

FROM A NEUTROPHILIC SYNOVIAL TISSUE INFILTRATE TO A CHALLENGING CASE OF RHEUMATOID ARTHRITIS

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Abstract

The herein report illustrates how a synovial tissue heavily infiltrated by neutrophils in the first weeks of arthritis, can evolve in few months to a synovial infiltration by lymphocytes with a characteristic pattern of rheumatoid arthritis (RA). This observation suggests a critical initial role of neutrophils in RA onset, which is eventually surpassed by the activation of the adaptive immune system. In addition, this patient, despite the absence of rheumatoid factors and anti-cyclic citrullinated peptide antibodies, progressed to a highly destructive and disabling disease, that was only controlled adequately with rituximab, due to the lack of response to methotrexate and serious adverse effects with TNF blockers therapy.

Keywords: Early Rheumatoid Arthritis; Synovitis; Neutrophils; Adverse Drug Reaction; Anti-Tumour Necrosis Factor Agents.

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease characterized by synovial hyperplasia caused by a large cellular leukocyte infiltrate and high expression of proinflammatory cytokines, leading to erosions and increased remodelling of joint cartilage and bone. The herein case report demonstrates how the presence of a syno-

vial tissue heavily infiltrated by neutrophils can occur during RA onset, being latter on converted into the classic synovial pattern of this disease. Despite the absence of rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (anti-CCP), the clinical evolution of this patient was poor. The difficulties in the clinical management were increased by the lack of response to methotrexate and to the occurrence of severe adverse events with TNF antagonists. These drawbacks led to the introduction of rituximab therapy with an adequate clinical response.

Case report

A 33 year-old woman presented with an acute asymmetric oligoarthritis initiated in the previous week, involving the left ankle, right knee and wrist with associated tenosynovitis. She also referred morning stiffness lasting 30 minutes and on clinical observation no skin lesions or fever could be detected. Her past and family history were irrelevant. Laboratorial evaluation showed normal blood count, elevated erythrocyte sedimentation rate (38 mm/1st hour) and C reactive protein (2.5 mg/dL). Serum RF, anti-CCP antibody, antinuclear antibodies were not detectable and HLA B27 was also negative. Serological tests to Human Immunodeficiency Virus, *Borrelia burgdorferi*, Cytomegalovirus, Epstein-Barr virus, B and C hepatitis virus were negative as well as urinary sediment and bacteriological exam of vaginal swab. Hands and wrists, ankles and knees, feet, chest and sacroiliac radiographs were normal. Synovial biopsy of the right knee revealed the presence of an acute inflammatory infiltrate with predominance of polymorphonuclear cells, suggesting an infectious process (Figure 1a). Despite of a negative synovial fluid culture she was treated with ceftriaxone (1 g im/day), du-

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ring 8 days, due to the diagnostic hypothesis of gonococcal arthritis, and with diclofenac 150mg/dL. As no clinical improvement occurred she was started on a low dose of oral prednisone with a partial clinical response. Two months later, she developed additional involvement of the left wrist and metacarpophalangeal joints of the left hand. By that time, she began treatment with sulphasalazine (up to 2.5 g daily), later associated with methotrexate (up to 20 mg weekly), again only achieving a partial clinical and laboratorial response. Due to signs of high inflammatory activity in the left wrist a second synovial biopsy was performed, 8 months after disease onset. This second biopsy showed fibrosis, moderate diffuse lympho-plasmocitary infiltrate and a few scattered neutrophils (Figure 1b). By this time, she already presented hand and feet erosions and clearly fulfilled the ACR classification criteria for RA¹.

The disease became aggressive and disabling, with the need for surgical synovectomy and partial arthrodesis of the wrist. At that time (two years after disease onset) she was started on infliximab (3mg/Kg iv every 8 weeks, plus 15 mg/week of methotrexate), due to intolerance to 20 mg/week of methotrexate and persistent disease activity (DAS28: 5.8). In the day after the first infusion she developed sneezing and on the second infusion a severe angioedema occurred after 10 minutes of perfusion, requiring hydrocortisone treatment. She was switched to adalimumab (40 mg sc eow) and after 2 months she developed erythematous-descamative plaques involving both hands, feet

and scalp with total alopecia (Figures 2a and 2b). The skin biopsy was compatible with a psoriatic like skin reaction (Figure 3). These skin lesions disappeared 4 months after stopping adalimumab therapy and application of calcipotriol+dipropionate of betamethasone in the lesions. As described, there was no family history of psoriasis and there was a complete remission of the skin lesions after stopping adalimumab without subsequent psoriatic lesions recurrence. She was then proposed for treatment with rituximab (DAS28: 5.6).

Currently, 6 months after rituximab treatment and on 15 mg/week of methotrexate, she has a low disease activity (DAS28: 2.8) with no side effects reported. She only maintains tenderness of the left ankle, which will be treated surgically due to progressive radiological damage.

Discussion

This case report has interesting implication for the concept of early RA pathogenesis. In fact, the first biopsy, obtained in the initial weeks of RA onset, showed a synovial tissue highly infiltrated by neutrophils, which evolved into a different synovial cellular pattern as the disease became chronic. This observation reinforces a critical initial role of neutrophils in RA onset, which is later surpassed by the activation of the adaptive immune system. Despite the fact that RA has been classically considered as a T cell driven disease, recent studies showed that neutrophils are also prominent players in this disease². In fact, neutrophils are the

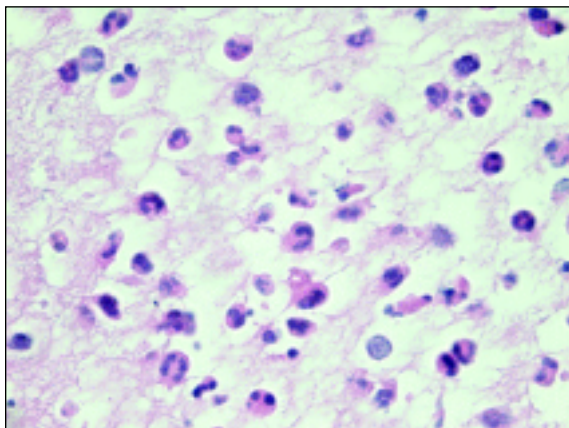


Figure 1a. Synovial biopsy of the right knee in the first weeks of the disease revealing the presence of an acute inflammatory infiltrate with predominance of neutrophils. (Hematoxylin- Eosin, 1000 X).

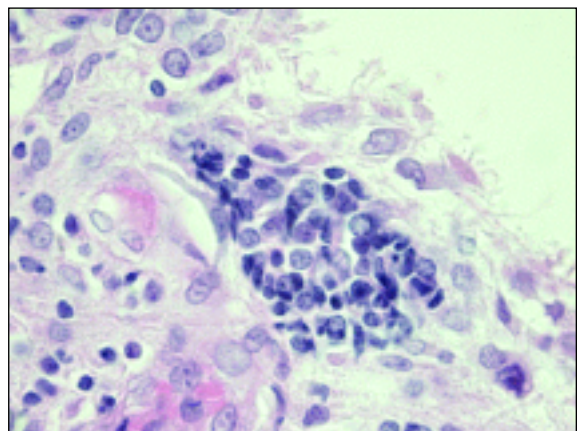


Figure 1b. Synovial biopsy of the left wrist 8 months after disease onset showing fibrosis and moderate diffuse lympho-plasmocitary infiltrate (Hematoxylin-Eosin, 1000 X).



Figure 2a. Erythematous and well demarcated papulosquamous lesion of left hand with a few sterile pustules on the palm.

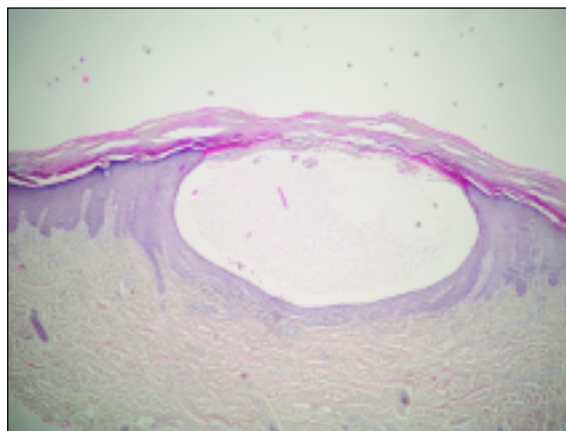


Figure 3. Spongiform vesicle with neutrophils on the top close to the corneal layer, with parakeratosis, compatible with psoriasis (Hematoxylin- Eosin, 1000 X).

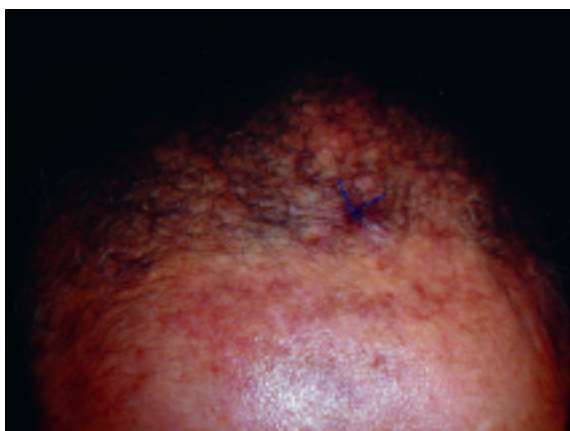


Figure 2b. Alopecia of the frontal area.

most abundant cells in the synovial fluid of patients with active RA and this fluid contains large quantities of cytokines that are secreted by these cells and macrophages [e.g. interleukin (IL) 1 β , IL6, IL8, tumour necrosis factor (TNF) and transforming growth factor (TGF) β]^{3,4,5,6}. Moreover, the disturbed neutrophils apoptosis that was previously reported both in synovial fluid and peripheral blood of RA patients^{7,8} may create the appropriate conditions for an inflammatory vicious cycle that might contribute to the self-perpetuation of an acute arthritis episode and creating the appropriate conditions for the onset of an unremitting joint inflammatory disease.

In addition, this case report also illustrates how a RF and anti-CCP antibody negative RA can be also aggressive and documents two serious adverse events that can occur with TNF antagonist the-

rapy: allergic reaction and psoriasis-like skin manifestations. Other reports of new-onset psoriasis during TNF blockers therapy have been published⁹⁻¹⁴. We emphasize the absence of a family history of psoriasis and the clear cut coincidence between starting adalimumab and the onset of the skin lesions in the absence of other treatment modifications. Moreover, there was a complete clearance of the skin lesions after stopping adalimumab without future psoriatic lesions recurrence. Finally, despite the possible reduced efficacy of rituximab in RF and anti-CCP antibody negative RA patients¹⁵, this particular patient exhibited an excellent clinical response.

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