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Panniculitis: an unusual presenting manifestation of rheumatoid arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is a systemic inflammatory disease affecting primarily the joints but also other organs including skin. Panniculitis is an extremely rare manifestation of the disease manifesting mainly as reddish, ulcerative painful nodules and papules, usually in the legs. Histopathologically, it is characterised by liponecrobiosis, granulocytic and histiocytic infiltrates and vasculopathy.

Herein, we describe a middle-aged woman with a past medical history of hypertension and diabetes mellitus, and unremarkable family history, who presented with symmetrical polyarthritis, low grade fever and painful subcutaneous nodules in the abdomen. Her laboratory tests showed high acute phase reactants, positive rheumatoid factor and anti-Ro autoantibodies and negative anti-CCP. Surgical resection and histological examination of the nodules revealed neutrophilic lobular panniculitis associated with RA. She was treated with low doses of glucocorticosteroids and methotrexate. The latter was substituted with leflunomide due to toxicity. The patient had significant clinical and laboratory improvement.

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disorder affecting mainly the joints. Extrarticular manifestations are common, involving skin, eyes, heart, lungs, and kidneys, nervous and gastrointestinal system (1). Skin involvement is described in less than 15% of RA patients (2). Rheumatoid nodules are the most common cutaneous manifestation (3) while panniculitis is encountered very rarely in the context of RA. In this report, we describe a middle-aged woman whose first manifestation of RA were subcutaneous painful abdomen nodules, histologically confirmed to be panniculitis. The case study was approved by the ethics committee of the Laiko General Hospital and informed consent was obtained from the patient.

Case presentation

A 65-year-old woman presented to our outpatient rheumatology clinic with bilateral arthritis of metacarpophalangeal and proximal interphalangeal joints, morning stiffness lasting for more than an hour, low grade fever, myalgias and painful nodules in the abdomen, for the last two months. Her family history was unremarkable while from her past medical history she had hypertension and non-insulin dependent diabetes mellitus. She neither smoked, nor referred increased consumption of alcohol. Her daily treatment included: metformin twice a day and amlodipine once a day. The patient also complained for weight loss (more than 15 kg in 6 months) and fatigue.

Physical examination was unrevealing except from bilateral arthritis of MCPs and PIPs and from numerous subcutaneous nodules in the abdomen. Chest and hand x-rays were without significant findings and abdomen ultrasound showed enlarged liver. From her blood tests, she had normal complete blood count, serum chemistry and urinalysis. Hepatitis C antibody and mantoux testing were negative. She had increased acute phase reactants and serum protein electrophoresis with hypergammaglobulinaemia without evidence of monoclonality. From her immunological profile she manifested high titers of antinuclear autoantibodies (ANA), normal values of serum C3 and C4, high positive rheumatoid factor and anti-Ro/SSA antibodies. Antibodies to cyclic citrullinated peptides (anti-CCP) were negative (Table I). Full evaluation for the existence of Sjögren's syndrome, systemic lupus erythematosus and other systemic autoimmune rheumatic diseases was negative. The patient fulfilled the ACR/EULAR criteria for rheumatoid arthritis (4) with a DAS28 score of 5.62.

Two of the nodules were surgically removed after patient's informed consent. Macroscopically they were grey-yellowish, adjacent to the adipose tissue and toughish to palpation.

The patient was treated with methotrexate (10 mg/week) and methylprednisolone (7.5 mg/day) until biopsy evaluation. She responded very well and 15 days later she had no arthritis, fever or fatigue. Additionally, the nodules have dramatically decreased in size and pain had been greatly alleviated.

Table I. Laboratory examination results at the time of diagnosis as well as during follow-up. 2nd and 3rd visit was 1 and 6 months following diagnosis, respectively.

Examination	1st Visit	2nd Visit	3rd Visit
Haematocrit (%)	40.0	41.5	38.6
Haemoglobin (mg/dl)	13.0	13.0	12.4
White blood cells	4750	3200	4900
Platelets	237.000	138.000	156.000
AST/ALT	36/29	107/131	34/32
ALP/γGT	39/21	34/35	35/34
T4/TSH	ND	1.6/0.7	ND
CRP[a]	2.0	0.7	0.2
ESR	43	23	20
ANA	1/2560	ND	ND
RF (IU/ml)[b]	80	ND	ND
C3 (mg/dl)	144	ND	ND
C4 (mg/dl)	32	ND	ND
Anti-dsDNA[c]	Negative	Negative	ND
Anti-CCP	Negative	ND	ND
Anti-Ro/SSA	Positive	ND	ND
Anti-La/SSB	Negative	ND	ND
Anti-U1RNP	Negative	ND	ND
c-ANCA	Negative	ND	ND
p-ANCA	Negative	ND	ND
DAS28	5.62	2.87	2.25

a = normal values <0.5 mg/dl, b = normal values <20 IU/ml, c = determined by ELISA, ND = not done

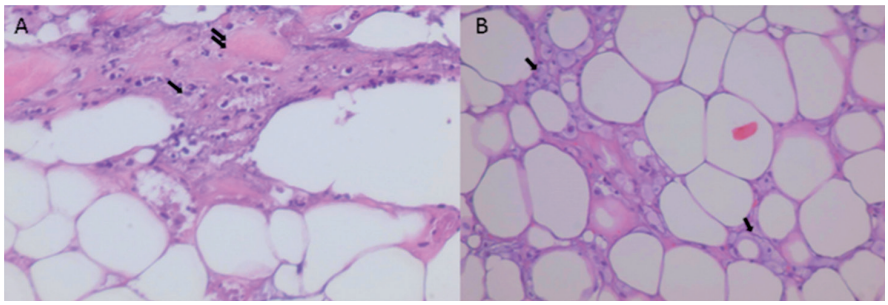

Fig. 1. Representative tissue section of nodules' biopsy stained with haematoxylin/eosin showing fat necrosis with (**A**) acute inflammation, as indicated by neutrophils lying in basophilic amorphous material (arrow), and thrombosed vessels (double arrow), (**B**) foamy histiocytes in-between fat globules (arrows). Original magnification: x250.

The biopsy of the nodules revealed adipose tissue with multifocal liponecrosis and scattered foamy histiocytes with mild fibrosis of the septae, focal necrosis with acute inflammation and fibrin deposition and extension to the adjacent adipose tissue. Nuclear dust was seen in the areas of acute inflammation (Fig. 1). No perivascular infiltrates or granulomatous lesions were identified and there was no evidence of acute necrotising vasculitis. The histopathological findings were compatible with the diagnosis of neutrophilic lobular panniculitis associated with RA.

In the laboratory exams one month later, the values of acute reactant proteins were decreased and the patient had low disease activity (DAS28=2.87) however the patient manifested increased liver enzymes and low white blood cells and platelets level. Methotrexate was discontinued and leflunomide was added to glucocorticosteroids. In the 6-month follow up, the patient was in clinical and laboratory remission (Table I).

Discussion

Skin involvement in the context of RA comprises of a variety of clinical pictures including: rheumatoid nodules, rheumatoid papules, neutrophilic dermatosis, pyoderma gangrenosum, rheumatoid vasculitis and lesions related to drugs (*e.g.* methotrexate) (3, 5). Histopathologically, three main patterns have been identified: diffuse interstitial granulocytic and histiocytic infiltrates along with liponecrobiosis and non-inflammatory vasculopathy, vasculitic lesions characterising by granulocytic infiltrates and less usually infiltrates by granulocytes in the dermis and the subcutis (6, 7).

Lobular panniculitis has been described for the first time to be associated with RA by Yaffee *et al*., in 1955 (8). Since then, less than 10 cases worldwide have been presented (2, 3, 5-7, 9-11). Histopathologically, they are characterised by liponecrobiosis, granulocytic infiltrates in lobules (lobular panniculitis) and septae (septal panniculitis), while vasculitic lesions may or may not occur (10). Mechanisms leading to these phenomena in RA patients are not yet understood, most probably due to the limited number of cases. Though, immunecomplexes have been proposed as possible mediators (9). The patients are usually middle-aged women with long lasting seropositive rheumatoid arthritis (10). A considerable number of them had also overlapping features with another autoimmune disease (*e.g.* Sjögren's syndrome, autoimmune hepatitis) (3, 5). Skin lesions are usually presented in legs or over joints, as reddish, and sometimes as ulcerative nodules or papules (5, 7). A variety of treatment modalities have been used. They include anti-malarials, dapsone, colchicine, glucocorticosteroids, methotrexate, azathioprine, cyclophosphamide and IL-1 receptor antagonist inhibitor (3, 5, 9, 12). Yet, there are no studies suggesting the most applicable regimen, which is usually determined according to the physician's experience.

Herein, we present a middle-aged woman who presented in our outpatient rheumatology clinic with symmetric polyarthritis, morning stiffness, fever and painful subcutaneous nodules in the abdomen. She had positive rheumatoid factor and anti-Ro autoantibodies. The patient fulfilled the 2010 diagnostic criteria for RA. Furthermore, the existence of another autoimmune rheumatic disease has been excluded after extensive work-up. To the best of our knowledge, this is the first time that panniculitis in RA patient is described as the initial symptom. Interestingly,

the nodules were observed in a rather unusual location and were not ulcerated. Histopathological features were fully consistent with the diagnosis of lobular panniculitis associated with RA displaying liponecrobiosis, granulocytic and hystiocytic infiltartes and thrombosed vessels (vasculopathy). Interestingly, the skin lesions were resolved upon treatment with methotrexate and low doses of glucocorticosteroids.

In conclusion, it should be taken into account that even a very rare skin manifestation like this one is a potential presenting symptom of rheumatoid arthritis.

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