocastra	1 : 100	trypsine	(+)	(–)
CD34	DAKO	1 : 25	citrate, pH = 6.0, MW	(–)	(–)
CD138	DAKO	1 : 100	citrate, pH = 6.0, MW	(–)	(–)
Epithelial Membrane Antigen	DAKO	1 : 100	none	(–)	(–)
HMB-45	DAKO	1 : 50	citrate, pH = 6.0, MW	(–)	(–)
cytokeratin 7	DAKO	1 : 50	citrate, pH = 6.0, MW	(–)	(–)
myeloperoxidase	DAKO	1 : 200	none	(–)	(–)
lysozyme	DAKO	ready to use	proteinase K	(–)	(–)

MW – microwave

ed PCR followed by melting point analysis with the LightCycler™ sequence detection system (ROCHE Molecular Systems, Mannheim, Germany) using the DNA Master Hybridization Probes kit, as described by the manufacturer. This methodology is described in detail elsewhere [6, 7]. Mast cells were found positive for the mutation. The mutation was not investigated in the histiocytic component or three-lineage haematopoiesis.

After a period of good symptomatic response to interferon alpha lasting for 10 months, the patient reported relapse of progressive fatigue, dyspnoea and bone pains. She declined further investigations and treatment and died shortly thereafter of cardiac arrest. No autopsy was performed.

This case, like many other cases of SM-AHNMD, presented not only a diagnostic challenge, but also a clinical dilemma, as selecting the optimal cytoreductive therapy for SM-AHNMD is frequently hampered by different biology of both neoplastic components. Contemporary indications to treat both SM and AHNMD independently are based on limited empiric experience [8]. Of note, due to the extreme rarity of histiocytic sarcoma, there is no universally adopted or even widely recommended therapy for this malignancy. In the present case the patient's age and cardiovascular comorbidities discouraged any aggressive approach. Monotherapy with interferon alpha proved to be a reasonable palliative regimen, resulting in 10-month remission.

To summarise, we presented a case of systemic mast cell disease associated with a histiocytic neoplasm, representing a new subtype of SM-AHNMD. This report makes the list of non-mast cells tumours comprising SM-AHNMD complete in regard to all the major WHO categories of haematopoietic malignancies.

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