Non-infectious pulmonary complications of myelodysplastic syndromes and chronic myeloproliferative disorders

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Summary

\textit{Introduction}. — Non-infectious pulmonary complications of myelodysplastic syndromes and chronic myeloproliferative disorders are not rare but remain little known to respiratory physicians who may be confronted with various clinical pictures corresponding to different pathophysiological causes.

\textit{Background}. — The few data in the literature only relate to isolated cases or small series. The non-infectious pulmonary complications of myelodysplastic syndromes and chronic myeloproliferative disorders can be classified into several clinical entities: tumour syndrome, pulmonary fibrosis or diffuse infiltrating pneumonia, autoimmune reactions including vasculitis, Sweet syndrome, organizing pneumonia, pulmonary alveolar proteinosis, pleural effusion and pulmonary arterial hypertension. The diagnosis is provided by the histology and management of these complications depends on the underlying pathology.

\textit{Viewpoints and conclusion}. — Myelodysplastic syndromes and myeloproliferative disorders are entities which are becoming better characterized and understood. Better knowledge of the pathophysiological mechanisms involved in these complications should improve their diagnosis and their management, which still remains complex.

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Non-infectious pulmonary complications of myelodysplastic syndromes

Introduction

The frequency of pulmonary complications of haematological malignancies is very high and most of them are attributed to infectious causes. These are the best known. However, non-infectious complications are not rare, especially in myelodysplastic syndromes and chronic myeloproliferative disorders, and should be recognized by respiratory physicians. In this literature review, we will not deal with complications such as pulmonary oedema or drug toxicity — the subject of a future dedicated article. We concentrate on the more specific complications of these entities, on which few data are available in the literature, and only based on isolated observations or small series.

In practice, respiratory physicians are confronted with varying clinical pictures. The most often the patient, whether treated or not for a blood disorder, will present at a given time respiratory symptoms for which their opinion will be requested. Sometimes investigations are triggered by the discovery of abnormal pulmonary images in a patient treated for a blood disorder. Respiratory investigations can sometimes provide the diagnosis of an associated blood disorder. This article concerns myelodysplastic syndromes (MDS) and myeloproliferative syndromes (MPS).

Myelodysplastic and myeloproliferative syndromes are becoming better known

Myelodysplastic syndromes (MDS) and myeloproliferative syndromes (MPS) are clonal disorders of haematopoiesis constituting the preleukemic conditions. Classification of these disorders has recently changed to include new developments in cytogenetics.

Myelodysplastic syndromes

MDS is characterized by a bone marrow maturation disorder with proliferation of immature cells resulting in one or more cytopenias, and dysplasia involving the three haematopoietic lineages with normal bone marrow counts [1]. These syndromes can be primary, or secondary to treatment (chemotherapy, radiotherapy), to professional or environmental exposure to bone marrow toxic substances, or can complicate a congenital disease (trisomy 21, Fanconi syndrome, neurofibromatosis).

MDS occurs the most often after 50, with a mean age of onset of 65 [2]. Obtaining a bone marrow biopsy with karyotyping is an indispensable stage in diagnosis.

The World Health Organization classification (WHO 2002), based on the morphologic, cytotoxic and immunophenotypic features of neoplastic cells has recently refined the previous Franco-American-British Cooperative Group classifications (FAB 1982) [3]. The FAB criteria classified MDS in five categories: refractory anaemia, refractory anaemia with ringed sideroblasts, refractory anaemia with excess blasts, refractory anaemia with excess of blasts in transformation, and chronic myelomonocytic leukaemia (CMLL). In the current WHO classification, the blast threshold in blood or bone marrow for the diagnosis of acute myeloid leukaemia has been reduced from 30 to 20%, thus removing refractory anaemia with excess of blasts in transformation from the criteria defining MDS. This classification also recognizes 5q- syndrome. Furthermore, CMML is not longer considered to be a MDS, but is a new entity called myeloproliferative syndrome with myelodysplasia, along with atypical chronic myeloid leukaemia, juvenile myelomonocytic leukaemia and chronic idiopathic myelofibrosis [3] (Table 1).

The prognosis of MDS is variable considering the heterogeneous nature of these entities, with life expectancy varying from a few weeks to a few years. The complexity of the karyotype established at the time of diagnosis of MDS is a major prognostic factor [4]. The International Prognostic Scoring System (IPSS) refines the prognosis of these diseases into four categories: low risk, intermediate 1 risk, intermediate 2 risk, and high risk, depending on the percentage of marrow blasts, the karyotype abnormalities, and the number of cytopenias [1].

- Myelodysplastic syndromes are characterized by a disorder of bone marrow maturation and proliferation of immature cells.
- The WHO classification separates myelodysplastic syndromes into refractory anaemia, refractory anaemia with ringed sideroblasts, refractory anaemia with excess of blasts, and 5q- syndrome.
- The prognostic criteria distinguish different risk levels: low risk, intermediate 1 risk, intermediate 2 risk, and high risk, depending on the percentage of marrow blasts, the karyotype abnormalities, and the number of cytopenias.

Myeloproliferative syndromes

Myeloproliferative syndromes, now referred to as myeloproliferative neoplasms, are chronic heterogeneous disorders with in common the transformation of a haematopoietic stem cell by a molecular event providing a proliferative advantage to the clone without blocking maturation, with bone marrow hypercellularity, megakaryocyte hyperplasia and dysplasia, and spontaneous progress towards blast transformation [5]. The phenotypic diversity of these disorders is attributed to a spectrum of mutations affecting different protein kinases or related molecules. Succinctly, two predominant entities are currently recognized: chronic myeloid leukaemia (CML) defined by the presence of the BCR-ABL fusion protein, and myeloproliferative neoplasms with JAK2V617F mutation, found in most patients with polycythaemia vera (PV) and nearly 50% of the two major phenotypes of MPS apart from CML, essential thrombocytosis (ET) and myeloid metaplasia (MM) with myelofibrosis [6]. Other oncogenic events have been identified in the rarer MPSS; these involve tyrosine kinase receptors such as KIT mutations in mastocytosis (recently added to the list of MPSS), and PDGFRα, PDGFRβ, and FGFR1 for MPS with hypereosinophilia [7]. These entities have recently been defined in the WHO 2008 classification of myeloproliferative neoplasms [7] (Table 2). The identification of these abnormalities is particularly useful as these disorders are likely to respond to targeted therapies already vali-
### Table 1  WHO classification of myelodysplastic syndromes [3].

<table>
<thead>
<tr>
<th>Disease</th>
<th>Blood findings</th>
<th>Bone marrow findings</th>
</tr>
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<tbody>
<tr>
<td>Refractory anaemia</td>
<td>Anaemia, no or rare blasts</td>
<td>Erythroid dysplasia alone, &lt; 5% blasts, &lt; 15% ringed sideroblasts</td>
</tr>
<tr>
<td>Refractory anaemia with ringed sideroblasts</td>
<td>Anaemia, no blasts</td>
<td>Erythroid dysplasia alone, &lt; 5% blasts, ≥ 15% ringed sideroblasts</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia</td>
<td>Cytopenias (bicytopenia or pancytopenia), no or rare blasts, no Auer rods, &lt; 1 billion monocytes per liter</td>
<td>Dysplasia in ≥ 10% of cells in ≥ 2 myeloid cell lines, &lt; 5% blasts, no Auer rods, ≥ 15% ringed sideroblasts</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia and ringed sideroblasts</td>
<td>Cytopenias (bicytopenia or pancytopenia), no or rare blasts, no Auer rods, &lt; 1 billion monocytes per liter</td>
<td>Unilineage or multilineage dysplasia, 5–9% blasts, No Auer rods</td>
</tr>
<tr>
<td>Refractory anaemia with excess blasts, type 1</td>
<td>Cytopenias, &lt; 5% blasts, no Auer rods, &lt; 1 billion monocytes per liter</td>
<td>Unilineage or multilineage dysplasia, 10–19% blasts, occasional Auer rods</td>
</tr>
<tr>
<td>Refractory anaemia with excess blasts, type 2</td>
<td>Cytopenias, 5–19% blasts, occasional Auer rods, &lt; 1 billion monocytes per liter</td>
<td>Unilineage dysplasia in granulocytes or megakaryocytes, &lt; 5% blasts, no Auer rods</td>
</tr>
<tr>
<td>Myelodysplastic syndrome, unclassified</td>
<td>Cytopenias, no or rare blasts, no Auer rods</td>
<td>Normal-to-increased megakaryocytes with hypolobated nuclei, &lt; 5% blasts, no Auer rods, isolated del (5 q)</td>
</tr>
<tr>
<td>Myelodysplastic syndrome associated with isolated del (5 q)</td>
<td>Anaemia, &lt; 5% blasts, platelet count normal to increased</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2  WHO classification of chronic myeloproliferative syndromes [3].

- **Chronic myeloid (or myelogenous) leukaemia**
- **Chronic neutrophilic leukaemia**
- **Chronic eosinophilic leukaemia, not classified elsewhere**
- **Hypereosinophilic syndrome**
- **Polycythemia vera**
- **Chronic idiopathic myelofibrosis**
- **Mastocytosis (mast cell disease)**
- **Essential thrombocythemia**
- **Unclassifiable chronic myeloproliferative diseases**

*Non-infectious pulmonary complications of myeloproliferative syndromes and myelodysplastic syndromes*

Management of the pulmonary complications of these blood diseases can be complex; presentations vary because of the different pathophysiological causes. Rather than approach the subject according to haematologic disease, we have chosen to present these complications based on their clinical presentation in respiratory medicine (Table 3).

### Tumours

**Appearance of parenchymal or mediastinal tumour masses**

**Extramedullary haematopoiesis**

Tumour-like intrathoracic presentations indicating extramedullary haematopoiesis have been reported. Extramedullary haematopoiesis is described in some haematologic diseases occurring as a compensatory response to ineffective haematopoiesis. Intrathoracic
Table 3  Pathophysiological mechanisms according to clinical presentation.

<table>
<thead>
<tr>
<th>Radiographic and clinical presentation</th>
<th>Associated aetiology or disease</th>
<th>Useful diagnostic tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour</td>
<td>Extramedullary haematopoiesis</td>
<td>Tc-99m lung scan</td>
</tr>
<tr>
<td></td>
<td>Chloroma (granulocytic sarcoma)</td>
<td>CT scan</td>
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<tr>
<td></td>
<td></td>
<td>Fine needle aspiration biopsy, biopsy</td>
</tr>
<tr>
<td>Infiltrating pneumonia</td>
<td>Extramedullary haematopoiesis</td>
<td>Thoracic CT scan</td>
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<tr>
<td></td>
<td>Autoimmune paraneoplastic</td>
<td>Tc-99m lung scan</td>
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<tr>
<td></td>
<td>syndrome</td>
<td>Bronchoalveolar lavage</td>
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<td></td>
<td>Sweet syndrome</td>
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<td></td>
<td>Hypereosinophilic syndrome</td>
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<tr>
<td></td>
<td>Pulmonary alveolar proteinosis</td>
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</tr>
<tr>
<td></td>
<td>Organizing pneumonia</td>
<td></td>
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<tr>
<td>Pleural and pericardial effusion</td>
<td>Tumour infiltration</td>
<td>Pleural puncture</td>
</tr>
<tr>
<td></td>
<td>Extramedullary haematopoiesis</td>
<td>Biopsy</td>
</tr>
<tr>
<td></td>
<td>Chloroma (granulocytic sarcoma)</td>
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</tr>
<tr>
<td></td>
<td>Immune mechanisms</td>
<td></td>
</tr>
<tr>
<td>Pulmonary artery hypertension</td>
<td>Association with MPS</td>
<td>Echocardiogram</td>
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<tr>
<td></td>
<td></td>
<td>Cardiac catheterization</td>
</tr>
</tbody>
</table>

haematopoiesis was first reported by Giuzetti [8] in 1912 during an autopsy, then described in MPS, particularly in myeloid metaplasia where extramedullary haematopoiesis compensates the bone marrow failure due to myelofibrosis. Commonly described in the spleen, liver, and lymph nodes, extramedullary haematopoiesis can occur in the kidney, thymus gland, adrenal glands, peripheral nervous system, fatty tissue, cartilage, and epidural space [9]. Thoracic involvement remains rare, the most often presenting as tumours in the posterior inferior mediastinum in paraspinal position [10], but cases involving the epidural space have been described. They vary between 2 to 10 cm in diameter. They can be uni- or bilateral, presenting as asymmetric well-delimited non-pulsatile and non-calcified paravertebral masses; they are often initially mistaken for neurogenic tumours [11]. Tumours in the anterior mediastinum are far rarer [12]. Ask-Upmark made the first diagnosis in a “live patient” by fine needle aspiration biopsy [13]. Such needle aspiration biopsies remain dangerous because of the risk of haemorrhage [13]. Diagnoses have been obtained by laminectomy or thoracotomy.

These masses are usually asymptomatic and are revealed on the occasion of routine radiological examinations. The differential diagnoses include neurogenic tumour (unilateral and posterior mediastinum), lymphoma — mainly parahilar, and even aortic aneurysm [14]. Descriptions of presentations with bilateral pulmonary nodules (haematopoetic tissue masses) or pulmonary infarction secondary to vascular thrombosis within these masses have been very rare [15,16]. Imaging is useful in obtaining a positive diagnosis when extramedullary haematopoiesis is suspected: a CT scan, or Tc-99m bone marrow scintigraphy showing tracer accumulation in the bone marrow as well as less intense uptake in the pulmonary localization [17]. Proof of diagnosis is provided by histology showing the presence of haematopoietic progenitor cells in the erythroid, granulocyte and megakaryocyte lineages.

Airway obstruction is very rare and can result in tracheal compression [18] by a paratracheal or subglottic extramedullary haematopoietic tissue mass [19]. Presentation with noisy breathing due to the possible onset of respiratory distress was resolved in one case with an emergency tracheotomy. Treatment, in the case of threatening localization, can be low-dose external beam radiotherapy [18].

• Extramedullary haematopoiesis is a compensatory response to ineffective haematopoiesis.
• The masses are often discovered on routine imaging studies.
• The diagnosis is based on the CT scan, Tc-99m bone marrow scintigraphy and histology.

Chloromas
Chloromas or granulocytic sarcomas are solid extramedullary tumours composed of immature myeloid cells. Chloromas have been reported in patients with acute myeloid leukaemia, myeloproliferative syndromes including CML, polycythaemia vera, myelofibrosis and hypereosinophilic syndrome. Neiman reported a series of 61 cases including 24 patients presenting known myeloproliferative syndrome [20]. Chloromas can also complicate myelodysplastic syndromes (in particular RAEB and refractory anaemia with blast crisis) [20–22] and are considered to be a factor of poor prognosis for the blood disease. Chloromas can affect all anatomical territories [20] and have been described in the orbit, skin, kidney, uterus, brain, skull, etc.
Intrathoracic chloromas remain rare but 50 cases have been described in the literature. They are the most often mediastinal tumours visible as a mass on standard radiographs; involvement of the pleura, lungs, pericardium and hila is also possible [23]. In one patient, multinodular involvement associated with enlarged lymph nodes was revealed on the occasion of onset of cough, dyspnoea and deterioration in general health; the diagnosis was confirmed by transbronchial biopsy of a nodule [24]. Hilar masses can result in bronchial compression [25] (Fig. 1). One case of isolated involvement of the tracheobronchial tree causing subglottic stenosis has been described [26], as well as a right atrial mass detected on an echocardiogram for signs of cardiac tamponade [27]. Finally, in a child, a nodular form that rapidly progressed to infiltrating pneumonia has been reported [28].

Chloromas or granulocytic sarcomas are solid extramedullary tumours composed of immature myeloid cells.

- They are a factor of poor prognosis for the blood disease.

Pleural or pleuropericardial effusion

*Specific pleural effusion*

Cases of specific pleural effusion have been reported in myeloproliferative syndrome and, in particular, in CML [29,30]. The pleural fluid is often haemorrhagic, and rich in both mature and immature cells (granulocytes, monocytes and blast cells in varying proportions). The occurrence of effusion is a factor of poor prognosis, indicating progress to the blast transformation stage [30]. In CML with Philadelphia chromosome, the translocation can be found in the pleural fluid granulocytic cells. Specific pleurisy has been described in other PMSs such as myelofibrosis, chronic eosinophilic leukaemia, and polycythemia. The mechanism involved is infiltration of the pleura at a blast transformation stage of the myeloproliferative syndrome.

In CML, the incidence of pleural effusion revealing blast transformation has considerably decreased since the introduction of tyrosine kinase inhibitors (imatinib, dasatinib, nilotinib). However, the use of dasatinib is accompanied by a high incidence of pleural effusion, in those cases attributed to dasatinib-induced toxicity [31].

- Specific pleural effusion can complicate myeloproliferative syndromes.
- The pleural fluid is often haemorrhagic, and rich in both mature and immature cells.
- Pleural effusion is a factor of poor prognosis.

*Extramedullary haematopoiesis*

In CML, extramedullary haematopoiesis can cause pleurisy. This is a rare event. The most often, involvement is microscopic and asymptomatic; however, pleural involvement can be seen as true effusion that can progress to haemothorax

by spontaneous laceration of extramedullary haematopoietic tissue [32,33]. Chemical pleurodesis is currently not recommended, but low-dose radiotherapy (4.5 Gy) has been effective [34].

*Chloromas*

Chloromas have also very rarely caused pericardial or pleural effusion. Histology provides the diagnosis.
Non-infectious pulmonary complications of myelodysplastic syndromes

Appearance of diffuse infiltrating pneumonia

Extramedullary haematopoiesis

Some cases of interstitial involvement with pulmonary fibrosis attributed to extramedullary haematopoiesis have been described [17,35,36]. These were patients admitted for dyspnoea in the context of known or unknown myeloid metaplasia. The clinical examinations and investigations did not provide differentiation: bilateral crepitant rales, interstitial syndrome on the radiographs, which in one case, was suspicious of cardiology pulmonary oedema, and hypoxaemia confirmed by blood gas analysis. The definitive diagnosis was made by transbronchial biopsy. Fibrosis can also affect the pleura. Acute respiratory failure in the context of diffuse pulmonary fibrosis can be fatal [37]. The mechanism of fibroblast growth factor production promoting fibrogenesis in the lung has been suggested. A case presenting as ARDS has been described in a patient treated for CML in acceleration phase [37].

The diagnosis should be suggested in any patient with known MDS/MPS presenting dyspnoea with hypoxaemia. Again, imaging is very useful: CT scans show diffuse septal thickening; Tc-99m scintigraphy reveals tracer uptake, moderate in both lungs, and intense in bone marrow; finally, only a lung or transbronchial biopsy provides a definitive diagnosis showing perivascular fibrosis, and foci of erythroblasts, immature granulocytes and dysplastic megakaryocytes [17]. Treatment of the pulmonary involvement requires treatment of the blood disease causing the extramedullary haematopoiesis, which can then improve the respiratory symptoms. However, progression to fatal acute respiratory distress is possible.

Autoimmune manifestations

Autoimmune manifestations associated with MDS can be limited to serological abnormalities (antineuclear antibodies, frequently antineutrophil cytoplasmic antibodies), or can cause true clinical syndromes such as Raynaud syndrome, Sjögren syndrome, systemic lupus erythematosus, or polychondritis whose clinical presentation can include pleural effusion.

Autoimmune manifestations associated with myelodysplasia are known as “autoimmune paraneoplastic syndrome”. In a series of 221 patients treated for MDS reported by Enright, associated autoimmune disorders were diagnosed in 30 patients, i.e. 7.4% [38]. These autoimmune manifestations may well be more frequent. Saif et al. found an incidence of 10 to 13% in reported data [39]. This diagnosis has a real impact. It has been reported that the association of autoimmune manifestations with myelodysplasia can worsen the prognosis and can be a predictive factor of poorer survival. This autoimmune paraneoplastic syndrome has also been described in rare cases of CMLM. Myelodysplasia preceded the autoimmune manifestations in half the cases in Enright’s series, but can be simultaneous (7/30) or even appear secondarily [38]. Acute pulmonary parenchyma involvement is not isolated; it is accompanied by other autoimmune manifestations: fever, joint pain, peripheral oedema, rashes and so on, as well as pericardial involvement, pleural effusion, myositis, and gastric and colon ulcers. Half of the patients with diffuse infiltrating pulmonary parenchyma opacities developed fatal acute respiratory failure.

Diffuse infiltrating pulmonary involvement related to acute autoimmune vasculitis has been described in patients with MDS. The clinical presentation of this vasculitis is variable: polyneuropathy, glomerulonephritis, polyarthritis, pyoderma gangrenosum, etc. [40]. In these cases pulmonary involvement presents as pulmonary fibrosis.

These autoimmune manifestations usually respond to corticosteroid therapy, which enables differentiation of immune and tumour origins, particularly in pleurisy [41].

Diagnosis of these immune disorders is important as they worsen the prognosis of MDS; their management requires treatment of the myelodysplasia, including immunosuppressants, chemotherapy, and immunotherapy.

Sweet syndrome

Sweet syndrome can be accompanied by diffuse pulmonary infiltrates. Acute neutrophilic dermatosis, or Sweet syndrome, was described by Robert Douglas Sweet in 1964 [42]. The disease is characterized by skin lesions with red or purple papules, usually on the upper limbs, head and neck. These lesions correspond to neutrophilic infiltration of the superficial dermis and respond rapidly to corticosteroid therapy. Extracutaneous manifestations are possible with fever, peripheral neutrophilia, kidney, liver, joint, muscle, eye, and pulmonary involvement. Sweet syndrome is associated with a malignant disease in 10 to 20% of cases, the most often a haematological malignancy. In a series of 79 patients with Sweet syndrome, Cohen reported 9% with MDS and 7% with CML in chronic or acceleration phase for 85% of the associated blood diseases [43].

Pulmonary involvement in Sweet syndrome is characterized by the appearance of infiltrates visible on the chest radiographs. Lung biopsies show neutrophilic infiltration comparable with that found in the dermis. Clinical progress of pulmonary involvement parallels that of the skin condition and is sensitive to corticosteroid therapy.

Hypereosinophilic syndrome

In addition to “neutrophilic” infiltration, pulmonary manifestations with hypereosinophilia have been described in MDS and MPS. Matsushima et al. [41] have reported a case of diffuse interstitial lung involvement, predominant in the bases, in a patient presenting authentic Sweet syndrome diagnosed with skin biopsies, and myelodysplasia with der(1q;7p) chromosomal abnormality. This patient presented bone marrow hypereosinophilia. Matsushima reported three cases of patients presenting this type of MDS with the same chromosomal abnormality, bone marrow hypereosinophilia and pulmonary involvement. One patient presented opacities in the right upper lobe and left lower lobe with bilateral pleurisy in the context of bone marrow and peripheral hypereosinophilia, for which the diagnosis of eosinophilic pneumonia was retained. Another patient presented bilateral pleural effusion with pericardial effusion and ascites (chapter on pulmonary infl-
treatment), for which the diagnosis of autoimmune vasculitis was retained. The incidence of der(1q;7p) chromosomal abnormality is 2% in MDS. An associated immune origin may be involved in the onset of complications, with anticipated response to corticosteroid therapy but poor prognosis with progress to acute worsening. Few cases have been published to date. Kuroda has also reported a clinical picture with eosinophilic pulmonary infiltration confirmed by autopsy, associated with MDS with chromosomal abnormalities ([47,XY,+1] der[1;7][q10;p10] and trisomy 8 syndrome) and clonal eosinophilia [44]. These publications indicate the importance of looking for an underlying blood disease when hypereosinophilia is associated with pulmonary infiltrates.

In addition to these specific presentations, pulmonary manifestations of hypereosinophilic syndrome are generally superimposable on those described in chronic idiopathic eosinophilic pneumonia [45].

### Pulmonary alveolar proteinosis

The association between pulmonary alveolar proteinosis (PAP) and haematological malignancies is well known, though rare. Described by Rosen et al. in 1958, PAP is characterized by the accumulation of surfactant-associated phospholipoproteinaceous material in the alveoli and terminal bronchioles [46]. The clinical picture is that of chronic diffuse infiltrating pneumonia. Among the causes found for secondary PAP, haematological malignancies are predominant, with MDS [47,48] and CML being the most frequently encountered [49–51]. Shoji et al. have reported a series of 103 autopsies of patients with blood diseases of which six presented PAP: the disease was myelodysplasia in four cases, acute myeloid leukaemia due to acute worsening of myelodysplasia in another case, and acute lymphoblastic leukaemia in the last case, but with Philadelphia chromosome [52]. In 20 of the 69 cases of PAP also reported by Shoji, the diagnosis of CML was made, and that of myelodysplasia in seven cases. Their frequency in patients presenting PAP requires systematic investigation of these blood diseases.

PAP in blood diseases is not specific and the diagnosis is obtained by bronchoscopy with bronchoalveolar lavage withdrawing fluid with a characteristic milky appearance. In blood diseases with PAP, the role of GM-CSF antibody level was low while levels for these antibodies are rather high in acquired PAP [53]. The mechanism could possibly be a reduction in the number of alveolar macrophages or a functional defect probably due to impaired macrophage maturation associated with MDS [54].

### Organizing pneumonia

In organizing pneumonia (formerly bronchiolitis obliterans organizing pneumonia [BOOP] in English-speaking countries), histology shows filling of the distal air spaces with granulation tissue composed of inflammatory cells, fibroblasts and collagen. Organizing pneumonia (OP) is characterized by non-specific inflammation associated with alveolar opacities on the radiographs that are low density, migratory, recurrent and highly sensitive to corticosteroids. Localized forms and presentations with diffuse interstitial pneumonia similar to fibrosis have also been reported [55].

OP has been described in patients presenting blood diseases, the most often due to infection, or related to chemotherapy or radiotherapy. The blood disease itself has more recently been implicated as a risk factor in the onset of OP in these patients. OP is a rare disorder with an estimated incidence of 34/100,000 in patients with a haematological malignancy.

The clinical and radiological presentation, and its response to corticosteroids, does not differentiate it from other organizing pneumonias. A Mayo Clinic study reported by Daniels found 11 cases of OP in 17,808 patients with a haematological malignancy; for six of them, no cause other than the blood disease could be found [56]. For one of the 11 patients presenting OP, the blood disease was myelodysplasia. This patient developed acute leukaemia 5 months later. When the clinical presentation is not specific, the diagnosis is made with lung or transbronchial biopsies. Other cases of OP in patients with MDS have been reported [57,58], with improvement of OP without corticosteroid therapy in a series of three cases, which questions the precise role of corticosteroids. OP associated with myeloproliferative syndrome seems to exist but is apparently rarer.

Diffuse infiltrating lung disease remains the most difficult diagnosis to make raising the problem of performing lung biopsies. Obtaining a specific diagnosis is useful in patients with haematological malignancies in terms of increased survival [59]. White also suggests that the presence of focal masses, nodules, and localized infiltrates, rather than diffuse infiltrates, indicates specific involvement. Dai et al. have shown that open lung biopsies can be performed in patients with blood diseases and can be useful in adjusting treatment [60].

- Diffuse infiltrating pneumonia can indicate extramedullary haematopoesis, autoimmune manifestations (autoimmune paraneoplastic syndrome), Sweet syndrome, hypereosinophilic syndrome, pulmonary alveolar proteinosis, and organizing pneumonia.

### Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is defined as a sustained elevation in pulmonary artery pressure of over 25 mmHg at rest or 30 mmHg with exercise, with pulmonary capillary wedge pressure and left ventricular end-diastolic pressure of over 15 mmHg [61]. In 2001, Dingli et al. reported pulmonary arterial hypertension in patients with chronic haematological malignancies associated with thrombocytosis [62]. Of the 26 patients with MDS or MPS associated with PAH of unknown cause, 12 presented myeloid metaplasia (MM), five essential thrombocythemia (ET), six polycythemia vera, one chronic myeloid leukaemia, and two myelodysplastic syndrome. Fourteen had high platelet counts exceeding 600,000.

Since this review, pulmonary arterial hypertension has become a common finding in MPS. In 2004, a prospective
study of 24 patients with chronic MPS found that 10 of the 24 patients, i.e. 41.7%, presented associated PAH. Half of the PAH cases were asymptomatic with the diagnosis requiring at the least a transthoracic echocardiogram [63].

The association of PAH with MPS is multifactorial in origin [64] related to the various characteristics of MPS: splenectomy, portal hypertension, chemotherapy, infiltration of the lungs by haematopoietic cells or extramedullary haematopoiesis, factors causing thrombocytosis, and also pulmonary artery thrombosis due to thrombocytosis and erythroblastosis. A correlation has been found between platelet count and severity of PAH. Obstruction of the pulmonary artery by megakaryocytes has been documented in two cases, suggesting a role of platelet lineage in the pathogenesis of PAH. PDGF and TGF-β could possibly play an important role. The onset of PAH in patients with a chronic haematological malignancy remains a factor of very poor prognosis because, once it develops, PAH follows an independent course even if treatment of the initial blood disease has provided an improvement. In these cases, median survival after the diagnosis of PAH is 18 months. Schermuly et al. reported that imatinib reversed vascular remodelling in animal models of chronic MPS with PAH [65]. A pilot study in humans is currently in progress. More recently, Guilpain et al. [66] reported a series of 10 patients with “pulmonary hypertension” associated with MPS (eight PV and two ET). The diagnosis was confirmed with cardiac catheterization, ventilation/perfusion lung scan, and pulmonary angiography. Six patients had thromboembolic pulmonary hypertension with concomitant diagnosis of MPS; the four other patients had PAH without other risk factors for MPS. PAH associated with MPS occurred later with a median of 162 months after the diagnosis of MPS. However, haemodynamic data do not enable differentiation of the two conditions.

Although the mechanisms are not perfectly understood, myelofibrosis, chronic MPS and PAH seem to have in common mediators involved in their pathogenesis. Clinically, there is no difference between primary and secondary PAH.

Considering the reported data, PAH should be sought whenever dyspnoea occurs in a patient with a chronic blood disease, and particularly with myeloproliferative syndrome (Fig. 2).

**KEY POINTS**
- Pulmonary arterial hypertension is a common complication of myeloproliferative neoplasia.
- The causes of pulmonary arterial hypertension in myeloproliferative syndromes can be multiple: splenectomy, portal hypertension, chemotherapy, extramedullary haematopoiesis, thrombocytosis, pulmonary artery thrombosis due to thrombocytosis and erythroblastosis.
- Pulmonary arterial hypertension is a factor of poor prognosis.

**Conclusion**

Leaving aside infectious complications, the pulmonary manifestations that can arise in patients with MDS and MPS are varied and involve multiple mechanisms, which make their management complex. Pleural effusion is certainly the most common sign. Other manifestations remain rare. A better understanding of these complex situations should enable better management of these patients.

**Disclosure of interest**

The authors declare that they have no conflicts of interest concerning this article.

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