# Extensive pulmonary sarcoid reaction in a patient with BMPR-2 associated idiopathic pulmonary arterial hypertension

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**Abstract.** Pulmonary arterial hypertension is a progressive life-threatening disease characterized by vascular remodeling. There is evidence that varied immune mechanisms play an important role in progression of pulmonary hypertension. We describe a case of a 35-year-old woman with idiopathic pulmonary arterial hypertension (IPAH) and a novel BMPR2 mutation, who underwent a successful lung transplantation. Extensive granulomatous inflammation was seen in the resected lungs. The granulomatous inflammation found in the histology supports a sarcoid-like reaction due to pulmonary hypertension in the context of the BMPR2 mutation. *(Sarcoidosis Vasc Diffuse Lung Dis 2016; 33: 182-185)*

**Key words:** pulmonary arterial hypertension, granulomatosis, sarcoidosis, lung transplant

## Introduction

Pulmonary arterial hypertension (PAH) is an uncommon and potentially fatal condition characterized by vasoconstriction and vascular remodeling of small to medium sized pulmonary arteries in association with formation of plexiform lesions (1,2). The sustained elevation of mean pulmonary artery pressure leads to hypertrophy and subsequent failure of the right heart (3). Varied immune mechanisms play an important role in the progression of PAH leading to remodeling of pulmonary vasculature (1,4-7)

We describe an unique case of PAH with excessive granuloma formation linked to a BMPR2 mutation.

A 35-year-old woman with dyspnea at rest, progressive since pregnancy was analyzed in 2004. There were no signs of no signs of skin, eye disease or underlying lung disease, nor risk factors for PAH. Chest X-ray revealed enlarged right ventricle and pulmonary vessels. At echocardiograph pulmonary arterial pressure was 94/40 mmHg, mean 58 mmHg. Right heart catheterization confirmed these results (wedge pressure 5 mmHg, RVEDD 18 mm). Blood results were negative for hepatitis A, B, C, TBC and HIV. Lupus anticoagulans, ANA, ANCA were also negative and ACE was within normal limits.

Ultrasonography of the liver and ventilation perfusion scan were normal. HRCT scan at presentation revealed no signs of interstitial lung disease but an enlarged truncus pulmonalis and pulmonary vessels. Spirometry was normal. Diffusion capacity was slightly decreased (7.87 mmol/min/kPa, normal
10.34 mmol/min/kPa). BMPR2 mutation analysis revealed a novel missense mutation in exon 9 that leads to a substitution of methionine into arginine (c.1217 T>G, p.Met406Arg).

Idiopathic PAH NYHA III was diagnosed. Initially, treatment started with bosentan and coumarines, later on sildenafil (2007) and remodulin sc (2008) were added. In 2011 she deteriorated further. Echocardiography revealed a patent foramen ovale and she was screened for lung transplantation. In 2013 she was admitted with severe heart failure and received a high urgency lung transplant.

The resected lungs showed extensive granulomatous inflammation. Numerous granulomas were observed around pulmonary vessels. The granulomas were also located underneath the pleural surface.

No peribronchial inflammation was seen. In the hilar lymph nodes abundant granulomas were found (Figure 1, 2). In the resected lungs no signs for infection (negative PCR for mycobacteria and no hyphae) were seen. Destruction of the pulmonary vascular bed was seen with signs of granulomatous angiitis. No evidence of pulmonary veno-occlusive disease was found. Dilated and plexiform vascular lesions were seen in the context of BMPR2 associated PAH.

**Discussion**

We describe a unique case of a patient with an idiopathic BMPR2 mutation driven PAH which may be aggravated by granulomatous angiitis. This

![Fig. 1. Plexiform vascular lesions in the explanted lungs compatible with Bone Morphogenetic Protein Receptor-2 mutation induced pulmonary hypertension. A, Dilatation lesion consisting of thin walled vessels around an artery with media hypertrophy. B, Elastin van Gieson staining of indicated area in A showing the dilation lesion and in the top of the figure an eccentric intimal lesion in an arterial branch. C and D, plexiform vascular lesions consisting of a plexus of vascular channels surrounded by wide thin walled vessels. A, B and D H&E staining](image-url)
A 35-year-old woman presented with dyspnea, had a typical clinical course of a patient with an idiopathic PAH, as seen by her young age (8), the initial response to PAH specific medication and the BMPR2 mutation in exon 9. This is a novel missense mutation that had not been described earlier. The BMPR2 gene located at 2q33 encodes a type 2 receptor for bone morphogenetic proteins (BMP’s), which belong to the transforming growth factor-beta superfamily. BMP’s are involved in control of vascular cell proliferation. We suspect this mutation is pathologic because this amino acid is located within the kinase domain of BMPR2. Mutations in this domain of BMPR2 have been described as pathological (3,9-11). Histology of the resected lung showed dilated and plexiform vascular lesions which are seen in context of BMPR2 associated PAH that supports the hypothesis of a pathological BMPR2 mutation as we found for the first time. Interestingly histology also showed an extensive granulomatous inflammation with granulomatous angiitis (Figure 1, 2). This sarcoid like inflammation could have played an additional role in the progression of her pulmonary hypertension leading to further remodeling of the pulmonary vasculature (1,4-7,12). We speculated that the granulomatous inflammation is an extensive sarcoid reaction as seen in a reaction to foreign bodies as seen after intravenous injection or inhalation. However, our patient did only receive subcutaneous injections of treprostinil and her pathology is not consistent with foreign bodies. Another possibility may be caused by an immune reaction in response to pulmonary hyper-

Fig. 2. Granulomatous disease of the explanted lungs and hilair lymph nodes. A, Numerous granulomas were observed around pulmonary vessels. B, the granuloma’s were also located underneath the pleural surface. C, detail of granuloma’s consisting of epithelioid and giant cells with focally only a little necrosis. D, abundant granulomas in the hilair lymph nodes. A-D H&E staining
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tension as described by Sawada et al. (2) rather than a second diagnosis sarcoidosis. Sawada et al. (2) state that a loss of BMPR2 results in enhanced secretion of granulocyte-macrophage colony-stimulating factor in response to TNF which will lead to stress granule formation as seen in our case. In case of a second diagnosis like sarcoidosis, the idiopathic pulmonary hypertension could be aggravated by a sarcoidosis associated pulmonary hypertension (SAPH) component. About 5–6% of unselected sarcoidosis patients have SAPH, this is not always associated with overt parenchymal involvement (13,14). The majority has granulomatous involvement of the pulmonary vessel wall at microscopy (15,16). However, having both diagnoses is extremely rare because of the low incidence of both diseases (12,17), but cannot be ruled out. Granulomatous angiitis as seen in our patient could have lead to more severe pulmonary hypertension as seen in sarcoidosis associated pulmonary hypertension without a BMPR-2 polymorphism.

This case describes an aggravated IPAH by granulomatous angiitis, probably due to an extensive sarcoid reaction in a patient with a never described BMPR2 mutation in exon 9. We suggest that screening for polymorphisms of BMPR2 should also be considered in patients with sarcoidosis associated pulmonary hypertension, especially in those with normal or mild restrictive lung disease, because in these sarcoidosis patients treatment with PAH specific medication will possibly be more effective and not result as fast in shunting and hypoxemia as seen in sarcoidosis patients with severe pulmonary manifestations of sarcoidosis.

References