Unusual association of diseases/symptoms

Pulmonary extramedullary haematopoiesis

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A 72-year-old Caucasian lady with myeloproliferative disorder was admitted for evaluation of progressive dyspnoea, weight loss, fatigue and mild hypoxia. A diffuse ground glass opacity was seen on CT pulmonary angiogram. Differential diagnoses included heart failure, infection, progression of myeloproliferative disorder with extramedullary haematopoiesis, thromboembolism or hydroxyurea-induced lung injury. Bronchoscopy and broncho-alveolar lavage were uninformative however lung biopsy with video-assisted thoracoscopy revealed extramedullary haematopoiesis within lung parenchyma. This is a very rare complication of myeloproliferative disorder and the authors discuss the significance of the case, review the literature and report the patient's progress.

BACKGROUND

Radiological abnormalities in patients with haematological malignancy can be the result of the underlying disease, a side effect of treatment or the result of immunosuppression and opportunistic infection. Myelofibrosis is a relatively common condition but pulmonary abnormalities are rare. We report a case where pulmonary infiltrates were due to extramedullary haematopoiesis and describe the diagnostic process. The case is interesting because of the rarity of this complication despite the fact that splenic and hepatic sites for haematopoiesis are relatively common.

CASE PRESENTATION

The subject, a 72-year-old retired Caucasian lady, was admitted with history of progressive dyspnoea for 8 months, associated with fatigue and weight loss.

Myeloproliferative disorder had been diagnosed 15 years before in the setting of polycythemia, thrombocytosis, raised lactate dehydrogenase and splenomegaly. It was confirmed with the presence of hypercellular bone marrow and JAK2 positivity. She had been treated with hydroxyurea for 8 years. A bone marrow aspirate 6 months before presentation showed unchanged myelofibrosis.

Six years previously polycythemia and thrombocytosis had led to an arterial thrombosis of her right lower leg and a below knee amputation. She also suffered from well-controlled type 2 diabetes mellitus, reflux oesophagitis and gout. She had ceased smoking 5 years previously with a ten-pack year history. Medications included metformin, hydroxyurea aspirin, rabeprazole and allopurinol.

Respiratory system examination showed fine diffuse bibasal crackles. There were no other cardiopulmonary abnormalities. There was massive splenomegaly extending up to the umbilicus but no hepatomegaly or ascites.

INVESTIGATIONS**Full blood count**

Haemoglobin	111 g/l (110–160)
Mean cell volume	88fl (80–100)
Reticulocytes	$226.0 \times 10^9/l$ (10–100)
White cell count	$22.2 \times 10^9/l$ (3.5–10.0)
Neutrophils	$19.3 \times 10^9/l$ (1.5–6.5)
Lymphocytes	$0.7 \times 10^9/l$ (0.8–4.0)
Monocytes	$1.1 \times 10^9/l$ (0.0–0.9)
Metamyelocytes	$0.44 \times 10^9/l$ (0.00–0.01)
Myelocytes	$0.22 \times 10^9/l$ (0.00–0.01)
Blasts	$0.44 \times 10^9/l$ (0.00–0.01)
Nucleated red cells	1.00/100 WBC (0.00–0.01)
Platelets	$308 \times 10^9/l$ (150–400)

Bone marrow aspirate*Myelogram*

- ▶ Blasts: 3.4%
- ▶ Lymphocytes: 5.4%
- ▶ Promyelocytes: 5.6%
- ▶ Monocytes: 3.2%
- ▶ Metamyelocytes and myelocytes: 15.8%
- ▶ Plasma cells: 0.4%
- ▶ Other cells: 0.0%
- ▶ Neutrophils: 45.4%
- ▶ Erythoblasts: 20.0%
- ▶ Eosinophils: 0.8%
- ▶ Myeloid/erythroid ratio: 3.4/1.0
- ▶ Cells counted: 600

Erythropoiesis is essentially within normal limits and shows normoblastic maturation. Granulopoiesis is mildly hyperplastic with a predominance of mature neutrophils. Lymphocytes are present in normal numbers and have normal morphology. Plasma cells appear normal.

Megakaryocytes appear mildly to moderately increased and include a number of large hyperlobulated forms. There are no fragments present for assessment of iron stores. No ringed sideroblasts are evident.

Bone marrow surface markers

Site: trephine

Three populations were analysed.

1. Lymphoid cells comprised 3% of the total.
T cells 87%; CD4:CD8 ratio 0.4; B cells 1%; Natural killer (NK) cells 3%.
There is no immunological evidence of lymphoid malignancy.
2. Myeloid cells comprised 84% of the total.
No abnormal phenotype is present.
3. CD34 positive cells comprised 1.6% (ref. range 2.0%) of the total.

Site: aspirate

Four populations were analysed.

1. Lymphoid cells comprised 1% of the total.
T cells 84%; CD4:CD8 ratio 0.5; B cells 1%; NK cells 7%.
No immunological evidence of lymphoid malignancy detected.
2. Strong positive CD38 positive cells (plasma cells) comprise <0.1% of the total.
Cytoplasmic immunoglobulin studies show no evidence of a monoclonal population.
3. Myeloid cells which comprised 88% of the total.
No abnormal phenotype detected.
4. CD34 positive cells comprised 2.1% (ref. range 2.0%) of the total.

Report on marrow trephine

Bone trabeculae appear normal.

Marrow cellularity is markedly increased (>90%) with disorganised architecture. Erythropoiesis is moderately reduced. Granulopoiesis is markedly increased with mild left shift. Blasts are not increased. Megakaryocytes are moderately increased with prominent clustering.

The majority are large hyperlobulated forms with nuclear atypia but there are a few smaller hypolobulated forms also. There is patchy fibrosis. Reticulin is markedly increased (grade 3).

Conclusion

Myelofibrosis arising from a preceding myeloproliferative neoplasm (JAK2 +). Respiratory function test revealed normal spirometry and lung volumes with moderate reduction in diffusion capacity.

CT chest showed diffuse ground glass opacity with mosaic hypoattenuation (figure 1).

Echocardiogram showed an elevated right ventricular systolic pressure at 50 mm Hg with normal right and left ventricular function.

Bronchoscopy and broncho-alveolar lavage did not reveal abnormal cytology and cultures of lavage fluid were sterile. Nucleic acid amplification did not suggest infection

Figure 1 CT chest – bilateral ground glass appearance at mid thoracic section.

with respiratory viruses, *Pneumocystis jirovecii* or other pathogens.

A video-assisted thoracoscopic lung biopsy was performed. Histopathology of the lung biopsy specimen showed atypical cellular infiltrates suggestive of myeloid origin. The immunohistochemistry stain for myeloid cells (myeloperoxidase and lysozyme) was highly positive suggestive of extramedullary haematopoiesis figures 2–4.

DIFFERENTIAL DIAGNOSIS

1. Thromboembolic disease
2. Opportunistic infection
3. Drug-induced lung disease from hydroxyurea
4. Cardiogenic/non-cardiogenic pulmonary oedema

5. Progression of myeloproliferative disorder/extramedullary haematopoiesis/leukaemic transformation
6. Vasculitis.

TREATMENT

- ▶ Interferon α 3 million units three times weekly
- ▶ Increasing dose of hydroxyurea.

OUTCOME AND FOLLOW-UP

Hospital admission was complicated by large bilateral extensive deep vein thrombosis. An inferior vena cava filter was placed and the patient anticoagulated with warfarin. To date despite vigorous treatment as above, clinical improvement has been minimal.

Figure 2 Histopathology of lung biopsy specimen – atypical cellular infiltrates showing features of myeloid origin.

Figure 3 Immunohistochemistry of lung biopsy specimen with lysozyme stain which picked up myeloid cells.

Figure 4 Immunohistochemistry of lung biopsy specimen with myeloperoxidase stain picked up myeloid cells.

DISCUSSION

Extramedullary haematopoiesis is a normal process in fetal life occurring predominantly in spleen and liver and in non-fetal life is a pathological compensation for abnormal bone marrow typically occurring in myelofibrosis with myeloid agnesis. It is also associated with thalassemia, polycythemia rubra vera, chronic myeloid leukaemia and myelodysplastic syndrome. Occasionally, tissues and organs other than the spleen and liver are involved, however, thoracic extramedullary haematopoiesis is very rare. It can present as pulmonary hypertension, haemothorax, pneumothorax or pleural effusion. Paraspinal masses, especially in the thoracic region, have been often described.¹ Presentation and progression are variable depending the underlying pathology and can vary from incidental findings to respiratory failure. Explanations for variation in phenotypic presentation of myelofibrosis have been attributed with variable dosage of JAK2 inheritance, acquired genetic defects.^{2 3}

Our patient progress was complicated by venous thrombosis, which is described in 10% of patients with myelofibrosis and is considered a poor prognostic sign.^{2 4} Ground glass appearance on CT chest as seen in our patient has been well described in case reports.^{5 6} Pulmonary hypertension as seen in our patient can result from a number of mechanisms, including pulmonary capillary obstruction, thrombotic events, interstitial pneumonitis and fibrosis, and alveolar airspace involvement, or from hematopoietic progenitor cell invasion of the pulmonary artery intima. Lung biopsy including transbronchial biopsy could be risky due to high risk of bleeding, depending on the degree of pulmonary hypertension and stability of the patient. Medical pleuroscopy has been described in establishing the diagnosis when patients present with pleural effusion.⁷ Much of the literature regarding extramedullary haematopoiesis is from articles in radiology, haematology and pulmonology.^{2 4-17}

Pulmonary interstitial extramedullary haematopoiesis is very uncommon and pose a diagnostic challenge and many diagnoses are made only at post mortem. We share here our experience with a similar complex case.

Learning points

- ▶ Extramedullary haematopoiesis is a pathological compensation of a long-standing bone marrow disease.
- ▶ Thoracic extramedullary haematopoiesis is a rare but a well-accepted progression of myeloproliferative disorder.
- ▶ Differential diagnoses include leukaemic transformation, heart failure, thromboembolism, infections and drug-induced lung injury.
- ▶ Diagnosis is difficult and early multi-specialty involvement is optimal.
- ▶ Imaging may assist but is usually non-diagnostic.

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Competing interests None.

Patient consent Obtained.

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