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Review Article

Importance of tenosynovitis in preventing the progression through rheumatoid arthritis continuum

Tomomasa Izumiyama[a,*] and Masaaki Miyazawa[b]

[a]Higashisendai Rheumatic Disease Clinic, Sendai, Miyagi, Japan
[b]Department of Immunology, Kindai University Faculty of Medicine, Osaka-Sayama, Osaka, Japan

*Correspondence: Tomomasa Izumiyama; tom.izu.556@gmail.com; Higashisendai Rheumatic Disease Clinic, 1-17-5 Shinden-Higashi, Miyagino-ku, Sendai, Miyagi 983-0039, Japan.

ABSTRACT

Rheumatoid arthritis (RA) has long been characterized by synovitis and bone erosions typically developing symmetrically in small joints. However, recent advances in imaging modalities have indicated frequent association of tenosynovitis with RA, and some consider tenosynovitis to be not just a complication but a major trait of RA. Furthermore, as there are cases with tenosynovitis preceding the clinical detection of inflammatory arthritis in predisposed individuals, tenosynovitis may constitute an important biomarker in defining the pre-RA phase of disease development. Tenosynovitis itself must be treated as it causes functional impairment and physical as well as socioeconomic burden, and its treatment may result in effective prevention of RA development at a pre-arthritic stage. Thus, further efforts need to be taken in detecting and treating tenosynovitis in the pre-RA stage, which can be facilitated by ultrasonography and magnetic resonance imaging.

KEYWORDS: Tenosynovitis; rheumatoid arthritis; diagnosis; preclinical stage; progression

Introduction

It is widely accepted to start prescribing methotrexate as an antirheumatic drug once the 2010 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) criteria [1] classifies a patient as having rheumatoid arthritis (RA). At the same time, it has also been shown through clinical trials that many patients can be benefited by early recognition of the disease process with prompt treatment, which can even achieve remission [2]. This leads to the idea of preventing the disease development at a preclinical stage by defining populations at risk of developing RA [3]. However, there is still no consensus on at what time point a patient can be diagnosed as having imminent RA. In this regard, it has recently been proposed to include tenosynovitis of the hand and foot as the third defining trait of RA along with classic features of synovitis and bone erosions in small joints [4]. Although this proposal is still arguable, EULAR task force has pointed out tenosynovitis as one of the predictive factors that indicate progression to classifiable RA [5].

In this critical review, we intend to discuss about pathophysiological and clinical importance of tenosynovitis in early recognition of the ongoing process of RA continuum at the pre-RA stage and the possible benefit of treating tenosynovitis in preventing its progression to established and even early RA. We also propose the possible significance of connective tissue pathologies in tendon-related structures in detecting pre-RA lesions.

Tenosynovitis as early pathology in RA development

Finger tenosynovitis is commonly detected in patients with untreated early RA by using ultrasonography (US) and/or magnetic resonance imaging (MRI) (Figures 1–3), and some report that MRI is more sensitive than US in detecting tenosynovitis in the fingers: in one report, flexor tenosynovitis was found in 48% of 50 patients on US compared to 82% on MRI [6]. A historic report described RA cases presenting with tenosynovitis as the initial manifestation [7], and frequent presence of tenosynovitis of the hand, especially flexor tenosynovitis, in RA had been repeatedly reported in the 1970s [8–10]. Anatomic distribution of tenosynovitis associated with risks of progression to RA is those of the extensor carpi ulnaris (ECU) and of flexor tendons of the second finger [11, 12]. There are cases in which carpal tunnel syndrome associated with flexor tenosynovitis preceded the development of RA [13–15]. Furthermore, in mice expressing the 3′-modified human tumor necrosis factor (TNF)-α transgene, tenosynovitis and following formation of osteoclasts precede the development of pannus-like lesions and chronic polyarthritis [16]. Thus, these clinical observations and the animal model indicate the importance of tenosynovitis as the initial lesion of RA.

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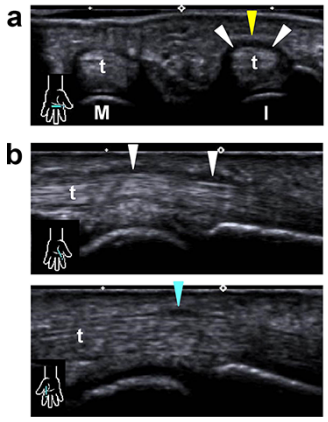


Figure 1. Representative US images of tenosynovitis.

(a) A transverse scanning image of flexor tendons (t) showing highly contrasted thickened tendon sheath (yellow vertical arrowhead) with anechoic synovial proliferation or fluid accumulation (white oblique arrowheads) of the index finger (I) in a 54-year-old female patient. M, middle finger. (b) Longitudinal scanning images of the left and right index finger flexor tendons showing an extended area of anechoic synovial proliferation or fluid accumulation (white arrowheads in the upper panel) and A1 pulley thickening (blue arrowhead in the lower panel) in a 49- or 47-year-old female patient, respectively. The latter is distinguishable from tenosynovitis by its anatomical location and size.

Importance of tenosynovitis in the diagnosis of RA

In the 1956 diagnostic criteria for RA [17], which was revised in 1958, tenosynovitis was regarded to be relatively nonspecific. On the other hand, in the 1981 clinical criteria of remission in RA [18], a lack of soft tissue swelling in joints or tendon sheaths was included in the six requirements to yield optimal discrimination of complete clinical remission, indicating that tenosynovitis was regarded to be one of the pathophysiologic manifestations of RA at that time. Later, however, with the advent of slow-acting antirheumatic drugs, as it was then called, disease activity and treatment response in RA were judged with the Ritchie Articular Index [19] or Disease Activity Score in 28 Joints [20], and tendons were not included as a variable in the 2010 ACR/EULAR RA classification criteria [1]. Nevertheless, it must be pointed out that morning stiffness was included as having a high diagnostic value in the 1956 diagnostic criteria for RA [17] and tenosynovitis has been shown to associate with and contribute to severity of morning stiffness in RA patients [21–23]. This indicates that the category of possible RA that was intended to pick up early and atypical cases [17] might actually have included some pre-RA cases presenting with tenosynovitis. The statement that *the inclusion of patients who do not have RA in the possible group will not be serious as errors in diagnosis will become apparent as the patients are followed* [17] may suggest that the difficulty in diagnosing cases with early RA was one focus of discussion at that time. Although some degree of differential diagnosis can be made based on the detection of disease-specific autoantibodies, when tenosynovitis precedes the manifestation of typical skin lesions or clinical signs of autoimmune diseases other than RA, it is practically unable to distinguish it from tenosynovitis in pre-RA even now. Thus, the above statement of not being afraid of making errors in diagnosis of early RA is worth listening to. Furthermore, it should also be noted that the above authors have emphasized that *the criteria should not be so strict that only cases of great severity or long duration can be included* [17]. As the importance of tenosynovitis in picking up early RA is revisited now, morning stiffness that is closely associated with tenosynovitis and can be a very sensitive manifestation of early RA must be re-evaluated.

Issues inherent in the concept of pre-RA

RA is autoimmune inflammatory arthritis that develops through a continuum of distinct progressive phases: namely,

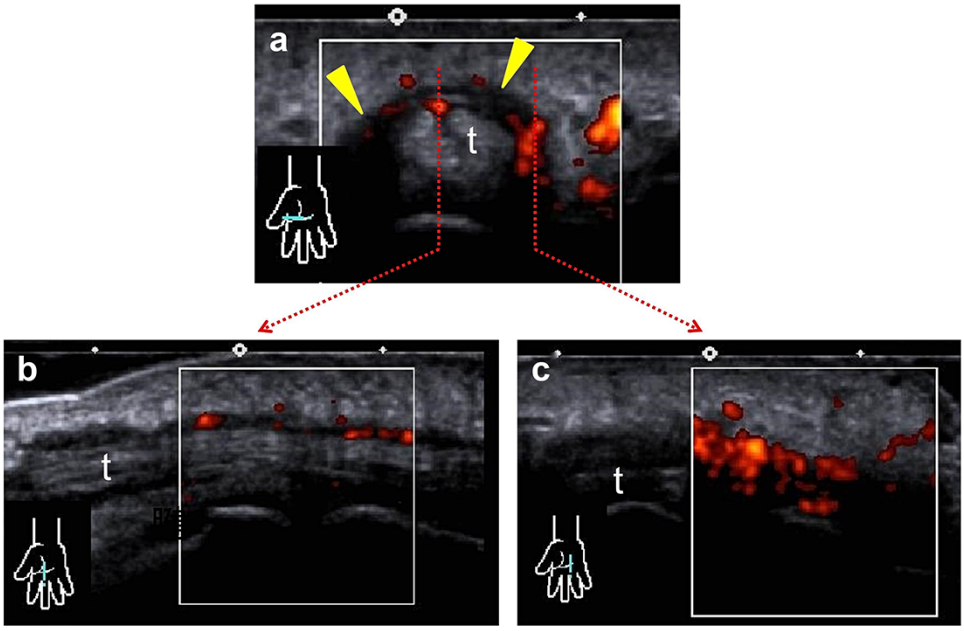


Figure 2. Colour Doppler ultrasound images of tenosynovitis with increased vascularity in a 35-year-old female patient.

A transverse scanning image of the third finger flexor tendon (t) shows inflamed hypervascular synovium (red coloured) within the tendon sheath (yellow oblique arrowheads) in panel (a). Longitudinal sections corresponding to dotted lines in panel (a) are shown in panels (b and c).

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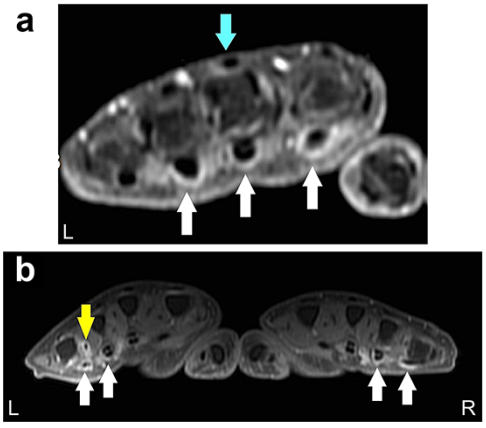


Figure 3. (a) A T1-contrasted MRI image of flexor tenosynovitis and extensor peritendinitis in a 42-year-old female patient.

Tenosynovitis of the left index, middle, and ring finger flexor tendons (white upward arrows) and extensor peritendinitis of the middle finger (blue downward arrow) are shown in the axial postcontrast image through the left hand. (b) An MRI image of bilateral tenosynovitis and peritendinitis of interosseous tendons in a 74-year-old female patient. Bilateral ring and little finger tenosynovitis (white upward arrows) and the third palmer interosseous peritendinitis (yellow downward arrow) are shown in the axial postcontrast image through the hands.

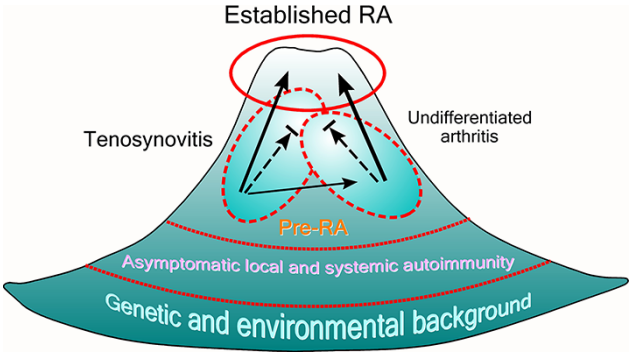


Figure 4. Diagrammatic representation of the pathogenesis of RA with emphasis on the importance of tenosynovitis as a pre-RA condition.

Tenosynovitis in predisposed individuals may (solid arrow) or may not progress to established RA (dashed arrow). Similarly, undifferentiated arthritis or PR may (solid arrow) or may not progress to classifiable RA (dashed arrow).

environmental factors added on predisposing genetic factors trigger local and then systemic autoimmunity (immunological onset), which leads to the development of inflammatory lesions in the musculoskeletal system represented by arthralgia (clinical onset) followed by undifferentiated inflammatory arthritis and classifiable RA [3, 24, 25] (Figure 4). As most RA patients do not return to pre-onset status of symptoms even with appropriate therapy once clinically apparent arthritis develops [26], the pre-RA stage of seropositive disease has been defined through several prospective studies with the intended goal of delaying or preventing the onset of clinical arthritis in at-risk individuals [24, 27]. However, the concept of pre-RA as currently defined can be used only retrospectively to describe stages prior to clinical manifestation of arthritis in individuals who eventually developed RA [27]. This means that extra-articular manifestations of patients who do not develop classifiable arthritis cannot be defined as those of pre-RA regardless of their severity or effects on quality of life. Furthermore, this definition connotes contradictions. First, palindromic rheumatism (PR) is thought to be a pre-RA condition [28–31] and periarticular soft tissue inflammation including tenosynovitis is frequently detectable in PR patients [32–34]. In one study, treatment of PR patients with antimalarials significantly reduced and delayed the secondary development of RA and other connective tissue diseases, but more than 60% in the untreated group did not progress to a secondary disease [35]. A more recent study estimated that about 20% of PR patients do not progress to RA even at 10 years from the PR onset [36]. Thus, although it is impractical to follow up patients all through their lives, these reports indicate that not all pre-RA conditions progress to RA. This may also apply for pre-RA patients presenting with tenosynovitis as the initial manifestation. Second, if treatment halts the progression to RA as in the above cases of PR given antimalarials, the target stage of treatment cannot be described as pre-RA by definition. Therefore, treatment strategies aiming at preventing the progression to RA undermine the presence of the pre-RA stage.

These issues indicate necessities to re-examine definitions of RA itself. As can be seen in the 1958 revision of diagnostic criteria that classified RA into classical, definite, probable, and possible cases [37], RA is a pleiotropic condition. There is no doubt that patients fulfilling the 2010 ACR/EULAR classification criteria must be treated, but it does not mean that those not classified should be left untreated, especially because the revision from the 1987 American Rheumatism Association (ARA) to 2010 ACR/EULAR criteria was made with emphasis on early enough intervention to prevent the joint destruction [38]. We would like to propose that not only those who would progress to classifiable arthritis but also those who demand treatment due to their pathophysiological condition must be treated regardless of their prospect of progression. As RA is a continuum of progressive stages [3, 25, 34], the entire process of the progression from systemic autoimmunity to classifiable inflammatory arthritis must be considered as putative RA [24], and any stage of this continual process can be a therapeutic target if applicable.

Necessities to treat tenosynovitis per se

RA has been defined and treated as inflammatory arthritis that can lead to joint destruction and resultant functional impairment associated with substantial socioeconomic consequences. However, tenosynovitis can also cause functional impairment and thus has to be treated. Tenosynovitis of hand flexor tendons causes trigger fingers and decreased gripping strength. Tenosynovitis that develops in the carpal tunnel induces carpal tunnel syndrome, which causes sensory disturbances and results in reduced daily functionality and significant socioeconomic burden [15]. Tendon rupture may even occur [39]. Furthermore, tenosynovitis of ECU can result in bone erosion [40]. Importantly, these tenosynovial lesions may develop prior to the onset of synovitis of a joint [40, 41] and become a target of therapeutic intervention. Thus, tenosynovitis must be treated when required and it may result in halting the progression of RA continuum before the development of arthrosynovitis.

Caution must be taken when treating seronegative RA

To facilitate early initiation of disease-modifying antirheumatic drugs (DMARDs) that are associated with better

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outcome [29, 42], it has been proposed to start treating patients with positive anticitrullinated protein antibodies and new nonspecific musculoskeletal symptoms [43, 44]. This approach is practical for seropositive cases at present; however, clinical diagnosis and decisions to initiate treatment of seronegative RA can only be made by an expert rheumatologist, while most patients visit general practitioners repeatedly without getting early referral. As a result, seronegative RA is shown to be delayed in diagnosis and treatment initiation, thus causing some patients to miss the window of therapeutic opportunity [45]. Therefore, negative autoantibodies in laboratory tests of possible early RA cases must be interpreted very carefully. Similarly, C-reactive protein levels less than the reference range do not necessarily mean a lack of local inflammation [29, 46]. Early RA should be diagnosed based on the presence of synovitis in joints or tendons, not based on laboratory test values. In this regard, dissemination of a deeper understanding on tenosynovial lesions would also be required for early diagnosis and treatment initiation of seronegative RA.

Usefulness of MRI and US in diagnosing pre-RA

For early detection of pre-RA manifestations, we have to depend on imaging technologies to objectively detect and describe tenosynovial lesions. In fact, MRI and US are included in biomarkers considered for identification of individuals with autoimmunity and musculoskeletal symptoms who could constitute a cohort with sufficient risk of progression to RA [3]. However, these imaging modalities have weakness in discriminating slight pathological changes in pre-RA from normal anatomy, and some have pointed out that further studies are required for daily diagnostic decisions based on imaging alone [26]. On the other hand, researchers from 16 countries have reported that US is a routinely available, noninvasive, and relatively inexpensive bedside technique that is reproducible and reliable in the evaluation and follow-up of tenosynovitis [47]. Similarly, MRI has been utilized in diagnosing RA patients presenting with tenosynovitis [11, 12] or peritendinitis of interosseous [48, 49] or extensor tendons [50]. As musculoskeletal lesions, especially tenosynovitis, are associated with significant levels of functional impairment and socioeconomic consequences, imaging modalities that can detect such lesions should be initiatively utilized in seronegative as well as seropositive individuals.

Management of pre-RA with tenosynovitis as its initial manifestation

There is no evidence-based treatment strategy currently adoptable for the management of presumable pre-RA presenting with tenosynovitis as its initial manifestation. Tenosynovitides of ECU and flexor tendons of the second finger are reported to be associated with risks of progression to RA [11, 12] and thus can be subjects of intervention aiming at halting the progression to RA. However, the possible effectiveness of preventative intervention is difficult to evaluate as it is unclear if and when the tenosynovitis progresses to RA and successful prevention denies its being a pre-RA lesion as discussed above. Progression from PR to RA was successfully prevented with antimalarials in some cases [35], but PR is widely accepted as a pre-RA condition with fairly well-documented kinetics of progression to RA [35, 36]. Nevertheless, managements aiming at the reduction of patients' burden can be considered. For example, in cases of severe flexor tenosynovitis that causes difficulties in daily activities, steroid injection can be efficacious as a temporary symptomatic treatment [51]. Caution must be taken, however, as steroid injection is a risk factor for postoperative surgical site infection when subsequent open surgical release is performed [52, 53]. The most significant pitfall in treating tenosynovitis is tuberculous tenosynovitis as a differential diagnosis of unilateral lesions [54]. It can even be associated with extensor lesions that may represent an RA-associated initial pathology [50]. If tuberculous tenosynovitis cannot be ruled out, treatment of tenosynovitis should be limited to patients with bilateral lesions, and simultaneous imaging of both hands by MRI or US can contribute to decision-making (Figure 3). As slight pathological changes in pre-RA can be difficult to discriminate from normal anatomy, further discussion is required in improving accuracy of clinical diagnosis of tenosynovitis made by using imaging modalities.

As to interventions other than steroid injection, reports on PR can also provide helpful information. Besides the above-described antimalarials that prevented progression of PR to RA in some cases [35], in PR cases in which acute arthritic attacks were not controlled with hydroxychloroquine and low-dose prednisolone use of DMARDs resulted in complete remission at a high frequency, and only a small fraction of treated patients progressed to RA [55]. This tight control strategy might be considered in cases of tenosynovitis in predisposed individuals. If long-term remission is achieved with such intervention, as in the above cases of PR treated with DMARDs, it can resultantly be interpreted that predicted progression through the RA continuum was successfully prevented at the pre-arthritic stage. There may be questions about how long the treatment should be continued in patients who are not readily showing signs of arthritis. However, once the disease process progresses to overt arthritis, it cannot be returned to the pre-arthritic phase in most cases [26]. Therefore, dedicated intervention by expert rheumatologists should be considered for patients who suffer from unbearable symptoms and daily burden of tenosynovitis.

Inflammation in connective tissues other than synovia

Although we have mainly discussed about tenosynovitis here, RA is one of the connective tissue diseases, not just a disease of synovia. As indicated by cases of RA with interstitial lung disease as its initial manifestation [56], inflammation in RA is not confined to synovial tissues, but inflammation of connective tissues other than synovia can be seen at the onset of clinical disease. Examples are peritendinitis of hand interosseous tendons [57], which lack tendon sheath or synovium [48, 49] or of metacarpophalangeal (MCP) extensor tendons [50] in early RA. Furthermore, enthesitis is frequently observed in RA patients [58, 59]. However, enthesitis must be comprehended through the anatomic basis of enthesis organ concept that has indicated structural similarities between classic and functional entheses as well as articular fibrocartilages [60]. Thus, mechanical microdamage in enthesis regions can initiate synovitis as a regenerative process on the tendon side and at the same time bone erosions with osteoclast formation as a

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remodelling process on the bone side. Osteoclast formation following inflammatory thickening of tendon sheath in the human TNF-α transgenic mouse model [16] can be comprehended in line with the above concept of enthesis organ, as the anatomic site of bone erosions co-localizes the wrap-around structures of peroneus longus muscle tendon on the calcaneus. This may suggest that mechanical stress on tendons and bones in the early inflammatory process can result in tenosynovitis and bone erosion. In fact, bone erosions in the proximal part of the MCP joints occasionally observed in RA patients are anatomically associated with mechanical microdamage that is prone to occur adjacent to collateral ligaments [61]. Although these extraarticular lesions, which are also observed in PR [32–34], are not directly contributing to the diagnosis of RA, further studies are required for more thorough understanding of the possible contribution of extraarticular inflammation in the pathophysiology of early RA.

Conclusions

Cases of RA presenting with tenosynovitis have long been recognized [7–10], and their importance is more and more emphasized in considering earliest possible intervention within RA continuum. It is time for rheumatologists to discuss the diagnosis of and treatment initiation in early RA based on the detection of not only joint synovitis but also tenosynovitis. This leads to the understanding of RA pathogenesis as autoimmune inflammation of the entire synovial tissue, not just an articular one. A number of recent reports utilizing imaging modalities indicate that tenosynovitis dominates the pathophysiology in some pre-RA cases, and not all patients at the pre-RA stage progress to classifiable RA. Thus, the whole picture of RA as systemic synovitis can be summarized as shown in Figure 4. Recognition of the presence of a pathogenetic course of RA that is clinically initiated with tenosynovitis may be important in exploring early diagnosis and treatment initiation at the pre-RA stage. To determine if and when slight inflammatory changes in tenosynovium that can only be detected with MRI or US should be treated, trials to initiate antirheumatic therapy in nonarthritic patients might be required. To encourage such trials, we would like to quote the authors' statement in the 1956 classification criteria again as it is very important: 'the inclusion of patients who do not have RA in the possible group will not be serious as errors in diagnosis will become apparent as the patients are followed' [17].

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Conflict of interest

None declared.

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