A Rare Presentation of Extramedullary Hematopoiesis in Post-polycythemic Myelofibrosis

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Abstract Polycythemia vera is a clonal proliferative disorder of the bone marrow that could possibly evolve into myelofibrosis in its natural course. Progression to myelofibrosis is usually a late stage complication and presents clinically with refractory cytopenias and extramedullary hematopoiesis (EMH). EMH can occur in any tissue during the course of post-polycythemic myelofibrosis. However, skin and cardiac involvements seems to be very rare. We present a 56-year-old woman with post-polycythemic myelofibrosis refractory to treatment, developing EMH after splenectomy in various organs, exceptionally the skin and the heart. Along with the case, the clinical presentations, treatment options, prognostic significance of EMH and the role of cytogenetics is discussed in the light of the literature.

Keywords Polycythemia vera · Myelofibrosis · Extramedullary hematopoiesis · Skin · Splenectomy · Heart

Abbreviations

EMH Extramedullary hematopoiesis
MF Myelofibrosis

PV Polycythemia vera
Post-PV MF Post-polycythemia vera myelofibrosis

Introduction

Post-polycythemia vera myelofibrosis (post-PV MF) is a long term clinical outcome in around 10 % of patients with polycythemia vera (PV) [1, 2]. No clear risk factors have been identified for such a transformation. Due to replacement of normal bone marrow with fibrous tissue, hematopoiesis pursues in various other organs with reticuloendothelial capacity such as liver, spleen and lymph nodes, and is denoted as “extramedullary hematopoiesis” (EMH). Along with these most frequently affected organs, hematopoietic cells may less frequently infiltrate other tissues as well; yet, skin and cardiac involvements are extremely rare manifestations.

Here we present a post-PV MF patient refractory to drug treatment and subsequently developed symptoms of EMH in various organs including skin and heart after splenectomy.

The Case

A 56-year-old woman admitted to our clinic with fatigue, profuse sweating and loss of appetite in April 2007. She had been diagnosed with post-PV MF 7 years ago when she admitted with similar symptoms. At the time of diagnosis, she had hepatosplenomegaly and leukoerythroblastic picture on blood smear with cell counts within normal limits. Red cell mass was elevated and erythropoietin level was low. Leukocyte alkaline phosphatase (LAP) score was elevated and Jak-2 mutation was positive. Bone marrow aspiration was a dry tap and bone marrow biopsy demonstrated marked fibrosis and low grade collagenization.

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Cytogenetic analysis of bone marrow cells revealed 46 XX with t(1;8) in 6 of 20 metaphases. Molecular study for bcr/c-abl translocation was negative.

Hydroxyurea at a dose of 500 mg/day had been started but discontinued after 3 months of treatment due to thrombocytopenia. Patient was switched to interferon therapy (3 million units/day, 3 days a week). After 8 months of treatment, interferon was discontinued because the patient suffered from profound fatigue after interferon injection and progressive liver and spleen enlargement developed despite treatment. She gradually became anemic and moderate leukocytosis developed. The patient's course was complicated by severe bone pain due to osteosclerosis, which could not be stabilized by analgesic agents.

Her physical examination at current admission revealed hepatomegaly measuring 10 cm and her spleen was extending to the inguinal region. The patient's hematology at admission was as follows: hemoglobin 16.8 g/dL, white blood cell $18.4 \times 10^9/L$ with a differential showing 49 % neutrophils, 23 % metamyelocytes, 8 % myelocytes, 3 % promyelocytes, 8 % basophils, 2 % eosinophils, 9 % lymphocytes, 3 % monocytes and 3 % normoblasts and platelet count was $179 \times 10^9/L$. She had a mean corpuscular volume of 70. Serum lactate dehydrogenase level was significantly elevated (1,100 U/L). Peripheral blood smear revealed a leukoerythroblastic picture with teardrop poikilocytes.

Since medical treatment was ineffective in controlling disease symptoms and she had progressive splenomegaly leading to abdominal fullness and early satiety, splenectomy was performed. Following splenectomy, her fatigue, early satiety and loss of appetite resolved. 4 months after splenectomy she developed generalized pruritus and multiple painless, violet-colored, patchy, papular lesions, 2–3 cm in diameter, on trunk and extremities (Fig. 1). Her leukocyte count was $131 \times 10^9/L$ with leukoerythroblastic picture, giant platelets, normoblasts and dyshematopoiesis at that time. The incisional skin biopsy revealed extramedullary myeloid tumor with cells immunohistochemically stained with MPO, CD34, lysosyme and CD43 (Fig. 2). Hydroxyurea 2 g/day was started. Skin lesions started to fade in a few days after the onset of therapy.

A few days later, the patient was readmitted with a sudden onset and short-lived confusion. She had a new onset high rate atrial fibrillation on ECG. She was given diltiazem and digoxin for rhythm control. The cardiac silhouette was enlarged on chest X-ray. Echocardiographic studies showed a conserved systolic function with ejection fraction of 67 %, dilated right atrium and ventricle with a pulmonary artery pressure of 85 mmHg. She had second degree mitral regurgitation and third degree tricuspid regurgitation. Pericardial effusion and a 14×12 mm mass in posterior atrioventricular groove were noted on echocardiography. After the patient was stabilized,

Fig. 1 Papular lesions on trunk and extremities revealing extramedullary hematopoiesis on skin biopsy

Fig. 2 Precursor hematopoietic cells infiltrating collagen fibers in skin biopsy (HE $\times 400$)

transesophageal echocardiography was performed, which confirmed a 19×7 mm mass close to the base of left ventricle in posterior atrioventricular groove. Cardiac MRI demonstrated a contrast enhanced lesion along the posterior atrioventricular groove, which may be interpreted as EMH. Pericardial fluid sampling was suggested but patient did not permit. The patient refused any further treatment and left the hospital on her own will. She was reported to be dead 1 month after discharge.

Discussion

In PV, less than 20 % of the patients may present with a certain degree of myelofibrosis (MF) at the time of diagnosis and transformation from PV to MF has been reported to occur at a ratio about 5–15 % after 15–20 years of

follow-up [2, 3]. Since the incidence of MF in first 10 years is low and it is usually manifested in patients with a long duration of disease, the occurrence of MF is rather early in our patient and may suggest an aggressive subgroup [4].

Among chronic myeloproliferative disorders, EMH is most commonly seen in idiopathic MF since it is associated with the highest rate of bone marrow fibrosis (up to 80 % at presentation) and circulating progenitor cells [5, 6]. Foci of EMH are most commonly found in the spleen, liver and lymph nodes, but may also infrequently occur at other sites as kidney, adrenal glands, pleura and peritoneum [7–11]. Skin and cardiac manifestations, as we have encountered in our patient, are extremely rare.

Up to 30 cases of cutaneous EMH have been reported in the literature. Very few of them developed in the setting of secondary MF. Tanaka et al. [12] reported four cases of secondary MF (three PV and one essential thrombocythemia) presenting with cutaneous manifestations, in their literature review. Whether due to primary or secondary MF, the skin lesions range from reddish–purplish macules, papules or erythematous plaques to nodules, ulcers and bullae. There seems to be no association between timing of skin manifestations and time to disease progression in the reported cases. Yet, there are reports of patients with blastic transformation shortly after development of skin manifestations, which may indicate that skin involvement may serve as a sign of disease acceleration or development of blastic crisis [13, 14]. In almost half of the cases, splenectomy preceded the occurrence of skin lesions but whether splenectomy has an effect on the development or progression of EMH is not clear. Any possible effect may be through shifting of EMH to other organs after splenectomy. Barosi et al. [15] observed an unexpectedly high rate of blastic transformation in splenectomized patients with MF. Not all skin lesions were responsive to hydroxyurea; it may be interpreted from the cases that hydroxyurea seems to control skin involvement as long as it is able to control stigma of disease activity as spleen size or transfusion dependence [16, 17]. Electron beam radiation seems to produce variable results on treatment of skin lesions [17–19].

Very few cases of EMH involving the heart have been reported in the literature. Most of the cases developed secondary to chronic myelogenous leukemia, and pointed out to an accelerated phase of the disease [20, 21]. Almost all patients presented with massive pericardial effusion, leading to cardiac tamponade [22, 23].

Pulmonary infiltration of hematopoietic cells has been reported in less than 30 cases of MF. Although we do not have a histopathologic evidence, pulmonary involvement by EMH may be an explanation for the increased pulmonary artery pressure observed on echocardiography in our patient [24]. Radiotherapy may be used for pulmonary hypertension due to EMH [25].

Although drug treatment may decrease transfusion dependence or spleen size, treatment is largely palliative in MF and has not been shown to improve survival [26]. Allogeneic stem cell transplantation is the only curative therapy that offers long-term relapse-free survival for patients with MF [27, 28]. Bone marrow transplantation causes regression of bone marrow fibrosis in MF but whether it has an effect on reversal of EMH is not known [29].

Several cytogenetic abnormalities have been associated with PV and MF. They are present in a small proportion (~15 %) of PV patients at the time of diagnosis [30] whereas new cytogenetic abnormalities develop in the majority (75–100 %) of cases during the course of the disease [31, 32], with the highest frequency in patients given multiple lines of treatment [33]. They are highly unspecific during the polycythemic phase with a predominance of chromosome 1(+1q), 8 and 9 (usually as trisomies) and chromosomes 13 (del13q) and 20 (del20q) abnormalities whereas monosomy or partial deletion of chromosomes 5 and 7 are more characteristic of therapy related leukemia [33]. Trisomy 1q is reported to be especially frequent after the development of “post-polycythemic myelofibrosis” [34, 35]. Translocations are frequent and chromosome 1 seems to be one of the commonly involved chromosomes as one of the partners [33]. Among reported translocations there are t(1;7), t(1;20), t(1;9), t(1;3) [36–39]. t(1;8) was present in our patient before disease progression. Staven et al. [40] reported a patient who had previously received radiophosphorus therapy for PV, later developed chronic granulocytic leukemia and had deletion of chromosomes 8 and 12, and translocation between 1 and 8. There is no data on whether t(1;8), specifically, affects prognosis in those patients; however Dingli et al. [41] reported cytogenetic abnormalities other than del13q or del20q to be the only adverse prognostic factors for survival in patients with post-polycythemic and post-thrombocytopenic myeloid metaplasia.

In conclusion, post-PV MF may present with EMH in various organs; such an entity may predict a widespread organ involvement and a grave course in patients with post-PV MF. The effect of splenectomy and specific cytogenetic abnormalities are not exactly known but current observations may suggest an unfavorable course.

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