

Idiopathic myelofibrosis with fatty bone marrow: an issue of sampling? A propos an unusual case

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Idiopathic myelofibrosis (IMF) is regarded as a chronic myeloproliferative disorder typically presenting with uniformly fibrotic bone marrow characterized by numerous clusters of strongly atypical megakaryocytes.¹ Although a very low content of hematopoietic cells in bone marrow is not a rare finding, it is usually attributed to diffuse fibrosis replacing both hematopoiesis and fat within the intertrabecular spaces.¹ Myelofibrosis with fatty bone marrow is a very rare variant of IMF in which abnormal hematopoiesis is dislocated to extramedullary sites, mostly to the spleen, whereas the histology of the bone marrow is compatible with the picture typical for aplastic anemia. Recently Gerli et al. reported a case of this unusual variant,² and four cases had been reported previously.³ Additionally, Antonucci et al. described an evolution of a picture interpreted as aplastic anemia into typical IMF in the course of 20 years, which could represent a similar condition.⁴ Here we present a case of IMF with a mixed (aplastic/ typical) histological picture in a large trephine biopsy.

A 63-year old male was referred to our institution for hematological consultation due to leukocytosis with a leukoerythroblastic peripheral blood picture and marked splenomegaly. These abnormalities were detected upon routine medical examination in the course of chronic ischemic heart disease, arterial hypertension and chronic peptic ulcer disease. At presentation his spleen reached the midline and protruded 10 cm below the umbilicus. Examination of peripheral blood showed anemia (Hb = 8.3 g/dL, Ht = 25.4%, RBC = $3.22 \times 10^{12}/L$), leukocytosis (WBC = $19.0 \times 10^9/L$), and mild thrombocytopenia (Plt = $138 \times 10^9/L$). The differential count of peripheral blood revealed 1% promyelocytes, 12% myelocytes, 18% metamyelocytes, 26% band forms, 30% segments, 2% eosinophil granulocytes, 3% basophils, 6% lymphocytes, and 2% monocytes. Additionally there were 3 erythroblasts per 100 peripheral blood leukocytes. Peripheral blood smears demonstrated anisocytosis, poikilocytosis and giant platelets. The RT-PCR for bcr/abl transcripts was negative. The retrospective review of the patient's records revealed slightly increasing leukocytosis, and thrombocytopenia as early as four years prior to the hematological consultation.

The trephine bone marrow biopsy consisted of two fixed fragments 22 mm and 11 mm long, both 1.9 mm in

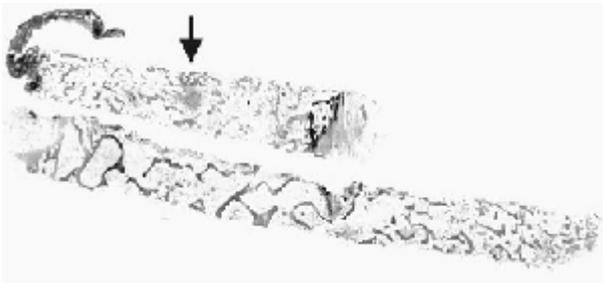


Figure 1. Low-power view of the whole trephine bone marrow biopsy consisted of two cores. An arrow points at the largest focus of hematopoietic tissue within the core containing areas compatible with idiopathic myelofibrosis. The other core shows bone marrow aplasia (hematoxylin& eosin).

diameter (Figure 1). Histologically the larger core demonstrated a picture almost compatible with bone marrow aplasia (Figure 2A). Notably, there was no stromal fibrosis, and osteopenic bone trabeculae had smooth, regular outlines. Scattered hematopoietic cells consisted mostly of small, typical lymphocytes. A few megakaryocytes did not show pathognomonic morphological alterations. They were mostly dispersed, but one small cluster was found at the periphery of the core. Contrarily, the smaller core contained clusters of hematopoietic cells residing in the stroma undergoing significant reticulin and collagen fibrosis (Figure 2B). These cells represented chaotically intermingled elements of all three major hematopoietic lines, and small typical lymphocytes, forming a diffuse nodule within the largest cluster. The megakaryocytes were characterized by marked variations in sizes, diversification in shapes of the cytoplasm, abnormally polymorphic nuclear profiles with atypical segmentation patterns, and occasionally hyperchromasia of chromatin. Some of the megakaryocytes formed small clusters. Dilated sinuses filled with hematopoietic cells, including atypical megakaryocytes, were easy to find (Figure 3). The stroma outside the clusters of abnormal hematopoiesis was slightly edematous, whereas the disfigured bone trabeculae were distinct from these contained in the larger core, bearing in mind early osteomyelosclerotic changes. Neither core contained

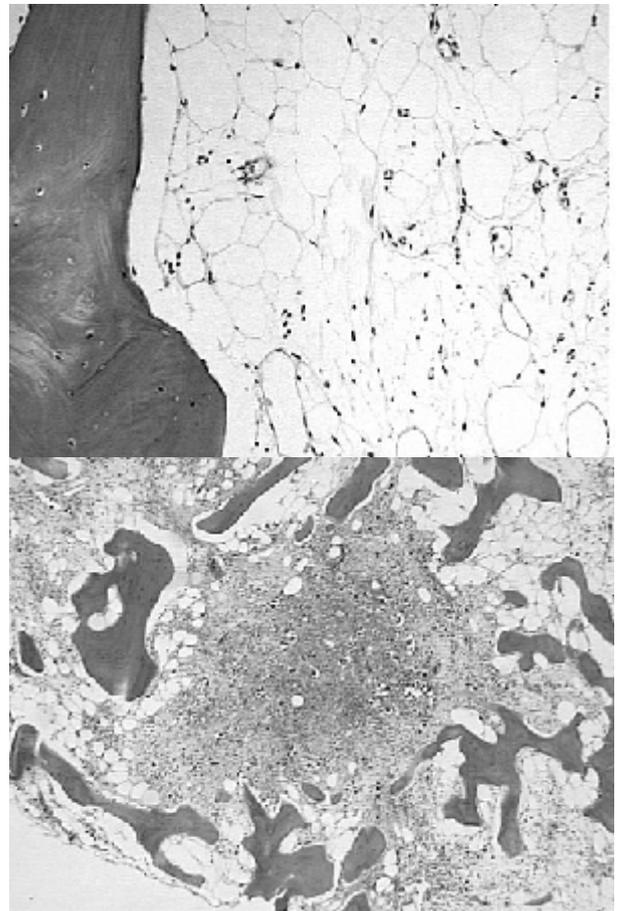


Figure 2. Different bone marrow and bone histology in the two cores. A. Bone marrow aplasia with normal bone trabeculae (hematoxylin& eosin, lens magnification 10x). B. Focal idiopathic myelofibrosis with irregular bone trabeculae (hematoxylin& eosin, lens magnification 2.5x).

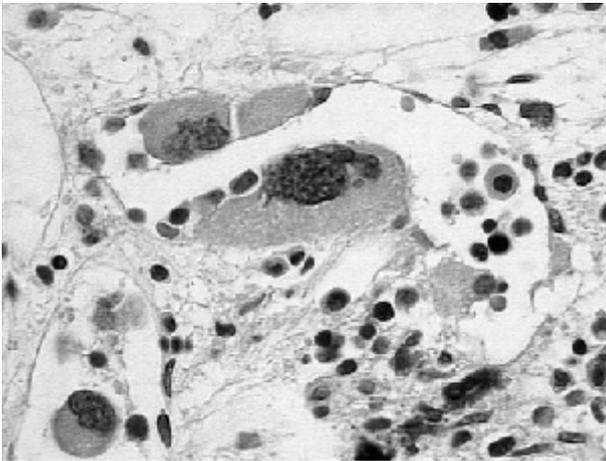


Figure 3. High-power view of the atypical intrasinusoidal megakaryocytes within the cluster of fibrotic hematopoietic tissue (hematoxylin& eosin, lens magnification 40x).

excess or clusters of blasts.

The whole picture was diagnostic of IMF with the focal bone marrow involvement and predomination of areas mimicking bone marrow aplasia.

The patient was released with steroid treatment (Danzol), and a recommendation for periodic hematological monitoring at intervals of six months, but was lost to follow-up.

Gerli et al. in their report discuss the possible explanations for fatty bone marrow found in an otherwise typical clinico-pathological context of IMF, proposing dislocation of hematopoiesis into distant bone marrow sites as a likely, but unproven mechanism behind this puzzling syndrome². Our case may provide some insight into the nature of at least some cases diagnosed as *IMF with fatty bone marrow*. In addition to almost exclusively

fatty zones, mimicking bone marrow aplasia, the large biopsy material may reveal clusters of densely aggregated hematopoiesis with all the hallmarks of IMF. Our findings point out the necessity of ample sampling of bone marrow in all cases demonstrating aplastic histology in patients with a hematological picture suggesting IMF. Although we were lucky to arrive at the diagnosis assessing a large unilateral sample, in such cases bilateral trephine bone marrow biopsy seems to be mandatory.

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Z. Rudzki, T. Sacha, K. Okon', A.B. Skotnicki

correspondence: Dr. Zbigniew Rudzki; Department of Pathomorphology, Collegium Medicum, Jagiellonian University, Grzegorzeczka 16, 31-531, Kraków, Poland

phone: (+48) 12 4215210, fax: (+48) 12 411 9725,

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