Case 324

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History

73 y/o woman first diagnosed with polycythemia vera (PV) in 1987. Beginning in 1989, patient was treated with anagrelide and then with hydrea two tablets daily plus intermittent phlebotomies, 2-4 times per year. Stopped hydrea in June 2009 because Hct decreased to 36. Since then, developed increasing leukocytosis (WBC > 30 and later >50 x10 e9/L) in association with increased splenomegaly, early satiety, weight loss. Referred to Weill-Cornell Medical College for further management. Diagnosed with post-PV myelofibrosis (8/2009), she was treated with pegintron first and later with pegasys with no response. Spleen size and WBC having continued to increase while the patient's symptoms have worsened with profound weakness, unable to eat adequately, fluid retention, and severe spleen pain. No response to trial of JAK2 inhibitor (incyte) as well as to panobinostat, a non-selective histone deacetylase inhibitor (HDAC inhibitor). Palliative splenectomy performed upon patient request on June 2010. She died on October, 2010.

Details

1. Bone marrow biopsy (4/2010): fixed in Bouin fluid 0.8x0.2 cm. decalcified in nitric acid. The biopsy shows a hypercellular bone marrow (100% cellularity) with diffuse myelofibrosis. The bone marrow cellularity is predominantly myeloid (M:E ratio 4:1). Mature neutrophils predominate. Erythropoiesis is decreased. Megakaryocytes are increased with pleomorphic cytological features and variably tight clustering. Blasts are 2%. Fibrosis is confirmed by reticulin and trichrome stains and is estimated as grade 4 (MF-3).

The corresponding CBC showed: Hb 10.5 g (MCV: 88.3fl); WBC: 50.2 x10^9/L (N:67%; Band 8%; Meta 6%; Myelo 9%; Promyelo 1%; Eos 1%; Baso 2%; Blasts 1%; Mono 1%; Lymph 4%). There were 1/100 NRBC. Plts. 192 x10^9/L. Aspirate is dry tap. Touch preparation only.

2. Spleen, splenectomy (6/2010): fixed in formalin. Spleen measures 35x16x12cm and weights 3000g., and appears homogenously beefy red upon sectioning. Microscopically the expanded splenic red pulp shows extensive extramedullary hematopoiesis. This is characterized predominantly by a maturing granulocytic proliferation largely neutrophilic, associated with foci of megakaryopoiesis. Erythropoiesis is predominantly intrasinusoidal. No blast accumulation is appreciated although myeloperoxidase immunostain highlights the presence of an increased proportion of promyelocytes.

Immunohistochemistry and Flow Cytometry

Immunohistochemistry:

1. Immunohistochemistry of bone marrow biopsy: MPO 80%; Glyco C 5-10%; CD34 <1%; CD117 <1% (mast cells); CD42b positive in megakaryocytes (no megakaryoblasts identified).

2. Immunohistochemistry of spleen: MPO highlighs increased number of myeloid cells. CD34 and CD117 do not show increased number of positive cells. No megakaryoblasts by CD42b.

Flow Cytometry:

1. Bone marrow dry tap. No flow was performed.

2. Spleen flow cytometry by gating on CD45 dim cells showed 2% blasts. Polyclonal B-cells and unremarkable T-cells.

Cytogenetic Findings

Karyotype: Peripheral blood corresponding to the submitted 2010 bone marrow and spleen showed 46,XX,del(13)(q12q14)[9]/46,XX,+add(1)(p11),-6[8]/46,X,-X+2,del(4)(q21)[2].

Molecular Findings

JAK2 V617F mutation confirmed by ARMS-PCR at multiple times both in PB and in the spleen. No allele burden determination was performed.

Interesting Features/Discussion

The case fulfills the WHO 2008 criteria for progression to post-PV myelofibrosis. In addition, the presence of persistent significant neutrophilic leukocytosis associated with an increased proportion (>10%) of circulating immature myeloid cells is also consistent with disease progression. Although the case does not fulfill the criteria for accelerated phase in a classical sense, nevertheless it may represent a yet not clearly established manifestation of acceleration similar to what recently reported in cases of primary myelofibrosis developing sustained monocytosis (Boiocchi L, et al. Development of monocytosis in patients with primary myelofibrosis indicates an accelerated phase of the disease. Mod Pathol. 2012 Sep 28. doi: 10.1038/modpathol.2012.165. [Epub ahead of print]. This conclusion is further supported by the presence of a complex karyotype (with three clones) which was confirmed multiple times by analyzing peripheral blood samples and spleen tissue. These abnormalities had not been detected before the evolution to post-PV myelofibrosis (per communication with clinical attending physician).

Proposed Diagnosis

Post-polycythemic myelofibrosis associated with neutrophilic proliferation.

Consensus Diagnosis

Post-polycythemic myelofibrosis associated with neutrophilic proliferation, JAK2 V617F mutation-positive