Case report

Pulmonary alveolar proteinosis (PAP) in idiopathic hypoparathyroidism

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SUMMARY

Idiopathic hypoparathyroidism (IH) and autoimmune pulmonary alveolar proteinosis (PAP) are rare disorders. A patient with IH and optimal calcaemic control on calcium and alfacalcidol was detected to have PAP after 8 years of follow-up. Patient had no respiratory complaints. Routine abdominal imaging for renal calcification showed patchy ground glass opacities in the lower lung fields leading to incidental diagnosis of PAP. Pulmonary function tests showed impaired diffusion capacity of the lung. Anti-granulocyte macrophage-colony stimulating factor autoantibodies were positive. Patient regularly attended the pulmonary clinic and showed progressive improvement in diffusion capacity of the lung during 2 years of follow-up. The calcaemic control in IH remained stable despite its presence with PAP. The autoimmune PAP in the presented case suggests a possible autoimmune basis of IH.

BACKGROUND

Hypoparathyroidism is characterised by tetany, cataract and hypocalcaemia with subnormal serum parathyroid hormone (PTH). It is a rare endocrine disorder with prevalence of 23–37 cases/100 000 person-years.^{1 2} Post-surgical hypoparathyroidism is the most common type and idiopathic hypoparathyroidism (IH) constitutes 10% of all cases. Underbjerg *et al*, observed only 47 cases of IH in the national registry of Denmark during 1977–2012.³ Similarly, pulmonary alveolar proteinosis (PAP) is a rare disease characterised by excessive lipoproteinaceous material in the alveoli, hypoxaemic lung failure, and risk of infection and frequency of 1–7 cases/million populations.^{2 4} Most cases of PAP are autoimmune in nature and demonstrate circulating autoantibodies against granulocyte macrophage-colony stimulating factor (GM-CSF) in 90% of cases.² High affinity GM-CSF autoantibodies decrease PU.1 transcription factor expression in alveolar macrophage leading to inefficient clearance of lipoprotein surfactant in the alveoli.²

In contrast, aetiopathogenesis of IH is under investigation. Currently, IH is considered to be a cluster of heterogeneous aetiologies with autoimmune and genetic basis as indicated by calcium sensing receptor autoantibodies in 13% and mutation of parathyroid transcription factor ‘GCM2’ gene in 11%.^{5 6} Presence of coexistent autoimmune diseases is considered as a surrogate for autoimmune basis of a given disease. The various subclinical and clinical autoimmunity observed in a large

cohort of patients with IH at our centre include thyroid peroxidase positivity in 16.3%, primary hypothyroidism in 7.6%, celiac disease in 3.3% and alopecia areata, alopecia totalis, vitiligo and psoriasis in 1% each.^{6 7} None of the patients with IH in our cohort had PAP and to the best of our knowledge, presence of PAP in IH has not been reported earlier. Here, we report clinical course and significance of PAP in a patient with IH.

CASE PRESENTATION

A 45-year-old woman presented to the endocrine clinic in 2008 for the management of IH. She had history of generalised tonic-clonic seizures, numbness and tingling of the extremities with recurrent carpo-pedal spasm since 2003. She was prescribed oral calcium and valporate by the local physician which she took intermittently. She also had history of haemoptysis and significant weight loss in 2007 for which she was treated with antituberculosis drugs under ‘Revised National Tuberculosis Control Program’.

INVESTIGATIONS

Her investigation at our centre in 2008 revealed serum total calcium of 5.1 mg/dL, inorganic phosphorus of 7.4 mg/dL, alkaline phosphatase of 238 IU/L, serum intact PTH of 24.4 pg/mL and serum 25(OH)D of 31.5 ng/mL. Her thyroid function tests including serum thyroid stimulating hormone (3.76 μ IU/mL), T4 (10.63 μ g/dL) and thyroid peroxidase antibody (9.7 IU) were normal. Cranial CT scan showed presence of basal ganglia calcification. She did not have anti-calcium sensing receptor antibodies and R110W mutation of GCM2. Other biochemical investigations were normal. She was prescribed a daily dose of 2.0 g of oral elemental calcium as carbonate salt and 1.0 μ g of alfacalcidol. Her hypocalcaemic symptoms improved and she maintained optimal serum calcium control between 8.0 and 8.5 mg/dL.

In mid-2016, patient underwent routine screening for renal calcification. Though ultrasonogram showed absence of nephrocalcinosis/renal stones, thick-walled renal cortical cysts of 1.7×1.05 cm were noted. Urologist advised CT for further evaluation which incidentally revealed multifocal areas of ground bilateral glass opacities in the lower lung field. Patient had normal body mass index (26.4 kg/m²), was afebrile and had no respiratory symptoms or signs, she was advised pulmonary function tests and CT of the thorax in view of previous history of

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Figure 1 Serial CT scan of the patient showing course of ground glass opacities in the lung parenchyma during 2017–2019 (A–C).

treatment for tuberculosis. The CT showed bilateral, asymmetrical basal peripheral subpleural multifocal ground glass consolidations with subjacent interstitial septal thickening, suggestive of organising pneumonia (figure 1A). Her pulmonary function tests showed restrictive defect with moderate impairment of diffusion capacity for carbon monoxide (DLCO, 41%, table 1).

TREATMENT, OUTCOME AND FOLLOW-UP

Patient was referred to pulmonary clinic for further follow-up. The repeat CT thorax at 6 months showed no remarkable change in lung lesions (figure 1B) and she underwent bronchoscopy, bronchoalveolar lavage and transbronchial lung biopsy. Bronchoscopic airway examination was normal. The bronchoalveolar lavage from right middle lobe was sent for cytopathology, staining for acid fast bacilli, pneumocystis carinii staining, Genexpert, bacterial and fungal cultures. Endobronchial and transbronchial lung biopsies were taken from right lower lobe. The lavage fluid showed degenerated cells, few alveolar macrophages and proteinaceous exudate. The acid fast bacilli (AFB) stain, cultures and expert were negative. Transbronchial lung biopsy showed features of PAP (figure 2). The serum GM-CSF antibody level was 27.7 µg/mL compared with normal (<5.0 µg/mL) and GM-CSF-stimulated phosphorylation of signal transducer and activator of transcription 5 (STAT5) could not be detected in peripheral blood cells suggesting an autoimmune PAP. Since the patient was asymptomatic, no medical treatment was advised except for deep breathing exercise, pulmonary function tests and CT thorax at yearly interval. The last follow-up CT chest in 2019, showed no remarkable change in lung lesions (figure 1C). There was mild reduction in forced vital capacity on follow-up but diffusion capacity improved (table 1).

DISCUSSION

Both IH and PAP are rare diseases and chances of missing such cases in combination are high. Asymptomatic nature of the PAP in a subset of cases may further underestimate its diagnosis in IH. This was exemplified in the present case where patient had no respiratory complaints. Detection of PAP and its treatment is important in view of its long-term complication of pulmonary fibrosis and restrictive lung disease. These complications can be prevented by close follow-up and early treatment of PAP with

Figure 2 Photomicrograph showing lung parenchyma with alveolar spaces filled with amorphous granular periodic acid–Schiff stain positive diastase resistant material (200×).

modalities such as lung lavage in cases with progressive deterioration in oxygen saturation.

Occurrence of PAP in the present case of IH might represent a chance or real association. However, this issue can be addressed only when more such cases are reported in literature. Alternatively, large cohort of patients with IH could be screened for presence of PAP to document its prevalence in IH. The course of PAP in the present case during 2 years of follow-up was unremarkable despite coexisting IH and maintenance of serum calcium in lower range of 8.0–8.5 mg/dL. In fact patient showed improvement in diffusion capacity of the lung over 2 years of follow-up. Spontaneous improvement and remissions without any treatment are reported in PAP and up to a quarter of patients may improve without treatment.^{8,9} This may be the likely cause of improvement in DLCO in our patient due to the dynamic nature of the disease process. Presence of PAP in the present case also did not lead to any difficulty in the management of IH and she maintained stable calcaemic control without any change in requirement of daily dose of calcium and vitamin D.

Most cases of PAP are autoimmune with evidence of GM-CSF autoantibodies as observed in the present case. This indicated, likelihood of autoimmune basis of IH in the given case since one of the characteristic of organ-specific and non-organ-specific autoimmune disorders is their frequent association. Thyroid autoimmunity is usually the most common coexistent illness in patients with various autoimmune diseases.^{6,7} In this regard autoimmune PAP is unique and shows only limited spread of autoimmunity to other organs and tissue. In fact, the largest series of 410 patients with PAP as reported by Seymour and Presneill, had only seven cases (1.3%) of coexistent autoimmunity.⁴ These included rheumatoid arthritis and positive smooth-muscle antibodies in two cases each and immunoglobulin nephropathy, multiple sclerosis and celiac disease in one case each.⁴ Inoue *et al*, also reported lack of increased prevalence of coexistent autoimmunity in 248 patients with PAP in Japan.¹⁰ This study observed only three cases of autoimmunity including polymyalgia rheumatic, haemolytic anaemia and Wegner's granulomatosis. The low prevalence of coexistent autoimmunity observed both in PAP and IH are in contrast to the 20%–25% prevalence of coexistent autoimmune thyroiditis in type 1 diabetes mellitus and autoimmune premature ovarian failure.¹¹

Table 1 Serial pulmonary function tests for the patient

Parameters (% predicted)	Serial pulmonary function tests			
	January 2017	May 2018	September 2018	April 2019
FEV ₁	2.32 L (87%)	2.09 L (75%)	1.80 L (72%)	1.56 L (66%)
FVC	2.01 L (87%)	1.67 L (71%)	2.08 L (71%)	1.81 L (65%)
FEV ₁ /FVC	86.4 (107%)	79.9% (96%)	86.5% (107%)	86.5 (107%)
DLCO corrected	9.83 (41%)	–	15.77 (67%)	21.27 (93%)

FEV₁, forced expiratory volume in one second; FVC, forced vital capacity.

Thus, patient with IH can have coexistent PAP. The patient may be asymptomatic and disease could be detected only on pulmonary function test and chest imaging. Screening of a large cohort of patient with IH for the PAP would help confirm the association, if any, between these two disorders.

In summary, here we report unique case of IH with autoimmune PAP. The course of PAP was benign during 2 years of follow-up with improvement of lung diffusion capacity. The calcaemic control in IH remained stable despite presence of PAP.

Patient's perspective

In retrospect, I was slightly uncomfortable with mild dyspnoea but thought it to be a part of the ongoing hypoparathyroidism. However, 2 years after the diagnosis of PAP and breathing exercise advised at respiratory clinic, there is remarkable improvement in dyspnoea.

Learning points

- ▶ Patient with idiopathic hypoparathyroidism (IH) was incidentally diagnosed with coexistent pulmonary alveolar proteinosis (PAP) after 8 years of follow-up.
- ▶ The patient had no symptoms of PAP, but had abnormal pulmonary function tests and imaging of the chest.
- ▶ Progressive improvement in diffusion capacity of the lung occurred during 2 years of follow-up. The calcaemic control in IH remained stable despite presence of PAP.

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