

A very rare cause of pre-capillary pulmonary hypertension: The PAMI syndrome

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Abstract

We report the first known case of PAMI syndrome associated with pulmonary arterial hypertension (PAH) with a positive response to cyclophosphamide and pulmonary vasodilators. The patient's history began at 7 months with severe pancytopenia and fever. As time progressed, migrating arthritis, hepatosplenomegaly, and a growth deficit manifested without a plausible explanation. At the age of 17, worsening dyspnea led to a diagnosis of severe pre-capillary pulmonary hypertension and, after a multidisciplinary evaluation, a dual therapy with both vasoactive and immunosuppressive agents led to rapid clinical improvement. After a decade of stability, stopping sildenafil caused deterioration, reversed upon reintroduction. Thirty years after the onset of signs and symptoms, a genetic test identified the underlying condition known as PAMI syndrome. As PAMI syndrome involves intense systemic inflammation similar to PAH related to systemic lupus erythematosus (SLE), parameters and functional autonomy appropriately responded to early immunosuppressive and vasoactive therapy. PAMI syndrome, a rare autoinflammatory disease, is linked to precapillary pulmonary hypertension but the exact cause and optimal treatment approach are not fully understood, requiring further research for clarification and improved treatment options.

KEYWORDS

inflammatory PH, interferonopathies, PSTPIP1 gene, pulmonary arterial hypertension (PAH), pulmonary circulation

Manuela Iseppi and Giulio Savonitto contributed equally as the first author.

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BACKGROUND

PSTPIP1-associated myeloid-related proteinemia inflammatory syndrome (PAMIs) is a very rare monogenic autoinflammatory disease caused by missense mutations in proline-serine-threonine phosphatase-interacting protein 1 (PSTPIP1) gene.¹

Its estimated prevalence is 1/1,000,000 with 35 cases reported.²

The PSTPIP1 gene encodes a protein involved in innate inflammatory response, which regulates interleukin-1 release and T-cell activation. Mutations in PSTPIP1 can increase the protein's ability to bind pyrin, an immunomodulatory protein, resulting in uncontrolled inflammasome activation and overproduction of IL-1 β .³ Furthermore, transcriptome studies also highlighted a strong activation of the nuclear-factor kappa B and the interferon pathways.⁴

Clinical manifestations partially reflect hyperactivation of innate immune response, including recurrent arthritis, cutaneous inflammation, lymphadenopathy, hepatosplenomegaly, and growth failure. Laboratory tests usually reveal pancytopenia, elevated inflammatory parameters, high serum zinc, and calprotectin levels.⁵

Mutations in PSTPIP1 have been strongly linked to a well-known autoinflammatory syndrome called PAPA, which shares common clinical features with PAMIs except pancytopenia. Furthermore, pathogenic mutations in PAPA syndrome are distinct with those identified in PAMIs (p.E250K and p.E257K). Zhang et al. described the first case of PAMIs associated with increased estimated pulmonary pressure at echocardiography.³ However, the diagnostic confirmation and classification of the subtype of pulmonary hypertension (PH) require the invasive hemodynamic assessment by right heart catheterization (RHC).⁶

We report a case of PAMIs associated with pulmonary arterial hypertension (PAH) with a positive response to cyclophosphamide and pulmonary vasodilators.

Case presentation

This case report presents a 31-year-old female from Southern Italy with a 46XX karyotype and a family history of spontaneous abortions on her father's side. At 7 months of age, she was hospitalized due to severe anemia, neutropenia, thrombocytopenia, and fever.

Deficient forms of anemia were excluded and bone marrow aspirate ruled out myelodysplasia and hemoglobinopathies.

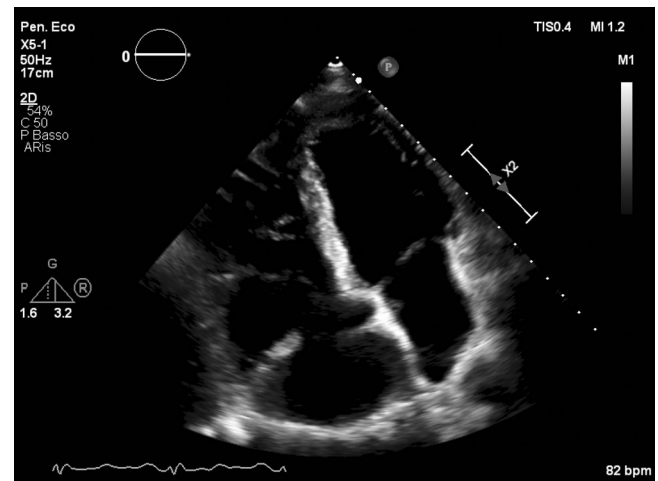


FIGURE 1 Echocardiogram in 2010—fractional area change (FAC): 23%—tricuspid annular plane excursion (TAPSE): 13 mm—systolic pulmonary artery pressure: 90 mmHg—right ventricular end-diastolic area (RVEDA): 28 cmq.

Both direct and indirect Coombs tests as well as standard autoantibody panels (ANA, ANCA, nDNA, ENA, and anti-cardiolipin) were negative.

The only abnormal laboratory findings were increased markers of systemic inflammation (erythrocyte sedimentation rate 100 mm/h and IgE 5000 IU/mL).

Total body computed tomography scan revealed hepatosplenomegaly, while electrocardiogram and echocardiogram showed no signs of cardiac involvement with normal intracardiac filling pressures.

At 2 years, the onset of migrating arthritis and recurrent fever, requiring steroid infiltrations and oral NSAIDs, complicated the course of the disease.

Persistent hepatosplenomegaly was investigated with a liver biopsy, revealing mild perivenular hepatitis with inflammatory cell infiltration and apoptotic bodies. Infectious (such as hepatitis B and C) and autoimmune etiologies were excluded. ACE test ruled out sarcoidosis, skin biopsy ruled out lysosomal disease, and urinary porphyrins were negative.

One year later, due to growth hormone (GH) deficiency, a replacement therapy with GH was initiated and continued until the patient reached 18 years of age.

In 2010, at the age of 17, the patient was hospitalized for worsening fatigue and dyspnea for mild efforts. Echocardiogram (Figure 1) showed a dilated right ventricle (RV) with impaired contractility. Estimated pulmonary artery systolic pressure (sPAP) was 90 mmHg. Left ventricle dimension and function were normal. Intracardiac shunts were excluded.

6-min walking test (6-MWT) revealed a poor functional capacity (i.e., 370 m).

TABLE 1 First right heart catheterization at our center.

Weight	44 kg
Height	149 cm
BMI	19.8 kg/m ²
BSA	1.35 m ²
Systolic pulmonary artery pressure (sPAP)	87 mmHg
Mean pulmonary artery pressure (mPAP)	54 mmHg
Diastolic pulmonary artery pressure (dPAP)	36 mmHg
Pulmonary capillary wedge pressure (PCWP)	11 mmHg
Right atrial pressure (RAP)	9 mmHg;
Cardiac index (CI)	3.04 L/min/m ² (thermodilution method)
Pulmonary vascular resistance (PVR)	11 Wood Units (879.1 dyn s/cm ⁵)
Pulmonary vascular resistance index (PVRi)	1130.4 dyn s/cm ⁵ m ²
SVO ₂ in pulmonary artery	72%

Abbreviations: BMI, body mass index; BSA, body surface area.

The patient was referred to our center for further investigations.

RHC revealed severe precapillary PH with preserved cardiac index (Table 1). The vasoreactivity test was negative.

Laboratory tests confirmed pancytopenia (Table 2) and a previously unknown proteinuria was detected. Imaging and pulmonary function test excluded parenchymal lung disease, DLCO was normal, and pulmonary scintigraphy ruled out chronic thromboembolic PH. Upfront double combination therapy with bosentan 62.5 mg b.i.d. and sildenafil 40 mg t.i.d was started for PAH in addition to double immune modulating (suppressive) therapy with cyclophosphamide 750 mg/month for 10 months and prednisone. However, bosentan was early discontinued due to an increase in hepatic aminotransferase.

During the 10-year follow-up at residency's clinic the patient showed gradual improvement in symptoms, functional capacity, and normalization of RV function. Due to clinical stability sildenafil was stopped in 2017.

After 2 years in 2019, a multidisciplinary re-evaluation at our center was performed to investigate the possible monogenic etiology and to re-stratify PH.

Arthritis flare-ups were improving while dyspnea and fatigue relapsed after treatment discontinuation. Echocardiography showed normal RV function and hemodynamic impairment was less severe (Table 3).

TABLE 2 Baseline laboratory tests at our center.

Hemoglobin	12 g/L
Platelets	334 × 10 ⁹ /L
White blood cells	3.52 × 10 ⁹ /L
Neutrophil count	0.67 × 10 ⁹ /L
Creatinine	0.46 mg/dL
Total bilirubin	0.51 mg/dL
GOT	38 U/L
GPT	17 U/L
GGT	52 U/L
Lactate dehydrogenase	1063 U/L
IgE	>5000 mUI/L
BNP	37.8 pg/mL
C3	129 mg/dL
C4	23 mg/dL
TSH	4.88 mU/L
ESR	35 mm/h

Abbreviations: BNP, B-type natriuretic peptide; ESR, erythrocyte sedimentation rate; GGT, gamma-glutamyl transferase; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; TSH, thyroid-stimulating hormone.

TABLE 3 Follow-up right heart catheterization at our center.

Systolic pulmonary artery pressure (sPAP)	62 mmHg
Diastolic pulmonary artery pressure (dPAP)	29 mmHg
Mean pulmonary artery pressure (mPAP)	42 mmHg
Pulmonary capillary wedge pressure (PCWP)	8 mmHg
Right atrial pressure (RAP)	5 mmHg
Cardiac index (CI) measured with thermodilution method	3.6 L/min/m ²
Pulmonary vascular resistance (PVR)	6.7 Wood Units

B-type natriuretic peptide (BNP) was 21 pg/mL and a 6-MWT confirmed functional capacity of 443 m classifying the patient at low risk. Monotherapy with PDE5i was started with rapid improvement of symptoms and reduction in sPAP levels.

The identification of a strong interferon signature (score 19.2, n.v. < 2.7) raised the suspicion of a monogenic interferonopathy, underpinning PH. However, a genetic analysis of autoinflammatory-related genes led to the detection of a known pathogenic variant associated with PAMIs: c.G748 (E250K) in the PSTPI1 gene, which was not considered so far an interferonopathy. Further

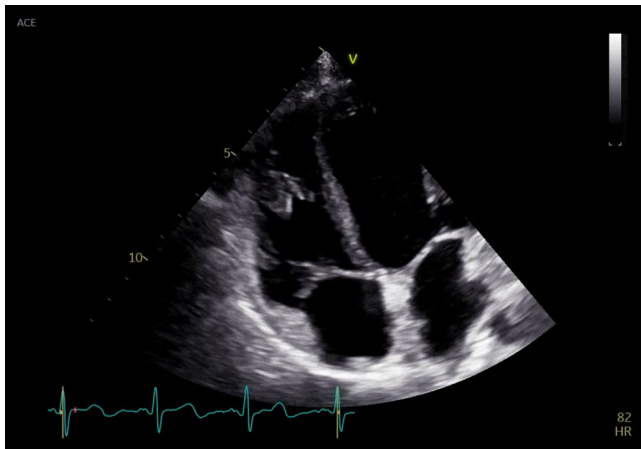


FIGURE 2 Echocardiogram in 2023—FAC: 47%—TAPSE: 24 mm—sPAP: 41 mmHg—RVEDA: 18 cmq.

transcriptomic analysis in the patient confirmed a hyperactivation of genes related to the interferon pathways and an upregulation of neutrophil activation genes like MPO, ELANE, and DEFA3. Moreover, the detection of mild proteinuria might be consistent with an inflammatory profile in the spectrum of systemic lupus erythematosus (SLE). Even if autoantibodies tested negative and complement levels were normal, hydroxychloroquine 200 mg b.i.d. was introduced to contrast interferon-mediated inflammation. After 4 years, the patient is asymptomatic (WHO 1), free from arthritis flare-ups for 2 years. Echocardiography (Figure 2) showed persistent normalization of RV function with an estimated sPAP of 41 mmHg.

DISCUSSION

Due to its extremely low prevalence and clinical heterogeneity, PAMIs can be easily misdiagnosed, resulting in delayed therapy initiation and disease progression. The best therapeutic strategy is not clear yet: glucocorticoids, monoclonal antibody therapies, colchicine, anakinra, and tacrolimus are the most reported treatments.²

This report describes the first documented case of precapillary PH associated with PAMIs, which presented with dyspnea and heart failure. We classified this specific case as type 1 PH after conducting classical examinations for diagnostic differentiation.⁶

Initially, the patient presented with a severe PH and an early combination therapy with vasodilators and immunosuppressants was promptly initiated, resulting in a stable initial clinical response. Subsequently, discontinuation of vasoactive therapy led to new relapses, easily controlled with PDE5i

monotherapy and hydroxychloroquine. Follow-up showed RV reverse remodeling and a significant decrease in sPAP.

We hypothesize that the predominant mechanism leading to a severe acute presentation was the hyperinflammation of pulmonary arterioles, which benefited from immunosuppressive therapy (cyclophosphamide + prednisone). After stabilizing inflammation, vasoactive monotherapy was sufficient to maintain excellent clinical and hemodynamic response. The slow progression of disease after the first withdrawal of treatments in 2017 supports this hypothesis.

The role of altered immunity and inflammation appears to be a prominent pathologic feature in PAH.⁷ Elevated serum levels of cytokines are characteristic of severe idiopathic PAH^{8,9} and other conditions such as connective tissue disease (CTD) and HIV-associated PAH.¹⁰

A crucial role is played by interferons as supported by the finding of PH in number of interferonopathies, including SAVI syndrome, COPA syndrome, and DNase2 deficiency. Notably, immune-therapy with cyclophosphamide and/or JAK inhibitors, together with vasodilators resulted in effective control of PAH in a few reported cases.¹¹

Even if transcriptomic analyses were performed only some years later, it is reasonable that an interferon-mediated inflammation was already present at the time when PH occurred, as it was considered dependent on the underlying genetic condition. Indeed, PAH is a recognized complication of several interferon-driven conditions, including CTD, mixed CTD (MCTD), and SLE^{12–14} and anti-inflammatory therapies like cyclophosphamide and JAK inhibitors showed an improvement in hemodynamics and clinical parameters in PAH associated with SLE^{15–17}, in DNase2 deficiency interferonopathy,¹⁸ and MCTD,¹⁶ although not in systemic sclerosis-associated PAH.¹⁷

Patients with SLE-associated PAH responded positively to immunosuppression alone, indicating the potential benefits of an early treatment.

As highlighted by Kumar and Graham,¹⁹ the exact nature of inflammation in human PAH remains uncertain, possibly involving different types of inflammation with contrasting effects on the vascular disease. Broad immune suppression may not effectively inhibit pathological processes while sparing beneficial mechanisms. Further questions persist, such as the role of inflammatory cells in inducing medial and intimal pathology and the adequacy of animal models in mimicking clinical immune drivers. Understanding inflammation's evolution throughout PAH progression remains crucial.

Current guidelines suggest that combination of immunosuppressive agents and PAH-specific agents may be considered for the treatment of PAH associated with SLE or MCTD.⁶

CONCLUSIONS

PAMIs is a rare monogenic autoinflammatory disease which can lead to pre-capillary PH. The pathophysiology of PH in this subset is unknown, but it is reasonable to infer that perivascular inflammation and subsequent vascular remodeling play an important role.

Periodical echocardiographic screening for cardiopulmonary involvement is advisable in PAMIs. Moreover, RHC should be performed when the echocardiogram supports the suspicion of PAH.

Similarly to PAH associated with SLE, our patient apparently derived the greatest benefit from immunosuppressive therapy at the initial phase. Treatment combination with immunosuppressive agents and pulmonary vasodilators might be the most rational approach to this rare form of PAH at the initial stage.

Additional studies are necessary to confirm the causal association between PAMIs and PAH and to better understand the underlying pathophysiological mechanisms and the optimal treatment approach.

AUTHOR CONTRIBUTIONS

Manuela Iseppi: Case design, data collection, manuscript writing. **Giulio Savonitto:** Case design, data collection, manuscript writing, critical review. **Alberto Tommasini:** Data collection, manuscript writing, critical review. **Alessia Pin:** Data collection, manuscript writing. **Gianfranco Sinagra:** Critical review. **Davide Stolfo:** Case design, manuscript writing, critical review.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

The research was conducted in accordance with ethical norms and appropriate regulations.

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