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CASE REPORT

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# Histopathological characteristics of early rheumatoid arthritis: a case one month after clinical onset

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**Abstract** A 68-year-old woman with early rheumatoid arthritis (RA) was admitted to the hospital because of tender and swollen knee joints. We performed a targeted synovial biopsy under arthroscopy to examine the histopathological characteristics 1 month after clinical onset. The synovia showed the typical histopathology of RA. Although the inflammatory changes were predominantly limited to the surface area of the synovia, associated with neovascularization and cell infiltrates composed mainly of T cells, plasma cells, and macrophages, lesions with fibrin deposition, mesenchymoid transformation and/or immature lymphoid follicles were also observed in part, indicating that this case was in the progression phase of RA. What we regularly call "early" might be "too late" even if it is within 1 month of clinical onset.

**Key words** Rheumatoid synovitis · Targeted biopsy · Immunohistochemistry

## Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease, characterized predominantly by persistent and proliferative inflammation of the synovia, associated with cell infiltrates composed chiefly of T cells, macrophages, and plasma cells, and neovascularization, followed by pannus formation leading to cartilage and bone destruction. Recently, "early RA" has been used as a clinical category which is expected to predict the prognosis of RA and allow for precise therapies in the early phase.[1,2] However, the histopathological features of the synovia specific to RA in the early phase and the potential prognostic value of this histopathology are still controversial.

In this paper we present a case of RA in the very early phase, only 4 weeks after its clinical onset, and show its histopathological characteristics. From this case study, we propose that histopathological analyses of synovial biopsy specimens obtained by targeted biopsy will be useful for defining RA.

## Case report

A 68-year-old woman developed a sudden onset of fever and polyarthralgia. The patient had been evaluated at another hospital 3 weeks earlier and treated with nonsteroidal anti-inflammatory drugs. She had no history of other disorders or treatment with corticosteroid. On admission to our hospital, the patient complained of bilateral knee pain accompanied by swelling and tenderness, as well as shoulder and wrist arthralgias, and morning stiffness.

On initial laboratory examination, the erythrocyte sedimentation rate was 114 mm in the first hour (Westergren), and C-reactive protein (CRP) was 4.39 mg/dl. Rheumatoid factor was negative, but antimitochondrial and antismooth muscle antibodies were detected. Radiographs showed no evidence of bony erosion or destruction. The patient was diagnosed as having early stage RA, according to the criteria proposed by the Japan Rheumatism Association.[3]

One month after clinical onset, a synovial biopsy was performed under arthroscopy. Based on the histopathological findings, which indicated RA, the patient was given three pulses of intravenous methylprednisolone (500 mg/pulse), and subsequently oral prednisolone (5 mg/day) and methotrexate (5 mg/week) with a good response. At a 1-year follow-up, she showed no recurrence of joint symp-

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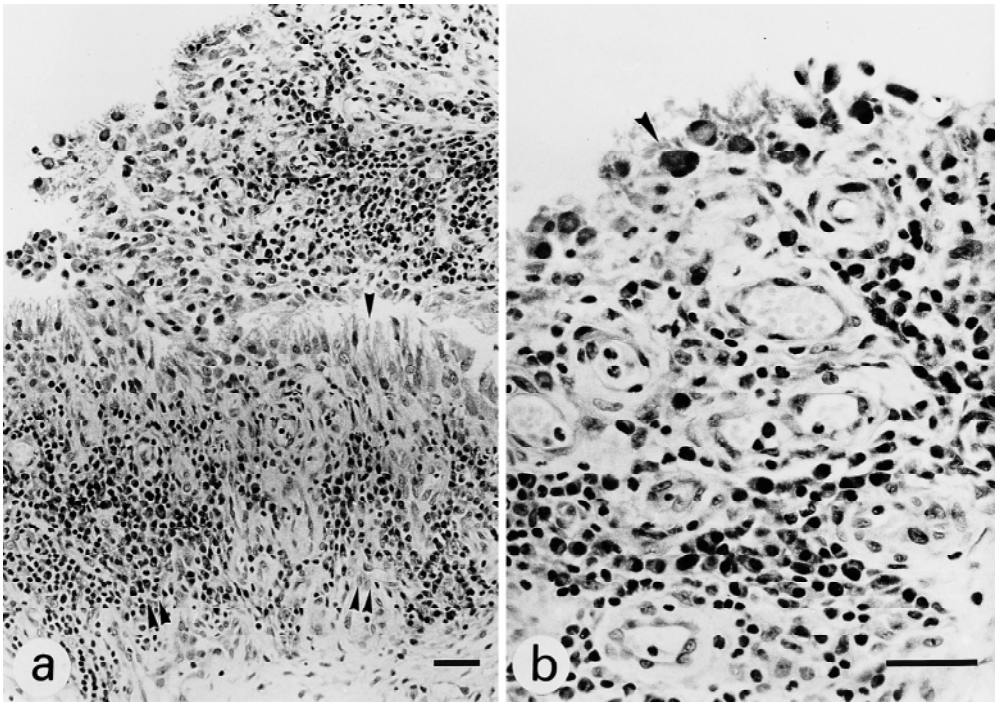


**Fig. 1.** Histological features of the superficial region of the synovia in this case (hematoxylin and eosin). **a** Proliferation of synovial lining cells with a palisading structure (*single arrow*) and many mononuclear cell infiltrates composed of lymphocytes and plasma cells in the sublining regions (*double arrow*). **b** Neovascularization at the arteriole level is prominent in the sublining layers. Nonforeign-body-type giant cells are observed in the lining layer (*single arrow*). *Bar* 100 μm

toms and continued to receive oral prednisolone (5 mg/day) and methotrexate (5 mg/week).

## Biopsy findings

A biopsy was performed at the Center for Rheumatic Diseases, Matsuyama Red Cross Hospital, 1 month after clinical onset of the RA. The synovia of the knee joint had a white cottony appearance at arthroscopy, was edematous and partially villous, and rich in vascularized and proliferative synovia. A total of eight specimens were obtained selectively from the areas of the suprapatellar pouch (the side walls, roof, and floor of the quadriceps bursa), the medial and lateral compartment, and the intercondylar notch region, and subjected to histopathological examinations.

Microscopically, several specimens manifested synovitis characteristic of RA. One specimen showed a proliferation of synovial lining cells, in over five broken layers, which were associated with several nonforeign-body-type giant cells. These lesions often had an underlying proliferation of blood vessels at the arteriole level, often associated with many cell infiltrates composed of lymphocytes and plasma cells in the sublining regions (Fig. 1). The proliferative lining layer showed a typical palisading structure of the lining cells which is partially associated with fibrin deposition.

In other specimens, there were erosive lesions of the synovia with a deficit in the superficial lining layer, in which the sublining tissue showed an incomplete or complete mesenchymoid transformation pattern characteristic of a massively proliferative lesion of fibroblast-like cells (Fig. 2a). There were foci of lymphocyte aggregates close to postcapillary venules (PCV) and resembling lymphoid follicles, but lacking germinal centers (Fig. 2b).

Immunohistochemical studies revealed that the lymphocytes invading the synovia and involving the synovial lining layer were mostly T cells, defined by CD3 staining (Fig. 3a). A few CD20-positive cells (B cells) existed near PCV only (Fig. 3b), although many plasma cells were accumulated in the sublining regions. Many CD68-positive cells were diffusely infiltrated into both the lining and sublining layers (Fig. 3c). Abundant proliferating-cell nuclear antigen (PCNA)-positive cells were detected in the sublining regions with a mesenchymoid transformation pattern. These were mainly mesenchymal cells, but there were no endothelial cells (data not shown).

## Discussion

Histopathological evaluations of synovitis to define RA have a long history, in which the characteristic features for rheumatoid synovitis have been defined as multilayered synovial lining layers (usually more than five layers), associated with a palisading structure of lining cells and the existence of nonforeign-body-type giant cells.[4] The formation of lymphoid follicles and massive accumulations of plasma cells and macrophages in the sublining region are also characteristic. Mesenchymoid transformation, fibrin deposition, and fibrinoid degeneration have been thought to be definite histopathological features of RA.[5] However, these findings

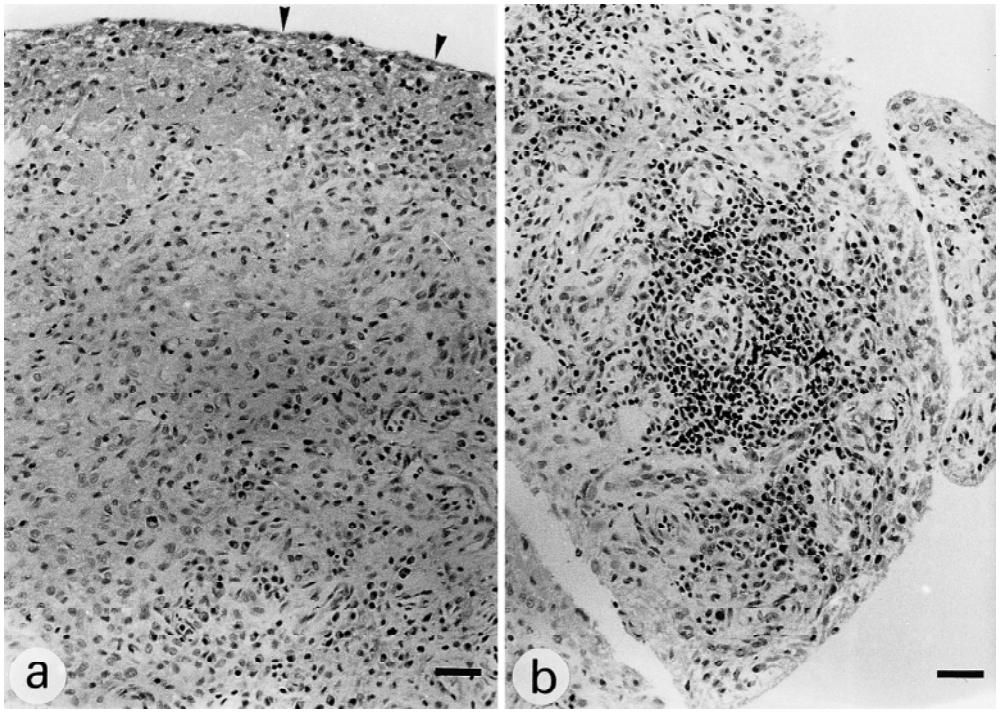


**Fig. 2.** Histological features of the synovia in this case (hematoxylin and eosin), in part showing: **a** mesenchymoid transformation, characterized by the massive proliferation of fibroblast-like cells, associated with a deficit in the synovial lining layers (*single arrow*); **b** immature lymphoid follicles near postcapillary venules (*single arrow*), which are lacking germinal centers. *Bar* 100 μm

have been described only in the joints of patients with advanced RA. Although the use of monoclonal antibodies for immunohistochemical staining has attracted much attention in histopathological studies of rheumatoid synovitis,[6,7] the value of histological assessment in clinical studies of early RA remains unclear, especially less than 1 month after clinical onset.

Previous studies of synovial tissues employing conventional histology in small numbers of RA patients may not be a reliable way to characterize the histopathological features specific to the early phase of RA.[8,9] Schumacher and Kitridou[10] reported the histopathological features characteristic of early RA in studies of six RA patients less than 2 months after clinical onset. These patients showed knee involvement in which synovial lining hyperplasia and vascular changes, as well as an accumulation of lymphocytes, but only occasional plasma cells and polymorphonuclear cells, were shown. In contrast, Konttinen et al.[11] studied synovial specimens obtained by blind-needle biopsy from RA patients 3 months after clinical onset, and compared these with those obtained surgically from RA patients more than 3 years after clinical onset. They concluded that the most prominent feature in the early phase of rheumatoid synovitis was abundant infiltration of mononuclear phagocytes, especially in the synovial sublining regions.

In this case, we observed four important histopathological features. (1) The synovia, even 1 month after clinical onset, showed the typical histopathology of RA, involving multilayers of synovial lining with a palisading structure and nonforeign-body-type giant cells, the accumulation of lymphoid cells with immature lymphoid follicle formation, mesenchymoid transformation, and fibrinoid degeneration. (2) These inflammatory changes were mainly limited to the surface area of the synovia, and associated with increased vascularity, capillary hyperemia, and in some areas, villus formation. (3) Cells infiltrating the synovia were mainly T cells and plasma cells, but with a few B cells and macrophages, partly involving multinucleated giant cells in the subsynovial tissue. (4) Many neutrophils were detected in synovial fluid, but there were few in synovial tissue.

It is worth noting that in this case a significantly increased number of macrophages were also found in the sublining regions, and a mesenchymoid transformation pattern was generated in other regions, since it has been thought that a mesenchymoid transformation is a result of a disease of long duration, and that macrophage infiltration is a characteristic of the progression of RA.[4,5] Thus, both T cells and macrophages, and perhaps plasma cells, seem to be characteristic of the early phase of rheumatoid synovitis. Previous reports of cytokine analyses in RA joints suggested that T cells contribute to the initiation of synovitis and macrophages to its perpetuation.[12,13] Considering this together with our evaluation in this case, suggests that synovial infiltration of abundant T cells, followed by macrophages, must be crucial for the initiation of the disease. Although the formation of lymphoid follicles in the synovia has usually been considered a specific feature of RA, which generates the maturation of B cells to plasma cells in situ, only immature lymphoid follicles were found in this case. Moreover, many mature plasma cells were distributed diffusely in the sublining region. These findings suggest that B cells are already systemically activated in the very early phase of RA, and differentiate to plasma cells in situ only following infiltration into the synovia. Based on these observations, we consider that the early process of RA is

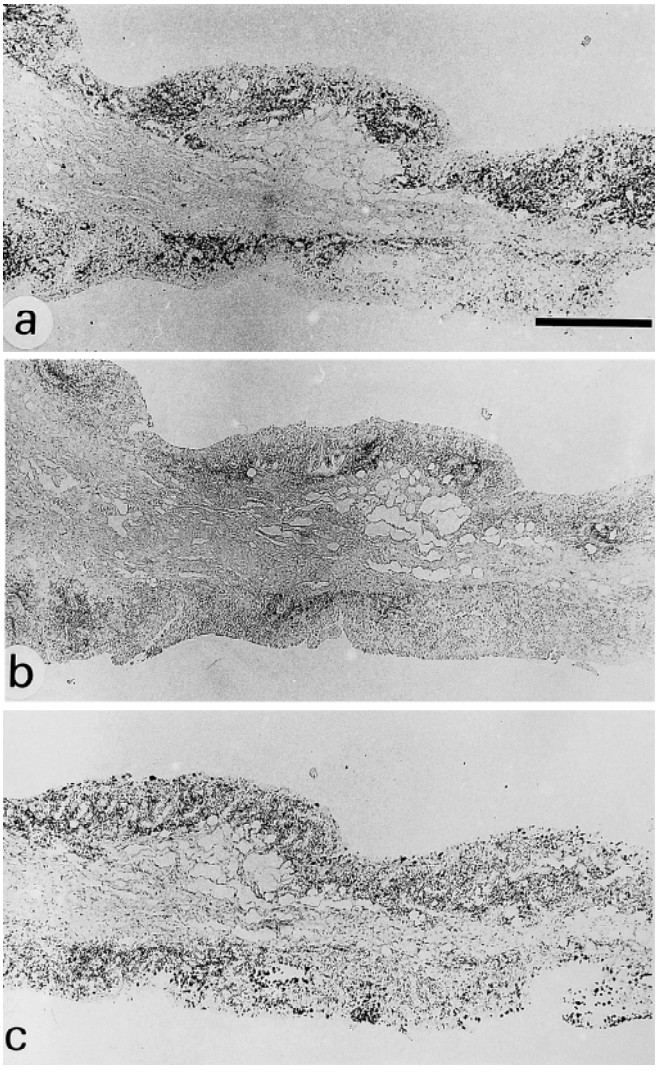


**Fig. 3.** Immunohistochemical features of the synovium in this case (avidin–biotin complex method), showing the distribution pattern of T cells, B cells, and macrophages in the serial sections. **a** Many CD3-positive cells infiltrate diffusely into the superficial regions. **b** A few CD20-positive cells locate near postcapilary venules only. **c** CD68-positive cells are observed in both the lining and sublining regions. *Bar* 500 μm

initiated by the immune response to particular antigens systemically, but not in situ. Then, the antigen-primed T cells accumulate in the synovia and clonally expand in situ, followed by the release of cytokines which lead to the activation of synovial lining cells and the migration of macrophages. Activated T cells in the synovia may also lead to the maturation of already activated B cells to plasma cells in situ.

Konttinen et al.[14] asked, "Is one year early, or too late?" That is, early RA diagnosed within 1 year after onset seems already to be in the chronic phase pathoetiologically. In this case, it should be emphasized that what we regularly call "early" might be "too late," even if it is within 1 month after clinical onset. A targeted biopsy of synovial lesions under arthroscopy is a powerful method, which led us to this conclusion. Diagnosing RA patients in the early phase is difficult and ambiguous. Histopathological studies of synovial biopsy specimens are important for diagnosing early RA prior to starting therapy. Orthopedic surgeons may need to understand the significance of a targeted biopsy of the synovia. This may also shed light on the characterization of T cell clonality and macrophage functions, thus providing valuable information for drug selection.

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