Human Pathology (2014) **45**, 2183–2191

ELSEVIER

Human PATHOLOGY

www.elsevier.com/locate/humpath

Progress in pathology

Autoimmune myelofibrosis: an update on morphologic features in 29 cases and review of the literature ☆

Maria E. Vergara-Lluri MD [a,*], Caroline I. Piatek MD [b], Vinod Pullarkat MD [c], Imran N. Siddiqi MD, PhD [a], Casey O'Connell MD [b], Donald I. Feinstein MD [b], Russell K. Brynes MD [a]

[a] *Hematopathology Section, Department of Pathology, University of Southern California–Keck School of Medicine, Los Angeles, CA 90033*
[b] *The Jane Anne Nohl Division of Hematology and Center for the Study of Blood Diseases, University of Southern California-Keck School of Medicine/Norris Cancer Institute, Los Angeles, CA 90033*
[c] *Division of Hematologic Oncology and Hematopoietic Cell Transplantation, City of Hope National Medical Center, Duarte, CA 91010*

Received 15 May 2014; revised 27 July 2014; accepted 30 July 2014

Keywords:
Autoimmune myelofibrosis;
Bone marrow fibrosis;
Morphologic criteria;
Autoimmune disorders;
Non-neoplastic fibrosis;
IgG4 related disease

Summary Autoimmune myelofibrosis (AIMF) is a distinct clinicopathological entity associated with diffuse bone marrow fibrosis and a benign clinical course. Distinction from neoplastic etiologies of marrow fibrosis, particularly primary myelofibrosis, is imperative, but few studies have documented histopathologic features in a large series. We describe 29 patients with AIMF, defined as marrow reticulin fibrosis and lymphocytic infiltration in the context of an established autoimmune disorder (secondary AIMF) or autoantibodies without a defined disorder (primary AIMF). Excluded were cases with atypical megakaryocytes, dysplasia, basophilia, osteosclerosis, unexplained splenomegaly, or neoplasms associated with myelofibrosis (MF). All cases were stained for reticulin, CD3, and CD20, with a subset additionally stained for CD138, κ, λ, immunoglobulin G (IgG), and IgG4. Lymphoid aggregates, where present, were classified into T-cell and B-cell patterns of distribution. Most patients (93%) presented with cytopenias. Sixty-nine percent (n = 20) were considered secondary AIMF and the remainder primary AIMF (n = 9). Peripheral blood showed absent-to-rare blasts and teardrop erythrocytes and absence of eosinophilia or basophilia. Characteristic bone marrow findings included hypercellularity with erythroid and megakaryocytic hyperplasias, mild reticulin fibrosis, intrasinusoidal hematopoiesis, T-cell pattern in lymphoid aggregates, mild polytypic plasmacytosis, and absence of IgG4-positive plasma cells. Primary and secondary AIMF were pathologically indistinguishable, except for an increased incidence of granulocytic hyperplasia in primary AIMF. This series confirms and expands the utility of the original diagnostic criteria for AIMF. Recognizing the characteristic morphology of AIMF and its associated clinical and laboratory features distinguishes autoimmune from neoplastic causes of MF and guides further evaluation and management.

1. Introduction

Autoimmune myelofibrosis (AIMF) is a benign and underrecognized cause of marrow fibrosis [1,2]. It is a distinct clinicopathological entity associated with autoimmune

☆ Disclosures: The authors have no conflicting interests or financial disclosures.

* Corresponding author. Department of Pathology, University of Southern California Keck School of Medicine, 2011 Zonal Ave HMR 308, Los Angeles, CA 90033.
E-mail address: Maria.Vergara-Lluri@med.usc.edu (M. E. Vergara-Lluri).

http://dx.doi.org/10.1016/j.humpath.2014.07.017
0046-8177/

phenomena, response to steroids, and a generally favorable outcome [1,2]. In the context of an established autoimmune disorder, like systemic lupus erythematosus (SLE), it is termed secondary AIMF. Primary AIMF refers to AIMF cases in which patients have autoantibodies but do not have a well-characterized autoimmune disorder. Although isolated case reports have been published, it remains a poorly recognized disorder [1-24].

Various benign and malignant disorders can cause or be associated with a diffuse increase in bone marrow reticulin fibrosis. These include myeloproliferative neoplasms (MPNs) with MF (eg, primary myelofibrosis [PMF]), lymphoid neoplasms (eg, hairy cell leukemia and T-cell large granular lymphocytic leukemia), metastatic solid tumors, pulmonary hypertension, chronic infections (eg, mycobacterial or fungal diseases), therapeutic agents (eg, granulocyte monocyte colony-stimulating factor), and metabolic disorders [25].

The natural history of PMF is that of limited overall survival, whereas AIMF typically follows a benign course and responds well to steroids and/or other immunosuppressive agents. On occasion, AIMF has been misdiagnosed as PMF [21,24] or another malignant disorder. Because the treatment and prognosis are so different, it is extremely important that pathologists are familiar with the distinct characteristics of AIMF.

Although the presence of lymphoid aggregates [21] and plasma cell populations [16,23] have been sporadically described in AIMF, a systematic evaluation of their prevalence and quality in AIMF has not been reported. Furthermore, the entity of immunoglobulin G4 (IgG4)–related sclerosing disease is an increasingly recognized fibroinflammatory condition with involvement in nearly every organ system [26]. Similar to AIMF, autoantibodies such as rheumatoid factor, antinuclear antibodies, and anti-Sjogren syndrome A antibody have been frequently identified in patients with IgG4-related disease. To our knowledge, however, no cases of IgG4-related disease have been reported to lead to bone marrow fibrosis. We investigated the possibility of IgG4-related disease involvement in the bone marrow in our AIMF cases with mild plasmacytosis. Here, we report the morphologic findings in a series of 29 patients that can aid in differentiating AIMF from neoplastic causes of MF.

2. Materials and methods

Twenty-nine patients (22-78 years; median age, 43 years; and 24 female, 5 male) with clinicopathological features of AIMF were identified from the bone marrow pathology records of our institution, with approval of the study by the Institutional Review Board of the University of Southern California. Inclusion criteria were the following: well-established autoimmune disorder and/or presence of autoantibodies, presence of reticulin fibrosis, and lymphoid infiltration as well as absence of atypical megakaryocytes, myeloid or erythroid dysplasia, basophilia, osteosclerosis, unexplained splenomegaly, and neoplasms known to cause MF. A reticulin stain and CD3 (LN10; Leica, Buffalo Grove, IL) and CD20 (L26; Dako, Carpinteria, CA) immunostains were performed on all cases. Reticulin was assessed using the European Consensus Classification [27]. Lymphoid aggregates, where present, were classified into a T-cell pattern or B-cell pattern, as detailed by Naemi et al [28]. These investigators defined 5 patterns of distribution for T and B cells within lymphoid aggregates: pattern 1, predominant T cells; pattern 2, mixed B and T cells; pattern 3, central core of T cells; pattern 4, predominant B cells; and pattern 5, central core of B cells. In a subset of cases, immunostains for IgG (RWP49; Leica), IgG4 (MRQ-44; Cell Marque, Rocklin, CA), CD138 (M115; Leica), κ (rabbit polyclonal; Dako), and λ (rabbit polyclonal; Dako) were available.

3. Results

Most patients (69%; n = 20/29) had established diagnoses of autoimmune disorders, including autoimmune hemolytic anemia, rheumatoid arthritis, SLE, Evans syndrome (autoimmune hemolytic anemia and immune thrombocytopenia), autoimmune hepatitis, antiphospholipid syndrome, autoimmune demyelinating polyneuropathy, dermatomyositis, type I diabetes mellitus, Hashimoto thyroiditis, polymyositis, primary sclerosing cholangitis, psoriasis, and vitiligo. Patients without well-established diagnoses of autoimmune disease had elevated titers of antinuclear antibodies, rheumatoid factor, and/or a positive direct antiglobulin test (Table 1). None met World Health Organization morphologic criteria for MPN [29].

Nearly all patients presented with cytopenias (93%; n = 27/29), with pancytopenia the most common manifestation (28%; n = 8/29). Anemia and thrombocytopenia (24%), isolated anemia (21%), and anemia plus leukopenia (14%) were less frequent. Two patients (7%), presented with leukocytosis and concurrent anemia and thrombocytopenia. In contrast to MPNs with MF, which invariably have prominent leukoerythroblastic features, leukoerythroblastosis and tear-drop poikilocytosis were absent in all but 1 patient (96%, Table 2). One case exhibited eosinophilia, whereas none of the cases displayed basophilia.

The bone marrow biopsies were hypercellular in most cases (74%; n = 22/30) (Fig. 1A). Most showed erythroid hyperplasia (77%; n = 23/30) or megakaryocytic hyperplasia (77%; n = 23/30). In just over half of the cases, combined erythroid and megakaryocytic hyperplasias were seen (55%; n = 16/29) (Fig. 1B). Granulocytic hyperplasia was observed in a third of cases (34%; n = 10/29). Although often subtle, sinusoidal dilation with intrasinusoidal hematopoiesis was found in nearly all cases (93%; n = 27/29) (Fig. 1C). Reticulin staining demonstrated mild fibrosis (MF-1) (86%; n = 25/29) in most cases (Fig. 1D); however, moderate-to-marked fibrosis (MF-2 or MF-3) (Fig. 1D and E) was found in a small minority of cases (10% and 4%, respectively). This corresponds to the originally reported Bauermeister grade 3 or 4 reticulin fibrosis of the bone marrow described in our initial reports [1,2].