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Case Report

Pericardial Extramedullary Hematopoiesis Associated with Metastatic Adenocarcinoma of Gastrointestinal or Pancreaticobiliary Origin: A Case Report

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Keywords
Extramedullary hematopoiesis · Pericardial fluid · Metastatic carcinoma

Abstract
Extramedullary hematopoiesis (EMH) is a rare complication of solid tumor malignancies. We describe the first case of a patient who developed EMH in the pericardium secondary to metastatic gastrointestinal or pancreaticobiliary cancer. A 58-year-old man presented with recurrent episodes of fatigue and shortness of breath and was treated with thoracocentesis and pericardiocentesis for pleural and pericardial effusions, respectively. Owing to a markedly elevated alkaline phosphatase, a bone scan was performed and demonstrated diffuse sclerotic lesions. Evaluation of pleural effusion diagnosed metastatic adenocarcinoma, and cytospin morphology of the pericardial fluid demonstrated EMH. While EMH secondary to solid tumors is commonly suggested to be due to cytokine signaling, we propose the mechanism of EMH in this patient was due to extensive disruption of bone marrow hematopoiesis, similar to what is seen in myeloproliferative neoplasms.

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Introduction

Extramedullary hematopoiesis (EMH) refers to the formation of blood cellular components outside of the bone marrow [1]. Physiologic EMH occurs in normal fetal development in the yolk sac followed by the liver and spleen [1–3] until the third trimester when the main site of hematopoiesis is the bone marrow and this persists into the remainder of adult life.

Pathologic EMH may be triggered by stress conditions such as infection or anemia [1, 2] but is most commonly observed in myeloproliferative neoplasms, such as myelofibrosis, polycythemia vera, and chronic myeloid leukemia [4]. In patients with myeloproliferative neoplasms, disrupted bone marrow hematopoiesis can trigger the release of hematopoietic stem cell/progenitor cells into the peripheral blood in a process called mobilization and homing to extramedullary sites [2]. Common sites of EMH include the spleen, liver, lymph nodes, and paravertebral regions [5, 6]. Less common tissues associated with EMH include the heart, fatty tissue, and adrenals. EMH occurs less commonly in cases of malignant solid tumors. When these cases are present, imaging techniques used for staging cancer may misdiagnose EMH as a site of metastasis [7]. We describe a rare case of EMH in the pericardium secondary to metastatic adenocarcinoma of gastrointestinal or pancreaticobiliary origin and review the literature on pericardial EMH arising in the context of malignancy.

Case Presentation

A 58-year-old gentleman presented with 6 weeks of worsening fatigue and dyspnea on exertion, as well as 36 h of new-onset cough with red-brown sputum. He had a history of testicular seminoma approximately 20 years prior, treated with orchiectomy and radiation, as well as severe esophagitis, celiac disease, hernia repair, and colonic polyps. Physical exam revealed significant bilateral wheezing and decreased breath sounds in the left lower lung zone but was otherwise unremarkable. Bedside point-of-care ultrasound revealed a pericardial effusion greater than 2 cm in depth surrounding the heart and a large left pleural effusion of over 5 cm. Sequence of events is provided in Table 1.

A complete blood count showed leukocytes 8.3 × 10^9 cells/L, hemoglobin 90 g/L, and platelets 278 × 10^9 cells/L. His electrolytes and renal function were within normal limits, but his alkaline phosphatase was markedly elevated at 2,592 U/L. Other liver enzymes were normal including gamma-glutamyl transferase, aspartate transaminase, alanine aminotransferase, and bilirubin. This led to a bone scan that revealed "multiple sclerotic metastatic lesions" (shown in Fig. 1). His CA19-9 was elevated at 377 U/mL, and his prostate specific antigen was within the normal range at 0.67 ng/mL. Serum protein electrophoresis and immunofixation did not detect any monoclonal protein. The patient underwent computed tomography imaging of the thorax, abdomen, and pelvis; colonoscopy; esophagogastroduodenoscopy; and ultrasound of his scrotum which did not identify a site of primary malignancy.

The patient underwent two thoracocenteses; the first at initial presentation which demonstrated borderline exudative fluid and another 10 days later which demonstrated transudative fluid. Fluid cytology found abundant reactive mesothelial cells and mildly atypical epithelioid cells. The atypical cells were positive for MOC31 and BerEP4 and negative for p40, calretinin, CK20, TTF-1, and NKX3.1. The immunoprofile was not conclusive.

Nine days later, he was admitted for worsening pericardial effusion with features of early tamponade requiring pericardiocentesis. The pericardial fluid cytology report was negative for malignancy; however, the cytospin morphology showed a hemorrhagic sample with a large number of erythroid precursors characteristic of EMH present (shown in Fig. 2). No nucleated

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Table 1. Timeline summarizing main events related to the case report

Time	Event
0 weeks	Routine blood test revealed elevated ALP 2,592 U/L
3 weeks	Presented with 36 h of new-onset cough and red-brown sputum Pleural effusion treated with thoracocentesis CT thorax demonstrated diffuse sclerotic osseous lesions concerning for metastatic disease, confirmed by bone scan
4 weeks	Presented with a 5-day history of shortness of breath upon exertion associated with orthopnea Pleural effusion managed with thoracocentesis
5 weeks	Bone marrow biopsy was performed demonstrating metastatic carcinoma cells
6 weeks	Admitted to cardiology for worsening pericardial effusion with features of early tamponade requiring pericardiocentesis Pericardial fluid cytospin morphology showed a hemorrhagic sample with a large of number erythroid precursors characteristic of EMH
10 weeks	Began palliative chemotherapy with capecitabine plus oxaliplatin
24 weeks	Patient passed away

ALP, alkaline phosphatase; CT, computed tomography.

RBCs were identified in the peripheral blood. A bone marrow biopsy demonstrated sclerotic trabecular bones and loose fibrous intervening stroma. Extremely few normal hematopoietic cells were noted as well as scattered aggregates of tumor cells showing signs of signet cell morphology. The neoplastic cells stained positive for CK-PAN and CK7 and negative for TTF-1, CDX-2, and CK20 (shown in Fig. 3). This along with another repeat thoracocentesis were consistent with adenocarcinoma, likely of gastrointestinal or pancreaticobiliary origin. Normally, a tumor of the pancreas has bone metastasis visible on computed tomography scan, which was surprisingly not identified in this case.

Discussion

This was a 58-year-old gentleman with metastatic adenocarcinoma, likely gastrointestinal or pancreaticobiliary origin, presenting with a very unique finding of EMH in his pericardium. We searched PubMed using the terms “extramedullary hematopoiesis,” “pericard*,” and “cancer” which returned 12 results. The results were all reports of EMH in myeloproliferative neoplasms, mainly chronic myeloid leukemia and polycythemia vera. However, none of these articles described EMH in the pericardium secondary to solid tumor malignancy. To our knowledge, this is the first report to describe this presentation.

EMH is a rare clinical finding for any malignant solid tumor. A 2018 literature review identified 42 patients with EMH and solid tumors [7]. The most common sites of EMH were lymph nodes, the liver, and kidneys. Additionally, the review described potential causes of EMH in these patients. First, administration of granulocyte colony-stimulating factor during chemotherapy, which stimulates mobilization of stem cells into the peripheral blood, can result in these cells homing to extramedullary sites. Second, secretions of cytokine or hematopoietic growth factors by tumors can initiate the same mechanism and result in EMH.

In our patient, however, we posit that extensive bone metastasis compromised the integrity of the bone marrow microenvironment and triggered EMH similar to what is seen in patients with myeloproliferative neoplasms. In these patients, EMH has been treated with hydroxyurea and blood transfusions to suppress hematopoiesis, thereby reducing EMH in the

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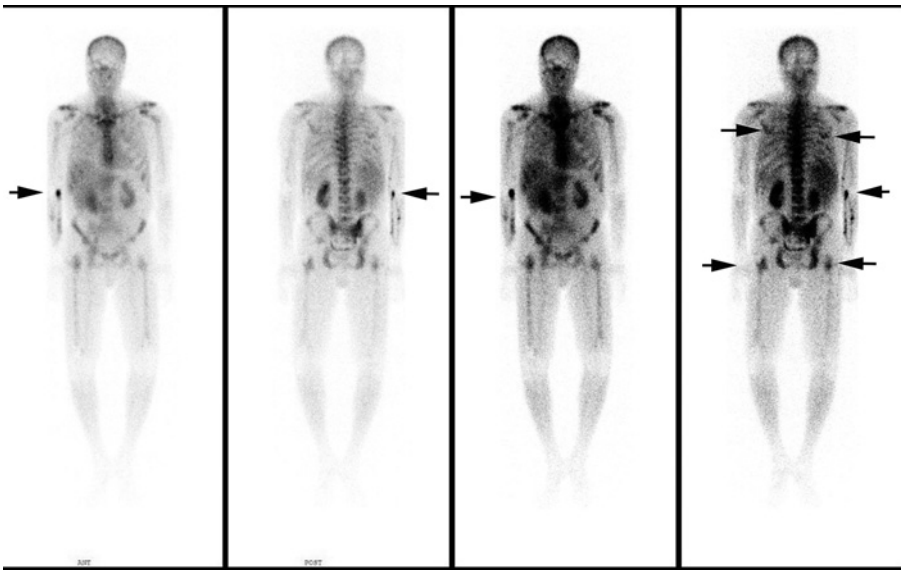

Fig. 1. Bone scan – panels showing anterior and posterior views demonstrating multiple foci of involvement. Arrows point to a select number of metastatic bone lesions.

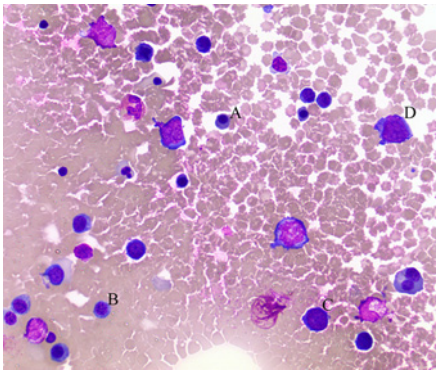

Fig. 2. Pericardial fluid on cytospin [Wright-Giemsa ×50] showed hemorrhagic fluid sample with erythropoiesis – erythroid precursors at various stages. A Orthochromic normoblast. B Polychromatic normoblast. C Basophilic normoblast. D Pronormoblast.

affected tissue [8]. In cases where EMH is a compensatory mechanism for disrupted hematopoiesis, replacing the diminished blood cellular components with transfusions reduces the need for EMH and, therefore, reduces EMH activity [9].

We suspected our patient to have an adenocarcinoma of gastrointestinal or pancreaticobiliary origin. Gastrointestinal cancer treatment is multimodal, involving a combination of radiation, chemotherapy, immunotherapy, and/or surgical resection. Immune checkpoint inhibitors (ICIs) are a novel advancement in immunotherapy. ICIs used for gastrointestinal cancers include nivolumab, pembrolizumab, and atezolizumab. Atezolizumab, an anti-PD-L1 monoclonal antibody, is approved for treatment of hepatocellular carcinoma and is undergoing clinical trials for gastric and pancreatic cancers [10]. To improve drug efficacy, novel steps in treatment personalization are being investigated, such as the potential to predict response to ICIs using characteristics like tumor mutational burden, microsatellite instability, and PD-L1 expression [11]. DNA damage repair pathway deficiency is another characteristic being investigated as a predictive biomarker of response to immunotherapy [12].

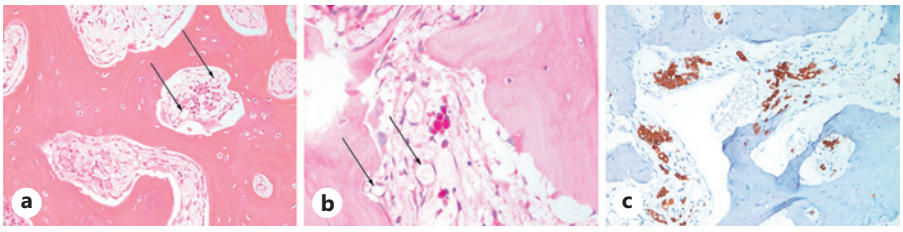

Fig. 3. Panel **a**: bone marrow biopsy [H&E ×20] showed aggregates of neoplastic cells having mostly signet cell appearance. Arrows point to a select number of signet ring cells. Panel **b**: bone marrow biopsy [PAS ×40] showed nuclei that were peripherally located and the cytoplasm was PAS [periodic acid Schiff] positive, indicating mucin production. Arrows point to a select number of signet ring cells. Panel **c**: bone marrow biopsy [Pan keratin ×20] showed neoplastic cells with strong staining for pan keratin marker, confirming the diagnosis of metastatic carcinoma.

The patient's management began with transfusion support, pleural catheter drainage for symptom management, and palliative chemotherapy. Specifically, the treating team chose to start capecitabine (and subsequently include oxaliplatin) immediately as molecular testing results were not yet available. This combination was felt to be a good first-line treatment for metastatic colorectal cancer [13] and provided a convenient regimen while awaiting further test results. No further pericardial drainage was required.

Fourteen weeks after chemotherapy treatment began, the patient passed away. He developed bilateral malignant pleural effusion, and his bony metastases had worsened. At the time of death, he was being treated with sorafenib and had completed five fractions of palliative radiation to his cervical spine. Despite this, he continued to decline clinically, had multiple electrolyte disturbances, and developed thrombocytopenia. The CARE Checklist has been completed by the authors for this case report, attached as supplementary material.

Conclusion

We describe the first case of EMH in the pericardium secondary to a metastatic adenocarcinoma. The pathophysiology in our patient differs from the mechanisms proposed in the literature (granulocyte colony-stimulating factor and cytokine signaling). Although a rare clinical complication of metastatic solid tumors, it is important that physicians consider this in their differential diagnosis in patients presenting with recurrent pericardial effusions.

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

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Author Contributions

Maud Ahmad reviewed the literature and drafted the manuscript. Cyrus C. Hsia, Benjamin Chin-Yee, Ian Chin-Yee, and Nikhil Sangle critically revised the manuscript. Kamilia Rizkalla performed pathological analysis and provided images. All the authors approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants. Further inquiries can be directed to the corresponding author.

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