HISTOPATHOLOGICAL ANALYSIS OF RHEUMATOID TENOSYNOVITIS

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INTRODUCTION
Clinical feature of rheumatoid arthritis (RA) is characterized by chronic polyarthritis, as its name indicates. Therefore, the prevailing concept for the etiology of RA is an autoimmune response to unknown auto-antigen(s) specifically expressed in the joints. Autoimmune nature of RA is supported by the high prevalence of auto-antibodies, such as rheumatoid factor (1). In addition, a massive infiltration of activated CD4+ T cells is found in the inflamed synovium in the joints. Thus, it is hypothesized that these CD4+ T cells recognize unidentified joint specific auto-antigen(s) presented on synovial macrophages or fibroblasts and activate them to produce inflammatory cytokines, leading to chronic inflammation and progressive destruction of the joints. On the other hand, it is noteworthy that chronic synovitis is also often observed in extra-articular regions in RA patients. Flexor and extensor tenosynovial tissues of the digits could even be the earliest symptom of RA in substantial percentage of RA patients (2, 3), surprisingly little is known about its histopathological features. In this study, we compared histopathological features of joint synovitis and tenosynovitis in RA. We found a striking similarity in the histological features between joint synovitis and tenosynovitis, including the proportion and distribution of the immune cell populations. These results suggest that the prevailing tenosynovitis is also a fundamental aspect of RA.

METHODS
Six RA patients with active arthritis in the radiocarpal joint and active synovitis in the extensor tendon of the digits were included in this study. Synovial tissues were obtained at the surgery when RA patients underwent synovectomy of both joints and the tendon on the same day. As controls, four patients with knee or hip osteoarthritis (OA), who underwent joint replacement surgery, were investigated. Synovial tissues were fixed with formalin and embedded in paraffin. They were evaluated by hematoxylin and eosin staining and by immunohistochemical analysis for CD4+ T cells, CD8+ T cells, CD20+ B cells and CD68 macrophages using a Mann–Whitney U-test was used for analyzing the differences in histological scoring. The paired t-test was used for the comparison between tenosynovium and joint synovium of RA. A P-value of less than 0.05 was considered statistically significant.

RESULTS
Synovial tissues from RA wrist joints showed typical histological features of RA synovitis (figure 1A), these included hyperproliferation of synovial lining cells, typically more than seven layers, and massive infiltration of inflammatory cells including lymphocytes and plasma cells. A formation of new blood vessels was also observed. Furthermore, the RA tenosynovial tissues showed quite similar phenotypes to the RA joint synovium, such as hypertrophy of the lining layer and massive cellular infiltration (figure 1B). In contrast, neither the hyperplasia of synovial lining nor severe infiltration of inflammatory cells was observed in OA synovium, although the OA synovium also showed villous-shaped hypertrophy of synovial tissue and new vessel formation in the sublining layer (figure 1C).

In the synovial tissues of both RA joint and RA tendon, most of CD4+ T cells were found in the form of aggregation, while some were diffusely distributed in the sublining layer. CD20+ B cells were found in a similar fashion to CD4+ T cells, while majority of CD8+ T cells were found scattered. CD68+ macrophages were found in the lining layer as well as the sublining layer. Thus there was a striking similarity even in the proportion and distribution of the inflammatory cell populations between joint synovitis and tenosynovitis. These features were quite different from those of OA synovium, which showed only marginal infiltration of these cell subsets. The difference was further confirmed by a quantitative analysis on the number of infiltrating cells in the synovium (figure 2). The synovial tissues from OA joints contained significantly less CD4+ T cells, CD8+ T cells, CD20+ B cells and CD68+ macrophages than either RA joint synovium or tenosynovium. Again, there was no significant difference in the number of these immune cells between RA tenosynovitis and RA joint synovitis. These results indicated that RA joint synovitis and tenosynovitis are histologically indistinguishable even in terms of the infiltrating cellular components.

DISCUSSION
There have been only a few studies examining RA tenosynovitis. One study demonstrated production of several proinflammatory cytokines and proteolytic enzymes by cultured RA tenosynovium (4). More recently, it was also reported that neutralization of IL-1 and TNF-a reduced production of MMP-1 and MMP-13 by RA tenosynovial tissue in vitro (5). These studies clearly indicate that RA tenosynovitis has biological activities to induce tissue damage, such as tendon rupture, similar to the joint synovitis, which induce progressive joint destruction. However, to date, there has been no detailed comparative study on the histopathology between RA tenosynovitis and joint synovitis. In this study, we for the first time found that RA tenosynovitis have almost identical histopathological features to RA joint synovitis, which was more evident by comparing these tissues from the same patient. Our study revealed that the histopathological features of rheumatoid tenosynovitis were strikingly similar to those of joint synovitis. Therefore, it is suggested that the ongoing inflammation in the tenosynovium and the joint synovium is driven by similar mechanisms, and thus RA may not be an organ specific disease targeting the joints but rather a tissue specific disease targeting the synovial tissues.

REFERENCES
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