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CASE REPORT
Other

Adult-onset hypoxaemia, diffuse lung lesions, and pulmonary hypertension in cobalamin C defect: a case report

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Background Cobalamin C (cbl-C) defect is an inherited autosomal recessive disorder that commonly affects the central nervous system of infants. Severe pulmonary hypertension (PH) and diffuse lung lesions are unusual clinical manifestations, especially among adults.

Case summary A 25-year-old man with hypoxaemia, diffuse lung lesions, and PH, suddenly developed nausea, vomiting, headache, and worsening of dyspnoea. Metabolic screening showed elevated serum levels of methylmalonic acid and homocysteine, and genetic testing revealed *MMACHC* gene mutations. He was eventually diagnosed with severe PH secondary to cbl-C defect and was successfully managed with vitamin B12, betaine, L-carnitine, folate, as well as ambrisentan and sildenafil.

Discussion cbl-C is a rare cause of PH and can present with severe PH and diffuse lung lesions in adults. Given that the condition is treatable, a careful metabolic screening should be considered when a diagnosis of PH is made.

Keywords Cobalamin C defect • • Pulmonary hypertension • • Diffuse lung lesions • • Case report

Learning points

- Cobalamin C (cbl-C) defect could present as pulmonary hypertension (PH), hypoxaemia, and diffuse lung lesions in adults. The lack of specifications of these manifestations poses a considerable diagnostic challenge, leading to delays in diagnosis and initiation of treatment.
- Most patients benefit from treatment of cbl-C defect and PH, so a metabolic screening should be considered when a diagnosis of PH is made.

Introduction

Pulmonary hypertension (PH) is a condition characterized by increased pressure in the pulmonary circulation.[1] Diffuse ground-glass shadows and nodular shadows with severe hypoxaemia are features of PH caused by idiopathic pulmonary arterial hypertension (PAH), interstitial lung diseases, pulmonary veno-occlusive disease (PVOD), and pulmonary capillary haemangiomatosis (PCH),[2] which usually requires lifelong combined therapy or lung transplantation. Here, we present a case of severe PH with diffuse lung lesions secondary to cobalamin C (cbl-C) defect that has been successfully treated.

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Timeline

2010	Diagnosis of IgA nephropathy
2015	Shortness of breath
May 2016	Hospitalization for hypoxaemia, diffuse lung lesions, and pulmonary hypertension (PH)
November 2016	PH worsening with nausea and vomiting. Haemolytic anaemia-associated PH suspected. Steroid and pulmonary arterial hypertension-specific therapies were administrated
September 2018	PH worsening with haemolytic anaemia. Cobalamin C defect confirmed, and relevant treatment initiated
May 2019	Improvement in dyspnoea
January 2021	Significant improvement in symptoms and clinical parameters

Case presentation

A 25-year-old man with normal cognition presented with a complaint of shortness of breath for 1 year. He had been having positive urinary occult blood tests since the age of two and was diagnosed with IgA nephropathy by renal biopsy at the age of 19. His parents are non-consanguineous and healthy. No family history has been revealed.

On arrival, he presented with a cyanosis of lips and clubbing fingers and toes. The arterial blood gas on room air showed a PaO_2 level of 51 mmHg. Computed tomography pulmonary angiogram (CTPA) showed diffuse centrilobular ground-glass shadows and nodular shadows (*Figure 1A–C*), dilated pulmonary artery, and enlarged right ventricle (RV, *Figure 2A and B*). In addition, the pulmonary function test revealed a severe decrease of diffusion function. As echocardiography indicated intermediate probability of suspected PH, right heart catheterization (RHC) and pulmonary angiography (*Figure 2C*) were performed, which showed an mean PAP (mPAP) level of 34 mmHg, a pulmonary artery wedge pressure of 10 mmHg, and a pulmonary vascular resistance of 5.8 WU. Furthermore, the screening test for autoimmune disease was negative. Therefore, PVOD/PCH was highly suspected, and oxygen therapy was initiated. To confirm the diagnosis, a genetic test for EIF2AK4 mutations was performed, and the result was negative.

Five months later (November 2016), the patient suddenly developed nausea and vomiting, with an elevation of the N-terminal prohormone of brain natriuretic peptide (NT-proBNP, 3000 pg/mL) and an increased echocardiography-estimated pulmonary arterial systolic pressure (PASP) (74 mmHg). The full blood count revealed macrocytic anaemia, with haemoglobin shown as 84 g/L. The total and direct bilirubin were elevated to 42 and 17 μmol/L, respectively (*Table 1*).

The anaemia workup showed positive direct Coombs test and normal levels of vitamin B12 and folic acid, and bone marrow aspiration revealed a megaloblastic change. Therefore, a diagnosis of haemolytic anaemia-associated PH was considered. Steroids were

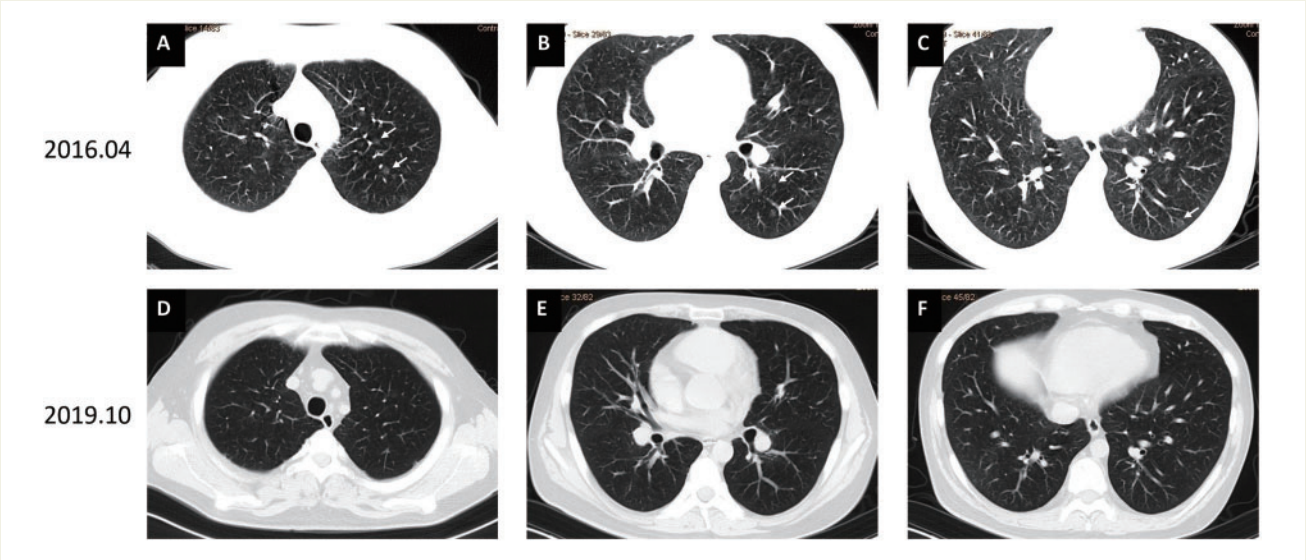

Figure 1 Computed tomography pulmonary angiogram at baseline (*A–C*) and 3-year follow-up (*D–F*) showed reduction in size and numbers of diffuse ground-glass shadows and nodular shadows (arrow).

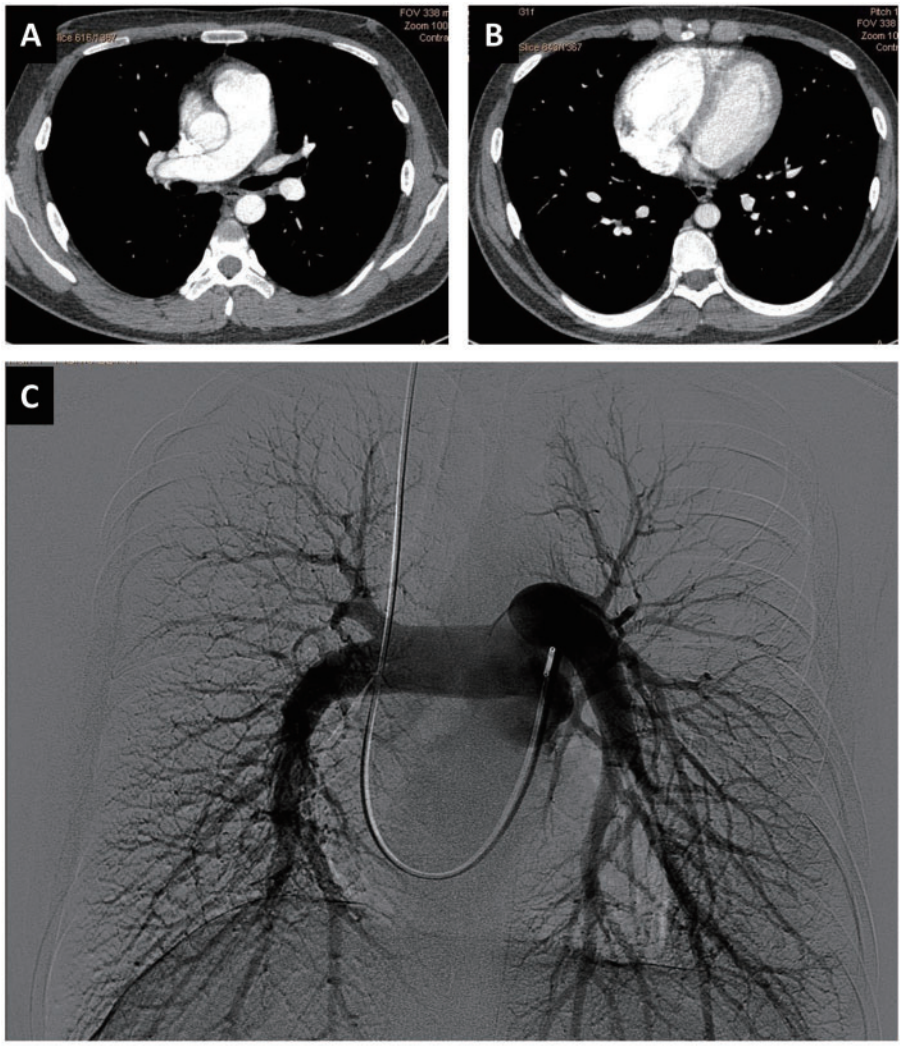

Figure 2 Dilated pulmonary artery (*A*) and right ventricular enlargement (*B*) are shown in computed tomography pulmonary angiogram, and pulmonary angiogram showed normal presentation (*C*).

administrated, ambrisentan (5 mg qd) and sildenafil (20 mg tid) were also administrated as off-label prescriptions. His shortness of breath was alleviated, and NT-proBNP and PASP were decreased within 6 months. However, his hypoxaemia was not improved. In 2018, the patient was admitted again, presenting with severe anaemia and worsening of PH. Previous investigations were thoroughly reviewed, and his clinical presentation was assessed. Metabolic workup revealed elevated serum homocysteine and methylmalonic acid {101.5 μmol/L [normal value (NV): 0.2–5.6 μmol/L]}. The mass spectrometric analysis of his urine sample demonstrated a significant increase of methylmalonic acid-2 [50.97 μmol/L (NV: 0.2–3.6 μmol/L)] and 2-methyl-3-hydroxybutyric acid-1–2 [50.97 μmol/L (NV: 0–0.3 μmol/L)]. The genetic analysis revealed heterozygous mutations of the *MMACHC* gene located on chromosome1 (GRCh37) c.80A>G, p.Gln27Arg and c.394C>T, p.Arg 132 X, which were inherited from his mother and father, respectively. The patient was, therefore, diagnosed with adult late-onset cbl-C defect.

Upon diagnosis, administration of vitamin B12, betaine, L-carnitine, and folate were initiated, and the patient's dyspnoea was relieved in 6 months. CTPA scans at 1-year post-initiation of the treatment showed a significant decrease of diffuse lung lesions (*Figure 1D–F*). A repeated echocardiography and RHC revealed mild PH with normal RV function (*Table 1*). Overall, the patient demonstrated an excellent response to treatment, with a significant improvement in exercise capacity and other clinical parameters.

Discussion

cbl-C defect is a rare inborn error of intracellular cobalamin metabolism caused by pathogenic variants in *MMACHC*.[3] MMACHC deficiency impairs conversion of dietary vitamin B12 to its two metabolically active forms, namely methylcobalamin and

Table 1 Clinical, biochemical, and echocardiography trends

	Initial (2016-5)	Disease progression (2016-11)	After PAH Tx (2017-5)	Disease progression (2018-9)	After cbl-C Tx (2021-1)
Clinical features					
NYHA class	2	4	3	3	1–2
Routine blood test and biochemical markers					
Haemoglobin (130–175 g/L)	152	84	119	65	182
RBC (10^{12}/L)	2.73	1.29	2.5	1.43	6.15
MCV (82–100 fl)	119	123.3	128	121	88
MCH (27–34 pg)	55.7	65.1	48	46	30
MCHC (316–354 g/L)	468	528	372	376	338
Tbil (4.7–24 μmol/L)	41	42	33	73	23
Dbil (0–5 μmol/L)	17	17	17	12.5	8
Scr (53–97 μmol/L)	84.5	70	82	100	90
Hcy (<15 μmol/L)	—	—	—	192	42.7
NT-proBNP (0–125 pg/mL)	22	3000	63.3	47.8	10
Blood gas analysis (without oxygen)					
PaO_2 (mmHg)	50	49	47	54	71
SpO_2 (%)	86.3	82.8	83.7	88.4	97
Echocardiography					
PASP (mmHg)	42	74	52	68	25
TR (m/s)	3.04	4.1	3.3	3.96	2.2
TAPSE (mm)	1.9	1.6	2.0	1.98	2.4
RA minor diameter (mm)	40	55	40	—	42
RA major diameter (mm)	44	46	41	—	45
RV transverse diameter (mm)	31	44	35	35	33
Pulmonary function					
DLCO SB (%)	30	—	—	23.6	46.7
DLCO/VA(%)	28.9	—	—	24.7	41.9
Right heart catheterization					
Mean PAP (mmHg)	34	—	—	—	27
PAWP (mmHg)	10	—	—	—	7
CO (L/min)	4.13	—	—	—	6.13
PVR (WU)	5.8	—	—	—	3.26

cbl-C, cobalamin C; CO, cardiac output; Dbil, direct bilirubin; DCLO/VA, diffusing capacity for carbon monoxide/alveolar volume; DLCO SB, DLCO single-breath method; Hcy, homocysteine; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; MCV, mean corpuscular volume; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PaO_2, oxygen partial pressure; PAP, pulmonary artery pressure; PASP, pulmonary artery systolic pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RA, right atrial; RBC, red blood cell; RV, right ventricle; Scr, serum creatinine; SpO_2, percutaneous oxygen saturation; TAPSE, tricuspid annular plane systolic excursion; Tbil, total bilirubin; TR, tricuspid regurgitation.

adenosylcobalamin, resulting in the accumulation of methylmalonic acid and homocysteine.[3,4]

Based on the age of disease onset, cbl-C defect is categorized as early-onset type (onset before the age of 12 months) and late-onset type (onset after the age of 12 months). Approximately 90% of reported patients were severe early-onset cases with poor prognoses.[3] In contrast, very few late-onset cases have been reported,[5,6] and the accurate incidence of this type remains unclear. Individuals with late-onset cbl-C defect often present with milder clinical manifestations and have more favourable outcomes,[5,7] except for those with haemolytic uraemic syndrome (HUS).[4] Cognitive impairment is the most frequent symptom of cbl-C defect, followed by myelopathy, ataxia, and seizures.[5] The symptoms of cbl-C defect are closely related to the age of onset. In preschool children, HUS and PH were the main presenting symptoms, while in older children/adolescents, psychiatric symptoms, cognitive impairment, and ataxia/dysarthria were the most frequent presentations. In adults, thromboembolic events, neuropathy/myelopathy, and non-HUS renal disease were also predominant features, in addition to cognitive decline and ataxia/dysarthria.[5,6]

PH is a severe but rare complication of cbl-C defect. In adults, only an 18-year-old man[7] and a 20-year-old woman[8] have been reported to be diagnosed with cbl-C defect with PH, severe renal thrombotic microangiopathy, and hypertension. cbl-C defect with PH and diffuse lung lesions has only been described in a few late-onset cases in children,[9–11] and therefore, to our knowledge, this patient might be the first adult cbl-C defect patient presenting with hypoxaemia and diffuse lung lesions as predominant symptoms. His unique features

posed a considerable diagnostic challenge, leading to a delay in diagnosis and initiation of treatment.

The pathogenesis of PH associated with cbl-C defect remains unclear. Previous study has revealed that the primary cause of PH is associated with pulmonary microangiopathy resulting from homocystinuria and methylmalonic acidemia.[9] These toxic metabolites may cause endothelial injury,[4] promote vasoconstriction and cell proliferation of vascular smooth muscle,[5,10] and enhance platelet aggregation,[5,10] which leads to formation of microthrombus,[7] and the subsequent pulmonary thrombotic microangiopathy.[3,9] In addition, coexistence of methylmalonic acidemia and hyperhomocysteinemia have been reported to increase the permeability of pulmonary capillaries that leads to diffuse ground-glass opacification.[10]

Treatment of cbl-C defect is based on a combined supplementation of vitamin B12, betaine, and folic acid. Good responses to these treatments have been reported in majority of patients with late-onset cbl-C defect.[3,4] Approximately 20 late-onset cases with severe PH have been reported to receive adequate cbl-C treatment and PAH-targeted therapy, which includes monotherapy and combined therapy.[11–13] After 2–3 months of treatment, most patients showed improvement in clinical symptoms and laboratory parameters, including hypoxaemia and PH. Though pulmonary artery pressure has been reported to return to normal in some patients within 6 months to 1 year,[14] some children died from RV heart failure in the first month of therapy.[15] Importantly, without the essential cbl-C treatment, PAH-targeted therapy alone has limited effect,[8,10] which demonstrates that making a correct diagnosis of PH is crucial for the selection of appropriate treatment.

In conclusion, we reported a case of cbl-C defect presenting with PH and diffuse lung lesions at early stage and has been misdiagnosed for a long period of time. The case suggests the importance of a careful metabolic screening in diagnosis of PH, and that metabolic disorders should be considered in differential diagnosis of PH.

Lead author biography

Qin-Hua Zhao, deputy chief physician, currently works in the Department of Pulmonary Circulation, Shanghai Pulmonary Hospital Affiliated to Tongji University. She has been engaged in the diagnosis and treatment of pulmonary vascular diseases for more than 10 years. She has certain expertise in the diagnosis of pulmonary vascular diseases and evaluation of right heart function by echocardiography. At present, as the first author, she has published many works in *Am J Cardiol*, *Clinical Cardiology*, the *Clinical Respiratory Journal*, etc. and participated in the publication of more than 20 papers.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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