CASE REPORT

JIACM 2026; 27 (3): 211-14

Autoimmune Polyglandular Syndrome Type II Presenting as Seronegative Autoimmune Addison's Disease with Mixed Connective Tissue Disease

Amit Sharma, Deepak Jain**, Divyajyoti Das*, Manjri Garg***, Shatakshi*****

Abstract

***Background:** Autoimmune Polyglandular Syndrome Type II (APS II) is defined by autoimmune primary adrenal insufficiency with autoimmune thyroid disease and/or type 1 diabetes. Mixed Connective Tissue Disease (MCTD) is characterised by anti-U1-snRNP antibodies. In MCTD, interstitial lung disease (ILD) typically presents as nonspecific interstitial pneumonia (NSIP), whereas usual interstitial pneumonia (UIP) is less common. The coexistence of APS II, seronegative autoimmune adrenalitis, MCTD, and UIP-pattern ILD is exceptionally rare, particularly in tuberculosis-endemic regions, where adrenal calcification is often presumed to be tubercular.*

***Case Presentation:** A 45-year-old woman with autoimmune hypothyroidism presented with weakness, hyperpigmentation, weight loss, and basal crackles. Morning cortisol was 3.75 µg/dL with ACTH >1250 pg/mL, confirming primary adrenal insufficiency. Anti-TPO >1300 IU/mL, ANA 1:1000, high anti-U1-snRNP, and anti-Sm positivity met Alarcón-Segovia criteria for MCTD. HRCT showed basal honeycombing and traction bronchiectasis consistent with UIP. CT abdomen revealed unilateral adrenal calcification; a CyTb induration of 2 mm indicated a negative test. Interferon-Gamma Release Assay (IGRA) was negative as well. She was treated with hydrocortisone, fludrocortisone, levothyroxine, and cyclophosphamide.*

***Conclusion:** This case represents an extraordinarily rare overlap of APS II, seronegative autoimmune Addison's disease, MCTD, and UIP-pattern ILD. This rare combination underscores the importance of distinguishing autoimmune adrenalitis from tuberculosis and demonstrates that unilateral adrenal calcification is not pathognomonic for TB.*

Introduction

Primary adrenal insufficiency is a life-threatening endocrine disorder and often presents with hyperpigmentation of the skin and mucosa, chronic fatigue, hypotension, hypoglycaemia, hyponatraemia and hyperkalaemia. A high degree of clinical suspicion is required for rapid diagnosis as delayed diagnosis may lead to adrenal crisis. Autoimmune adrenalitis is now the predominant cause of primary adrenal insufficiency, although tuberculosis still remains an important cause in endemic regions[1,2]. Autoimmune adrenalitis characteristically progresses with lymphocytic infiltration and cortical destruction of the adrenal glands. Anti-21-hydroxylase antibodies are highly specific but may be absent in up to 20% of advanced cases[2,3]. Autoimmune Polyglandular Syndrome (APS) type II reflects a genetically determined clustering of autoimmune adrenal, thyroid, and other endocrine disorders[4].

Mixed Connective Tissue Disease (MCTD) is defined by high-titre anti-U1-snRNP antibodies and overlapping features of Systemic Lupus Erythematosus (SLE), systemic sclerosis, and polymyositis[5]. ILD occurs in up to 75% of MCTD patients, but UIP is significantly less common[6].

Here we present an extraordinary overlap of APS II, seronegative autoimmune adrenalitis, MCTD, and UIP ILD with unilateral adrenal calcification.

Case Report

A 45-year-old woman with a 10-year history of autoimmune hypothyroidism on levothyroxine presented with progressive generalised weakness for 15 months, diffuse hyperpigmentation for 6 months, and unintentional weight loss of approximately 5 kg. She did not have a history of fever, cough, haemoptysis, night sweats, tuberculosis, diabetes, or prior glucocorticoid use. She had longstanding secondary amenorrhoea for nearly a decade and had never conceived. She also reported episodic cold-induced discolouration of the fingers suggestive of Raynaud phenomenon. On examination, she was thin with a body mass index of 16 kg/m^2; blood pressure was 90/60 mmHg without postural drop, pulse was 84/min, respiratory rate was 20/min, and oxygen saturation was 95% on room air. There was no pallor, icterus, cyanosis, clubbing, lymphadenopathy or pedal oedema. There was marked diffuse hyperpigmentation involving

**Resident, **Senior Professor, ****Assistant Professor, Department of Medicine, ***Professor, Department of Pathology, Pandit BD Sharma University of Health Sciences, PGIMS Rohtak - 124 001, Haryana.*
Corresponding Author: Dr Deepak Jain, Senior Professor, Department of Medicine, Pandit BD Sharma University of Health Sciences, PGIMS Rohtak - 124 001, Haryana. Tel: 9416147887, E-mail: jaindeepakdr@gmail.com

the face, neck, knuckles, elbows, palmar creases, tongue, and buccal mucosa (Fig. 1). Fine end-inspiratory "Velcro-like" crackles were audible over both lung bases, while cardiovascular, abdominal, and neurologic examination was unremarkable. Laboratory evaluation showed haemoglobin 10.3 g/dL, total leukocyte counts 6,300/mm^3, platelet counts 2.2 lakh per mm^3, MCV 91.1 fL, MCH 27.3 pg, MCHC 32.1 g/dL, fasting glucose 72 mg/dL, sodium 131 mmol/dL, potassium 4.9 mmol/L, and elevated ESR of 79 mm/hr. HbA1c was 5.6 %, corrected calcium 9.7 mg/dL, and phosphate 3.3 mg/dL. Liver and renal functions were normal. Endocrine evaluation revealed a markedly low morning serum cortisol concentration of 3.75 µg/dL (reference 5.27 - 22.40 µg/dL) with profoundly elevated ACTH levels >1250 pg/mL (reference 0 - 46 µg/mL), confirming primary adrenal insufficiency[1]. Thyroid profile showed elevated TSH of 22.56 µIU/mL with anti-thyroid peroxidase antibody titres >1300 IU/mL. Evaluation for infectious aetiologies revealed a negative interferon-gamma release assay (IGRA) and a CyTb skin test induration of 2 mm, interpreted as negative[7]. ECG showed, sinus rhythm. Chest X-ray showed mild bilateral basal reticular opacities with reduced lung volumes, without focal consolidation or pleural effusion. Pulmonary function testing showed a restrictive ventilatory defect with reduced diffusing capacity for carbon monoxide, consistent with interstitial lung disease. An echocardiography revealed preserved left ventricular systolic function without pulmonary hypertension. High-resolution CT scan of the chest demonstrated basal and subpleural honeycombing, traction bronchiectasis, and a straight-edge sign consistent with a usual interstitial pneumonia pattern[8] (Fig. 2). Contrast- enhanced CT scan of the abdomen revealed a bulky right adrenal gland with coarse calcification and a normal left adrenal gland, with no lymphadenopathy or features of active granulomatous disease. Extractable nuclear antigen analysis demonstrated a high-titre antinuclear antibody with a speckled pattern (1:1000; reference <1:80). Anti-U1-snRNP antibody levels were markedly elevated (>200 U/mL; reference <20 U/mL), with concomitant positivity of anti-RNP (>180 U/mL; reference <20 U/mL) and anti-Sm antibodies (65 U/mL; reference <20 U/mL). Antibodies to double-stranded DNA (anti-dsDNA 8 IU/mL; reference <30 IU/mL), SSA/Ro and SSB/La (both <10 U/mL; reference <20 U/mL), Scl-70 (<5 U/mL; reference <20 U/mL), Jo-1 (<5 U/mL; reference <20 U/mL), rheumatoid factor (6 IU/mL; reference <14 IU/mL), and anti-cyclic citrullinated peptide antibodies (4 U/mL; reference <20 U/mL) were negative. This ENA profile was strongly supportive of mixed connective tissue disease. As the patient had ILD and features of autoimmune serology, based on high-titre anti-U1-snRNP positivity along with Raynaud phenomenon, hand oedema, and synovitis, the patient fulfilled Alarcón-Segovia criteria for mixed connective tissue disease[9]. She was diagnosed with autoimmune polyglandular syndrome type II with seronegative autoimmune Addison's disease and UIP-pattern interstitial lung disease and was initiated on hydrocortisone, fludrocortisone, and levothyroxine after steroid replacement. Patient was started on IV Cyclophosphamide 600mg/m^2 every 4 weeks for interstitial lung disease[10]. She is on regular follow-up currently, and has improved significantly.



Fig. 1: *Progressive hyperpigmentation of face, neck and dorsum of hands.*

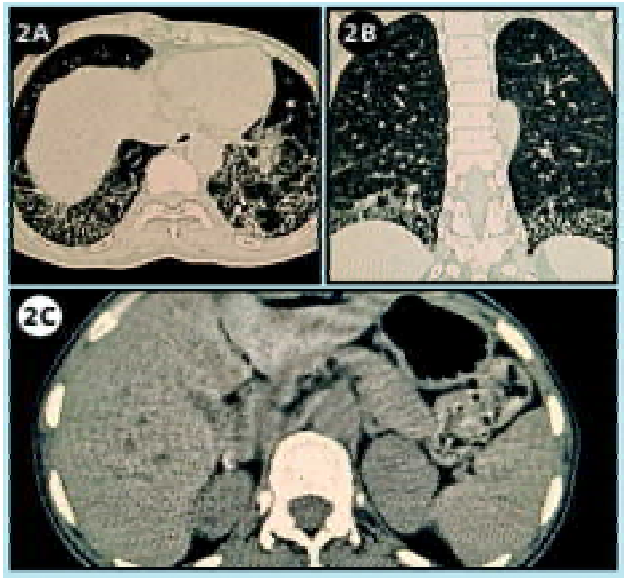


Fig. 2: *High-resolution computed tomography of Chest and contrast enhanced computed tomography of Abdomen.*

Discussion

This case represents an exceptionally rare and diagnostically challenging coexistence of autoimmune polyglandular syndrome type II, seronegative autoimmune adrenalitis, mixed connective tissue disease, and usual interstitial pneumonia-pattern interstitial lung disease. Primary adrenal insufficiency was unequivocally established by the biochemical profile of markedly low cortisol with disproportionately elevated ACTH, and the coexistence of autoimmune thyroiditis strongly supported the diagnosis of APS II[1,4]. Although anti-21-hydroxylase antibodies are highly specific markers of autoimmune adrenalitis, up to 10 - 20% of patients may be seronegative, particularly in advanced disease when extensive cortical destruction leads to antigen depletion, making seronegativity a recognised and clinically important phenomenon[2,3]. In tuberculosis-endemic regions, adrenal calcification often leads to diagnostic anchoring toward tuberculous adrenalitis; however, classical tuberculous involvement typically produces bilateral adrenal enlargement followed by coarse bilateral calcification, whereas unilateral adrenal calcification, as observed in this patient, is atypical and broadens the differential diagnosis to include autoimmune adrenalitis, prior haemorrhage, vascular insult, or idiopathic calcification[11,12]. The absence of constitutional symptoms, lack of pulmonary or nodal tuberculosis, a negative interferon-gamma release assay, and a negative CyTb skin test (2 mm) significantly reduced the likelihood of both active and latent tuberculosis, favouring an autoimmune aetiology[7]. Hence , unilateral adrenal calcification should be interpreted in the overall clinical context rather than being considered diagnostic of tuberculous adrenalitis[11]. Mixed connective tissue disease was confirmed using Alarcón-Segovia criteria[9], and although interstitial lung disease is common in MCTD, the predominant pattern is nonspecific interstitial pneumonia; usual interstitial pneumonia occurs in a minority of cases and is associated with a more fibrotic phenotype, poorer response to corticosteroids, and worse long-term prognosis[6,13].

The high-resolution CT findings of basal honeycombing, traction bronchiectasis, and a straight-edge sign in this patient were characteristic of a UIP pattern, necessitating immunosuppressive therapy with cyclophosphamide, extrapolated from evidence in other connective tissue disease-associated fibrotic interstitial lung diseases[8,10,14]. Epidemiologically, autoimmune polyglandular syndrome type II (~14-20 per million), mixed connective tissue disease (~1-4 per 100,000), seronegative autoimmune adrenalitis (~10-20% of autoimmune Addison's disease), and UIP-pattern interstitial lung disease in MCTD (~8-20%) are individually uncommon[3,4,15]. Their coexistence therefore represents an exceptionally rare convergence of low-prevalence disease entities, even after accounting for autoimmune clustering. Autoimmune adrenalitis is initiated by loss of immune tolerance, leading to autoreactive T-cell infiltration and antibody-mediated targeting of steroidogenic enzymes, most notably 21-hydroxylase, resulting in progressive destruction of the adrenal cortex[2]. Over time, chronic inflammation culminates in cortical atrophy, fibrous replacement, and in some cases dystrophic calcification; advanced disease stages may lack detectable circulating autoantibodies due to near-complete loss of antigenic tissue, accounting for seronegative presentations[2,3]. Autoimmune polyglandular syndrome type II arises from shared immunogenetic susceptibility, particularly HLA-linked defects in central and peripheral immune tolerance, enabling simultaneous or sequential autoimmune involvement of multiple endocrine organs[4]. Mixed connective tissue disease is driven by anti-U1-snRNP-mediated immune activation, with downstream interferon signalling, endothelial dysfunction, and fibroblast activation contributing to systemic manifestations[13]. In the lung, repeated immune-mediated alveolar epithelial injury with aberrant repair mechanisms leads to interstitial fibrosis, manifesting most commonly as nonspecific interstitial pneumonia; however, in a subset of patients, dysregulated wound healing and fibroblast proliferation result in the usual interstitial pneumonia pattern, characterised by fibroblastic foci, architectural distortion, honeycombing, and irreversible fibrosis, which confers a more aggressive disease course and poorer prognosis[8,13]. To our knowledge, the coexistence of APS II with seronegative autoimmune Addison's disease, MCTD, UIP-pattern ILD, and unilateral adrenal calcification has rarely, if ever, been reported in the published literature, highlighting the diagnostic complexity of autoimmune endocrine–rheumatological overlap syndromes[4,15].

Key Learning Points

1. Unilateral adrenal calcification is not pathognomonic of tuberculosis; evaluate for autoimmune, vascular, or other causes.
2. Seronegative autoimmune adrenalitis occurs in up to 20% and must be considered despite negative 21-OH antibodies.
3. CyTb induration of 2 mm should be interpreted as negative and reduces the likelihood of TB in the appropriate clinical context.
4. UIP-pattern ILD in MCTD is uncommon but signals a fibrotic phenotype with worse prognosis.
5. Cyclophosphamide is an evidence-based induction therapy for severe fibrotic CTD-ILD.

Conclusion

This patient's combination of APS II, seronegative autoimmune Addison's disease, MCTD, and UIP-ILD is exceptionally rare. Unilateral adrenal calcification, negative CyTb testing, and strong autoimmune serology guided correct diagnosis and avoided inappropriate anti-tubercular therapy. Early identification and appropriate immunosuppression were essential to address the progressive fibrotic lung disease and life-threatening adrenal insufficiency.

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