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CASE REPORT: ATYPICAL ANTI-SAE1 AUTOANTIBODY MANIFESTATION WITH SPLINTER HEMORRHAGES AS ONSET, AND RELATED TO UROTHELIAL CANCER

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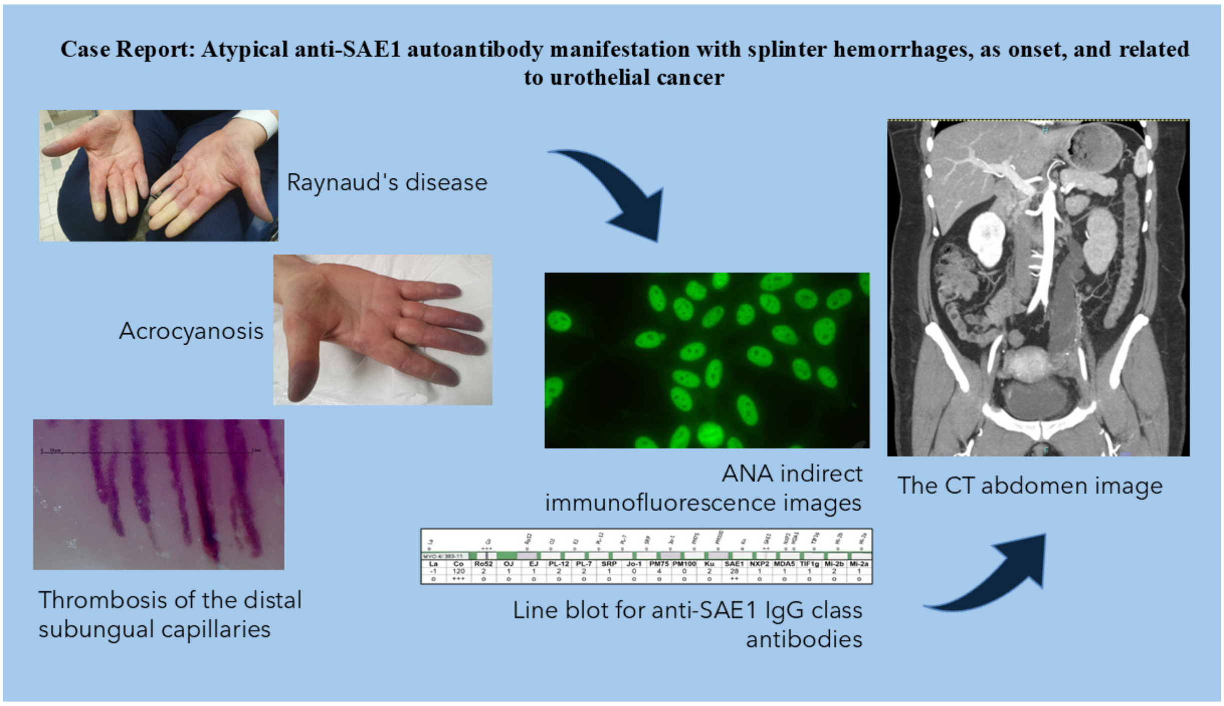
ABSTRACT – ***Background:*** Subungual splinter hemorrhages may represent an expression of infective endocarditis as well as autoimmune diseases or neoplasms. Anti-SAE1 autoantibody is directed against a small ubiquitin-like modifier-activating enzyme that plays a role in regulating transcription, cell cycle, and apoptosis. It is specific for dermatomyositis with skin rash and mild muscle involvement, and it can be associated with cancer.

Case Report: We describe the case of a patient who developed subungual splinter hemorrhages and acrocyanosis. Infections were excluded, and autoimmunity resulted in anti-SAE1 autoantibodies. A cancer screening found a high-grade urothelial carcinoma. The splinter hemorrhages disappeared after the carcinoma enucleation.

Conclusions: Our case describes an atypical onset of anti-SAE1 dermatomyositis with splinter hemorrhages, potentially linked to urothelial cancer. This highlights the importance of comprehensive cancer screening in patients with unusual dermatomyositis presentations.

KEYWORDS: Subungual splinter hemorrhages, Autoimmune diseases, Neoplasms, anti-SAE1 autoantibody, Dermatomyositis, Urothelial carcinoma, Paraneoplastic syndrome.



Graphical Abstract. From clinical symptoms and subungual splinter haemorrhages to positive immunoblot for anti-SAE1 antibodies, leading to urothelial carcinoma diagnosis confirmed by CT scan.

INTRODUCTION

Subungual splinter hemorrhages may be an expression of infective endocarditis as well as autoimmune diseases[1] or, as described in some case reports, neoplasms[2]. The anti-SAE1 autoantibody is directed against a ubiquitin-related protein that plays a role in regulating transcription, the cell cycle, and apoptosis. It is specific for dermatomyositis, where skin involvement is the most common initial manifestation, followed by late-onset mild myositis. Dysphagia may occur, and cases of organizing pneumonia have also been reported[3]. Cutaneous manifestations include the classical dermatomyositis signs such as Gottron's sign, Gottron's papules, heliotrope rash, as well as the "V-sign" and "Shawl sign." In addition, a diffuse dark-red or hyperpigmented rash has also been described in the literature[4]. Anti-SAE1 autoantibody can be associated with neoplasms in approximately percentage of around 20% of cases, with colorectal, esophageal, and uterine cancer being the most commonly reported[5]. However, no cases of urothelial neoplasms have been previously documented.

CASE PRESENTATION

We present the case of a 50-year-old woman with no history of smoking or occupational exposure to toxic substances. She had a familiarity with lung cancer from her father and breast cancer from her mother. In December 2023, she developed urinary burning symptoms and was treated with Levofloxacin for a suspected urinary tract infection, with symptomatic relief. Shortly thereafter, she presented with Raynaud's phenomenon (RF) and subsequent splinter hemorrhages in the distal portion of all fingernails and persistent acrocyanosis (Figure 1). The blood test showed a slight elevation of C-reactive protein (CRP) 1.42 mg/dL and erythrocyte sedimentation rate (ESR) 45 mm/h; white blood cell count, creatinine, electrolytes, and liver enzymes were all normal; blood cultures were negative. Vascular pathological findings were excluded by arterial and venous upper limbs Doppler ultrasound and CT chest angiography. Nailfold capillaroscopy was negative for the presence of giant capillary vessels, but multiple flame hemorrhages and thrombosed capillaries were detected, especially in the distal part of the nail (Figure 2). A transesophageal echocardiogram did not reveal valvular vegetations. Autoimmune testing revealed positive ANA 1:80 with a nuclear fine speckled pattern (AC-4) and a cytoplasmic dense fine speckled pattern (AC-19). Anti-ENA, ANCA, and anti-phospholipid antibodies were all negative and the Lupus anticoagulant test (LAC) was absent. Blotting rare myositis-specific autoantibodies resulted in a positive for Ab anti-SAE1 (Figure 3).

Figure 1. Clinical symptomatology images; (**A**) Raynaud's disease, (**B**) Splinter hemorrhages and acral ulcers in the right hand, (**C**) Detail of splinter hemorrhages in the 3rd and 4th fingers of the right hand, (**D**) Acrocyanosis.

Intravenous iloprost was started due to clinical acrocyanosis worsening with ischemic-like pain. Anyway, we assisted only in a partial skin manifestation improvement. A first-level cancer screening was then performed: left kidney third-degree hydronephrosis and the ipsilateral ureter dilatation up to its outlet, in the bladder, was found at abdominal ultrasound. Abdominal CT with contrast medium confirmed an inhomogeneous, polylobate mass causing pelvic and

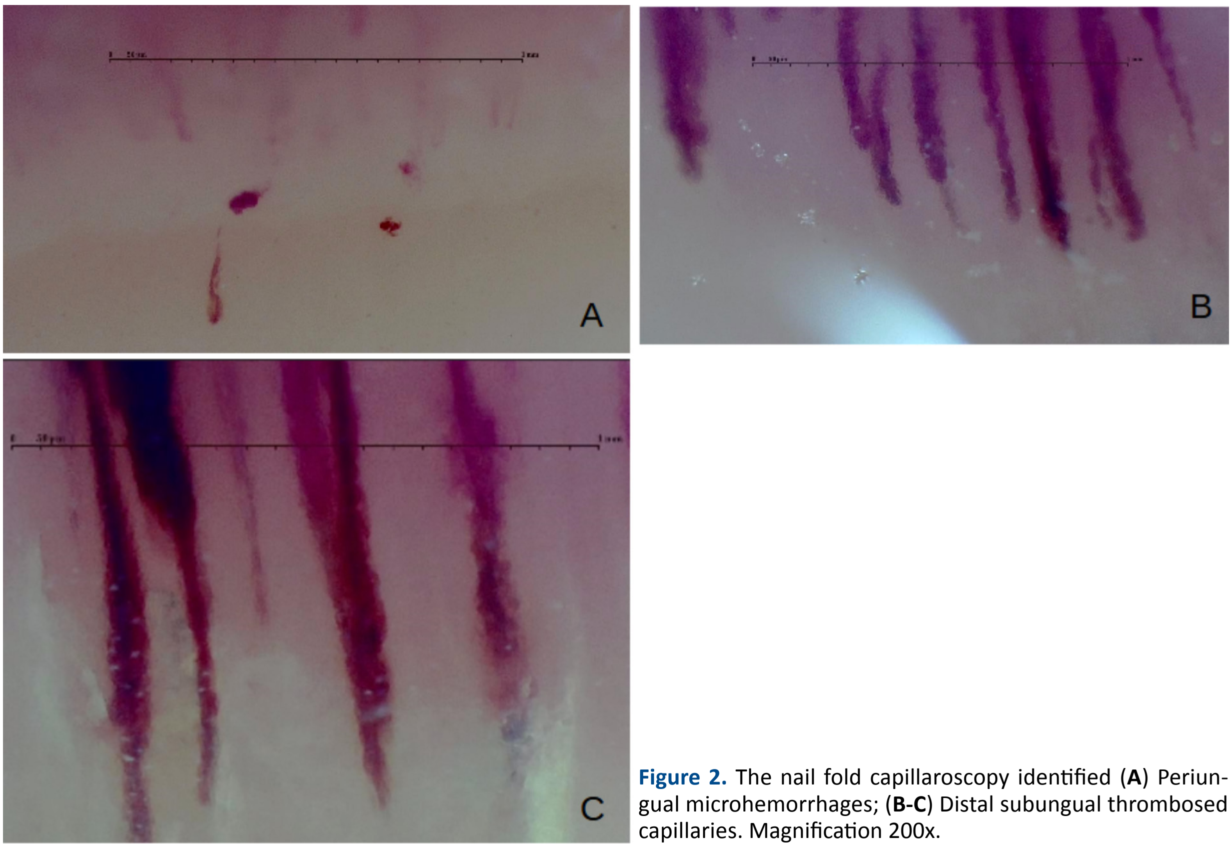


Figure 2. The nail fold capillaroscopy identified (**A**) Periungual microhemorrhages; (**B-C**) Distal subungual thrombosed capillaries. Magnification 200x.

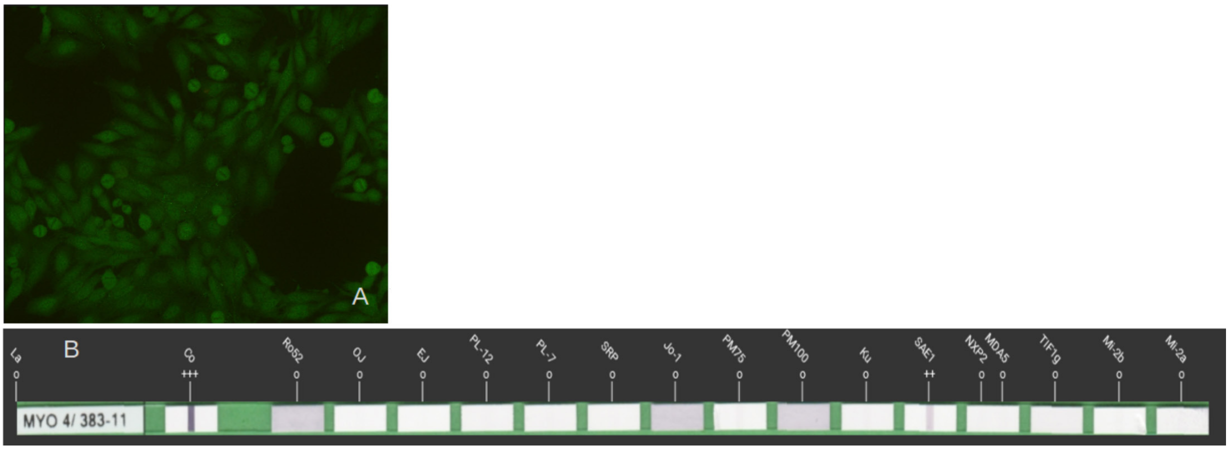


Figure 3. **A**, autoimmunity tests resulted positive for ANA 1:80 with nuclear fine speckled pattern (AC-4) and cytoplasmic dense fine speckled pattern (AC-19). **B**, Myositis profile blot, the immuno blot detects IgG antibodies to anti-SAE1.

ureteral dilatation up to 53x35 mm, suspected to be a pathologic, confluent, bundled lymphadenomegaly as the first hypothesis. Additionally, thickening of the left posterior bladder wall with endoluminal vegetations was observed (Figure 4). Incomplete thrombosis of the left external iliac and femoral veins was also detected, prompting initiation of anticoagulant therapy. Cystoscopy confirmed bladder neoformation, and radical cystectomy was performed. Histological examination revealed a high-grade urothelial carcinoma pT3b N3 with eleven positive lymph nodes out of thirty-seven removed. RF, acrocyanosis, and sub-ungual hemorrhages regressed until a complete resolution after the neoplasm enucleation.

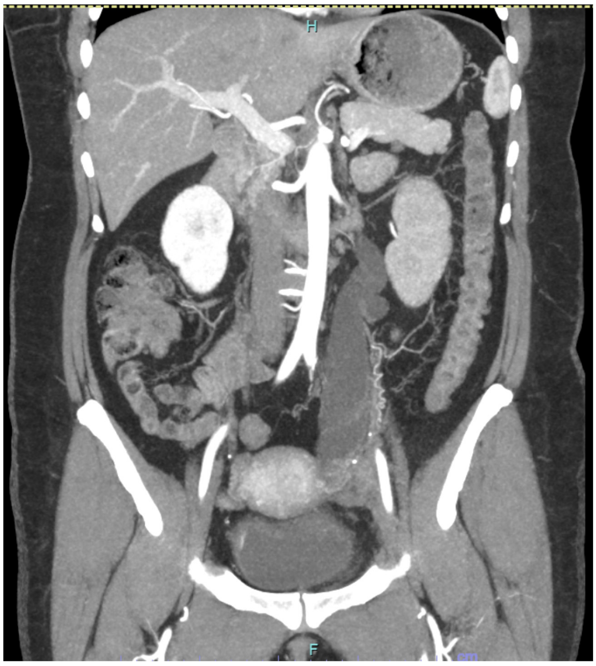


Figure 4. CT abdomen with contrast medium shows an inhomogeneous polylobate mass as the cause of the pelvis and ureter dilatation up to 53x35 mm, suspected to be a pathologic confluent bundled lymphadenomegaly as the first hypothesis. Moreover, there was a thickened, with endoluminal vegetations to the left lateral posterior, bladder wall and there was incomplete external iliac and left femoral veins thrombosis.

DISCUSSION

ANA was detected by indirect immunofluorescence (IIF) using EUROIMMUN test kits. (Euroimmun Luebeck, Germany). The confirmatory test was performed by line-blot technology following the manufacturer's instructions. The test is specific for the following antigens: Mi-2 alpha, Mi-2beta, TIF1g, MDA5, NXP2, SAE1, Ku, PMScl100, PMScl75, Jo-1, SRP, PL-7, PL-2, EJ, OJ, Ro-52 (Figure 4).

The anti-SAE1 autoantibody targets a ubiquitin-related protein involved in regulating transcription, cell cycle, and apoptosis. It is recognized as a specific marker of dermatomyositis but is found to be associated with neoplasms[3,4,6] and in around 20% of different anti-SAE myositis courts[4].

Sub-ungual splinter hemorrhages may be an expression of infective endocarditis, but also of autoimmune diseases or neoplasms.

The uniqueness of our case lies in the paraneoplastic manifestation of splinter hemorrhages in association with the presence of anti-SAE1 antibodies, which are typically linked to dermatomyositis. However, in this instance, they were associated with neoplasia and without the classical skin onset. To the best of our knowledge, no similar cases have been reported. Although rare cases of anti-SAE1-positive myositis without skin involvement have been described[3,7], particularly as an initial presentation, a North American cohort has also reported an association with Raynaud's phenomenon[6]. Additionally, a monocentric Italian cohort documented periungual telangiectasia in 4 out of 10 patients[8]. The 2023 international guidelines on cancer screening in idiopathic inflammatory myopathies highlight dermatomyositis as being associated with a high risk of cancer development[9]. Our case shows an atypical clinical manifestation without skin rashes, with splinter hemorrhage and Raynaud phenomenon, yet associated with autoantibodies that can be cancer-related. It is, therefore, important, if this autoantibody is found, to conduct a comprehensive screening for occult neoplasms, considering also a paraneoplastic manifestation, even though unusual, such as splinter hemorrhages. The anti-SAE1 autoantibody has been associated with malignancies in approximately 20% of cases; however, to date, no reports in the literature have linked it specifically to urothelial carcinoma.

CONCLUSIONS

The peculiarity of our case is the unusual clinical onset of anti-SAE dermatomyositis with splinter hemorrhages. The association between anti-SAE autoantibody and splinter nail hemorrhages in relation to urothelial cancer has not been previously documented. We believe that our case contributes to the understanding of atypical dermatomyositis presentations and highlights the need for comprehensive cancer screening in the presence of unusual clinical manifestations.

Conflict of Interest

Lisa Agatea is an employee of Euroimmun Laboratory, Padua, Italy. The other authors declare that they have no conflict of interest to disclose.

Funding

No funding was obtained for this study.

Ethics Statement

All procedures performed in the study were in accordance with the Ethical Standards of the Institutional and/or National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable Ethical Standards.

Informed Consent

The patient was informed of the scientific and clinical interest in her disease as well as of this anonymous publication. She provided a written informed consent for the anonymous publication of this case report including figures.

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Authors' Contributions

A. Biglia—collection and interpretation of data, first draft; MC. Sacchi—immunology data, first draft; F. Maggiore, V. Morandi, E. Cammarata—collection and interpretation of data, critical review of the manuscript; M.M. Ciriello—immunology data, critical review of the manuscript; M.R. Pellico, L.M. Castello—clinical interpretation of data, critical review of the manuscript; L. Agatea—critical review of the manuscript; C. Pelazza, critical review of the manuscript and corresponding author; A. Roveta—critical review of the manuscript.

Availability of Data and Materials

Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

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