CASE REPORT

Extramedullary haematopoiesis presenting with cardiac tamponade in a patient with polycythaemia vera

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SUMMARY

A 71-year-old man with a history of polycythaemia vera, diagnosed 4 years ago, presented to the emergency room with shortness of breath. A bedside echocardiogram revealed a large pericardial effusion with features concerning for pericardial tamponade. A left anterior thoracotomy and a pericardial window were emergently performed in the operating room and relieved the patient's symptoms. Histology evaluation of the pericardial fragments and pericardial fluid revealed the presence of trilineage haematopoietic elements without any increase in the blasts. A bone marrow core biopsy revealed an increase in reticulin fibre and increase in the number of blasts of 5%–10%, whereas peripheral blood testing was positive for JAK2 V617F mutation. This case report reviews the literature for cases of extramedullary haematopoiesis associated with myeloproliferative neoplasms.

BACKGROUND

The detection of mutations in *JAK2*, *MPL* and *CALR* has improved our understanding of myeloproliferative neoplasms (MPN) and aided in the diagnosis. However, additional factors predicting progression to myelofibrosis or leukaemic transformation have yet to be identified. This patient presents with an unusual progression of his polycythaemia vera (PV) to myelofibrosis with extramedullary haematopoiesis (EMH) involving the pericardium and causing tamponade. We also reviewed the literature for a handful of similar presentations involving MPN.

CASE PRESENTATION

A 71-year-old Ethiopian man with a history of PV, diagnosed 4 years previously and maintained on hydroxyurea 1000 mg daily and daily aspirin, presented to the emergency room with worsening shortness of breath with a dry cough, anorexia and night sweats of 3-week duration. A complete blood count showed a modestly elevated leucocyte count of 15×10^9 cells/L, haemoglobin of 9 g/dL and platelet count of 654 000/L. The peripheral blood smear showed marked neutrophilia with bandemia; the erythroid lineage was notable for rare nucleated red blood cells and occasional teardrop cells. The patient's blood count 3 weeks prior to presentation showed a leucocyte count of 8.66×10^9 cells/L, haemoglobin of 12 g/dL and platelet count of 244 000/L.

INVESTIGATIONS

A bedside echocardiogram in the emergency room revealed a large pericardial effusion with features concerning for pericardial tamponade. A follow-up formal echocardiogram demonstrated a large circumferential pericardial effusion and hyperdynamic systolic function with an ejection fraction of 70%. The patient was emergently taken to the operating room for a left anterior thoracotomy and a pericardial window. He was found to have dense pleural adhesions, with 700 mL of sanguineous fluid drained from the pericardial space. Evaluation of the pericardial fragments and pericardial fluid revealed the presence of haematopoietic elements (both myeloid and erythroid precursors) suggestive of proliferative haematopoietic cells. No increase in the number of blasts was noted on immunohistochemistry stains for CD34 and CD117 (figure 1).

DIFFERENTIAL DIAGNOSIS

The patient's presentation with EMH with concomitant anaemia was concerning for progression of the PV to myelofibrosis and possibly leukaemic evolution. The patient subsequently underwent a bone marrow biopsy with pathology of the core biopsy significant for an increase in reticulin fibre deposition and focal osteosclerosis, consistent with post-PV myelofibrosis. An increased number of blasts of 5%–10% was also noted without overt leukaemic transformation (figure 2). An aspirate could not be obtained due to the dry tap; FISH and cytogenetic analyses were consequently unavailable. *JAK2* V617F mutation was detected, whereas the *BCR-ABL* gene was negative on the peripheral blood.

TREATMENT

Hydroxyurea was discontinued on admission, with the patient's clinical course improving after the pericardial window; he was discharged on postoperative day 6.

OUTCOME AND FOLLOW-UP

On a follow-up visit as outpatient 8 weeks after his initial presentation, his complete blood count showed a leucocyte count of 13.6×10^9 cells/L, haemoglobin of 9.9 g/dL and platelet count of 556 000/L.

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Figure 1 Pericardium with megakaryocytes and immature erythroid and granulocytic cells consistent with extramedullary hematopoiesis ((A) H&E, 200x). A megakaryocyte with large multilobated nucleus ((B) H&E, 400x).

DISCUSSION

MPN are a group of clonal bone marrow disorders manifesting with excess circulating cells. The 2016 revision to the WHO classification of myeloid neoplasms and acute leukaemia lists PV, essential thrombocythaemia (ET), chronic myeloid leukaemia (CML), primary myelofibrosis (PMF), chronic eosinophilic

Figure 2 Hypercellular bone marrow with increased megakaryocytes, and erythroid and granulocytic hyperplasia. Note the cellular streaming indicative of fibrosis ((A) H&E, 200x and (B) H&E, 400x). Reticulin fibrosis consistent with progression to the fibrotic polycythaemic phase of PV in this patient with anaemia, a leukoerythroblastic blood picture and a history of PV ((C) reticulin, 200x). PV, polycythaemia vera

leukaemia and chronic neutrophilic leukaemia under the banner of MPN.¹ Of all the MPNs, gain of function driver mutations in the *JAK2* gene are readily detected in PV, ET and PMF, with nearly all cases of PV and approximately 60% of individuals with PMF harbouring a mutation. Furthermore, evolution of PV to myelofibrosis is thought to occur in around 12%–21% of cases.^{2,3} The risk of progression to acute leukaemia and myelodysplastic syndrome varies between each entity with PMF carrying the highest risk of leukaemic transformation among the *BCR/ABL*-negative MPN.⁴

PV, ET and PMF are closely related entities with phenotypic similarities and share characteristic somatic aberrations. The course of PV and other MPN disorders is far from homogeneous with diverse clinical outcomes varying from indolent disease to thrombosis, fibrotic and leukaemic progression that cannot be predicted solely based on the driver mutations.⁵ Additional molecular testing and karyotyping could prove to be valuable in predicting leukaemic transformation but has not been correlated with fibrotic progression. In our case the absence of such testing is a drawback.

The significance of the development of secondary myelofibrosis after PV has been debated with some experts reporting this feature as a sign of myeloid metaplasia while others describing it as part of the natural history of the disease.^{6,7} Furthermore, the quantification of reticulin and subsequently diagnosis of myelofibrosis are dependent on manual scoring by the haematopathologist rendering the precise estimation of the degree and frequency of fibrosis in PV problematic issue.⁸ At the time of diagnosis of PV, grade 1 or higher bone marrow reticulin fibrosis has been reported in several studies with a frequency of 20%–50%.^{9–11} Early fibrotic changes predict for a higher incidence of progression to overt myelofibrosis based on two series without a significant association with overall or leukaemia-free survival.¹² This has led to the recognition of prefibrotic/early PMF by the latest WHO classification in 2016 as a distinct entity based on bone marrow morphology and a worse clinical outcome with a higher propensity to evolve into myelofibrosis and acute leukaemia.^{13,14}

Myelofibrosis has the worst prognosis of the MPN disorders and is characterised by anaemia, hepatosplenomegaly and EMH. Evaluation of the bone marrow typically reveals increased reticulin staining and increased collagen. In the prefibrotic phase of the disease, bone marrow hypercellularity with granulocytic proliferation and decreased erythropoiesis is also seen on a bone marrow biopsy.^{2,4} Osteosclerosis and angiogenesis may also be seen. EMH is a common complication of PMF and is characterised by increased marrow production of haematopoietic progenitors. The pathogenesis of EMH remains poorly understood, however studies have pointed towards reactivation of stem cell niches, producing embryonic patterns of haematopoiesis.¹⁵ EMH commonly involves the liver, spleen, lymph nodes, para-vertebral regions and, less commonly, serosal surfaces. Ascites and pleural effusions secondary to EMH, although rare, have been more frequently reported in the literature, with pericardial involvement being a rare phenomenon.

Pericardial EMH without leukaemic involvement has been reported in several patients with MPN. In addition to the case presented above, a review of the literature reveals a total of eight patients with EMH involving the pericardium presenting with tamponade or pericardial effusion and an underlying PV, ET or PMF (table 1).^{16–23} PMF was thought to be the primary pathology in five patients with three of them having secondary myelofibrosis to either PV or ET; a *JAK2* mutation was detected in all three recently reported cases. Additionally, several similar

Table 1 Literature review of published cases of EMH involving the pericardium in patients with an underlying MPN

Year published (reference)	Age/gender	Diagnosis	EMH diagnosis	Splenomegaly	Outcome	Genetic analysis
Current report	71/M	Post-PV myelofibrosis	Pericardial fluid and biopsy	No	Alive at fourth month	JAK2 V617F
2016 (Mahadevan <i>et al</i>) ¹⁶	67/M	PMF	Autopsy/pericardium	Prior splenectomy	Death, 5 days	JAK2 V617F del (13q) in 9/20
2015 (Hofkens <i>et al</i>) ¹⁷	59/M	Post-PV myelofibrosis	Pericardial fluid and biopsy	Not reported	Follow-up not reported	JAK2 positive
2014 (Konca Degertekin <i>et al</i>) ¹⁸	56/F	Post-PV myelofibrosis	Pericardial fluid	Yes	Death, 1 month	JAK2 positive 46 XX t(1;8) in 6/20
1997 (Vilaseca <i>et al</i>) ¹⁹	67/M	PMF	Pericardial fluid and biopsy	Yes	Lost to follow-up	N/A
1985 (Bubley <i>et al</i>) ²⁰	57/M	PMF	Autopsy/pericardium	Not reported	Death	N/A
1983 (Imam and Doll) ²¹	32/M	PMF	Pericardial biopsy	Prior splenectomy	Pericardiocentesis, fenestration and radiotherapy	N/A
1977 (Averback and Moinuddin) ²²	58/F	Post-ET myelofibrosis	Pleural fluid	Yes	Death, pulmonary embolism	N/A
1985 (Haedersdal <i>et al</i>) ²³	52/M	PMF	Pericardial biopsy	Prior splenectomy	Not reported	N/A

EMH, extramedullary haematopoiesis; ET, essential thrombocythaemia; PMF, primary myelofibrosis; PV, polycythaemia vera.

presentations have been described in patients with chronic myelogenous leukaemia in chronic phase and in a case of chronic myelomonocytic leukaemia.^{24–28}

In conclusion, we herein discuss a case of JAK2 V617F mutated secondary myelofibrosis with extramedullary trilineage haematopoiesis presenting with pericardial tamponade. Observation of EMH in PV should raise the suspicion of fibrotic or leukaemic transformation. Further description and understanding of morphological and genetic features beyond the somatic aberrations in JAK2, CALR and MPL are needed to better characterise the diverse clinical outcomes within MPN.

Learning points

- Progression to myelofibrosis should be considered in patients with a history of polycythaemia vera.
- Extramedullary haematopoiesis (EMH) is a common complication of primary myelofibrosis and typically involves the spleen or the liver.
- EMH involving the pericardial cavity is rare and can lead to pericardial effusion and tamponade.
- Cardiac tamponade requires prompt recognition and urgent drainage of the pericardial fluid.
- The diagnosis of EMH can be made through the analysis of the pericardial fragments and pericardial fluid in patients with myeloproliferative neoplasm presenting with a pericardial effusion.

Contributors All authors: contributed to the writing and editing of this manuscript. VE: acquired the data and conducted the literature review. FH: planning, design, reporting and reporting final edits. AC: acquired, interpreted and reported the data. EL: involved in the planning, design and editing.

Competing interests None declared.

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