Not only synovitis but also tenosynovitis needs to be considered: why it is time to update textbook images of rheumatoid arthritis

Rheumatoid arthritis (RA) is typically represented as synovitis and bone erosions of small joints. This classic picture resulted from comparing patients with RA with other rheumatic joint diseases for clinical and radiographic characteristics. Although different classification criteria for RA have been developed over time, this classic picture has not changed since the mid-20th century. During the last decennium, advanced imaging modalities, such as MRI and musculoskeletal ultrasound (US), have refined our understanding of tissues involved in RA. We will argue that tenosynovitis at the level of the hand and feet joints is a feature that deserves to be added as the third classic trait of RA.

A feature can be considered as a disease trait when it occurs frequently and is specific, and when a new trait is considered its connection with the disease is not a substitute of an already acknowledged classic feature. We will study the occurrence of tenosynovitis in RA in the light of these principles.

Many, but not all, tendons at the hand and feet joints are surrounded by a sheath.[1 2] Tendon sheaths have a cell composition similar to the synovial lining of joints.[3]

Fiona McQueen was the first to describe tenosynovitis in early RA using MRI.[4] The reported prevalence of tenosynovitis depends on the number of tendon sheaths studied (wrist, metacarpophalangeal (MCP) and/or metatarsophalangeal (MTP) joints, unilateral or bilateral). A prevalence of ~50% is described,[5 6] but most were higher (~80%).[7–11] MRI studies in consecutive early RA showed a sensitivity of tenosynovitis of 75%–87%.[7–9] Figure 1A–C presents imaging examples (MRI, US) in early RA. Imaging studies in persons from the general population repetitively showed a prevalence of tenosynovitis at small joints ranging from 0% to 3%,[12–14] corresponding with a specificity of 97%–100%. The specificity in patients with other arthritides as reference is also high. A study at the tendon level of the wrist and MCP joints, comparing consecutive patients with RA and other early arthritis (including psoriatic arthritis), reported a specificity ranging from 82% to 99%.[8] Thus, tenosynovitis at the level of small joints (MCPs, wrist, MTPs) has high sensitivity and specificity for RA.

Studies in an experimental mouse model showed that tenosynovitis was the first sign of inflammation.[15] Infiltration of the tendon sheaths by granulocytes and macrophages was the first pathological event in the preclinical phase; only few T cells were present and B cells were initially absent (figure 1D). Hyperplasia of the joint synovial lining was observed at the onset of clinical arthritis but not in the preclinical disease.[15] The question if tenosynovitis is also the initiating feature of arthritis in humans with RA is still unsolved. However, a serial MRI study in pre-RA revealed that tenosynovitis and synovitis occurred very early, before the development of clinical arthritis and erosions.[16] The notion that tenosynovitis is a very early feature of RA is further supported by the consistent finding that tenosynovitis is an independent predictor for developing RA in patients with clinically suspect arthralgia and undifferentiated arthritis, whereas synovitis is not constantly predictive in multivariate analysis (online supplementary table).

Finally we explored whether tenosynovitis contributes to symptoms and signs that are characteristic of RA. A summary of currently available data reveals that tenosynovitis is related to
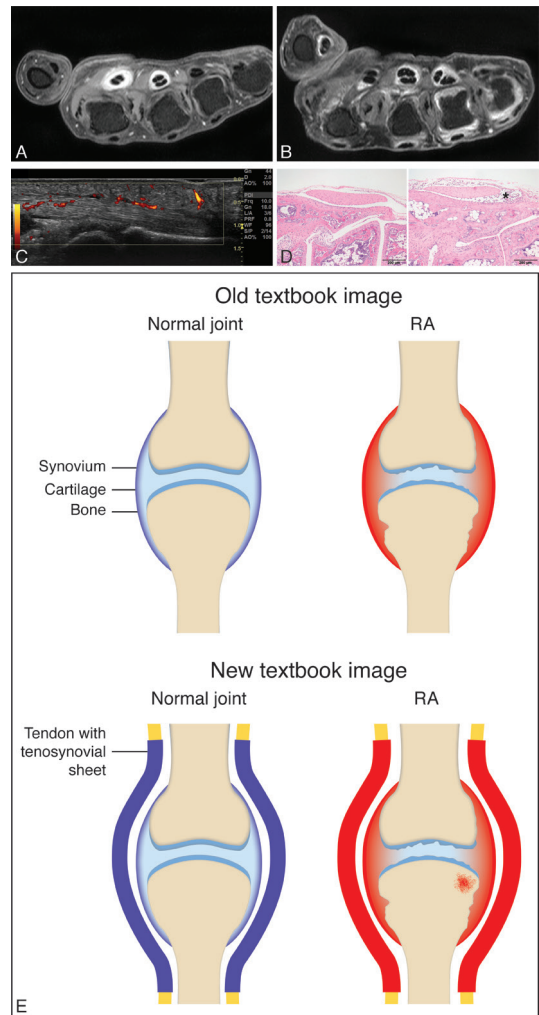

Figure 1 Tenosynovitis as an early trait in RA (A–C) and experimental arthritis (D), and the proposed new textbook image of RA including tenosynovitis (E). (A–B) MRI (axial plane after contrast enhancement, 1.5T MRI) of two patients with early RA with flexor tenosynovitis at MCP 2 and 3 (A) and flexor tenosynovitis at MCP 1, 3 and 4, and synovitis at MCP 4 and 5 (B). (C) Ultrasound (longitudinal plane) in a patient with early RA showing flexor tenosynovitis at MCP 2. (D) H&E–stained transverse section planes of the hind paw of 4-week-old wild-type (left) and hTNFtg (right) arthritis mice with tenosynovitis (*infiltration of lymphocytes and inflammation of the tendon sheath) in the preclinical phase of arthritis (magnification 100×). (E) Proposed new textbook image with tenosynovitis and osteitis. MCP, metacarpophalangeal; RA, rheumatoid arthritis.

the presence of joint swelling, joint tenderness, morning stiffness and functional impairments in RA and in earlier disease phases (online supplementary table). Associations were independent of possible concomitant imaging-detected synovitis.

To summarise, tenosynovitis at the level of small joints has high sensitivity and specificity for early RA. Tenosynovitis occurs early during RA development. It underlies symptoms and signs that are characteristic of RA, both in preclinical stages and in clinical RA. Based on this we propose that, in addition to synovitis and structural damage, future textbook images from now on also depict tenosynovitis as a classic trait of RA, as portrayed in figure 1E. In addition, if classification criteria for the earliest phases of RA were to be derived or modified, tenosynovitis could be included.

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Retinal vasculometric characteristics and their associations with polymyalgia rheumatica and giant cell arteritis in a prospective cohort: EPIC-Norfolk Eye Study

Both polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) have been associated with an increased future risk of cardiovascular disease (CVD).[1] However, it remains uncertain whether this is a consequence of inflammatory disease or relates to a common underlying mechanism. Retinal vascular images are a sensitive measures of vascular health, which are emerging as important biomarkers of future cardiovascular risk with changes affecting arterioles and venules.[2] In this study, we assess whether vasculometric features associated with CVD are detectable prior to the onset of PMR and GCA.

We analysed data from initially healthy subjects enrolled in the EPIC-Norfolk Study, a prospective population-based cohort which enrolled participants between the years 1993 and 1997.[3 4] Digital photographs of the retinal fundus were taken of 8112 participants between 2004 and 2011 using a TRC-NW6S non-mydriatic retinal camera and IMAGEnet Telemedicine System (Topcon Corporation, Tokyo, Japan) with a 10 MP Nikon D80 camera (Nikon Corporation, Tokyo, Japan). Retinal vessel widths were measured using the QUARTZ (QUantitative Analysis of Retinal vessel Topology and siZe) programme.[5] The fully automated algorithm uses an ensemble classifier of bagged decision trees to allocate vessels into arterioles and venules at 80% probability and calculates summary measures for each participant with an averaged measure between right and left eyes.

Cases of PMR and GCA were identified by three methods: (1) free text questionnaire responses at enrolment, and thereafter, 18 months, 3, 10 and 13 years; (2) linkage to hospital electronic discharge summaries containing International Classification of Diseases (ICD) codes (3) linkage to keyword searches (*polymyalgia or rheumatica or giant or arteritis*) of out-patient clinic letters. To be identified as PMR or GCA, participants were required to have received at least two prescriptions for oral glucocorticoids within 6 months following their diagnosis.

Table 1 Retinal vasculometric characteristics and their association to diagnoses of PMR and GCA

	Incident cases*	Incident cases meeting classification sets	Control n=5477
PMR (n)	30	24	
Venular width (µm) and SD	96.6 SD 12.5	100.0 SD 11.3	91.1 SD 10.6 from 5036 controls
Difference in venular width (µm) (95% CI) 80% probability†	5.5 (1.7 to 9.3) p=0.005	8.9 (4.7 to 13.2) p=<0.001	
Adjusted for age at time of retinal photograph capture and sex	4.4 (0.7 to 8.2) p=0.021	7.8 (3.6 to 12.0) p=<0.001	
Arteriolar width (µm) and SD	75.6 SD 7.6	76.9 SD 7.8	75.0 SD 6.3 from 5037 controls
Difference in arteriolar width (µm) (95% CI) 80% probability†	0.7 (–1.6 to 2.9) p=0.575	0.6 (–1.6 to 2.9) p=0.57	
Adjusted for age at time of retinal photograph capture and sex	1.0 (–1.2 to 3.3) p=0.366	1.1 (–1.1 to 3.4) p=0.32	
GCA (n)	16	13	
Venular width (µm) and SD	93.0 SD 9.4	93.7 SD 10.3	91.1 SD 10.6 from 5036 controls
Difference in venular width (µm) (95% CI) 80% probability†	1.9 (–3.3 to 7.1) p=0.47	2.6 (–3.2 to 8.4) p=0.38	
Adjusted for age at time of retinal photograph capture and sex	1.1 (–4.1 to 6.2) p=0.68	1.5 (–4.2 to 7.2) p=0.60	
Arteriolar width (µm) and SD	74.4 SD 5.9	73.8 SD 6.0	75.0 SD 6.3 from 5037 controls
Differences in arteriolar width (µm) (95% CI) 80% probability†	–0.6 (–3.6 to 2.5) p=0.73	–1.2 (–4.7 to 2.2) p=0.48	
Adjusted for age at time of retinal photograph capture and sex	–0.03 (–3.1 to 3.0) p=0.98	–0.7 (–4.1 to 2.7) p=0.70	

*Incident cases—median time period 2.9 years between retinal image capture and subsequent diagnosis with >75% having an interval of >1 year.
†Probability of vascular segment type (arteriole or venule) weighted by segment length, 95% CI.
GCA, giant cell arteritis; PMR, polymyalgia rheumatica.

This approach follows classification methodology validated in the Clinical Practice Research Datalink.[6] Cases were excluded from analysis if the diagnosis in the case record was refuted or changed within the first 6 months. Case assignment was carried out independently by two rheumatologists (MY, RW). Only incident cases with retinal images captured before their PMR or GCA diagnosis were included.

Among 5532 participants who had retinal images analysable by QUARTZ, we identified 30 cases of incident PMR (median age at diagnosis: 74.8 years, range (60.5, 87.0); mean erythrocyte sedimentation rate (ESR) at diagnosis: 48 mm/hour; 70.0% female) and an additional 16 cases of GCA (median age at diagnosis: 75.0 years, range (62.1, 84.0); mean ESR at diagnosis: 80 mm/hour; 81.3% female). Vasculometric measures of those subsequently developing PMR (table 1), showed wider venules compared with controls (5.5 µm increased width 95% CI 1.7 to 9.3, p=0.004), which remained significant after adjustment for age at time of retinal image capture, and sex (4.4 µm wider, 95% CI 0.7 to 8.2, p=0.021). Some who were diagnosed with disease did not meet the classification criteria. A stronger association was present when the analysis was limited to those cases which fulfilled current classification criteria sets. Although, on average those subsequently developing GCA had wider venules compared with controls (93 vs 91.1 µm) the difference failed to reach statistical difference. There was no association between arteriolar measures for either PMR or GCA.

Using a novel retinal marker in a longitudinal population-based setting, this analysis shows that participants who developed PMR already had wider retinal venules prior to the onset of their inflammatory disease. The data are limited by the relatively small number of cases with incident disease and need to be replicated in other settings. They nevertheless lend weight to the hypothesis that vascular changes precede the onset of PMR.

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Dupilumab as a novel steroid-sparing treatment for IgG4-related disease

IgG4-related disease (IgG4-RD) is a rare fibroinflammatory, multisystemic condition with a relapsing-remitting progression.[1]

The level of serum IgG4 correlates with inflammatory activity and organ involvement.[1] Glucocorticoids are first line for IgG4-RD, but there are numerous adverse effects with chronic use.[2] Dupilumab is a monoclonal antibody that acts on the interleukin 4 (IL-4) receptor alpha, shared by the IL-4 and IL-13 receptors.[1] IL-4 causes isotype switching from IgM to IgG4 and IL-13 is implicated in fibrosis.[3] Thus, it was postulated by the authors to investigate dupilumab as a novel steroid-sparing treatment for IgG4-RD.

A 67-year-old man with no known allergies and a history of sensory neural hearing loss, recurrent bronchitis, spinal stenosis, moderate positional obstructive sleep apnoea, asthma, atopic dermatitis (which caused swelling around his eyes) and allergic rhinoconjunctivitis underwent extensive investigations over the past 2 years due to suspected IgG4-RD.

The patient's initial complaint was pruritic erythematous lesions on the legs, arms, chest and palms. Further investigations revealed parotitis, sinusitis, normocytic anaemia and eosinophilia. An MRI showed retroperitoneal and genitourinary fibrosis (figure 1A). Total IgG and IgG_4 levels were found to be 32.40 g/L and 20.60 g/L, respectively. The patient had a prostate biopsy which revealed 50 IgG4 cells per high power field and an IgG4+/IgG+ cell ratio of 40%. This result is exactly borderline as per the IgG4-RD comprehensive diagnostic criteria,[4] making the result of the biopsy probable for IgG4-RD. Interventional radiologists determined the retroperitoneal fibrosis to be inaccessible for biopsy and the patient declined a repeat prostate biopsy. Although the biopsy was borderline, given that the imaging, clinical features and laboratory investigations fulfilled the remainder of the comprehensive diagnostic criteria (1 to 3a), IgG4-RD was the consensus diagnosis.[4]

A treatment plan of a 40 mg daily dose of prednisone was suggested by rheumatology, with the option of adding the adjuvant immunosuppressant azathioprine. The patient was on 40 mg prednisone daily but declined other agents due to the risk of adverse effects.

Laboratory investigations revealed haemoglobin counts of 131 g/L (normal range 135–175 g/L), haematocrit levels of 0.391 L/L (normal range 0.4–0.5 L/L), eosinophil levels of 1.4×10^9 cells/L (normal range $0.0–0.5 \times 10^9$/L) and alkaline phosphatase serum levels of 34 U/L (normal range 40–129 U/L). On examination, atopic dermatitis was present with 50% body surface area (BSA) involvement with an Investigator Global Assessment (IGA) score of 4, indicating severe disease. An initial 600 mg subcutaneous injection of dupilumab, followed by a 300 mg subcutaneous injection every other week for 12 months was given to treat atopic dermatitis, asthma and potentially IgG4-RD.

After 3 months on dupilumab, the patient's eye swelling resolved, and his skin and asthma noticeably improved to IGA1 and <10% BSA. Both total IgG and IgG4 levels reduced substantially to 19.41 g/L and 11.43 g/L, respectively. After 12 months on dupilumab, the patient's retroperitoneal fibrosis improved dramatically corresponding with the decreased IgG4 levels (figure 1B). It is noted that dupilumab is in itself an IgG4 monoclonal antibody.

Current treatments for IgG4-RD are associated with many long-term adverse effects. The first-line treatments are glucocorticoids, second-line treatments are chemotherapeutic immunosuppressants and the third-line treatment is B-cell depleting rituximab, an anti-CD20 monoclonal antibody. The adverse effects associated with these therapies include increased risks of infection and potentially lasting immune deficiency.[5]

Dupilumab has been observed to be safe with long-term use across multiple indications.[6] In this patient, IgG4-RD was
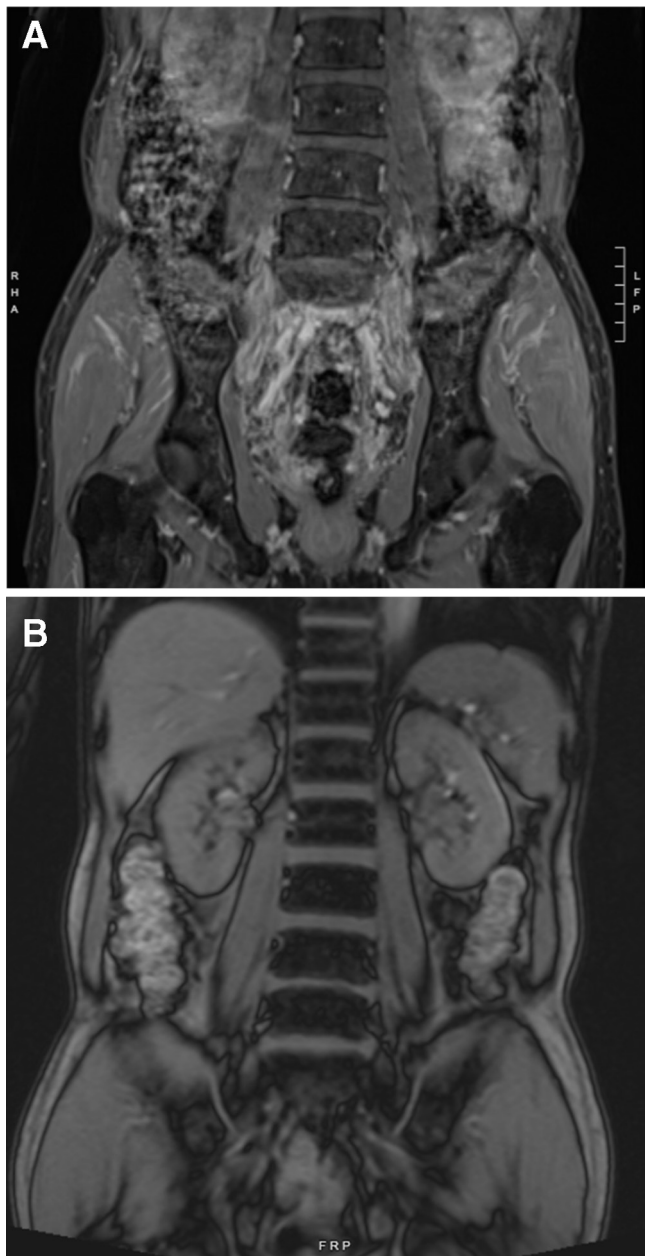
Figure 1 (A) Patient's initial MRI findings before dupilumab treatment showed extensive retroperitoneal and extraperitoneal fibrosis. (B) MRI taken approximately 1 year after dupilumab treatment showed dramatic resolution of fibrosis.

controlled with no further relapses across all affected organ systems with no significant long-term adverse events and prednisone withdrawal within 2 months. Dupilumab's efficacy in the treatment of IgG4-RD also highlights the importance of IL-4 and IL-13 in the pathological mechanisms of this condition.

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Correction notice This article has been corrected since it published Online First. Figure 1 has been updated.

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