

C A S E R E P O R T

A persistent cough as atypical clinical presentation of intrathoracic extramedullary hematopoiesis (EMH) in a female with thalassemia intermedia

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Summary. Extramedullary hematopoiesis (EMH) is a rare disorder, defined as the appearance of hematopoietic elements outside the bone marrow or peripheral blood. The most common sites of EMH are liver and spleen, but it has been documented in other organs such as the mediastinum, lymph nodes, breast, and central nervous system. EMH occurs as a compensatory mechanism for bone marrow dysfunction in severe thalassemia. We report a case of EMH presenting as a posterior mediastinal mass in a 34-year-old woman with thalassemia intermedia with chronic cough and shortness of breath on exertion. The diagnosis of EMH was confirmed by a CT-guided fine needle biopsy. All symptoms disappeared after surgical removal of the mass. (www.actabiomedica.it)

Key words: extramedullary hematopoiesis, thalassemia intermedia, differential diagnosis, treatment

Introduction

Cough is a nonspecific reaction to irritation anywhere from the pharynx to the lungs. Cough can be divided into acute self-limiting cough, lasting less than three weeks, or chronic persistent cough, which usually lasts for more than eight weeks. Cough lasting for an intermediate period of 3-8 weeks is called subacute cough. Most cases of troublesome cough reflect the presence of an aggravant (asthma, drugs, environmental, gastro-oesophageal reflux, upper airway pathology) in a susceptible individual. The most common causes of chronic cough, other than smoking in adults, are postnasal drip, asthma and gastro-oesophageal reflux disease (GORD). Chronic refractory cough also often

occurs after a viral infection (1). We report a case of extramedullary hematopoiesis (EMH) presenting as a posterior mediastinal mass in a 34-year-old woman with thalassemia intermedia (TI) with chronic cough and shortness of breath on exertion. The diagnosis of EMH was confirmed by a CT-guided fine needle biopsy. All symptoms disappeared after surgical removal of the mass.

Case presentation

A 34-year-old female with a history of BTI, persistent dry cough for 6 weeks duration, and breathlessness for the past 12 months. She was referred for

investigation to Hematology Section, National Center for Cancer Care and Research She denied fever, wheeze, haemoptysis, back pain or any other relevant complaints.

Physical examination revealed mild pallor, a brownish skin, a blood pressure of 130/80 mmHg, pulse rate of 76 beats per min, respiratory rate of 16 breaths per min and scars of previous splenectomy and cholecystectomy. She was occasionally transfused in the past years. Chest auscultation was negative.

On admission, her laboratory investigations showed haemoglobin=8 g/dL, white blood cell count: $5.7 \times 10^9/L$, platelet count: $676 \times 10^9/L$, mean corpuscular volume; 76 fl. The liver function test showed ALT: 32 U/L (normal 0-40), total bilirubin: 16 mmol/L (normal: 4-18), direct bilirubin: 1 mmol/L (normal: 0-4). Serum ferritin level was 6350 ng/mL (normal: 20-200).

The initial chest radiography showed a right hilar mass and an increased trabecular pattern (Figure 1). A magnetic resonance imaging (MRI) of the chest demonstrated a well circumscribed paravertebral thoracic mass, measuring 4.5x3.5x4.3, without adenopathy, or erosion of the vertebral bodies and the ribs (Figure 2).

A CT-guided needle biopsy of the right mass was performed. Histological findings (Figure 2 D) re-



Figure 1. Chest X-ray showing homogenous round opacity on right para hilum side

vealed three lineage hematopoietic cells with markedly increased erythroid precursors and scattered hemosiderin laden macrophages, consistent with extramedullary hematopoiesis (Figure 3). Flow cytometry analysis performed on the core biopsy confirmed involvement by EMH (Figure 4).

Because of severe iron overload and alloimmunization we started treatment with hydroxyurea (HU). However, the treatment with HU remained inefficient. A surgical excision of the largest mass was performed. Cough and breathlessness improved markedly after the operation.

Discussion

EMH is a rare entity that was first described by Guizetti during an autopsy in 1912 (2). Most cases present in adulthood and with a male predominance. Mediastinal extramedullary hematopoiesis in individuals as young as 7-year-old boy, known to have HbE- β thalassemia presenting with cough for one-week duration has been reported (3). These intrathoracic tumors often localize between the 6th and 12th thoracic vertebrae (4). They can present as unilateral, bilateral or as multiple masses in the paravertebral area, anterior mediastinum, pericardium and pleura (4-6).

It is mainly observed in combination with chronic anaemia resulting from conditions such as thalassaemia, sickle-cell anaemia or spherocytosis (7-9). It can also be associated with myeloproliferative syndromes (e.g. chronic myeloid leukaemia, osteomyelosclerosis or polycythaemia vera) and advanced stages of neoplasia with bone marrow infiltration or destruction.

The pathogenesis of this outside-bone marrow hematopoiesis is not clear. It may originate from extension of hyperplastic marrow through the thin cortex of ribs and vertebral bodies; the capsule of the mass is formed by the periosteum. Another explanation is that EMH results from transforming of embryonal rests of osteogenic tissue into hematopoietic one under stress conditions in order to maintain sufficient red cell production (10-12).

The differential diagnosis of an intrathoracic paravertebral tumour includes all kinds of soft tissue, neurological or pleural tumours or metastasising extra

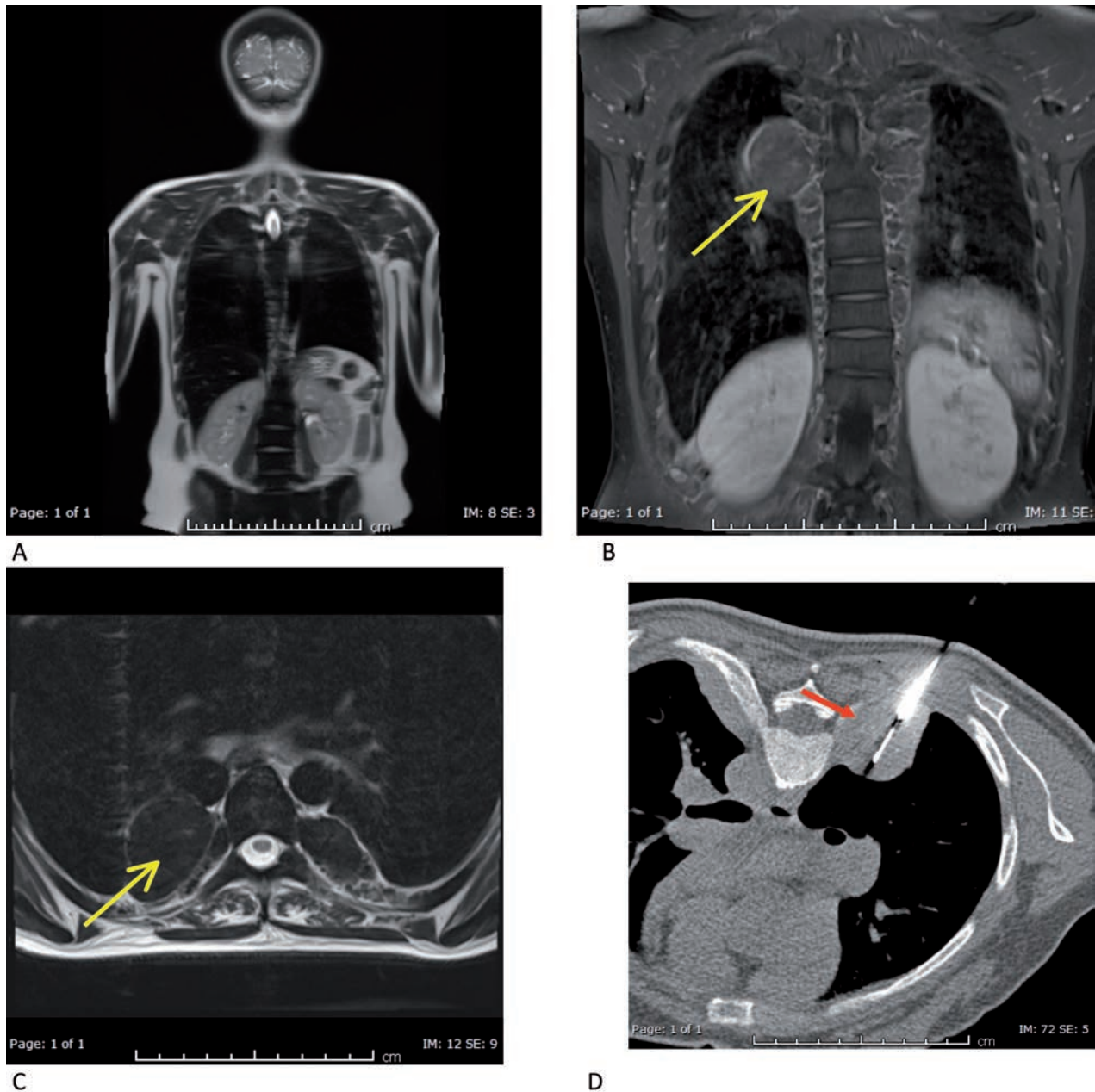


Figure 2. A) MRI Coronal haste localizer shows marked decrease T2 signal intensity of the liver and bone marrow due to iron overload and absent spleen. B) MRI Coronal post contrast fat saturated image shows right posterior paraspinal mass extending from T3-4-disc level to T6-7-disc level (yellow arrow) with no significant enhancement, measuring about 4.5x3.5x4.3 cm C) MRI Axial T2 image shows the right posterior paraspinal mass (yellow arrow) with decreased T2 SI of the mass and vertebral bone marrow D) Thoracic computed tomography (CT) guided needle biopsy of the right mass in the prone position with the needle inside (red arrow)

thoracic malignomas, with a special emphasis on (non-Hodgkin's) lymphomas (2, 4, 6, 8).

A number of non-invasive diagnostic procedures have been recommended to reach a diagnosis of

EMH. These include chest roentgenograms, contrast enhanced CT, magnetic resonance imaging and technetium-99m sulfur colloid radionuclide bone marrow scanning. While radiologic studies often demonstrate

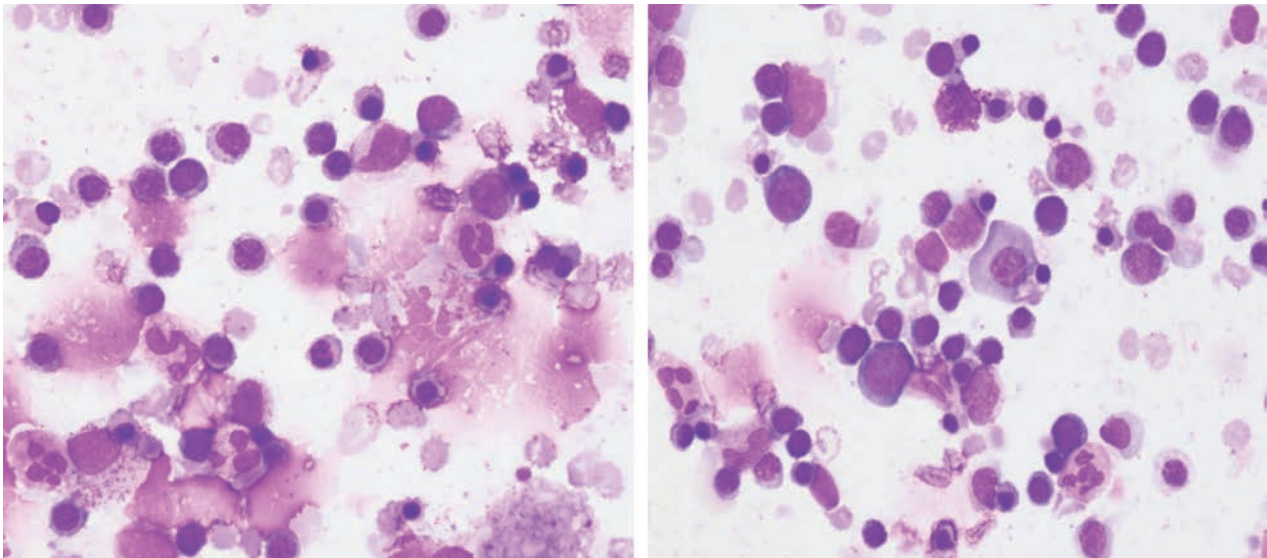


Figure 3. Haematoxylin and eosin-stained histological appearance of the paravertebral tumour showing numerous erythroid precursors, some granulocytic cells (at different stages of maturation), few lymphocytes and scattered histiocytes

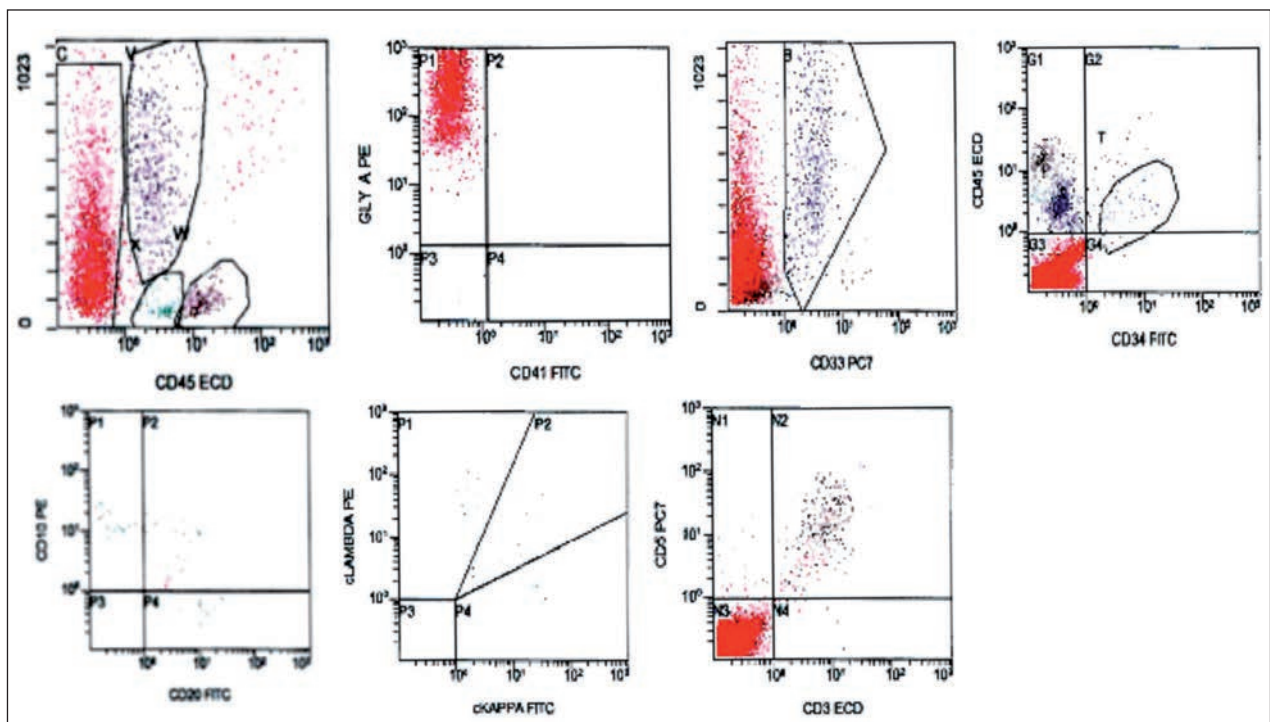


Figure 4. Flow cytometry on paraspinal mass shows a large population of erythroid precursors ~ 69% expressing glycoprotein (red colored population). Granulocytes comprise ~10%. There are less than 0.5% B-cells with no immunophenotypic evidence of monocytic B-cell population. CD3/CD5-positive T-cells comprise approximately 3%

findings suggesting intrathoracic extramedullary hematopoiesis, histology is usually required for diagnostic purposes.

There are no clear guidelines or consensus regarding the management of such cases, it is largely based on case reports and personal experience. Treatment

options include: surgery, radiotherapy, blood transfusions, hydroxyurea or a combination between them. Most of the cases reported presenting with spinal cord compression are treated either with surgical excision or radiotherapy. Surgery has the benefit of immediate relief of the compression and histological confirmation of the diagnosis, but has drawbacks including risk of bleeding and risk of recurrence (16). Radiotherapy is reported in conjunction with surgery, and reported as the sole treatment with good results, this is because hematopoietic tissue is sensitive for radiation, dose used is reported between 10-30 Gy (17). Hydroxyurea, is an inhibitor of ribonucleotide reductase and a well-tolerated cytostatic agent. It increases fetal hemoglobin synthesis and decrease the need for EMH. It is also reported as the sole treatment with good response (18).

Intrathoracic EMH is most often asymptomatic and treatment is usually unnecessary, except in the presence of complications (19, 20). Massive haemothorax (19, 21), symptomatic pleural effusion (22), and spinal cord compression (23) are complications of intrathoracic EMH.

Because in some cases radiation may be disadvantageous and worsen anemia due to the destruction of the sources of compensatory hematopoiesis and a high risk of recurrence, up to 19-37%, has been reported (25) as the main drawback of radiotherapy (26), we decided for the surgical removal after the presentation of pros and cons of treatment with the patient.

Video-assisted thoracic surgery carries the advantages of an open biopsy by direct visualization of the mass. In addition, any hemorrhage that results from the biopsy can be better controlled compared with the percutaneous approach. Furthermore, the lesion can be resected in the same operation with minimal trauma.

In conclusion, EMH should be considered in the differential diagnosis of an intrathoracic mass particularly, if a history of thalassemia or chronic anemia is discovered. Surgical resection and radiation therapy should be considered as treatment options for EMH.

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