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Case study

Two cases of concomitant acquired aplastic anemia and systemic mastocytosis

Natalia Golardi MD[a,1], Jacob E. Sramek MD[a,b,1], Jerome B. Myers MD, PhD[b], Helene Saffer MD[c], Tracy I. George MD[a], David R. Czuchlewski MD[a,*]

[a]*Department of Pathology, University of New Mexico, Albuquerque, NM 87102, USA*
[b]*Penrose - St. Francis Hospital, Department of Pathology, Colorado Springs, CO, USA*
[c]*Analytic Pathology Medical Group, Sharp Grossmont Hospital, La Mesa, CA, USA*

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Summary Reactive bone marrow mast cells reliably lack the morphologic, immunophenotypic, and molecular features of systemic mastocytosis (SM). We report two unusual cases of acquired aplastic anemia (AA) in which multifocal aggregates of bone marrow mast cells fulfilled morphologic and immunophenotypic criteria for SM according to the World Health Organization 2008 classification. In the absence of clinical symptoms attributable to SM, the patients were treated with immunosuppressive therapy directed towards AA. Clinical follow-up and subsequent bone marrow examination revealed no evidence of overt SM in either patient. These cases represent, to our knowledge, the first reported instances in which criteria for SM have been fulfilled in the presence of AA. However, given the clinical courses followed by our patients, the incidental identification of mast cell lesions consistent with indolent SM may be of uncertain significance in the setting of AA.

1. Introduction

Mastocytosis is a myeloproliferative neoplasm of clonal, bone marrow-derived mast cells with a wide array of clinical and morphologic presentations ranging from cutaneous to systemic, and indolent to aggressive, disease. Among the subtypes of mastocytosis is systemic mastocytosis (SM), defined in the World Health Organization 2008 classification as showing specific combinations of morphologic, immunophenotypic, clinical, and/or molecular findings (Table) [1]. Systemic mastocytosis is diagnosed when the major criterion and one minor criterion, or, alternatively, at least three minor criteria, are present. Adherence to these requirements is recommended to avoid a misdiagnosis of SM in cases of reactive mast cell hyperplasia.

Aplastic anemia (AA) is a bone marrow failure disorder characterized by pancytopenia and marrow hypocellularity in the absence of an abnormal marrow infiltrate or increased reticulin deposition [2]. It is most often acquired, and an autoimmune mechanism is typically implicated [3]. Mast cells are frequently noted in the bone marrow in cases of AA, and in some cases, they are relatively or even absolutely increased in number. These mast cells are benign, reactive in nature, and do not fulfill criteria for a diagnosis of SM. In particular, they are usually scattered in an interstitial distribution and do not form clusters of morphologically atypical cells, they do not show

* Corresponding author. TriCore Reference Laboratories, Albuquerque, NM 87102, USA.
E-mail address: dczuchlewski@salud.unm.edu (D. R. Czuchlewski).
[1] These authors contributed equally.

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Table WHO 2008 criteria for diagnosis of SM

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

NOTE. Originally published by Horny et al., 2008 [1].

aberrant expression of CD2 or CD25, and no *KIT* mutation is detectable. In fact, so reliably can these mast cells be differentiated from SM that one authority expressly notes that SM has never been diagnosed in the setting of AA [4]. It is in this light that we report two unusual cases of AA in which the current World Health Organization (WHO) 2008 diagnostic criteria for SM are, in fact, met.

2. Case histories

A 48-year-old male presented to the emergency room with massive epistaxis and fever preceded by a one-week history of lower extremity petechiae. A complete blood count revealed a neutrophil count of $<0.05 \times 10^9$/L, platelet count of 11×10^9/L, and hemoglobin of 12.0 g/dL. Eosinophilia was not present. A bone marrow biopsy was performed. The aspirates contained numerous hypocellular spicules with a predominance of lymphocytes, plasma cells, and mast cells. Although evaluation was limited by the paucity of hematopoietic cells, no dysplasia was noted in the erythroid and myeloid precursors present, and blasts were not increased. The trephine biopsy showed a markedly reduced cellularity of approximately 5% (Fig. 1) and two aggregates composed predominantly of mast cells with admixed lymphocytes in a targetoid configuration. One of the aggregates was perivascular, while the other was paratrabecular. The mast cells had moderately abundant cytoplasm and ovoid nuclei (Fig. 1); more than 15 were present in each aggregate, and the majority of the mast cells were either hypogranular or spindled. Giemsa, tryptase, and CD117 stains highlighted the mast cells (Fig. 1). CD25 was strongly and diffusely positive within the mast cells (Fig. 1). The mast cell nuclei stained for pSTAT5, a feature associated with neoplastic mast cells in the setting of SM [5,6]. They were negative for CD2. *KIT* mutation status and serum tryptase level were not determined; nevertheless, the case fulfilled WHO 2008 criteria for diagnosis of SM (major criterion, and minor criteria 1 and 3 [via CD25 expression], Table).

Flow cytometry of the aspirate material showed a predominance of immunophenotypically normal lymphocytes, and normal expression of CD55 and CD59 by red blood cells. Mast cells were not specifically examined in the flow cytometric analysis. Conventional cytogenetic analysis was hindered by hypocellularity of the aspirate and culture failure, but the one evaluable metaphase cell had a normal karyotype. Serologies for Epstein-Barr virus, HIV, and cytomegalovirus were negative.

Due to the patient's lack of symptoms directly attributable to SM, immunosuppressive therapy for AA with anti-

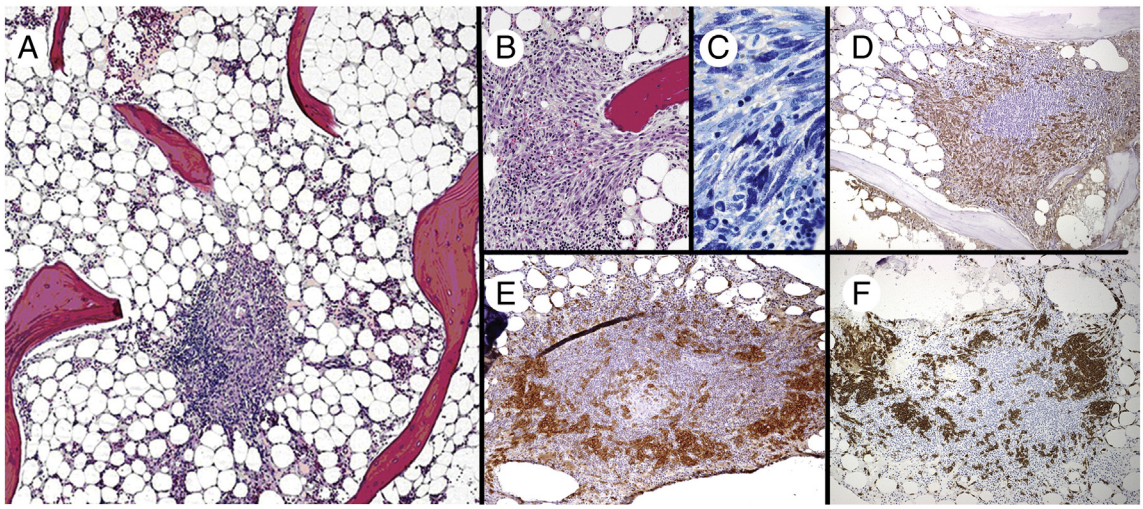

Fig. 1 A and B, The bone marrow trephine biopsy from case 1 shows a representative mast cell aggregate in the background of a hypocellular bone marrow. The mast cells are positive for Giemsa (C), tryptase (D), CD25 (E), and CD117 (F).