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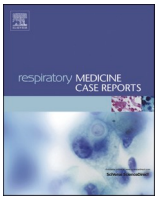

Case Report

Unusual cause of dyspnea in patient with Myelofibrosis: The Ruxolitinib lung

Antoine El Kik [a,*], Maarten Vander Kuylen [b], Benjamin Bailly [c], Jennifer Fallas [d], Benjamin Bondue [a]

[a] Department of Pneumology, Hôpital Universitaire de Bruxelles, Université Libre de Bruxelles, Brussels, Belgium
[b] Department of Thoracic Surgery, Hôpital Universitaire de Bruxelles, Université Libre de Bruxelles, Brussels, Belgium
[c] Department of Hematology, Hôpital de La Louvière – Site Jolimont, Haine-Saint-Paul, Belgium
[d] Department of Pathology, Hôpital Universitaire de Bruxelles, Université Libre de Bruxelles, Brussels, Belgium

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ABSTRACT

Although pulmonary complications are frequent in patients suffering from hematological diseases, secondary pulmonary alveolar proteinosis is a very rare complication of myelofibrosis. We describe the case of a 65-year-old male patient treated by Ruxolitinib for myelofibrosis who developed a secondary pulmonary alveolar proteinosis complicated by a *Mycobacterium avium* infection. We believe that this respiratory complication might be related to the myelofibrosis and to the initiation of the Ruxolitinib according to its temporal relationship. Pulmonologists should be aware that respiratory symptoms in myelofibrosis patients taking Ruxolitinib may be related to pulmonary alveolar proteinosis.

1. Introduction

Pulmonary complications are frequent in patients suffering from hematological diseases including myelofibrosis. Although infectious causes are common, noninfectious complications are possible as thromboembolic disease, pulmonary hypertension, and thoracic extramedullary hematopoiesis. Among these, secondary pulmonary alveolar proteinosis (PAP) is a very rare complication of myelofibrosis. We describe the case of a 65-year-old male patient treated by Ruxolitinib for myelofibrosis who developed a secondary PAP complicated by a *Mycobacterium avium* infection. We believe that this respiratory complication might be related to the myelofibrosis and the initiation of the Ruxolitinib according to its temporal relationship. As this association was rarely suggested in the literature and not currently described in Pneumotox, the worldwide drug-induced database, we believe that this case report is of interest for both pulmonologists and hematologists.

2. Case presentation

In our case, the patient was diagnosed with myelofibrosis (Normal karyotype; IDH1+; SRSF2+; ASXL1+; CALR+) in June 2021 with a high-risk disease (MIPPS70+: 5) and a splenomegaly. The patient was a candidate for allograft stem cell transplantation but had no good donor. After initially being treated with Hydroxyurea, the patient started a treatment with Ruxolitinib in October 2021 at the dose of 15 mg twice a day, then increased to 20 mg twice a day after a month.

In March 2022, the patient presented a progressive worsening dyspnea at exertion, without any fever. In July 2022, the dose of

* Corresponding author.
E-mail address: drantoinekik@hotmail.com (A. El Kik).

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Ruxolitinib was increased to 25 mg twice a day. A chest CT scan showed increased ground-glass opacities together with condensations in August 2022. A bronchoscopic lung cryobiopsy was compatible with a hypersensitivity pneumonitis at that time. Methylprednisolone was introduced at the posology of 1 mg/kg daily. However, the dyspnea did not improve. Between August and December 2022, the patient was treated four times for pneumonia with various antibiotics without any improvement.

In February 2023, the dyspnea worsened. There were no other respiratory symptoms nor fever. The patient was referred to our hospital with an oxygen requirement of FiO_2 27 % at rest. The arterial blood gas analysis at admission showed hypocapnia (29 mmHg) with a high alveolar to arterial oxygen gradient (80 mmHg). Laboratory data showed an increased level of CRP (31 mg/L), lactate dehydrogenase (2036 U/L), white blood cell count (30690 cells/mm^3) and a decreased level of hemoglobin (7.2 g/dL). The patient had a restrictive syndrome on pulmonary function tests (VEMS/CVF: 82.66 %; CVF z-score: −3,80; CPT z-score: −3.41) with a decreased diffusing capacity for carbon monoxide (DLCO z-score: −0.89). The chest CT scan showed a crazy paving pattern predominant in the upper lobes (Fig. 1). The bronchoscopy revealed a 'milky' bronchoalveolar lavage (BAL) fluid. The total cell number in the BAL fluid was 5538 cells/mm^3, with 80 % neutrophils, 11 % macrophages and 8 % lymphocytes. The histopathological examination of the BAL fluid and transbronchial biopsies revealed intra-alveolar PAS-positive acellular eosinophilic material (Fig. 1). The alveolar architecture was preserved without any significant inflammatory infiltrates or signs of fibrosis.

The diagnosis of secondary PAP was done and a gradual withdrawal of Ruxolitinib and Methylprednisolone was achieved. The patient was negative for serum anti-granulocyte-macrophage colony-stimulating factor (GM-CSF) antibody and for GATA2 mutation. Of note, the BAL fluid revealed a *Mycobacterium avium* after 16 days of culture. No others germs were found in the extensive microbiological cultures or at the histological examination. The pathogenic role of the *Mycobacterium avium* was questioned in the absence of typical lesions at the chest CT scan and the decision was made not to treat it.

A first whole lung lavage (WLL) of the left lung was done in march 2023. At that time, the oxygen requirement of the patient gradually increased to FiO_2 50 % (Fig. 2) and the inflammatory markers level were higher (CRP: 230 mg/L). Other WLL were subsequently performed on the right lung beginning of April and then in May (day 52 and 73 after admission respectively). After the three WLLs, the oxygen requirement of the patient improved to FiO_2 27 % with an alveolar to arterial oxygen gradient of 48 mmHg (Fig. 2).

A *Mycobacterium avium* was found again in the culture of the first WLL. A follow-up chest CT scan done after the WLLs (day 81) showed new bilateral pulmonary cystic lesions in the upper lobes and in the left lower lobe (Fig. 1). Based on these new findings, a treatment by inhaled GM-CSF (300 mcg daily) was started as an alternative to WLL (day 86), and the patient began a quadruple-drug therapy with Amikacin (1 g three times per week), Rifampicin (600 mg daily), Azithromycin (500 mg daily) and Ethambutol (1600 mg daily). Amikacin was then stopped after two months because the antibiogram showed a resistance.

Serial follow-up chest CT scans showed a favorable evolution of the crazy paving pattern of the PAP but an increase in size of the cystic lesions (Fig. 1). By the end of June 2023, the oxygen requirement of the patient progressively increased to FiO_2 33 % (Fig. 2) with an alveolar to arterial oxygen gradient of 95 mmHg. A second BAL was judged too risky to perform because of the oxygen needs and the poor general condition of the patient. Indeed, the patient had lost more than 15 kg during the six months of hospitalization despite a close dietary monitoring and the introduction of an enteral nutrition. No signs of an acute leukemic transformation were detected. A marked asthenia and amyotrophy was also present and a request for euthanasia was made by the patient and approved by our medical department according to the general condition and the absence of possible treatment of the underlying hematological condition.

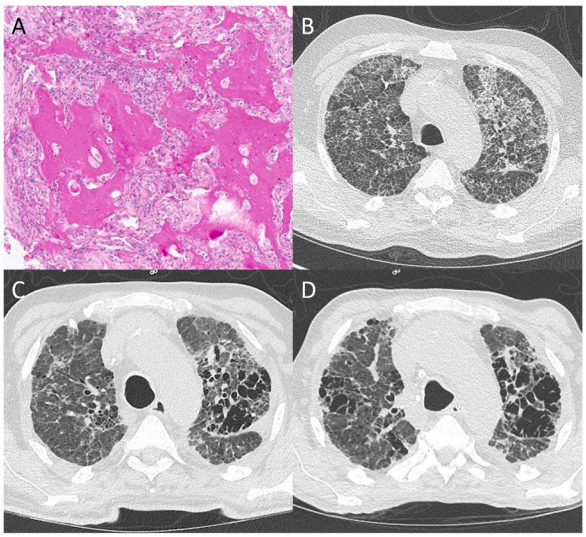

Fig. 1. A- Histopathological examination of the transbronchial biopsies (Periodic Acid Schiff staining at x 200 magnification); B- Chest CT scan at admission; C- Chest CT scan after the three whole lung lavages (three months after admission; day 81); D- Chest CT scan after two months of quadruple treatment for MA (five months after admission; day 134).

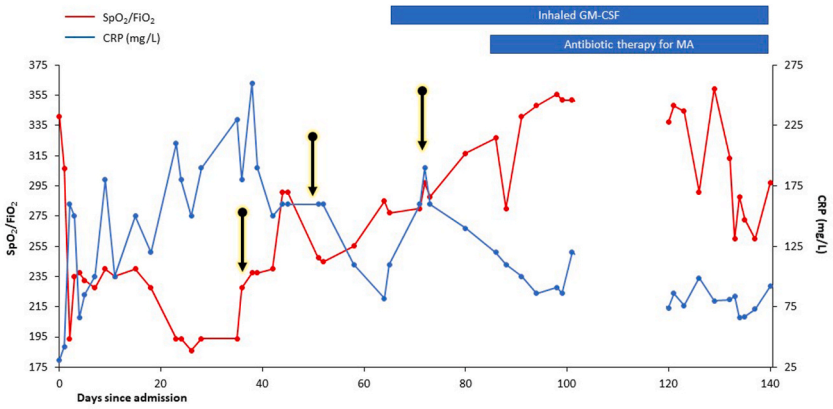

Fig. 2. Evolution of the oxygen requirements (SpO2/FiO2) and the CRP (mg/L). Arrows indicate the dates of whole lung lavages. The patient went home with oxygen supplemental between days 102 and 116. He died at day 140.

3. Discussion

Even if we cannot definitely rule out the direct role of the myelofibrosis in the occurrence of PAP, the role of Ruxolitinib in our patient is supported by several points:

- *The rarity of PAP-Myelofibrosis association*

PAP is a rare disease with an incidence of 0.2 per million inhabitants per year [1]. PAP is classified into four categories:

- Primary, which can be either auto-immune or hereditary;
- Secondary to hematological diseases, chronic infections, malignancies, medications;
- Congenital;
- Unclassifiable [1,2].

Among the hematological diseases associated with PAP, the myelodysplastic syndrome is the most common cause followed by the chronic myeloid leukemia [3]. The association of PAP and myelodysplastic syndrome can also be part of a specific syndrome, the GATA2 deficiency [4]. However, among the hematological diseases, only three patients with myelofibrosis, not treated by Ruxolitinib and having developed PAP, were reported in the literature [5,6]. This makes myelofibrosis unlikely to be the single cause of PAP in our patient.

- *A compatible physiopathology*

PAP results from an intra-alveolar accumulation of the surfactant secondary to a dysfunction of the alveolar macrophages involved in its clearance [1,2]. The GM-CSF pathway in the alveolar macrophages is involved in the surfactant clearance [1,2]. Accordingly, its impairment related to the presence of anti-GM-CSF antibodies causes the auto-immune PAP [1,2]. Ruxolitinib may theoretically also disrupt the GM-CSF signaling by inhibiting the JAK2 factor coupled to the GM-CSF receptor, supporting its possible relationship to PAP [7].

- *A compatible temporal relationship*

Respiratory symptoms appeared a few months after the Ruxolitinib initiation, increase with higher dose, and spontaneously decrease when tapered and stopped (before the first WLL).

- *Previous reports in the literature*

A similar case of PAP and a *Mycobacterium avium* infection occurring in a 70-year-old patient with myelofibrosis (JAK2V617F negative) treated with Ruxolitinib has been reported in the literature [7]. Another case described PAP and Mycobacterium abscessus infection in a 66-year-old patient taking Ruxolitinib after an allogeneic stem cell transplantation administered for a myelodysplastic syndrome [8]. Interestingly, in all three cases an atypical mycobacterial infection complicated the PAP with a delayed onset [7,8].

Therefore, our group introduced the idea of a Ruxolitinib lung: a PAP and an atypical mycobacterial infection developing in a patient with myelofibrosis or myelodysplastic syndrome treated with Ruxolitinib. Both combined, myelofibrosis or myelodysplastic syndrome and Ruxolitinib may increase the risk of PAP and atypical mycobacterial infection [7]. Indeed, Ruxolitinib having an immunosuppressive effect may increase the risk of opportunistic infections [7,9]. PAP patients are also more likely to develop lung infections (usual or opportunistic pathogens such as Actinomyces, Aspergillus, Cryptococcus, Mycobacteria and Nocardia) [1,7].

Spontaneous improvement is possible in auto-immune PAP and survival at 5 years is above 90 % [1]. Conversely, mortality seems to be important in Ruxolitinib lung since the patients died in two of the three reported cases. This could be explained by the fact that, in contrary to auto-immune PAP, the effectiveness of the WLL could be limited in secondary PAP and that the effectiveness of the

subcutaneous or inhaled GM-CSF therapy remains to be established [1,2].

It is important to note that PAP and atypical mycobacterial infection are not the only complications of Ruxolitinib. Ruxolitinib, in addition to myelofibrosis, is known to be associated with pulmonary hypertension [10]. Moreover, one case of Ruxolitinib associated acute respiratory distress syndrome in a patient with primary myelofibrosis has been described in the literature [11].

In conclusion, hematologists and pulmonologists should be aware that respiratory symptoms in myelofibrosis patients taking Ruxolitinib may be related to PAP. A prompt diagnosis, based on a 'milky' BAL showing a PAS-positive acellular material at histological examination and a compatible chest CT scan showing a crazy paving pattern, should lead to the discontinuation of Ruxolitinib [1].

4. Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

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The authors received no founding for this study.

CRediT authorship contribution statement

Antoine El Kik: Formal analysis, Writing – original draft, Writing – review & editing. **Maarten Vander Kuylen:** Formal analysis, Writing – review & editing. **Benjamin Bailly:** Writing – review & editing. **Jennifer Fallas:** Writing – review & editing. **Benjamin Bondue:** Formal analysis, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

A. El Kik, M. Vander Kuylen, B. Bailly and J. Fallas have no conflict of interests to report. B. Bondue discloses no conflict of interest in relationship with the present work. However, he discloses consultancy fees from Boehringer Ingelheim Medtronic and Lys Medical and research funding from the Fonds Erasme and Boehringer Ingelheim.

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