Leukemia Research Reports 6 (2016) 20–23

Contents lists available at ScienceDirect

Leukemia Research Reports

journal homepage: www.elsevier.com/locate/lrr

A remarkable hematological and molecular response pattern in a patient with polycythemia vera during combination therapy with simvastatin and alendronate

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ARTICLE INFO

Article history:
Received 14 April 2016
Received in revised form
15 June 2016
Accepted 19 June 2016
Available online 27 June 2016

Keywords:
Myeloproliferative neoplasms
Polycythemia vera
JAK2-V617F mutation
Simvastatin
Alendronate

ABSTRACT

We report a 57-year old man with polycythemia vera, who had a remarkable hematological and molecular response during treatment with simvastatin and alendronate. The patient was treated with this combination for 56 months, and during this period the patient has been in complete hematological remission. The JAK2-V617F allele burden has dropped from 64% to sustained values below 20%, and follow-up bone marrow biopsies have revealed no change in PV features, without any regular cytoreductive treatment.

1. Case report

In 2008 a 57-year old man was referred for treatment of polycythemia vera (PV). One year earlier he had been admitted with symptoms resembling an episode of transitory cerebral ischemia (TCI). The patient also had a history of multiple sclerosis (MS), vitamin B12 deficiency and tobacco smoking. The MS was not being treated at this point and the B12 deficiency was treated with cyanocobalamin 1 mg/day. At that time the hemoglobin concentration (Hgb) was elevated at 18.5 g/dL, the hematocrit (HCT) was 54%, and the white blood cell count (WBC) was 11.0×10^9/L. The platelet count was 502×10^9/L. Mean corpuscular volume (MCV) was normal 97 fL. A cerebral CT-scan showed a hypodense area compatible with an infarction of indeterminable age. The patient was treated with acetylsalicylic acid 75 mg/day, dipyridamole 200 mg 2 times/day along with simvastatin 40 mg/day. The patient was phlebotomized once before discharge. Unfortunately, although the elevated blood cells should have raised the suspicion of PV, the patient was not referred to a department of hematology, and no JAK2-V617F mutation analysis was done at this time.

The patient was referred to the department of hematology in 2008 by his general practitioner because of sustained elevated Hgb-concentrations and platelet counts along with fatigue. At the time of the PV diagnosis the Hgb concentration was 19.2 g/dL and the HCT 0.60. The WBC was 12.0×10^9/L, and the platelet count 485×10^9/L, the MCV 91 fL and B12 vitamin was elevated at 882 pmol/l. MCV remained normal and B12 normal or elevated. The red cell mass and plasma volume were both expanded, and serum-EPO was lowered at 1 IU/L. The JAK2-V617F mutation was positive with an allele burden of 64%. A bone marrow biopsy was compatible with PV with a slightly hypercellular bone marrow with panmyelosis and depleted iron stores, displaying no reticulin fibrosis and a peripheral blood-smear was without leucoerythroblastosis. Immunohistochemical staining with CD34 showed dilated vessels, but no increase in vascular density. An abdominal ultrasound showed normal spleen size. Based on the above findings the diagnosis PV was made.

During the following year 11 phlebotomies were performed and no cytoreductive treatment was administered. Fig. 1 illustrates the treatment and responses in hematological parameters along with the JAK2-V617F allele burden. Approximately 13 months after the PV-diagnosis, treatment with hydroxyurea (HU) 500 mg/day was initiated in order to reduce the need of phlebotomies and to normalize elevated leukocyte and platelet counts. Eighteen days later the patient was admitted to a department of neurology with convulsions and fever, being suspected of an attack of MS. Clinically a pneumonia was suspected, and a chest x-ray revealed

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http://dx.doi.org/10.1016/j.lrr.2016.06.004

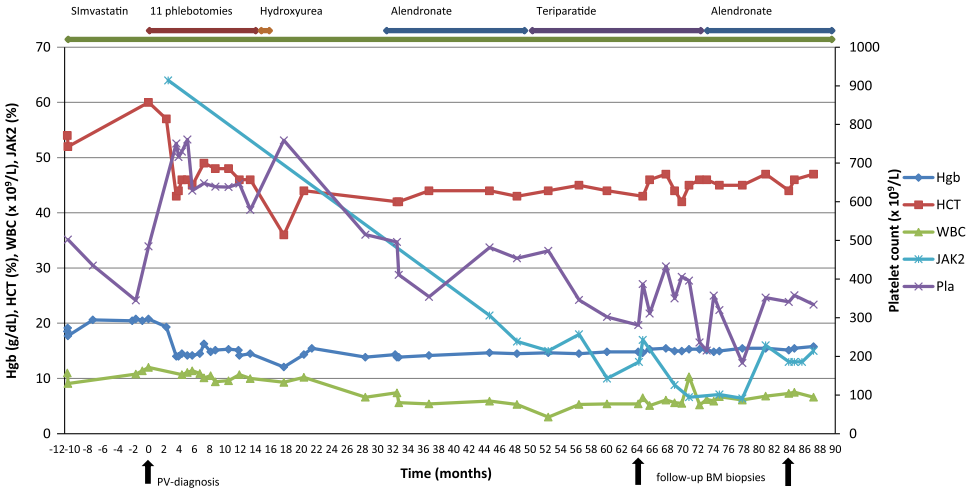
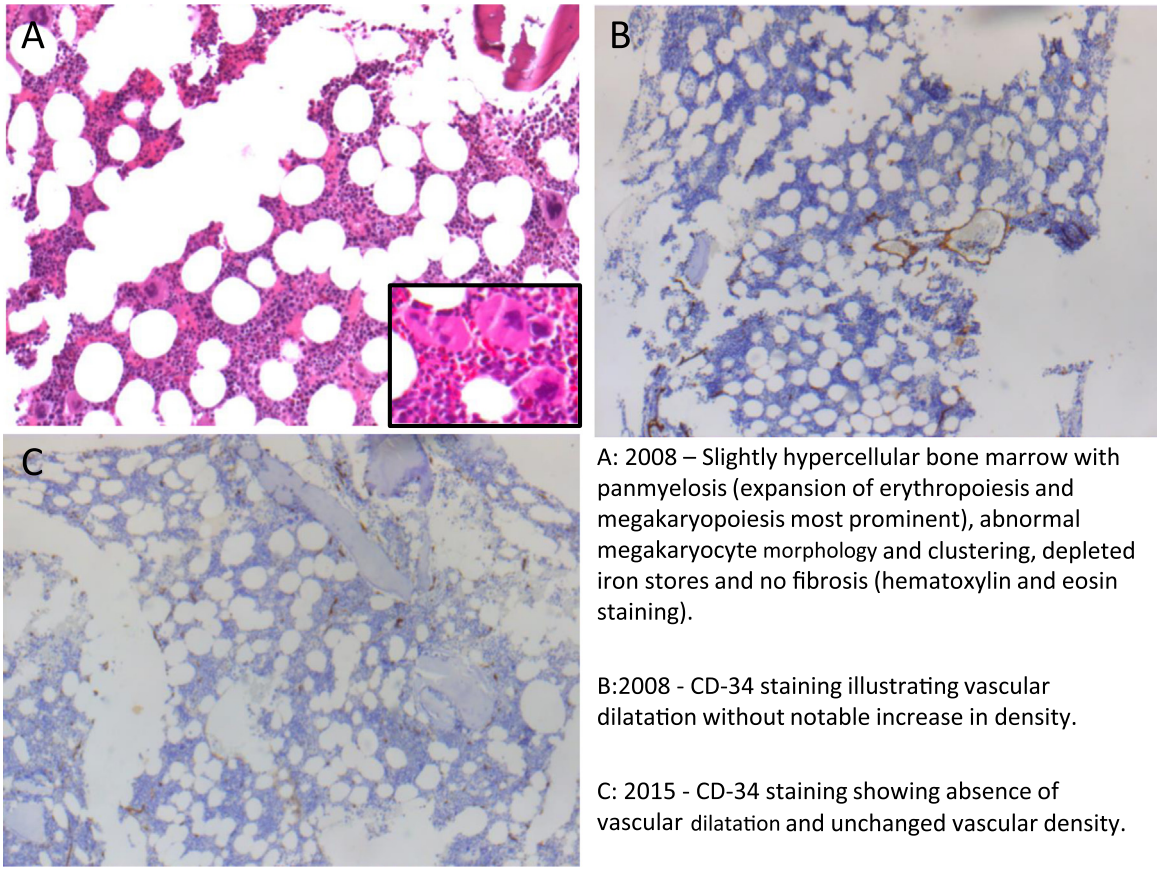


Fig. 1. The development of hematological parameters and the JAK2-V617F allele burden and an overview of the treatment.

multiple pulmonary infiltrates. Accordingly, treatment with antibiotics was initiated. No bacterial growth from blood, urine or sputum was recorded. After 3 days of admission HU was discontinued. Later, the patient developed shock and was transferred to the intensive care unit. A CT-scan of the chest and abdomen revealed signs of pulmonary alveolitis. A bronchoscopy was normal. No biopsy was performed. It was concluded that the alveolitis likely was induced by HU, since the patient steadily improved after HU was discontinued.

At follow-up in the hematological out-patient clinic the patient had a normal HCT and the platelet count was slightly elevated at 515×10^9/L. However, no further cytoreductive treatment was initiated. At the beginning of 2011 (31 months after the PV-diagnosis) osteoporosis was diagnosed. Consequently, treatment with alendronate 70 mg/week was initiated and continued for 18 months, until the patient changed treatment to Teriparatide – a PTH analog – for two years. Afterwards alendronate was reintroduced. During these 56 months, after initiation of alendronate, the patient was largely in complete hematological remission (the platelet count was temporarily above 400×10^9/L on some occasions) without need for further phlebotomies, and the JAK2-V617F mutation status 44 months after PV-diagnosis revealed a marked decrease in the allele burden from 64.0% to 21.4% (Fig. 1). The patient had no need of phlebotomies or cytoreductive



A: 2008 – Slightly hypercellular bone marrow with panmyelosis (expansion of erythropoiesis and megakaryopoiesis most prominent), abnormal megakaryocyte morphology and clustering, depleted iron stores and no fibrosis (hematoxylin and eosin staining).

B:2008 - CD-34 staining illustrating vascular dilatation without notable increase in density.

C: 2015 - CD-34 staining showing absence of vascular dilatation and unchanged vascular density.

Fig. 2. Bone marrow biopsies from 2008, 2013 and 2015.