

Reynolds Syndrome: A Rare Autoimmune Overlap Syndrome — A Case Series and Literature Review

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Abstract

Background

Systemic sclerosis (SSc) and primary biliary cholangitis (PBC) are chronic autoimmune diseases whose overlap defines a rare clinical entity known as Reynolds syndrome (RS). Knowledge regarding its pathophysiology, optimal diagnostic screening, and long-term prognosis remains evolving.

Case Presentation:

We report the case of a 52-year-old female presenting with profound fatigue, sicca symptoms, myalgia, arthralgia, and exertional dyspnea. Physical examination revealed sclerodactyly, puffy fingers, and bilateral parotid enlargement. Laboratory evaluation demonstrated systemic inflammation, polyclonal hypergammaglobulinemia, and a prominent cholestatic liver enzyme profile. Indirect immunofluorescence on HEp-2 cells exhibited a strongly positive antinuclear antibody titer (1:1280) with centromeric (AC-3), mitochondrial-type cytoplasmic (AC-21), and nuclear envelope (AC-11) fluorescence patterns. Line blot immunoassay confirmed high positivity for anti-centromere B and antimitochondrial M2 (AMA-M2) antibodies. Minor salivary gland biopsy confirmed grade 4 chronic sialadenitis. The patient was diagnosed with Reynolds syndrome combining limited cutaneous SSc and PBC, complicated by secondary Sjögren's syndrome. Treatment with ursodeoxycholic acid, hydroxychloroquine, anethole trithione, and a tapering course of oral corticosteroids yielded complete normalization of liver function parameters.

Discussion & Review:

A synthesis of current literature highlights shared autoimmune mechanisms, including common HLA susceptibility alleles and potential nuclear envelope protein alterations (such as *LBR* mutations). Cross-screening remains paramount: AMA testing in SSc allows early detection of subclinical PBC, while testing for anti-centromere antibodies and nailfold capillaroscopy in PBC aids early SSc identification. Although hepatic progression in RS appears comparatively indolent relative to isolated PBC, overall outcomes are dictated by visceral SSc manifestations.

Conclusion

Concomitant PBC and SSc requires heightened clinical vigilance and systemic cross-screening to optimize early detection and targeted management. Further multi-center cohort studies are warranted to elucidate shared pathophysiological pathways and standardized therapeutic approaches.

LEARNING POINTS

- The chronological relationship between SSc and PBC is variable, and both conditions may be diagnosed simultaneously. This temporal variability underscores the importance of systematic cross-screening: patients with SSc should be evaluated for cholestatic liver abnormalities and AMA, while patients with PBC should be assessed for clinical and serological features of SSc.
- The absence of ACA does not exclude SSc in patients with RS, as illustrated by the second case.
- Early recognition of visceral involvement, particularly interstitial lung disease and portal hypertension, is essential for appropriate management and prognostic assessment.

INTRODUCTION/BACKGROUND

Systemic sclerosis (SSc) and primary biliary cholangitis (PBC) are two chronic autoimmune diseases whose association, known as Reynolds syndrome (RS), represents a rare clinical entity (1). Although this association is now well recognized, its epidemiological, clinical, immunological, and prognostic characteristics remain incompletely defined, and knowledge regarding its pathophysiology, diagnosis, and management is still limited.

We report two cases of RS and provide a review of the literature to summarize the current knowledge regarding its epidemiological, genetic, pathophysiological, and diagnostic features.

CASE DESCRIPTION

CASE 1

A 52-year-old woman with a history of well-controlled type 2 diabetes mellitus and arterial hypertension was admitted to the internal medicine department for evaluation of severe ocular and oral dryness associated with myalgia, diffuse arthralgia, profound fatigue, and exertional dyspnea.

Physical examination revealed sclerodactyly and puffy fingers. Bilateral parotid enlargement was also noted. Abdominal examination showed no hepatomegaly or splenomegaly. No clinical signs of cardiac or pulmonary involvement were observed.

Laboratory investigations showed biological inflammation, with an erythrocyte sedimentation rate of 41 mm in the first hour, a C-reactive protein level of 24.8 mg/L, and polyclonal hypergammaglobulinemia of 16 g/L on serum protein electrophoresis. A cholestatic liver profile was also found, characterized by elevated gamma-glutamyl transferase, alkaline phosphatase, and total bilirubin levels, reaching two to three times the upper limit of normal, after exclusion of viral, drug-induced, and obstructive causes. Renal function was preserved.

Antinuclear antibodies (ANA) were tested by indirect immunofluorescence (IIF) on HEp-2 cell and monkey liver substrates (Human Epithelial type 2; EUROIMMUN Medizinische Labordiagnostika AG, Lübeck, Germany), using an initial dilution of 1:160. The test showed strongly positive fluorescence, with a titer of 1:1280, characterized by a centromeric pattern corresponding to AC-3 according to the

International Consensus on ANA Patterns (ICAP) nomenclature. This was associated with reticular cytoplasmic mitochondrial-type fluorescence (AC-21), suggestive of antimitochondrial antibodies (AMA), as well as nuclear envelope fluorescence (AC-11) (Fig. 1).

The profile of antibodies directed against extractable nuclear antigens (ENA), including Sm, RNP/Sm, SSA/Ro52, SSB, Jo-1, Scl-70, nucleosomes, centromere antigens, PM-Scl100, PCNA, histones, AMA-M2, ribosomal P proteins, and DFS70, was assessed using the Immunodot ANA Profile 3 Plus DFS70 kit (EUROIMMUN Medizinische Labordiagnostika AG, Lübeck, Germany). The bands were analyzed and quantified using EUROLineScan software (EUROIMMUN Medizinische Labordiagnostika AG, Lübeck, Germany). This analysis confirmed the presence of strongly positive anti-centromere B antibodies and antimitochondrial M2 antibodies (AMA-M2) (Fig. 2).

Abdominal ultrasonography revealed no abnormalities of the biliary tract or liver parenchyma. Non-invasive assessment of hepatic fibrosis using FibroTest® showed no significant fibrosis (F0 stage).

A minor salivary gland biopsy showed grade 4 chronic sialadenitis according to the Chisholm and Mason classification, compatible with Sjögren's syndrome.

The final diagnosis was Reynolds syndrome, combining limited cutaneous systemic sclerosis and PBC, complicated by secondary Sjögren's syndrome. Oral corticosteroid therapy was initiated, followed by gradual tapering. Background treatment with hydroxychloroquine and anethole trithione was also introduced, together with symptomatic measures for sicca syndrome. PBC was treated with ursodeoxycholic acid, resulting in normalization of the cholestatic liver parameters.

CASE 2

This was a 57-year-old man with no significant medical history who was admitted to the gastroenterology department for evaluation of dysphagia associated with generalized pruritus and deterioration of his general condition. From a gastrointestinal standpoint, he reported dysphagia to solid foods, associated with chronic, intermittent, moderate-intensity right upper quadrant pain. He also reported dyspnea and Raynaud's phenomenon.

On physical examination, mild scleral icterus was noted. The abdomen was soft, nondistended, and non-tender, with no palpable mass or organomegaly. There were no clinical signs of hepatocellular insufficiency or portal hypertension. The cardiopulmonary examination was unremarkable. Dermatological examination revealed smooth skin and facial skin, reduced facial expression, a slightly tapered nose, limited mouth opening, sclerodactyly, and multiple telangiectasias on the back and lower limbs.

Laboratory investigations showed a moderate inflammatory syndrome, with a CRP level of 17.95 mg/L, as well as moderate cholestasis characterized by γ -glutamyl transferase and alkaline phosphatase levels approximately twice the upper limit of normal. This was associated with mixed hyperbilirubinemia at

31.4 mg/L, without evidence of hepatocellular injury. Serum protein electrophoresis revealed polyclonal hypergammaglobulinemia. Indirect immunofluorescence testing for antinuclear antibodies showed a reticular cytoplasmic mitochondrial pattern (AC-21), suggestive of antimitochondrial antibodies.

The profile of extractable nuclear antigen antibodies was assessed using the Immunodot kit and confirmed the presence of strongly positive anti-mitochondrial M2 antibodies (AMA-M2) (Fig. 2).

A thoracoabdominopelvic CT scan performed during hospitalization revealed diffuse interstitial lung disease with a nonspecific interstitial pneumonia (NSIP) pattern, as well as chronic liver disease associated with signs of portal hypertension, without ascites. Esophagogastroduodenoscopy showed grade I esophageal varices without red wale signs, together with portal hypertensive gastropathy.

Overall, the clinical, laboratory, and radiological findings were consistent with systemic sclerosis associated with primary biliary cholangitis, defining Reynolds syndrome, with interstitial lung involvement and complications related to portal hypertension.

Oral corticosteroid therapy was initiated, followed by gradual tapering. Primary biliary cholangitis was treated with ursodeoxycholic acid, resulting in normalization of the cholestatic parameters. Raynaud's phenomenon was treated with isosorbide mononitrate. Given the interstitial lung disease associated with systemic sclerosis, immunosuppressive therapy with mycophenolate mofetil was initiated. Prophylaxis against variceal bleeding was also implemented using a non-selective beta-blocker.

DISCUSSION

The association between PBC and SSc was first reported in 1934 by Milbradt et al. (2) and was later recognized as a distinct clinical entity by Reynolds et al. in 1971 under the name Reynolds syndrome (RS) (1). Since then, case reports and case series have confirmed this overlap and helped characterize its clinical, serological, and evolutionary features (3–16).

From an epidemiological perspective, the prevalence of PBC among patients with SSc is estimated at 2–2.5%, whereas the prevalence of SSc among patients with PBC is approximately 8% (8, 10, 11). Most reported cases involve the limited cutaneous form of SSc (8, 11, 12, 14, 17–21), as observed in our patient.

The association between SSc and PBC suggests the existence of shared pathophysiological mechanisms that remain incompletely understood and involve genetic, epigenetic, environmental, and infectious factors. PBC and SSc share several susceptibility genes, including HLA-DRB1, HLA-DQA1, HLA-DQB1, IRF5, and STAT4, supporting the hypothesis of a shared autoimmune background. However, some associations differ between the two diseases, as the HLA-DR11 allele, which is associated with an increased risk of SSc, appears to be protective in PBC (22, 23).

From a pathophysiological perspective, Gaudy-Marqueste et al. (24) suggested that, in some patients, RS may result from abnormalities in nuclear envelope proteins caused by a heterozygous mutation in the

****LBR**** gene (Lamin B Receptor). This mutation was absent in 400 control subjects and was associated with altered expression of nuclear envelope proteins, including lamins A/C, B1, B2, and HP1 α , in skin fibroblasts, suggesting a tissue-specific mechanism that may contribute to the overlap phenotype. However, these findings are based on a single observation, and the hypothesis of a genetic laminopathy remains speculative (25).

Infectious agents may also act as potential cofactors in the pathogenesis of both diseases. *Helicobacter pylori* and *Chlamydia* species have been implicated in the pathogenesis of SSc and PBC (26–29). However, the role of *Chlamydia* remains controversial, as several studies have failed to confirm this association (30–32). An expansion of CD8 + T lymphocytes expressing a specific variable region of the beta chain of the T-cell receptor (TCRBV3) has also been reported in patients with RS and may contribute to disease pathogenesis (33).

Several studies indicate that there is no consistent chronological sequence in the development of RS. Different series have reported PBC preceding SSc, SSc preceding PBC, or simultaneous diagnosis of both diseases (1, 8, 12, 14–16, 34, 35). Our case illustrates this heterogeneity, as both diseases were diagnosed concomitantly.

Sicca syndrome is one of the most frequent autoimmune associations in RS, with reported prevalence rates ranging from 20% to 66% (6, 8, 20). Launay et al. also described, on minor salivary gland biopsy, a periductal lymphocytic infiltrate associated with epithelial necrosis of the excretory ducts, representing histological lesions suggestive of PBC (13). These findings suggest the existence of a common autoimmune process targeting biliary and salivary epithelia, supporting the hypothesis of a shared antigenic target.

Cross-screening for PBC and SSc is recommended. In patients with SSc, the presence of AMA may precede the clinical manifestations of PBC, justifying regular monitoring of liver function. Conversely, in patients with PBC, testing for ACA, assessment of SSc-related clinical features, and nailfold capillaroscopy may facilitate the early detection of systemic sclerosis (2, 36).

AMA are the main serological marker of PBC, with a sensitivity of 90–95% and a specificity of approximately 95%. They are directed against several enzymes of the 2-oxoacid dehydrogenase complexes located in the inner mitochondrial membrane, mainly the E2 subunit of pyruvate dehydrogenase (PDC-E2), as well as E3BP, OGDH-E2, and BCOADH-E2 (37).

In AMA-negative disease, PBC-specific antinuclear antibodies, particularly anti-gp210 and anti-Sp100 antibodies, have important diagnostic and prognostic value. Anti-gp210 antibodies, directed against a nuclear pore glycoprotein and associated with a punctate nuclear envelope pattern on IIF, are detected in 10–40% of patients with PBC and in 20–50% of AMA-negative cases. Their high specificity, estimated at 90–95%, and their association with adverse hepatic outcomes make them important diagnostic and prognostic markers (38).

Anti-Sp100 antibodies, directed against a nuclear protein involved in transcriptional regulation, produce a characteristic multiple nuclear dot pattern on IIF. They are detected in 15–30% of patients with PBC. Although less specific than anti-gp210 antibodies, they are useful diagnostic markers, particularly in AMA-negative cases, and their positivity has been associated with more severe disease progression (39).

ACA are a serological marker suggestive of SSc. They are primarily directed against the centromeric proteins CENP-A, CENP-B, and CENP-C and are detected in 6–30% of patients with PBC (2, 12, 40, 41). However, their presence is not essential for the diagnosis of SSc. In a cohort of 43 patients with PBC-SSc overlap, 13 patients (approximately 30%) were ACA-negative, as was the case in our second patient. Conversely, AMA are detected in approximately 22–25% of patients with SSc, particularly in those with limited cutaneous disease. As no cross-reactivity between mitochondrial and centromeric antigens has been demonstrated, the pathogenic role of ACA in biliary involvement remains uncertain to date (2).

PBC associated with SSc, particularly the limited cutaneous form, appears to have a more favorable hepatic prognosis than isolated PBC (8, 16). However, this hepatic benefit does not necessarily translate into improved overall survival, as prognosis may be influenced by visceral complications of SSc (8). More recent data nevertheless suggest that this overlap may correspond to a milder SSc phenotype, which could contribute to a relatively favorable overall prognosis (15).

CONCLUSION

This case highlights the importance of increasing clinicians' awareness of the potential association between PBC and SSc and of implementing appropriate cross-screening strategies to improve early diagnosis and optimize patient management. Multicenter studies involving larger cohorts are needed to better characterize the pathophysiological mechanisms underlying this association and to refine diagnostic, therapeutic, and prognostic strategies.

Declarations

DISCLOSURE

Conflict of interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Patient Consent: Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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Figures

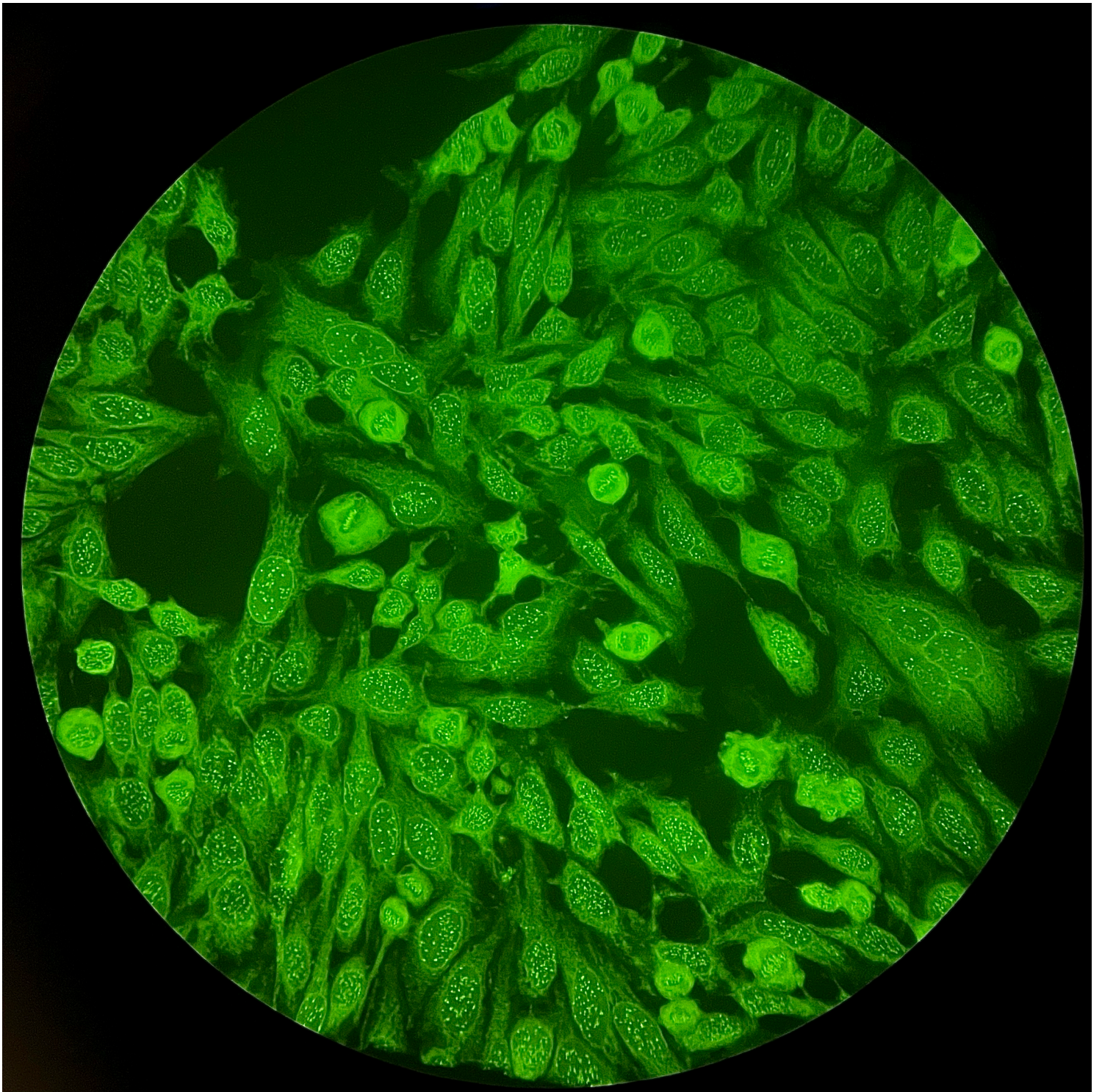


Figure 1

Indirect immunofluorescence on HEp-2 cells : strongly positive antinuclear antibody fluorescence at a titer of 1:1280, with a centromeric pattern (AC-3), associated with reticular mitochondrial-type cytoplasmic fluorescence (AC-21) and nuclear envelope fluorescence (AC-11), according to the ICAP classification.

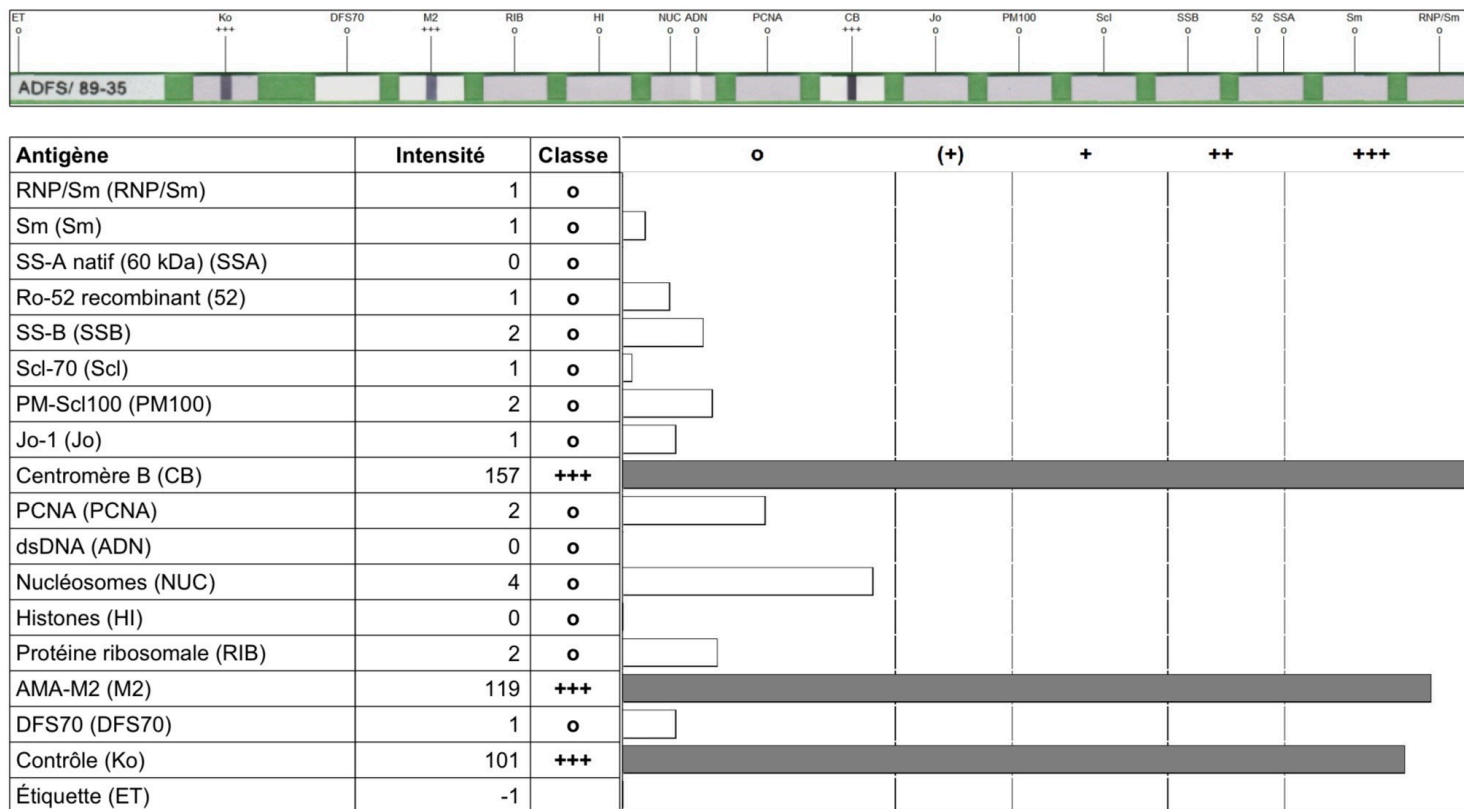


Figure 2

Identification of autoantibodies by immunoblotting using the Immunodot ANA Profile 3 Plus DFS70 assay : strong positivity for anti-centromere B and anti-AMA-M2 antibodies. Manufacturer's interpretation thresholds: negative (0–5), equivocal (6–10), positive (11–50), and strongly positive (>50).