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CASE REPORT

Pulmonary arterial hypertension in a patient with stage II sarcoidosis and Hashitoxicosis

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ABSTRACT: Although pulmonary arterial hypertension is usually associated with advanced stages of sarcoidosis, its occurrence in early stage disease is rare. Herein, a case of associated pulmonary arterial hypertension in the setting of Hashitoxicosis and stage II pulmonary sarcoidosis is reported. The case of associated pulmonary arterial hypertension occurred in a young female without clinically significant medical history and who completely recovered after receiving oral corticotherapy only. Furthermore, this case report suggests the presence of an interaction between pulmonary arterial hypertension, sarcoidosis and Hashitoxicosis.

KEYWORDS: Corticosteroids, Hashitoxicosis, pulmonary arterial hypertension, sarcoidosis, thyroid disorders

Pulmonary arterial hypertension (PAH) is a rare but well recognised complication of sarcoidosis, usually reported in advanced stages. Hashitoxicosis, an autoimmune thyroid disorder, is characterised by hypothyroidism and intermittent or sporadic periods of hyperthyroidism, similar to Graves' disease [1]. Antibodies against thyroid peroxidase and thyroglobulin are both present in Hashitoxicosis and result in thyroid cell destruction and thyroid-stimulating hormone (TSH) receptor stimulation. Although thyroid disorders have been identified as possible risk factors for PAH according to the Venice Classification [2], Hashitoxicosis has not been previously described in association with associated PAH (APAH). The present authors report the case of a patient presenting with APAH associated with sarcoidosis and Hashitoxicosis.

CASE REPORT

A 28-yr-old female was admitted for cough, haemoptysis, precordial pain, New York Heart Association class II, dyspnoea and weight loss (18 kg in 3 months). Her family and personal medical histories were unremarkable aside for a smoking habit that had ceased 3 yrs previously (13 packs·yrs). She denied taking any medications or illicit drugs at time of admission or in the past.

Physical examination revealed shortness of breath and lower extremity oedema. Her body temperature was 36.2°C, pulse rate was 100 beats·min^{-1} and arterial pressure was 135/70 mmHg. Breath sounds were symmetric, without adventitious sounds.

An incomplete right branch block was detected by electrocardiogram. Cardiac ultrasound displayed an enlarged right ventricle and a normal left ventricular ejection fraction, as well as normal echogenicity. A chest radiograph showed a bilateral interstitial pattern, along with bilateral hilar lymph nodes. High-resolution computed tomography and computed tomography angiography (CTA) of the chest displayed diffuse ground-glass opacities and small nodules throughout the lungs, as well as bilateral hilar and mediastinal enlarged lymph nodes without significant compression on the pulmonary arteries (fig. 1a). Pulmonary embolism was excluded by ventilation/perfusion lung scan and CTA. Room air arterial blood gas analysis revealed a pH of 7.44, arterial oxygen tension of 72 mmHg, arterial carbon dioxide tension of 26.3 mmHg, bicarbonates of 18 mEq·L^{-1} and oxygen saturation of 95%. Pulmonary functional tests showed a forced expiratory volume in one second (FEV_1) of 2.61 L (74% predicted), forced vital capacity (FVC) of 3 L (73% pred), FEV_1/FVC ratio of 78%, total lung capacity (TLC) of 3.99 L (71% pred) and diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) of 14.91 mL·min^{-1}·mmHg^{-1} (50% pred). Pulmonary haemodynamics obtained at rest by right heart catheterisation were as follows: elevated mean pulmonary arterial pressure ($\bar{P}_{pa}$) 34 mmHg; normal pulmonary capillary wedge pressure 5 mmHg; elevated pulmonary vascular

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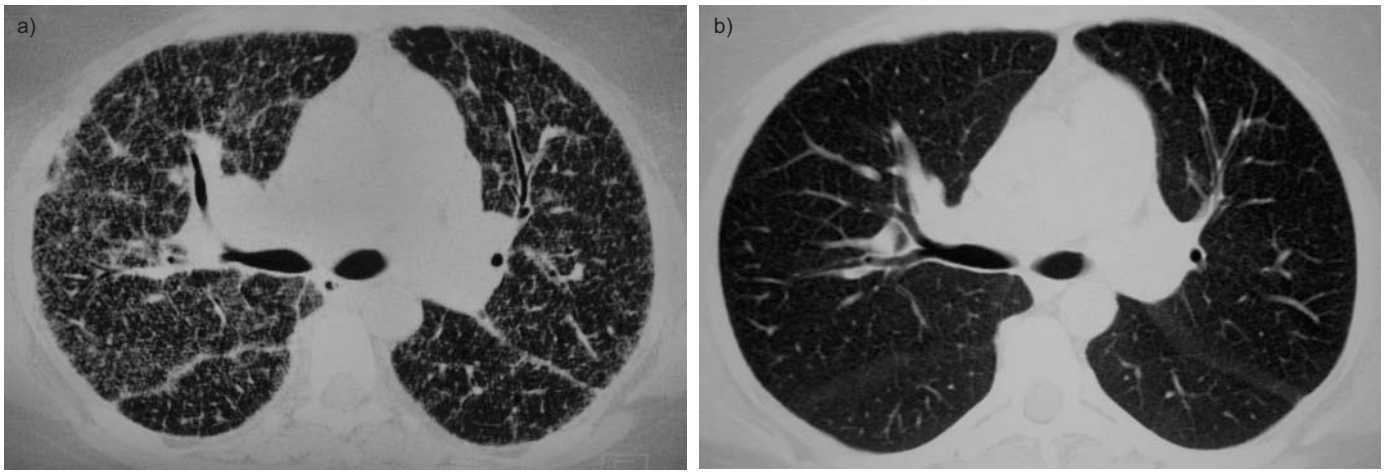

FIGURE 1. High-resolution computed tomography scan at tracheal carina level. a) Before treatment multiple small nodules and areas of ground-glass opacities with bilateral hilar enlarged nodes are visible. b) Following steroid treatment the abnormalities are no longer visible.

resistance (PVR) 290 dyn·s·cm^{-5} with normal systemic vascular resistance 957 dyn·s·cm^{-5}; and normal cardiac index 3.8 L·min·m^{-2}. Flexible bronchoscopy revealed mucosal secretions in the right bronchus. Bronchoalveolar liquid consisted of 275×10^6 cells with 7% lymphocytes, 17% neutrophils and 76% macrophages; there was no hemosiderophage. An elevated CD4/CD8 ratio of 6.5 was also noted. Multiple bronchial biopsies showed chronic and moderate inflammation. Thoracoscopic-guided lung biopsy (TGLB) from the left upper lobe measured $6 \times 3 \times 1.5$ cm. Four representative sections, each measuring 1.8–2 cm in the longest diameter, were available for microscopic examination. Histological sections stained with haematoxylin and eosin, periodic acid-Schiff with and without diastase digestion, Masson Trichrome and elastin revealed small to medium-sized noncaseating granulomas located along the bronchovascular bundles and within the lung parenchyma (fig. 2). Granulomas were found in ~50% of the biopsy specimen area, which corresponds to a grade 2 granulomatous angeitis according to Rosen's classification (three grades of severity) [3]. There was minimal involvement of pulmonary veins, characterised by granulomas within the vessel walls and destruction of the lamina elastica. Arterioles and larger vessels (both arteries and veins) were spared. There were no signs of hypertension such as intimal thickening or fibrosis and hypertrophy of the media. Plexogenic arteriopathy and thrombosis were also absent. There was no evidence of interstitial fibrosis, scarring or honeycombing. Microorganisms such as acid-fast bacilli were not found and a Mantoux test was negative. An abdominal ultrasound found no evidence of portal hypertension. Blood tests revealed a C-reactive protein level of 2 mg·dL^{-1} (normal: <0.8 mg·dL^{-1}), D-dimer level of 210 ng·mL^{-1} (normal: <130 ng·mL^{-1}) and an angiotensin converting enzyme level of 124.3 nmol·mL^{-1} (normal: 12.4–52.1 nmol·mL^{-1}). Hepatic enzymes and bilirubin levels were within normal limits. Antinuclear antibodies showed a mixed pattern, with titres of 1:40 uniform and 1:160 nucleolar patterns. HIV infection was excluded. Thyroid function tests showed TSH plasma levels <0.004 μUI·mL^{-1} (normal: 0.350–5.500 μUI·mL^{-1}), free T3 of 7.1 pmol·L^{-1} (normal: 2.7–6.4 pmol·L^{-1}), free T4 of 27.6 pmol·L^{-1} (normal: 11.0–24.0 pmol·L^{-1}), anti-microsomal antibodies of 70 UI·Ml^{-1} (normal: <35 UI·Ml^{-1}), anti-thyroglobulin antibodies of 73 UI·mL^{-1} (normal: <40 UI·mL^{-1}) and anti-TSH receptor antibodies of 2 UI·L^{-1} (normal: <1 UI·L^{-1}). A technetium thyroid scan showed heterogeneous uptake throughout the gland.

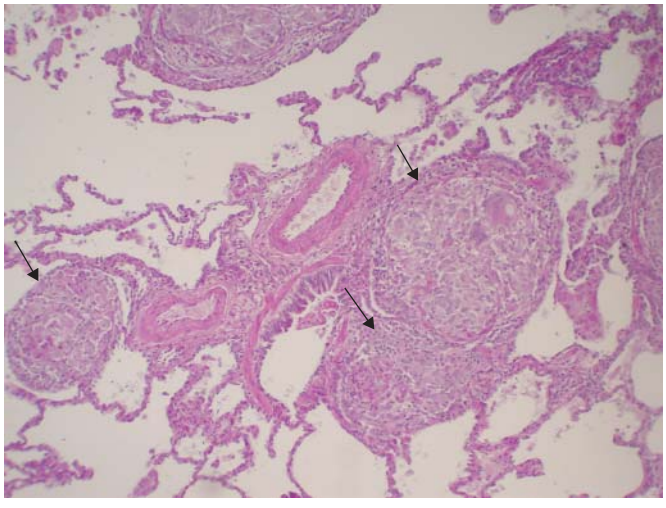

FIGURE 2. Histological lung biopsy stained with periodic acid-Schiff. Sarcoid granulomas (arrows) are located along lymphatics in the bronchovascular bundles. Arteries are normal without compression, intimal or medial hyperplasia and fibrosis.

After having ruled out the other causes of PAH, the present authors considered the diagnosis of APAH in the setting of autoimmune thyroiditis (Hashitoxicosis) and stage II pulmonary sarcoidosis. Because of the severity of the symptoms, oral methylprednisolone was administered at a dose of 64 mg daily. The patient became asymptomatic 6 weeks later with normalisation of $\bar{P}_{pa}$ (15 mmHg), PVR (91 dyn·s·cm^{-5}), thyroid hormones and TSH plasma levels (table 1). The cardiac output was 3.65 L·min^{-1}. In addition, complete clearance of interstitial infiltrates and total disappearance of previously enlarged lymph nodes were observed on the follow-up chest computed tomography (CT) scan (fig. 1b). Corticosteroids were then gradually tapered off and completely discontinued after 6 months. At that point, the pulmonary function tests were

TABLE 1 Effects of oral corticotherapy

	$\bar{P}_{pa}$ mmHg	PVR dyn·s·cm^{-5}	Cardiac output L·min^{-1}	TSH μUI·mL^{-1}	T4 free pmol·L^{-1}
Before treatment	34	290	3.8	<0.004	27.6
6 weeks after initiation of treatment	15	91	3.65	2.16	14.3

$\bar{P}_{pa}$: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; TSH: thyroid-stimulating hormone.

completely normal (FEV1 3.61 L (103% pred), TLC 5.75 L (102% pred) and $D_{L,CO}$ 23.95 mL·min^{-1}·mmHg^{-1} (80% pred)). After 24 months the patient remained asymptomatic and had a favourable outcome.

DISCUSSION

Herein, the authors report a case of moderate PAH in the setting of stage II sarcoidosis and Hashitoxicosis which affected a young female who completely recovered after oral corticotherapy.

The prevalence of PAH with sarcoidosis ranges from 1% to 28%, depending on detection technique, disease stage and screening method (systematic or not). PAH is usually described in stage IV sarcoidosis. It is commonly reported that sarcoidosis-associated PAH results from pulmonary capillary bed destruction by granulomatous inflammation and fibrosis, but the severity of PAH is sometimes not well correlated with the degree of pulmonary fibrosis. In a significant proportion of cases, PAH is also described in nonfibrotic stages [4, 5], wherein alternative mechanisms contribute to PAH development (table 2).

The patient did not present extrinsic compression of the pulmonary artery by enlarged lymph nodes or fibrosing mediastinitis. The available lung tissue did not show intimal/medial infiltration or compression of pulmonary arteries. In addition, there was no evidence of pulmonary veno-occlusive disease, which has been reported in some cases of sarcoidosis [6]. Hypoxaemic vasoconstriction might also contribute aetiologically to PAH but hypoxaemia in our observation was mild. Portal hypertension secondary to liver sarcoidosis was not found either [7]. Of note, no cardiac factors secondary to direct myocardial involvement by sarcoidosis were found. Furthermore, normal cardiac output, along with normal left ventricular systolic function and normal filling pressure were not consistent with haemodynamic changes related to hyperthyroidism [8].

TABLE 2 Physiopathology of pulmonary arterial hypertension in sarcoidosis

Most frequent (in advanced stages)
Destruction of pulmonary capillary bed by parenchymal fibrosis
Others
Extrinsic compression of large pulmonary arteries
By enlarged hilar or mediastinal lymph nodes
By fibrosing mediastinitis
Vascular infiltration by noncaseating granulomas and/or perivascular fibrosis
Of pulmonary arteries
Of pulmonary veins (with pulmonary veno-occlusive disease)
Myocardial infiltration by noncaseating granulomas
Pulmonary vasoconstriction
By hypoxaemia
By other vasoactive factors
Liver sarcoidosis (with portal pulmonary arterial hypertension)

Of note: multiple aetiologies can co-exist.

In a recent retrospective study of 22 patients with sarcoidosis and PAH, NUNES *et al.* [4] suggested the existence of two very distinct sarcoidosis phenotypes based on the presence or absence of pulmonary fibrosis on the chest radiograph. The seven fibrosis-free patients had low $D_{L,CO}$. NUNES *et al.* [4] hypothesised the role of a specific vasculopathy. However, their study lacks histological data. However, to the best of our knowledge, existing histological studies on the pulmonary vascular involvement in sarcoidosis [3, 9] have not directly correlated granulomatous angiitis and pulmonary haemodynamics. Nevertheless, in patients with sarcoidosis, pulmonary vessel involvement has been reported to be usual, ranging from 69% (open lung biopsy cases, mean patient age: 29 yrs) [3] to 100% (autopsy cases, average patient age: 60 yrs) [9], while PAH is rare in early stages and currently attributed to fibrosis. Further studies are needed to clarify the links between histological data and PAH.

The patient had no sign of fibrosis either on the CT scan or on the lung biopsy, her pulmonary function tests showed low $D_{L,CO}$ before treatment, and only focal minimal sarcoid involvement of small pulmonary veins was observed on lung biopsies. Vasculitis is not a fully recognised cause of PAH [2]. Thus, it is possible that the patient's PAH (which completely regressed under steroid treatment) was not directly related to the limited sarcoid involvement of small veins observed by histological analysis, even when considering that TGLB may offer an incomplete sampling. Since vasoreactivity was not tested, PAH secondary to a vasoreactive component cannot be excluded in our patient. This hypothesis would be in line with the reported favourable response to pulmonary vasodilators in sarcoidosis-related PAH [10].

Despite the fact that thyroid autoimmune disorders and PAH may be two distinct complications of sarcoidosis, interaction between these disorders has not been previously described and this deserves further characterisation and understanding. Indeed, higher prevalence of anti-thyroid autoantibodies and/or thyroid disorders (*e.g.* Hashimoto's disease) has been reported in several studies of sarcoidosis. In a recent matched case–control study (sex and age) of 111 patients, ANTONELLI *et al.* [11] demonstrated a significantly higher prevalence of

hypothyroidism (22% *versus* 7%) and anti-thyroperoxidase antibodies (34% *versus* 19%) in female patients with sarcoidosis compared with controls. However, pulmonary arterial pressure was not evaluated in this study, or in other published studies in the same field. Nevertheless, several studies reported a high prevalence (up to 49%) of thyroid disturbances (*e.g.* elevated levels of anti-TSH, anti-thyroglobulin or thyroperoxidase antibodies) in the setting of idiopathic PAH (IPAH) [12, 13]. It was suggested that autoantibody-induced immune disorders may contribute to IPAH, through pulmonary arterial endothelial dysfunction (*e.g.* imbalance between vasodilators and vasoconstrictors such as endothelin-1) [14].

PAH is a well-known predictor of poor outcome in sarcoidosis [15]. Its detection may prompt earlier referral to a transplant centre or introduction of therapy that may improve outcomes [10, 15]. As shown in a large retrospective cohort of patients, simple clinical criteria have failed to identify patients with concomitant sarcoidosis and PAH [16]. However, the $D_{L,CO}$ level which was low in our patient (50% pred) has recently been reported as a significant predictor of PAH in sarcoidosis [17, 18].

To the best of our knowledge, this is the first report supporting a potential interaction between PAH, sarcoidosis and thyroid disorders. According to the Venice Classification [2], we considered the PAH of our patient as an APAH. Other aetiologies of PAH were reasonably excluded by the work-up. Without ruling out a fortuitous association, we believe that the likelihood that these diseases coexist without being related is low, and this leads us to consider thyroid disorders in PAH associated with nonfibrotic stages of sarcoidosis. The favourable outcome with normalisation of the pulmonary artery pressure and $D_{L,CO}$ after a few weeks of oral corticosteroids suggests a potential common pathway between both diseases. Interestingly, reversibility or improvement of PAH under steroid treatment has been reported in HIV/human herpes virus 8-associated Castleman's disease [19] and POEMS syndrome [20]. Similar results under immunosuppressants and glucocorticoids have also been reported in systemic lupus erythematosus- or mixed connective tissue disease-associated PAH [21].

These data emphasise the relevance of immune and/or inflammatory processes contributing to PAH genesis or progression. This has led to the recommendation of first-line immunosuppressive therapy in patients with connective tissue diseases in New York Heart Association class I or II with a clinical and haemodynamic assessment after 3–6 months before considering a pulmonary vasodilator regimen. Because of the significant improvement of pulmonary haemodynamics reported, not only by us but by NUNES *et al.* [4] in three out of their five patients, a similar therapeutic attitude using corticosteroids alone could be considered in the cases of PAH associated with the nonfibrotic stages of sarcoidosis.

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