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Pulmonary arterial hypertension in systemic sclerosis—when criteria and pathobiology differ

Rheumatology key message

- Haemodynamic definitions of SSc-associated pulmonary arterial hypertension are sometimes not reflected in histological examination of lung vasculature.

Dear Sir, At the 2018 World Symposium on Pulmonary Hypertension, it was suggested that the haemodynamic definitions of pulmonary hypertension be revised, but that the diagnosis of pulmonary arterial hypertension (PAH) should still rely purely on right heart catheterization (RHC) measurements, after excluding pulmonary and left heart disease with other diagnostic modalities. We here report on two cases illustrating discordant haemodynamic and microscopic characteristics, questioning the validity of the current criteria with regard to pathobiology [1].

A 69-year-old female smoker (case A) was diagnosed with adenocarcinoma of the lung and underwent left lower lobe resection. Six months later she was diagnosed with SSc with nucleolar antinuclear antibodies and limited skin involvement, with an estimated disease duration of 10 years. High-resolution CT showed subtle signs of emphysema and interstitial lung disease. She had dyspnoea and increased systolic pulmonary arterial pressure on echocardiography. RHC revealed a normal mean pulmonary artery pressure (MPAP, 18 mmHg), but increased pulmonary vascular resistance (PVR, 3.6 WU), thus not fulfilling the criteria for PAH. Histology of the resected left lower lobe, explanted 6 months earlier, showed severe arteriolar abnormalities with medial/intimal thickening and small-vessel fibrosis, no plexiform lesions, but focal affection of venules with mild wall thickening (Fig. 1A–C). 'Early' SSc-associated PAH (SSc-APAH) was suspected and ambrisentan monotherapy was initiated. Renewed RHC, 7 months later, revealed elevated MPAP (26 mmHg) with reduced PVR (3.1 WU), now fulfilling the diagnostic criteria for SSc-APAH. She died of her malignancy 1 year and 8 months after SSc-APAH diagnosis.

The second case was a 50-year-old woman, who had never smoked (case B), with 11 years of stable limited cutaneous Jo-1 positive SSc and overlap with severe arthritis, mild myositis and interstitial lung disease who presented with dyspnoea. Lung function testing revealed low diffusing capacity of the lung for carbon monoxide (28% of predicted) and she underwent RHC. She fulfilled the criteria for SSc-APAH (MPAP 33 mmHg, PVR 4.0 WU) and ambrisentan monotherapy was initiated. She continued immunosuppressive therapy with rituximab and azathioprine, and improved haemodynamically. Eight years after PAH diagnosis she was also diagnosed with adenocarcinoma of the lung and underwent a partial left lower lobe resection. Histological examination revealed very few altered arterioles with wall thickening and no plexiform lesions or pathological venules. These altered arterioles were only present in areas with dense fibrosis with architectural distortion and honeycombing. No signs of wall thickening or other alterations were observed in the arterioles in areas showing inflammation, interstitial fibrosis with preserved architecture or other non-fibrotic lung tissue (Fig. 1D–H).

The clinical characteristics of the patients are presented in Supplementary Table S1 and Figs S1–S3, available at *Rheumatology* online. Case A challenges the current European Society of Cardiology/European Respiratory Society 2015 definition of PAH [2], as histological examination showed the presence of typical SSc-APAH abnormalities before the haemodynamic criteria for PAH were fulfilled. It cannot be ruled out that the vasculopathy was secondary not only to SSc but also to the adenocarcinoma [3]. However, the histological examination was consistent with previous reports of SSc-APAH [4, 5].

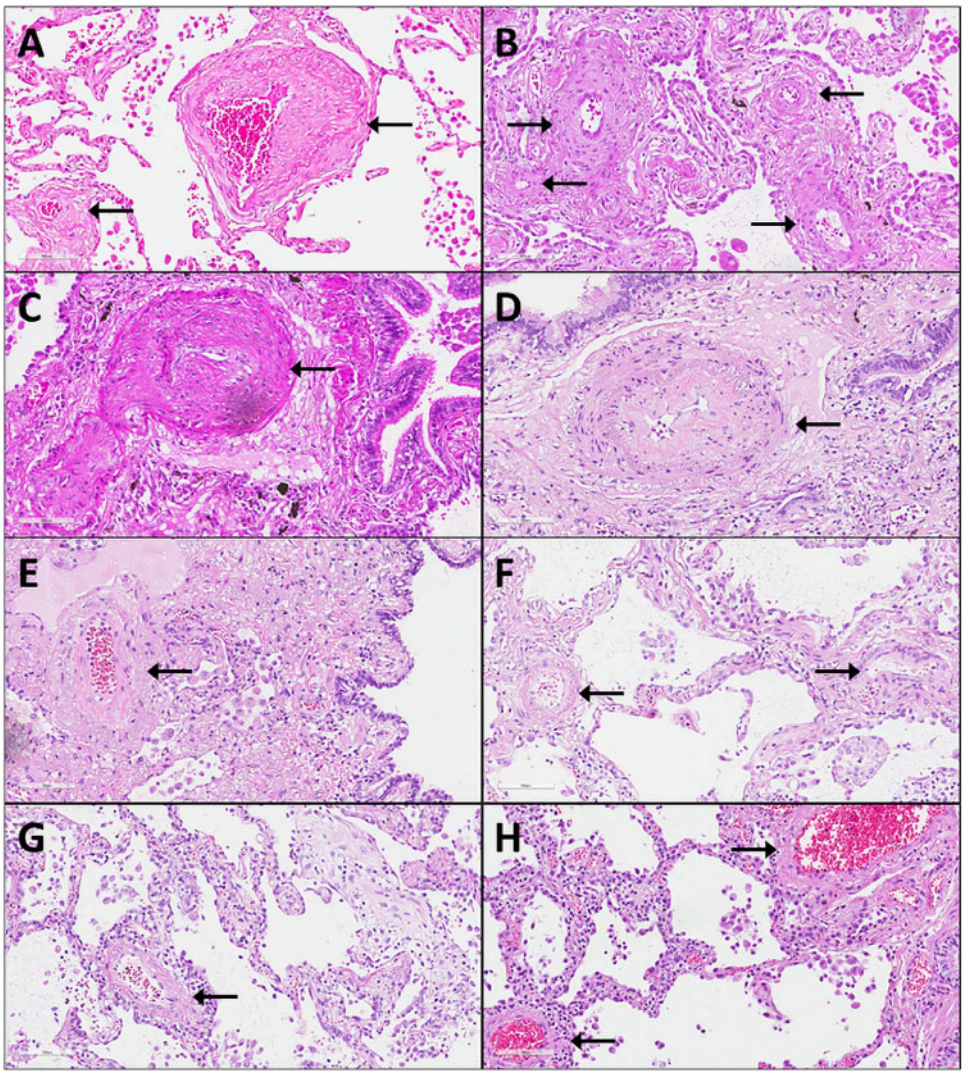
In case B, no PAH-specific alterations were identified in the histological examination of the left lower lobe despite the fact that PAH had been diagnosed 8 years before lobectomy. Lung fibrosis, present already early in disease, might have aggravated pulmonary hypertension. However, repeated high-resolution CT examinations before and after initiation of ambrisentan and rituximab have consistently regarded the overall extent of lung fibrosis as mild [6].

SSc-APAH is another disease than idiopathic PAH. In contrast to idiopathic PAH, plexogenic arteriopathy is absent in SSc-APAH, while small-vessel fibrosis is common [4, 5]. Even after the advent of modern vascular therapy, the prognosis for patients with SSc-APAH remains poor, and earlier initiation of treatment has been suggested to improve survival [7].

We suggest that not only haemodynamics but also vascular pathobiology should be included in the future classification of SSc-APAH by the European Society of Cardiology/European Respiratory Society. Ultimately, a biomarker specific for the pathobiology of lung arterioles is warranted. In the absence of such a tool, we appreciate the recent proposal that pre-capillary PH may be defined in patients with PVR $\geqslant$3 WU, pulmonary arterial wedge pressure $\leqslant$15 mmHg and mPAP $>$20 mmHg [1]. These patients often have underlying right ventricular dysfunction and could benefit from a more thorough examination of the right ventricle during stress, including the assessment of pulmonary arterial compliance. At present, we agree with previous studies suggesting that exercise RHC offers an opportunity to correctly diagnose early SSc-APAH [8].

In conclusion, early and correct identification of SSc-APAH still poses a considerable challenge [1]. We suggest that the current definitions do not completely reflect

Fig. 1 Histopathology of lung not fulfilling and fulfilling criteria for PAH associated with SSc



Case A: severe arteriolar abnormalities in areas without (**A**) and with (**B**, **C**) fibrosis. Case B: very few thickened arterioles in areas with fibrosis with architectural distortion (**D**), but normal in most such areas (**E**), as well as in areas with fibrosis with preserved architecture (**F**), organizing pneumonia (**G**) and interstitial inflammation (**H**). Scale bars: 100 μm.

the microscopic pathobiology of this disease, and that these classification criteria occasionally fail to identify early SSc-APAH. For future classification criteria, a biomarker specific for the SSc-APAH pathobiology is warranted.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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Early onset sarcoidosis (Blau syndrome): erosive and often misdiagnosed

Rheumatology key message

- Although uncommon, early severe radiological joint erosions do not preclude a diagnosis of EOS/Blau syndrome.

Dear Editor, Early-onset sarcoidosis (EOS) is an uncommon paediatric-onset arthritis caused by *de novo* mutation of *NOD2*; its rarity lends itself to misdiagnosis with systemic JIA. EOS when inherited via an autosomal dominant pathway is termed Blau syndrome; the two conditions are clinically identical. Deforming arthritis in the absence of significant radiographic erosions has been cited as a distinguishing feature of EOS. We report a case of proven EOS demonstrating clear evidence of progressive radiographic erosions.

A 31-year-old caucasian female diagnosed with systemic JIA in 1989 at 18 months, has been managed by our adult rheumatology service since 2007. Our patient's disease phenotype was composed of extensive deforming polyarthritis associated with bilateral panuveitis. Clinical examination revealed small joint synovitis as well as flexion contractures at the elbows. There has never been any cutaneous or nail changes. Eye examination showed the legacy of uncontrolled inflammatory activity with reduced visual acuity, bilateral vitritis and chorioretinal scarring. She had no significant family history.

Investigations reveal a negative rheumatoid factor, antinuclear antibody and anti-neutrophil cytoplasmic antibody alongside normal complement and elevated inflammatory markers. Hand radiographs 18 years after diagnosis showed widespread symmetrical erosive damage (Fig. 1). Pelvic and spinal radiographs have never demonstrated features of axial spondyloarthropathy.

Disease activity remained high despite conventional DMARDs and biologic DMARDs, including: anti-TNF (infliximab, adalimumab, etanercept, certolizumab, golimumab); anti CD-20 (rituximab); anti IL-6 (tocilizumab) and anti IL-1 (anakinra) agents. Consequently, she has required continuous daily oral corticosteroids to limit progression.

Her son, aged 4 years old, developed a symmetrical polyarthritis with uveitis and fever and following this, was diagnosed with EOS/Blau syndrome. At this point our patient's diagnosis was reviewed. Genetic testing in our patient confirmed the c.1000C>T mutation in the *NOD2* gene (16q12.1) leading to the pathological p.R334W protein change. Subsequently, her diagnosis was changed to that of EOS and her son's confirmed as Blau syndrome.

EOS is a sporadic auto-inflammatory condition, clinically and pathophysiologically distinct from other forms of sarcoidosis [1], characterized by the clinical triad of arthritis, recurrent uveitis and granulomatous skin dermatitis. Blau syndrome describes the inherited form, phenotypically indistinct from EOS; an initial genetic locus was located in 1996, with later localization of this to the *CARD15/NOD2* region [2]. Over 22 mutations of this gene have been identified, with p.R334Q and p.R334W found to account for a significant majority of EOS [3]. It is thought that these mutations lead to *NOD2* protein activation following antigen exposure, and may initiate an activation cascade terminating in the activation of end proteins, such as NF-kappa B, implicated in the inflammatory pathway [4].

The largest observational study to date reported findings from 24 patients (13 children and 11 adults, equating to radiographs of 45 hands and wrists in total) with Blau [5]. Significant abnormalities (for example, carpal dysplasia and crowding) were seen, but were notable for the total absence of radiographic erosions. Not all patients recruited to the study had radiological findings discussed, nor have they recorded the characteristics of the patients used (i.e. specific *NOD2* genetic mutation), limiting interpretation of these findings to the whole EOS/Blau cohort; nonetheless, this large study was unable to demonstrate erosive disease in these patients. Smaller reports again make no reports of patients with erosive disease [3, 6].