Calcinosis cutis in the course of systemic sclerosis overlapped by anti-MDA5 positive dermatomyositis: a case report

Wapnica skóry w przebiegu twardziny układowej z nakładaniem anty-MDA5 dodatniego zapalenia skórno-mięśniowego: opis przypadku

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Streszczenie

Wprowadzenie
Twardzina układowa (SSc) jest układową chorobą tkanki łącznej charakteryzującą się postępującym włóknieniem skóry, narządów wewnętrznych, wapnicą oraz zaburzeniem morfologii i funkcji naczyń. Przeciwciała anty-MDA5 rzadko występują w SSc będąc znacznie częściej obecne w idiopatycznej miopatii zapalnej (IIM) z kalcyfikacją skóry.
Cel
Celem badania jest przedstawienie pierwszego przypadku pacjenta z wapnicą skóry w przebiegu zespołu nakładania się SSc/IIM z klinicznie istotnym mianem przeciwciał anty-MDA5.
Materiał i metody
Badanie przedstawia 57-letnią pacjentkę, która po infekcji COVID-19 rozwinęła masywne owrzodzenia skórne na kończynach dolnych, które pojawiły się 8 miesięcy przed przyjęciem. Badania serologiczne wykazały wysokie miano przeciwciał anty-Ro52, anty-MDA5 i anty-Th/To, podczas gdy inne typowe przeciwciała dla SSc nie zostały znalezione. Pacjentce włączono leczenie cyklosporyną i amlodypiną. W dalszej części opisujemy również wpływ poszczególnych autoprzeciwciał na obraz kliniczny pacjenta, ze szczególnym uwzględnieniem przeciwciał anty-MDA5, w tym ich prawdopodobne powiązanie z wirusem SARS-CoV-2. Omawiamy także inne choroby autoimmunologiczne przebiegające z wapnicą skóry oraz aktualne podejścia terapeutyczne.
Wyniki
Badanie kontrolne pacjentki po trzech miesiącach wykazało znaczną regresję owrzodzeń i zwapnień. Nie uwidoczniono nowych zmian skórnych, a jedynym objawem niepożądanym pozostaje zwiększona częstość infekcji górnych dróg oddechowych.
Wnioski
Do tej pory nie istnieją konkretne wytyczne terapeutyczne dotyczące wapnicy skóry w przebiegu zespołu nakładania się SSc/IIM z dodatnimi przeciwciałami anty-MDA5. Wierzymy, że przedstawiona skuteczność zastosowanego leczenia zachęci badaczy do prowadzenia dalszych prospektywnych badań dotyczących stosowania cyklosporyny w leczeniu wapnicy skóry w przebiegu zespołu nakładania się SSc/IIM.

Słowa kluczowe: twardzina układowa, wapnica, SARS-CoV-2, cyklosporyna, przeciwciała, zapalenie skórno-mięśniowe

Summary

Introduction
Systemic Sclerosis (SSc) is an autoimmune connective tissue disease characterized by progressive fibrosis of the skin and internal organs, calcification, and vasculopathy. Anti-MDA5 antibodies are rather uncommon in SSc while being often associated with idiopathic inflammatory myopathy (IIM) with calcinosis cutis.
Purpose
The study aims to present the first ever reported case of a patient suffering from calcinosis cutis in the course of SSc/IIM overlapping syndrome with clinically relevant anti-MDA5 titers.
Material and methods
The study reports a 57-year-old post-COVID-19 female patient with massive cutaneous ulcerations of lower extremities that appeared 8 months before admission. Serology revealed high titers of anti-Ro52, anti-MDA5, and anti-Th/To, while other typical SSc antibodies were not found. We discuss the clinical impact of various autoantibodies with an emphasis on anti-MDA-5 including its probable association with SARS-CoV-2. Other autoimmune disorders with calcinosis cutis and its current therapeutic approaches were reviewed.
Results
The patient's follow-up examination after three months showed significant regression of ulcerations and calcifications, with no new skin lesions being noted. An increased frequency of upper respiratory tract infections was the only adverse effect of the introduced treatment.
Conclusions
Until now there are no specific therapeutic approaches for the calcinosis cutis in anti-MDA5 positive overlapping SSc/IIM syndrome. We believe this study can help attract clinicians to run further prospective studies concerning the use of cyclosporine in calcinosis cutis in the course of SSc/IIM overlapping syndrome.

Key words: scleroderma, systemic, calcinosis, SARS-CoV-2, cyclosporine, autoantibodies, dermatomyositis

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SSc - systemic sclerosis
IIM - idiopathic inflammatory myopathy
DM - dermatomyositis
ACTD - autoimmune connective tissue disease
MDA5 - melanoma differentiation-associated gene-5
ILD - interstitial lung disease
ICU - intensive care unit
CADM - clinically amyopathic dermatomyositis
RP-ILD - rapidly progressive ILD

1. Introduction

Systemic Sclerosis (SSc) is an autoimmune connective tissue disease (ACTD) with an unknown etiology, characterized by progressive fibrosis of the skin and internal organs. It leads to organ failure and systemic complications, with pulmonary involvement being the main cause of death.

Anti-melanoma differentiation-associated gene-5 (MDA5) antibodies are not typically associated with SSc but with idiopathic inflammatory myopathy (IIM), severe interstitial lung disease (ILD), ulcerations, and a higher risk of death [1]. Furthermore, their production could be triggered by SARS-CoV-2 which in turn is speculated to be able to lead to the development of autoimmune disorders or exacerbation of the current ones [2].

Calcinosis cutis, despite being a rare clinical entity, often accompanies ACTD. It is present in 25-40% of SSc cases and 30% of adults with dermatomyositis (DM) [3]. Although numerous therapeutic options are already available, the literature shows its various, often not satisfying, efficacy.

2. Case report

2.1. History and examination

A 57-year-old woman presented to the Department of Rheumatology with cutaneous ulcerations on her lower extremities that appeared eight months before admission. Before seeking medical help, she had not received any pharmacological treatment for this condition and had no history of trauma contributing to the ulcers. Surgical intervention, performed five months earlier, involved evacuating calcium/bone-like deposits. A biopsy from the wound border confirmed necrotic-ulcerative lesions with nonspecific granulation.

In 2021 the patient developed short-term memory impairment, and psychomotor retardation as a complication of a cardiac arrest caused by SARS-CoV-2 infection as a result of which she was hospitalized in the intensive care unit (ICU) for fifty-two days.

The patient had no family history of rheumatic diseases. She denied any allergies, excessive use of alcohol, or smoking.

On examination, the patient was in good general condition with slightly impaired cognitive functions and short-term memory defects. She presented not only swollen, bloodshot, ulcerated skin, and visible calcified masses on the shins bilaterally, but also edentulousness, obesity, telangiectasias present on facial skin, sclerosis of the skin including sclerodactyly and Raynaud's phenomenon. Normal symmetrical muscle strength was noted. No other abnormalities were observed.

2.2. Laboratory tests

Laboratory tests revealed several abnormalities including elevated acute phase markers. No laboratory features of muscular damage were noted. Significant titers of autoantibodies were found, such as anti-Ro-52, anti-MDA5, and anti-Th/To (Table 1).

Table 1. The table presents abnormalities found in the laboratory tests. The confirmation test for anti-dsDNA on *Crithidia luciliae* was negative. The patient was not tested for the autoantibodies panel prior to COVID-19.

Laboratory test	Patients' value	Normal value
ESR	23 mm/h	<12 mm/h
ferritin	392.3 µmol/l	13-150 µmol/l
neutrophils	7.58x10³/µL	2,20-4.80x10³/µL
vitamin D3	23.5 ng/ml	31-50 ng/ml
vitamin B12	631 pmol/l	145-569 pmol/l
total cholesterol	5.65 mmol/l	3,00-5,00 mmol/l
LDL	3.63 mmol/l	<3,00 mmol/l
triglycerides	1.73 mmol/l	<1.70 mmol/l
creatine	108.3 µmol/l	49,0-90,0 µmol/l
urea	8.8 mmol/l	2,8-7,2 mmol/l
NT-proBNP	203 pg/ml	<125 pg/ml
ANA	1:2560 (nucleolar pattern) 1:2560 (speckled pattern) 1:320 (mitochondrial pattern)	
anti-Ro-52	+++	
anti-MDA5	++	
anti-dsDNA	+	
anti-Th/To	+++	

ESR - Erythrocyte Sedimentation Rate, LDL - Low-density lipoprotein, ANA - Antinuclear antibody, NT-proBNP - N-terminal pro–B-type natriuretic peptide

2.3. Imaging tests

To better assess the patient's condition and disease progression several imaging and function tests were conducted. Lower extremities X-ray presented symmetrical subcutaneous disseminated reticular saturated calcifications on the crura, mainly on the anterior side, suggesting soft tissue calcinosis. The bones themselves showed no structural abnormalities.

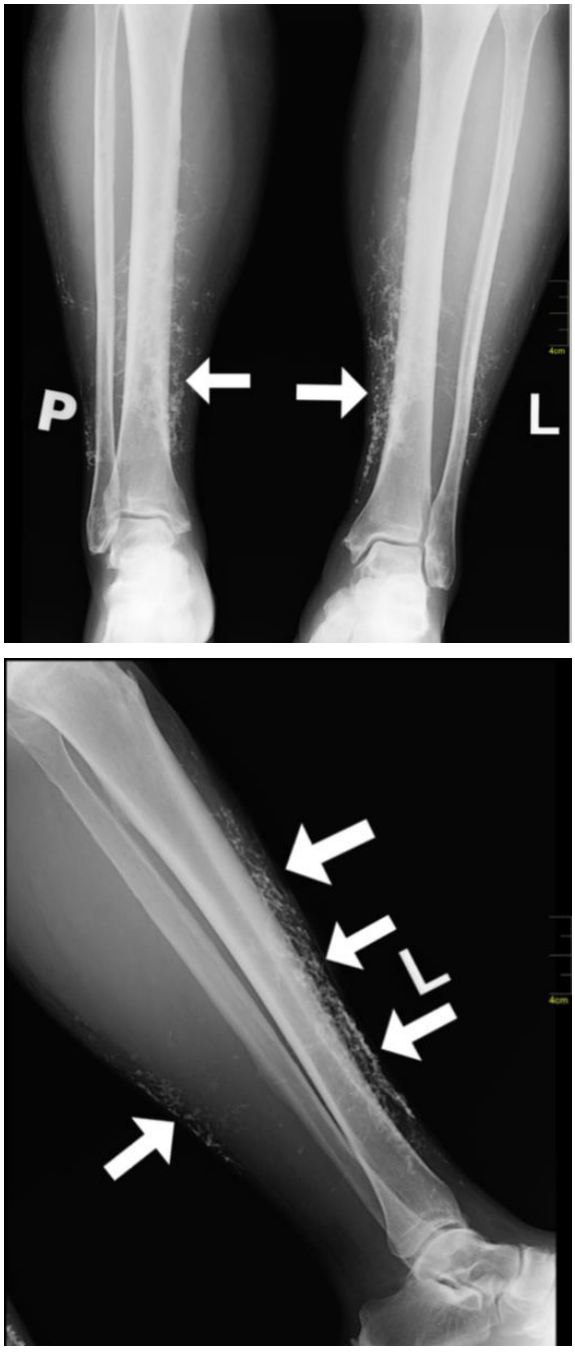

Figure 1. X-rays of the shin with symmetrical subcutaneous disseminated reticular saturated calcifications on the crura.

Spirometry showed features suggestive of a restrictive disorder - relatively minor changes in FEV1%VCmax (92,37%, percent predicted 116%) and FEV1 (2,42l, percent predicted 93%) with lower VCmax (2,62l, percent predicted 74%). The bronchodilator reversibility test was negative. Body plethysmography presented decreased vital capacity (3,54l, percent predicted 79%) with total lung capacity within the normal range (5,35l, percent predicted 102%). The transfer factor of the lung for carbon monoxide (TLCO) was decreased (5,69mmol/min/kPa, percent predicted 81%).

Capilaroscopy revealed unspecific/very early changes. Due to the especially low number of vessels (6-7/mm), stromal edema, and widened capillaries the capillaroscopic image should be successively monitored for further lesions.

2.4. Management and follow-up

Based on the EULAR/ACR criteria the patient with the clinical presentation including skin thickening, telangiectasia, ILD, and Raynaud's phenomenon achieved a score of 16 points that indicated the diagnosis of SSc. Despite the presence of myositis-specific antibodies (anti-MDA-5), the patient did not fulfill the EULAR/ACR classification criteria for IIM, however, the clinical utility of these criteria in patients with the predominance of extramuscular involvement is limited [4,5]. Based on the clinical features including calcinosis cutis together with the specific autoantibody profile implied the overlap of anti-MDA5-positive myositis sine myositis. The patient did not fulfill the ACR/EULAR criteria for Systemic Lupus Erythematosus and Sjogren syndrome.

To manage the disease, Raynaud's phenomenon and stop the progression of sustained lesions cyclosporine (100mg 2x per day) and amlodipine (5mg 1x per day) were introduced.

Comorbidities such as heart failure (II/III NYHA) with preserved ejection fraction (LVEF=58%), light tricuspid and mitral regurgitation, first-degree AV Block, HT, chronic kidney disease (G3,A1,KDIGO2012), hyperlipidemia, cholecystolithiasis, Vitamin D3 and folic acid deficiency, discopathy in C4/C5 and C5/C6, gastritis in the prepyloric part, hyponatremia, hyperuricemia were diagnosed following both the laboratory and imaging results and were treated based on appropriate guidelines. Owing to pulmonary hypertension suspicion, the patient was referred to the corresponding clinic.

After 3 months the patient was contacted remotely to assess the outcomes of treatment. A significant regression in the degree of ulceration and calcification was observed. The occurrence of new wounds was not noted. A higher frequency of upper respiratory tract infections is the only side effect of immunosuppressive treatment that was observed.

3. Discussion

To the best of our knowledge this is the first documented case of severe calcinosis cutis with clinically relevant anti-MDA5 titers in the SSc and DM sine myositis overlap patient. The Pubmed Database was searched to find similar cases but none were found.

Calcinosis cutis is characterized by hydroxyapatite crystal depositions in the skin and subcutaneous tissue extracellular matrix. It is clinically presented as subcutaneous nodules, sometimes with whitish masses. In the majority of SSc calcinosis cutis cases, the lesions are present on the hands, however, other common locations include proximal upper extremity, proximal lower extremity, knee, and hip [6]. So far there is no widely accepted treatment for calcinosis cutis. For smaller deposits warfarin, rituximab, ceftriaxone, or intravenous immunoglobulin are being used whereas larger lesions require surgical excision or curettage, and pharmacotherapy with bisphosphonates, aluminum hydroxide, probenecid or diltiazem [3,6].

Anti-MDA5 targets MDA5, a retinoic acid-inducible gene I-like receptor that detects viral RNA in cytoplasm, thus taking part in innate immune defense mechanisms [7]. Anti-MDA5, also known as anti-CADM-140, is usually found in patients with clinically amyopathic dermatomyositis (CADM) and has also been proven to increase

the risk of rapidly progressive ILD (RP-ILD) and cutaneous ulcers [1].

Furthermore, the patient's past medical history of severe pneumonia in the course of SARS-CoV-2 infection 18 months before admission to the Rheumatology Department raises a question, of whether the patient's serology has contributed to the severe course of COVID-19 or whether the infection itself was a trigger for autoimmunization. The anti-MDA5 antibodies were found to be associated with a more severe manifestation of COVID-19. On the other hand, because of molecular mimicry SARS-CoV-2 may induce the production of anti-MDA5 leading to autoimmune disorders [2].

Regarding pharmacotherapy in the described case, amlodipine and cyclosporine were administered. Amlodipine, a dihydropyridine calcium channel antagonist, shows its efficacy in managing Raynaud's phenomenon. Meta-analyses reveal that calcium channel antagonists reduce the number as well as the severity of Raynaud's episodes, compared to placebo [8]. The reason for the latter, a calcineurin inhibitor cyclosporine, is its efficacy in controlling the disease in patients with DM, including those with pulmonary and cutaneous involvement. Cyclosporine is documented to stabilize and in some cases reverse pulmonary fibrosis. [9,10].

4. Conclusion

We believe this is the first-ever reported case of severe calcinosis cutis in the course of SSc overlapped with anti-MDA5 positive DM in a post-COVID-19 patient. It underlines the significance of screening for less prevalent antibodies, such as anti-MDA5, in IIM- or SSc-suspected patients to better forecast the possible course of the disease and apply proper disease-modifying drugs. Furthermore, the case presents a possible impact of novel SARS-CoV-2 infection on the development of auto-immunological disorders. The implemented treatment shows satisfying effects in a 3-month-long follow-up period, suggesting the effectiveness of cyclosporine in anti-MDA5 positive calcinosis.

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