STILL out of Breath?

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Abstract

Adult onset Still’s disease (AOSD) is a rare inflammatory syndrome mostly seen in young adults. Known for its wide range of clinical manifestations, AOSD often presents with non-remitting systemic signs and symptoms. Many rare case associations have been described with AOSD, but only few with pulmonary hypertension (PAH). We are presenting a sixth known case of a young female adult with AOSD and PAH in the literature.

Keywords: Adult onset Still’s disease; Pulmonary hypertension; Young female adult; Yamaguchi criterions; Mycophenolate mofetil; Anakinra

Introduction

Adult onset Still’s disease (AOSD) is a rare inflammatory syndrome mostly seen in young individuals, usually of ages between 15 and 36 years old [1]. Notably known for its wide range of clinical manifestations, Still’s disease often presents itself by non-remitting systemic signs and symptoms: fever, arthralgia, leucocytosis, marked inflammatory profile, etc.

The diagnosis of AOSD is derived from the application of different sets of clinical diagnostic criteria [2-5]. The most widely used are those introduced by Yamaguchi [6] (Table 1). These criteria for the diagnostic of Still’s disease have proved to have better sensitivity than others previously proposed, in an analysis by Masson et al [7]. Multiple laboratory tests also help for the diagnostic of AOSD. Although it is not exclusive to the disease, a highly elevated ferritin level is commonly associated with AOSD [8].

Other manifestations of the disease may consist in arthritis, pharyngitis, lymphadenopathy, organomegaly (especially liver and spleen), etc. Many rare case associations have been described with AOSD: pure red cell aplasia, disseminated intravascular coagulation, hemolytic anemia. However, although many rheumatologic diseases are associated with pulmonary arterial hypertension (PAH) (systemic sclerosis [9, 10], CREST syndrome, systemic lupus erythematosus, Sjogren’s syndrome [11], rheumatoid arthritis [12-14]), only a few reports have made a direct link between AOSD and PAH.

The following will present de case of AOSD associated with PAH.

Case Report

We present a case of a 36-year-old Vietnamese woman known for a 2-year course of an AOSD with frequent relapses treated with corticosteroids and an immunosuppressant agent (Mycophenolate Mofetil, Cellcept®).

The diagnosis of AOSD was based on the presence of non-remitting systemic symptoms (fever, weight loss) and the presence of 3 major criteria (fever, arthralgia/arthritis, persistent leucocytosis) and 4 of the minor criteria (lymphadenopathy, hepato-splenomegaly, elevated serum hepatic aminotransferases and the absence on multiple occasions of ANA, anti-DNA or RF) from the Yamaguchi criterions [6]. She did not initially present a salmon-pink rash or a sore throat. The exclusion of multiple systemic, infectious and neoplastic syndromes had been done prior to the establishment of the diagnosis. Of note, the patient often presented levels of ferritin > 100,000 ng/mL during her relapses.

She presented herself at the emergency ward of our university teaching hospital in late 2008 for acute dyspnea. She had been experiencing slight dyspnea on exertion for the past 3 - 4 months. She denied any infectious symptoms and had been compliant with her medication. Two to three days before her hospitalization, she gradually not-
ed an increase in her dyspnea without any other associated symptoms.

Her physical examination revealed a young woman with marked respiratory distress. The patient was tachypneic at a rate of 40/min and had a SaO2 of 80% on room oxygen. Oxygen via facemask was administered and her condition improved greatly. Empiric antibiotics were administered to treat what was thought to be pneumonia.

A ventilation-perfusion scintigraphy and a multibarret thoracic angioscan were performed to rule out a pulmonary embolism and were normal. There were no abnormalities upon reviewing the films. The lung parenchyma was normal. The heart did not display an abnormal left ventricle and pulmonary vessels were normal apart for a dilatation of the pulmonary arteries. To complete the investigation, a trans-thoracic cardiac sonography was performed. It revealed a normal left ventricle but a severely dilated right heart with a pulmonary artery hypertension, systolic reaching the 73 mmHg + CVP. Also noted was a severe tricuspid insufficiency. A year prior to this cardiac evaluation, the patient had undergone a cardiac sonography. Neither valve dysfunction nor elevated pulmonary artery pressure were noted at that time. The only abnormality was a small pericardial effusion without consequence on the ventricular dynamic.

Over the next few days, her condition stabilized and she was then referred to a specialized clinic of pulmonary artery hypertension. She was again evaluated for possible aetiologies related to her new pulmonary hypertension, but none were found. A repeat thoracic scan showed no abnormal parenchyma, only dilated pulmonary arteries; her right cardiac catheterization showed a pulmonary capillary wedge pressure (PCWP) of 13mmHg and a mean pulmonary artery pressure of 43 (normal < 25 mmHg at rest [15-18]. A left cardiac catheterization demonstrated a left ventricular end diastolic pressure (LVEDP) of 15 mmHg. The patient’s final diagnosis was a PAH associated with AOSD.

A treatment with Anakinra, Kineret® had been started on her follow-up visits to try to prevent clinical worsening of her AOSD. She was also to begin treatment for her PAH. Unfortunately, the patient died of a septic shock a few weeks later. The family refused an autopsy.

**Discussion**

We have just portrayed a case of pulmonary artery hypertension (PAH) in the setting of an adult onset Still’s disease (AOSD). Lack of evidence toward any other etiology makes us believe that this PAH was a direct consequence of Still’s disease. Furthermore, the patient’s PAH developed a few years after the beginning of her AOSD. It is improbable that the patient would be diagnosed with two very uncommon diseases without their being an association between the two pathologies. Thus, idiopathic pulmonary artery hypertension (iPAH) is, in our view, not a diagnosis to retain. As mentioned earlier, other causes (classification groups 2 through 5) [15, 19] of PAH had been excluded (Table 2).

No pulmonary venous hypertension was detected on cardiac echography and right heart catheterization showed a normal pulmonary artery occlusive pressure. There was no evidence of left heart dysfunction on the left cardiac catheterization. Multiple contrasts enhanced thoracic scans and pulmonary ventilation-perfusion scintigraphy did not denote the presence of a chronic or acute thromboembolic process. A schistosomiasis infection had also been excluded to rule out a possible Katayama syndrome [20] with a presentation.
of PAH [21-23]. No parenchymal abnormalities have been seen on all the thoracic scans and a nocturnal saturometry did not correlate with the presence of sleep apnea. No HIV infection or drug abuse was documented.

The diagnosis of group 1 PAH is based on the absence of other known or common causes [14, 15]. In group 1, collagen tissue diseases are established causes of PAH, scleroderma being the most frequently cited. However, this association does not apply to AOSD. In actual medical literature, it is not a widely recognized etiology of PAH. This could probably be in part due to a weak incidence of both diseases [24]. Nonetheless, the association of both pathologies in the same patient must arouse suspicion as to whether it is only an uneventful situation or if there could be a direct causality between the two entities. In recent years, a few papers have made the case for this association [25-28]. Only five cases have now been described. This would be the sixth.

The pathologic hallmarks of idiopathic PAH are intimal thickening, media hypertrophy and plexiform lesions. Plexiform lesions are associated with a monoclonal proliferation of endothelial cells in the intralobular arteries of the lung and are associated to some extent with disease severity. On histological examinations, these lesions are also found in PAH associated with connective tissue diseases [29, 30]. Although many resemblances are found between iPAH and PAH associated with connectivitis, the exact mechanisms of pulmonary artery hypertension in the later are not completely understood. Infiltration of macrophages and T lymphocytes has been observed in the perivascular space of patients with iPAH and PAH induced by scleroderma [31]. The inflammatory process thus induced with the release of cytokines and growth factors by these cells may contribute to the vascular remodeling seen in these patients. Furthermore, some reports advocate a role of autoimmunity in the pathologic genesis of PAH [32]. Cases of regression of PAH with treatment of the underlying inflammatory process gives more weight to this argument. However, inference of these histo-pathologic mechanisms to AOSD patient’s needs to be addressed with further studies; the main of the scientific data on PAH associated with rheumatic disorders coming from lupus and scleroderma patients.

As for our patient, a treatment of Anakinra had been initiated because of worsening symptoms. A decrease in her inflammatory profile was seen within the first days of the therapy. A week later, the ferritin level dropped from over 100,000 to nearly 6,000 ng/mL. This is in line with some other reports showing a dramatic response to Anakinra within days of onset of therapy [33]. Other reports show that Anakinra can be effective in treatment-refractory Still’s disease [34-36]. It would have been informative to observe the evolution of the PAH after a few weeks of treatment with this IL-1 antagonist. However, the patient died of septic shock shortly after the initiation of the Anakinra.

In conclusion, this patient presented a case of severe PAH in the setting of an adult onset Still’s disease. To our knowledge, this is the sixth documented case of such an as-

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<tr>
<th>Table 2. WHO Classification of Pulmonary Artery Hypertension (PAH)</th>
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<td><strong>Group 1 PAH:</strong> pulmonary arterial hypertension</td>
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<tr>
<td>Sporadic PAH</td>
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<td>Familial PAH</td>
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<td>PAH associated with small arteriolar diseases (collagen vascular disease, anorexigens, HIV, etc)</td>
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<td><strong>Group 2 PAH:</strong> pulmonary venous hypertension</td>
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<td>Mainly left heart disease</td>
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<td><strong>Group 3 PAH:</strong> PAH associated with respiratory system disorder</td>
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<td>Sleep apnea</td>
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<td>Interstitial lung diseases</td>
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<td>Chronic obstructive pulmonary disease</td>
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<td><strong>Group 4 PAH:</strong> PAH associated with thrombotic disorders</td>
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<td>Thrombotic occlusion of pulmonary arteries (pulmonary embolisms)</td>
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<td>Non-thrombotic occlusion of pulmonary arteries (Katayama disease seen with schistosomiasis)</td>
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<td><strong>Group 5 PAH:</strong> PAH of extrinsic nature</td>
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<td>Mechanical compression of pulmonary vasculature (sarcoidosis, histiocytosis, etc)</td>
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sociation. Further studies are needed to better understand the causality between the two entities. We need to better characterize the epidemiologic profile of patients with severe adult onset Still’s disease to determine which patients are at risk of PAH. However, its infrequency may prove to be the major limitation in accomplishing this goal.

Grant Support

No grant support.

Conflict of Interest

No conflict of interest.

References

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