

CASE REPORT

Undifferentiated vasculitis or an evolving systemic autoimmune rheumatic disease?

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Abstract

Undifferentiated connective tissue diseases usually present with arthralgias, sicca symptoms, Raynaud's phenomenon and leucopenia. This case presents the atypical presentation of an undifferentiated connective tissue disease with extensive cutaneous involvement of fingers and toes leading to gangrene with absence of typical rheumatological symptoms. The autoimmune profile showed positive ANA and anti-Ro/SS-A. Thromboembolism was ruled out on the basis of transthoracic and transesophageal echo. She was treated with I/V corticosteroids and cyclophosphamide that halted the disease progression.

INTRODUCTION

Autoimmune connective tissue diseases (ACTDs) are known to have protean manifestations ranging from mild cutaneous involvement to life-threatening major organ failures. Many evidence-based criteria have been developed to classify ACTDs but the existence of rheumatic diseases not fulfilling any particular criteria is not uncommon in clinical practice [1–3]. However follow-up studies have shown varying percentages of patients with initially undifferentiated ACTDs either evolved into differentiated rheumatic diseases or reverted completely [4, 5].

Common clinical manifestations of undifferentiated ACTDs include arthralgias, Raynaud's phenomenon, photosensitivity and sicca symptoms. The autoimmune profile shows positive ANA usually with no disease-specific autoantibodies [4, 5].

An interesting case with extensive atypical cutaneous manifestation of vasculitis associated with positive ANA and anti-Ro/SS-A is hereby presented with absence of typical rheumatological symptoms.

CASE REPORT

A 27-year-old married female with two children presented to us with sudden onset of severe burning pain in all the digits of her left hand; the pain was followed by reddish discoloration of the digits within 24 h. Over a few days the colour of the digits changed from red to blue and eventually to black. The pain was associated with paraesthesias. Similar changes occurred in her right hand as well as the toes of both feet, in the next 20 days. There were no other rheumatological symptoms. She had no history of miscarriages or deep venous thrombosis.

On physical examination, she had a BMI of 36.3 kg/m². All the upper limb pulses were palpable bilaterally while the dorsalis pedis could not be palpated on either foot. On examination, both her hands showed blackish discoloration of the skin of the distal phalanx of the index, ring and little finger and was very tender to touch (Fig. 1). There was no well-developed line of demarcation at the time of presentation. The big toe and the second toe also showed blackish discoloration and were very tender. Rest of the examination was unremarkable.

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Figure 1: Gangrene of fingers of both the hands at the time of presentation.

Her baseline investigations showed haemoglobin of 12.4 g/dl with neutrophilic leucocytosis; her ESR was 70 mm/h and CRP was 48 mg/l and the coagulation profile was within normal limits. Her liver function and renal function tests were within the normal limits and she had proteinuria up to 300 mg/d. Urine complete examination showed ++ proteins but there were no sediments or cellular casts. Renal biopsy was planned but even after adequate counselling, she refused, so the biopsy was deferred. Protein C, protein S and anti-thrombin-III levels were normal, and anti-cardiolipin, lupus anticoagulant and anti- β 2-glycoprotein antibodies were negative. Her ANA levels came out to be homogenous (+++), while anti dsDNA was negative. RA factor was negative and complement levels were normal. The ENA profile showed increased titre of anti-Ro (SS-A) while the rest of the extractable nuclear antigens were negative. c-ANCA and p-ANCA were negative. Her serum was tested for cryoglobulins and the cryocrit was detected on day 8 of the serum being placed at 4 degree Celsius. The hepatic viral serology, HBsAg and Anti HCV by ELISA was negative.

Bilateral upper and lower limb Doppler studies were done which showed decreased irregular blood flow in both the right and left anterior tibial and dorsalis pedis arteries with normal blood flow in femoral and popliteal arteries. Upper limb Doppler studies showed dampened flow in brachial, radial and ulnar arteries with systolic drops while the right upper limb was unremarkable. Transthoracic and trans-oesophageal echoes were unremarkable. No thrombus was seen in left atrial appendage, left atrium or left ventricle. Chest X-ray and abdominal scan showed no abnormality.

Based on the clinical and immunological findings the diagnosis of mixed cryoglobulinemia associated with vasculitis



Figure 2: A well-defined line of demarcation that developed after treatment with cyclophosphamide (taken on the first follow-up visit).

secondary to undifferentiated autoimmune disease was made. During this time, she was given a pulse therapy of methylprednisolone with a total dose of 4.8 g in divided doses over 13 days followed by high dose oral corticosteroids. Intravenous low molecular weight heparin was instituted simultaneously and oral modified release nifedipine and cilostazol were also given. She responded partially to pulse therapy, therefore I/V cyclophosphamide along with mesna was given after which a clear line of demarcation developed on the involved digits of hands and feet (Fig. 2) and the gangrene stopped progressing. A second dose of cyclophosphamide was given after 2 weeks.

For the gangrenous digits, vascular and general surgeons were consulted and it was decided that the digits will be left to auto-amputate. Glyceryl trinitrate ointment was given for local application on the digits of the hands and feet. She was discharged on high dose oral corticosteroids, azathioprine and hydroxychloroquine and was called for follow-up after 2 weeks. It was planned that disease modifying anti-rheumatic drugs and oral corticosteroids will be adjusted keeping in view her symptoms on follow-up visit.

DISCUSSION

Undifferentiated connective tissue diseases (UCTDs) have been defined by many researchers in various ways. Any disease with signs and symptoms consistent with CTDs, but not fulfilling the defined criteria for CTDs comes under the umbrella of UCTDs. However, follow-up studies have shown that varying percentage of patients who had undifferentiated disease at the time of presentation went on to develop full blown classifiable CTD usually within the fifth year of the disease [6, 7]. Although the UCTDs have been seen to evolve to classifiable CTDs depending on the autoantibody profile at the onset but the data are less convincing.

UCTDs usually present with arthralgias, Raynaud's phenomenon, leucopenia, sicca symptoms and ANA positivity [4, 5]. Such patients usually have a milder clinical course and the symptoms usually settle with low dose corticosteroids with little, if any, need of immunosuppressant.

In our case, the patient did not have any rheumatological symptoms associated with UCTDs, rather she presented with severe vasculitis leading to gangrene of the digits of both hands and feet. Although ANA was found to be homogenous (+++), but in her ENA profile, only anti-Ro/SS-A was found to be positive with negative anti dsDNA. Anti-Ro/SS-A is associated with Sjogren's syndrome but it has also been shown to be present in

small percentage of SLE patients and poses a greater risk of congenital heart blocks and neonatal lupus syndrome [8]. Our patient has two children who were physically and mentally fit with no evidence of neonatal lupus/heart blocks. The proteinuria could not be adequately explained because we could not do the renal biopsy but in the light of literature it did not fit into the criteria of lupus nephritis as proteinuria was less than 500 mg/d and there were no urinary sediments or casts on urine examination [9]. As per treatment, the disease progression was halted by high dose corticosteroids and cyclophosphamide.

In conclusions, CTDs are a vast entity of autoimmune disorders with myriad of manifestations. Being chronic disorders, they evolve over a course of time involving major organs. It is only when the typical signs and symptoms are absent that the clinician is faced with a diagnostic challenge and such a scenario is not uncommon in clinical practice. The criteria for the diagnosis of UCTDs need to be clearly defined and moreover the already defined criteria for classifiable CTDs need to be revisited to encompass latent lupus, dormant systemic sclerosis and other similar diseases. From the clinical perspective, this will help in decision making regarding adequate follow-up, appropriate treatment and reduction in psychological stress of the patient. Moreover, the UCTDs may help researchers study the pathogenic roles of various autoantibodies via randomized controlled trials and may aid in devising disease-specific treatment modalities.

ACKNOWLEDGEMENTS

None declared.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICAL APPROVAL

The ethical approval was sought from the Institutional Review Board, National Health Research Council, Shaikh Zayed Medical Complex, Lahore, Pakistan.

CONSENT

We thank our patient for her consent to publish the case and the related pictures.

GUARANTOR

A.R. is considered as a guarantor.

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