



Case Report

Case report and literature review: cardiac tamponade as a complication of pericardial extramedullary hematopoiesis ☆☆☆



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ABSTRACT

Pericardial effusion can cause cardiac tamponade physiology with resultant cardiogenic shock and death. Myelofibrosis, the replacement of marrow cavity by fibrous connective tissue, is a secondary complication of a group of disorders known as myeloproliferative neoplasms, which are clonal processes characterized by abnormal proliferative growth of one or more hematopoietic lineages. One consequence of myelofibrosis is the development of hematopoiesis at other anatomic sites, most commonly the spleen and liver, a phenomenon known as extramedullary hematopoiesis (EMH). Herein we report a case of a man who died from pericardial tamponade due to a subacute pericardial effusion secondary to EMH in the pericardium in the setting of myelofibrosis. This case highlights an unusual etiology for pericardial effusion and tamponade that should be considered in cases of myelofibrosis and stimulates a discussion regarding the mechanisms and anatomic distribution of EMH.

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1. Introduction

Pericardial effusions have several etiologies, including infection, post-acute myocardial infarction, uremia, idiopathic causes, and malignancy. Cardiac tamponade with resulting cardiogenic shock occurs when the pressure from an accumulating pericardial effusion equalizes with intracardiac pressures, leading to impaired filling of one ventricle or usually both ventricles. The reported frequency of a malignant etiology of pericardial effusion and tamponade varies between studies, but several large series indicate that 13–23% of medium-large (>10 mm echo-free pericardial space) pericardial effusions have a malignant cause [1,2]. Ben-Horin et al. found that malignancies accounted for a third of symptomatic pericardial effusions [3]. Metastatic lung tumors most commonly cause pericardial effusion; metastatic breast cancer and melanoma, as well as leukemia/lymphoma, are also known to involve the pericardial space.

Primary myelofibrosis (PMF) is a myeloproliferative neoplasm (MPN) characterized by an abnormal clonal proliferation of granulocytes and megakaryocytes within the bone marrow cavity, with resultant bone marrow fibrosis due to nonclonal fibroblast proliferation and hyperactivity induced by microenvironmental growth factors [4]. Myelofibrosis can also arise as a complication of other types of MPNs such as essential

thrombocytopenia or polycythemia vera. Through incompletely understood mechanisms, a frequent consequence of myelofibrosis within the marrow space is the displacement of hematopoiesis to other anatomic sites, known as extramedullary hematopoiesis (EMH). EMH occurs most frequently in the spleen and liver and can also be present in other tissues, including lymph nodes and paravertebral regions [5].

Herein we report a case of a man who died from pericardial tamponade arising from a subacute pericardial effusion secondary to EMH in the pericardium in the setting of myelofibrosis. We also review and summarize published cases of cardiac tamponade with underlying pericardial EMH, and we discuss pathogenic mechanisms of EMH.

2. Case description

The patient was a 67-year-old man with a past medical history significant for a perforated T3N0 mucinous colonic adenocarcinoma, low-grade, status-post resection and colostomy 2 years prior to his death. At the time of colon resection, he also underwent splenectomy due to incidentally found massive splenic enlargement (3162 g). Pathologic examination of the spleen revealed extensive EMH without an increase in blasts, prompting additional molecular testing that revealed the presence of a *JAK2* c.1849G>T (p.Val617Phe) mutation. A complete blood count revealed a markedly elevated white blood cell (WBC) count of 104.4 K/ μ l with left shift (70% neutrophils, 6% bands, 5% metamyelocytes, 2% myelocytes, 1% promyelocytes, 3% lymphocytes, 4% monocytes, 8% eosinophils, and 1% basophils), mild anemia with hematocrit of 33.6%, and a normal platelet count of 347 K/ μ l. In addition, nucleated red blood cells were present at 10 per 100 WBC. Based on this clinical scenario and molecular findings, a presumptive diagnosis

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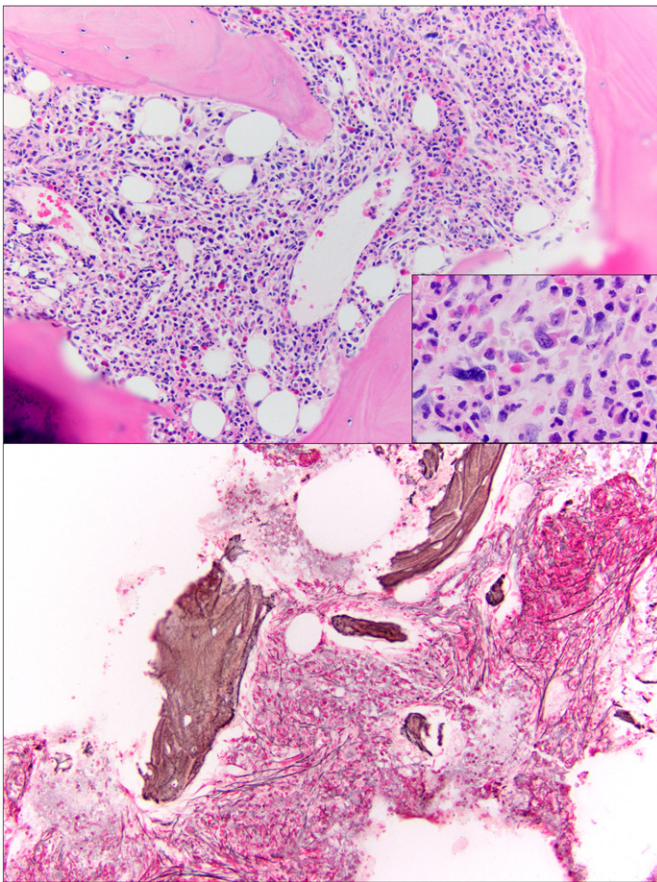


Fig. 1. Bone marrow biopsy demonstrating myelofibrosis. Top panel: The bone marrow biopsy is hypercellular for age showing myeloid predominance with full maturation and an increased number of eosinophilic forms. Megakaryocytes are hyperchromatic with atypical nuclear morphology (hematoxylin and eosin (HE), 200 \times and inset, 500 \times). Bottom panel: A reticulin stain highlights a moderate diffuse increase in reticulin fibrosis (reticulin, 200 \times).

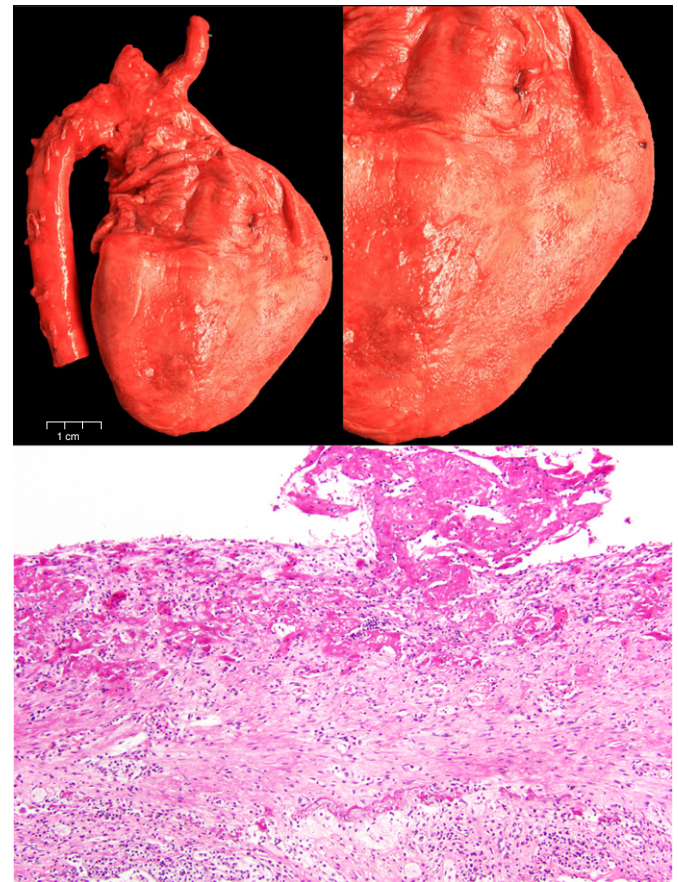


Fig. 2. Fibrinous pericarditis. Top panel: The epicardial surface of the heart macroscopically displays a shaggy exudate indicative of fibrinous pericarditis (area highlighted in right panel). Bottom panel: The epicardial surface displays fibrosis, fibrin deposition, and chronic inflammation consistent with fibrinous pericarditis (HE, 100 \times).

of MPN complicated by myelofibrosis was rendered, which was confirmed upon bone marrow biopsy that showed findings best classified as the fibrotic stage of PMF (Fig. 1). Cytogenetic analysis revealed that 9 of 20 metaphases demonstrated deletion of the long arm of chromosome 13, a finding that is nonspecific but indicative of clonal hematopoiesis. The patient was subsequently managed on hydroxyurea. The clinical course was complicated by chronic kidney disease (serum creatinine: 1.4–1.6 mg/dl) diagnosed 1 year status-post surgery as a sequela of anaplasmosis infection in the setting of chronic amoxicillin administration. His subsequent colostomy reversal was complicated by persistent colcutaneous fistula and *Clostridium difficile* colitis requiring hospitalization (admitted 20 days prior to death). He was discharged in stable condition after a course of oral antibiotics. At discharge, routine laboratory values were within normal limits except for an elevated WBC count of 19 K/ μ l, attributed to the underlying PMF. A chest X-ray showed a normally placed PICC catheter, unremarkable lung anatomy without pleural effusions or pneumothorax, and a normally sized heart.

Five days following hospital discharge, the patient was found lifeless at home, 2 h after last contact. Consent for an unrestricted autopsy was obtained from the decedent's daughter. At autopsy, 630 ml of serosanguinous fluid was found in the pericardial space, and the pericardium and epicardium displayed gross fibrinous pericarditis (Fig. 2, top panel). Cardiac examination revealed an enlarged heart weighing 650 g (typical male adult heart = 270–360 g) with no gross evidence of acute myocardial infarction, ventricular wall rupture, or coronary artery/great vessel dissection.

Microscopic examination of the epicardium demonstrated subacute fibrinous and fibrous pericarditis (Fig. 2, bottom panel). In addition, there was a hematopoietic cell infiltrate composed chiefly of maturing myeloid cells, involving approximately 80% of the ventricular epicardial surfaces (completely sampled circumferentially in one cross-section). Immunohistochemical staining confirmed the myeloperoxidase-expressing myeloid elements of the infiltrate (Fig. 3, top and bottom panels), consistent with EMH, in a background of chronic inflammation. While CD34 staining highlighted background vasculature, there was no evidence of increased numbers of CD34-positive blasts (data not shown). Sections of the liver also showed robust EMH (Fig. 3, bottom panel).

Sections of the myocardium showed interstitial and focal remote replacement fibrosis in the posterior left ventricle, indicative of prior remote ischemic myocyte injury associated with complex atherosclerosis with 70% chronic stenosis of the right coronary artery. There was minimal atherosclerotic involvement of the left anterior descending (20% luminal occlusion) and circumflex (10% luminal occlusion) coronary arteries. There was no microscopic evidence of acute plaque rupture or acute myocardial infarction.

3. Discussion

Common differential diagnoses of pericardial effusion include infection, metabolic disturbances, drugs/toxins, radiation, postmyocardial infarction, and malignancy — all conditions that were not present or clinically suspected in the reported case. Cardiac tamponade as a complication of pericardial EMH in the setting of myelofibrosis has been

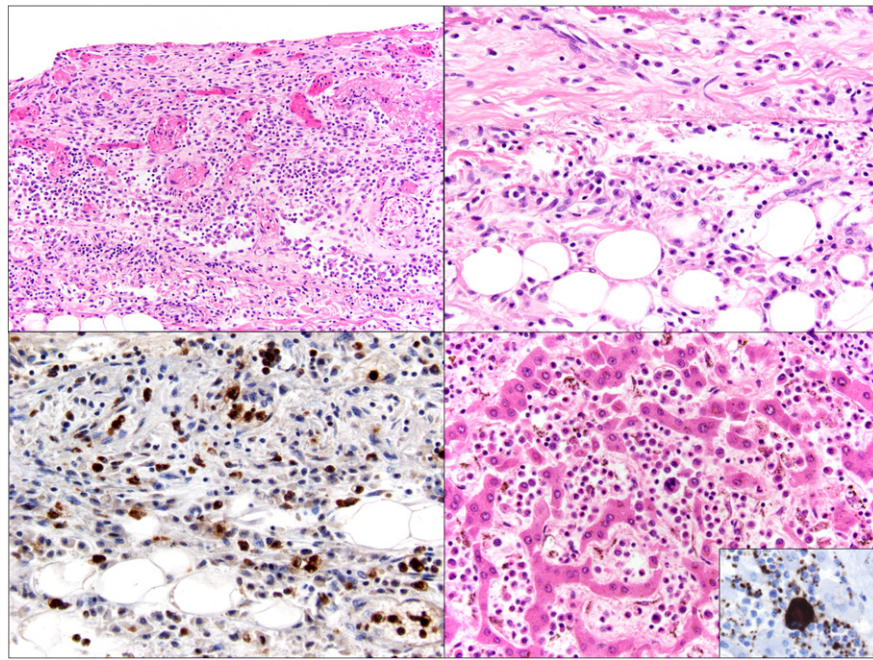


Fig. 3. EMH in pericardium and liver. Hematopoietic cell infiltrate in pericardial surface composed chiefly of maturing myeloid cells, as confirmed by immunohistochemistry for myeloperoxidase (top/bottom panels: upper left, HE, 200×; upper right, HE, 400×; lower left, MPO, 400×). Infiltration of liver sinusoids by maturing myeloid cells and occasional atypical megakaryocytes, as confirmed by immunohistochemistry for CD61 (bottom panel: lower right, HE, 400× and inset, CD61, 400×).

reported occasionally in the literature [6] (Table 1). Most cases have occurred in patients with PMF; although myelofibrosis in the setting of other MPNs, overlap myelodysplastic neoplasms/MPNs or secondary acute myeloid leukemia have also been described. In leukemic cases, no evidence of leukemic involvement of the pericardial fluid or pericardium was documented. In the most recently reported PMF case [2], a

pericardial effusion with clinical features of tamponade was found in a 59-year-old man presenting with exercise-induced dyspnea. A diagnostic and therapeutic pericardial fenestration was performed, yielding normoblasts suggesting EMH, which was confirmed by pericardial biopsy. Subsequent bone marrow biopsy revealed involvement by a *JAK2*-positive MPN with myelofibrosis. Other reports of cardiac tamponade

Table 1
Literature review: cardiac tamponade with underlying pericardial EMH

No.	Patient age/sex	Diagnosis	Presentation	Diagnosis of EMH	Tamponade treatment	Prior splenectomy?	Outcome	Reference
1	67/M	PMF	Death	Pericardial tissue	None	Yes	Death	Current report
2	59/M	Chronic MPN with myelofibrosis	Exercise-induced dyspnea	Pericardial biopsy and fluid cytology	Pericardial fenestration	No	Complete resolution	[6]
3	67/M	PMF	Dyspnea, malaise, and chest pain	Pericardial biopsy	Pericardial fenestration	No	Immediate improvement, lost to follow-up	[15]
4	52/M	PMF	Unknown	Pericardial biopsy	Pericardiocentesis/ pericardial fenestration	Yes	Unknown	[16]
5	57/M	PMF	Dyspnea, edema	Pericardial tissue	Pericardiocentesis/ pericardial fenestration	No	Death	[17]
6	32/M	PMF	Post splenectomy complication	Pericardial biopsy	Pericardiocentesis/ pericardial fenestration/ radiotherapy	Yes	Complete resolution	[18]
7	58/M	Atypical chronic myeloid leukemia with myelofibrosis	Systolic heart murmur and increasing oxygen requirement	Pericardial exudate cytology	Pericardial fenestration/ tomotherapy-based intensity-modulated radiation therapy	No	Decreased oxygen requirement, increase in functional status	[19]
8	16/F	Acute myeloid leukemia evolved from PMF	Exertional dyspnea	Pericardial fluid cytology	Pericardiocentesis/ radiotherapy	Yes	Partial resolution	[12]
9	60/M	Chronic myelomonocytic leukemia with increased reticulin fibrosis	Dyspnea	Pericardial fluid cytology	Pericardiocentesis	No	Complete resolution	[20]
10	65/M	MPN without documented myelofibrosis	Dyspnea, anorexia, fatigue, fever	Pericardial biopsy	Pericardial fenestration	No	Complete resolution	[21]
11	48/F	Chronic myelogenous leukemia	Unknown	Pericardial fluid cytology	Pericardiocentesis	Unknown	Complete resolution	[22]

with underlying pericardial EMH in the setting of myelofibrosis relate similar clinical presentations and treatment by pericardiocentesis or pericardial fenestration and, in one case, radiotherapy. Interestingly, two additional patients with myeloid neoplasms developed pericardial EMH and subsequent tamponade without documented marrow fibrosis [14–15] (Table 1). Overall, outcomes were varied ranging from complete resolution in a majority of cases to death in two cases.

The mechanisms underlying effusion in the setting of EMH have not been investigated, though it is possible that they involve increased vascular permeability due to the actions of vasoactive cytokines produced during EMH. For instance, it is known that to establish the vascular niche during EMH, macrophages (especially erythrophagocytic macrophages), fibroblasts, and activated lymphocytes secrete cytokines including IL-4, IL-6, VEG-F, and FGF-4 [7], known to increase vascular permeability in experimental models in vitro [8–11]. For instance, IL-4 influences the permeability of human vascular endothelial monolayers in vitro, increasing the passage of albumin in a dose-dependent fashion [9]. Similarly, IL-6 augments the permeability of bovine vascular endothelial cells, an effect that is abrogated by the addition of an anti-IL-6 antibody [10]. The impact of splenectomy on the development of EMH in the pericardial space in this case is uncertain. It is possible that there may be a compensatory increase of EMH at other anatomic sites in the absence of a spleen, which is a reported, though unpredictable and poorly understood, long-term complication of splenectomy [12]. However, it is notable that fewer than half of patients with cardiac tamponade and pericardial EMH in our review of the literature had prior splenectomy (Table 1). There may also be cell-extrinsic and cell-intrinsic contributions of *JAK2*-mutant bone marrow cells. Acute infection with *Anaplasma phagocytophilum* in a mouse model has been associated with a decrease in bone marrow granulocytic macrophage and erythroid colony forming units and compensatory increases in splenic myeloid and erythroid lineage formation [13]. However, zoonotic *Anaplasma* infection in humans has not been reported to be associated with EMH, including in the pericardium. Lastly, to our knowledge, EMH in the setting of colon adenocarcinoma has not been documented.

4. Conclusion

Herein, we report a case of subacute pericardial tamponade secondary to pericardial effusion due to pericardial EMH in the setting of PMF, ultimately resulting in death. Pericardial EMH in the setting of myelofibrosis is a rare but reported etiology of pericardial tamponade [6] should be considered in the appropriate clinical setting; treatment consists of symptomatic therapy with continued management of the underlying neoplastic process. The pathogenesis of pericardial hematopoiesis in the setting of myelofibrosis is likely similar to that being elucidated in other extramedullary sites and may involve active and passive release of hematopoietic precursors from diseased bone marrow [14]. In sum, pericardial EMH can be a source of lethal pericardial effusion even in the absence of frank malignant involvement of the pericardium.

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