

Review

Ankle arthritis – an important signpost in rheumatologic practice

Patrick D.W. Kiely ^{1,2} and Mark E. Lloyd³

Abstract

Ankle arthritis is a useful clinical signpost to differential diagnosis in rheumatic disease. Biomechanical features and differences in cartilage physiology compared with the knee may confer protection of the ankle joint from factors predisposing to certain arthritides. The prevalence of ankle OA is low, and usually secondary to trauma. Primary OA of the ankle should be investigated for underlying causes, especially haemochromatosis. New presentations of inflammatory mono/oligo arthritis involving the ankle are more likely due to undifferentiated arthritis or spondyloarthritis than RA, and gout over CPPD. The ankle is often involved in bacterial and viral causes of septic arthritis, especially bacterial, chikungunya and HIV infection, but rarely tuberculosis. Periarticular hind foot swelling can be confused with ankle arthritis, exemplified by Lofgren's syndrome and hypertrophic osteoarthropathy where swelling is due to subcutaneous oedema and osteitis respectively, and the ankle joint is rarely involved.

Key words: ankle, osteoarthritis, spondyloarthritis, septic arthritis, haemochromatosis, gout, rheumatoid arthritis, sarcoidosis

Rheumatology key messages

- Primary OA of the ankle is rare and should prompt screening for haemochromatosis.
- Incident inflammatory arthritis involving the ankle is more likely due to SpA than RA.
- In Lofgren's syndrome, hind foot swelling is due to periarticular oedema rather than ankle arthritis.

Introduction

Despite recent major advances in management of rheumatic diseases, clinical diagnosis can remain challenging. Pattern recognition is an important part of this process, encompassing all aspects of the patient, history, examination and results of investigations. Assessment of the individual joints affected is particularly important in formulating a differential diagnosis, with, for example, characteristic involvement of the DIP and first carpo-metacarpal joints in OA, whereas these joints are generally spared in RA.

This review article focuses on the ankle joint across the spectrum of rheumatic conditions, where it is differentially affected in certain arthritides and spared in others. In this regard, the ankle is an interesting and perhaps neglected signpost in the process of differential diagnosis. We also draw attention to peri-articular mimics of ankle arthritis, as the hind foot is a complex region requiring careful clinical examination to assess the cause of pain and swelling.

Ankle joint anatomy

Evolutionary considerations

The ankle joint is a complex structure comprised of a diarthrosis between the tibia and talus (talocrural) and an interosseous syndesmosis between the tibia and fibula [1]. Stability is provided by the medial (deltoid) and lateral collateral ligaments, with movements occurring predominantly as a hinge providing dorsi-plantar flexion with additional rotation and inversion/eversion [1].

¹Department of Rheumatology, St George's University Hospitals NHS Foundation Trust, ²Institute of Medical and Biomedical Education, St George's University of London, London and ³Department of Rheumatology, Frimley Health NHS Foundation Trust, Frimley, UK

Submitted 31 May 2020; accepted 24 July 2020

Correspondence to: Patrick D.W. Kiely, Department of Rheumatology, St George's University Hospitals NHS Foundation Trust, Blackshaw Road, London SW17 0QT, UK. E-mail: patrick.kiely@nhs.net

Compared with the hip and knee, the range of movement of the ankle while walking is relatively small, maximum 30°, increasing to 56° when descending stairs [1].

Development of the ankle joint in homo sapiens occurred after the knee by many thousand years. Knee (proximal tibia) specimens dating 2 million years ago are the same morphologically as in homo sapiens, acknowledged to have evolved ~300 000 years ago. In contrast, the morphology of the ankle (distal tibia) in specimens dating 1.6 million years ago is primitive compared with the evolved homo sapiens ankle [2]. While this is a striking evolutionary difference, the consequences in terms of susceptibility to arthritis are not established.

Cartilage differences compared with knee

Ankle (talar dome) cartilage is distinctive in being denser and stiffer than knee cartilage, due to higher proteoglycan and sulphated glycosaminoglycan content, lower water content and hydraulic permeability [3, 4]. Differences in partition coefficient support the hypothesis that differences in transport properties of ankle and knee cartilage may explain differences in the incidence of OA between these joints [3, 4]. Furthermore, ankle chondrocytes are eight times less responsive than knee chondrocytes to the inhibitory effect of interleukin-1 on proteoglycan synthesis, and (unlike knee chondrocytes) resistant to the depleting effects of fibronectin fragments on proteoglycan, meaning less susceptibility to matrix loss in a proinflammatory state [4].

Osteoarthritis

Palaeopathology studies of human skeletal remains from archaeological sites generally find no evidence of ankle OA, or a very low prevalence <8% [5]. Contemporary series report that while ~15% of the world's population are affected by symptomatic OA of any joint, 6–10% by symptomatic knee OA, only 1–4.4% are affected by ankle OA [4, 6–8].

The ankle differs from the hip and knee in terms of aetiology of OA. A primary aetiology, i.e. arising in the absence of trauma or adverse biomechanical factors, accounts for most cases of hip and knee OA (65% and 82% respectively) with trauma a much less frequent cause, attributed to 8% and 12.5%, respectively [9]. In contrast, the aetiology of ankle OA is much more frequently due to trauma, reported in 70% and 78% of cases in two orthopaedic series, compared with a primary aetiology in just 7.2% and 9% [8, 9]. Thus, the ankle seems protected from primary OA, in contrast to the hip and knee.

The very low prevalence of primary OA of the ankle is surprising given the forces transmitted through the ankle are 5 to 13 × body weight during activities such as running, and much greater than through the hip and knee [1, 10]. Protective factors, compared with the hip or knee, may include (i) a relatively high level of congruency, with most load applied to the talar dome, (ii) a

large load bearing area, (iii) a narrow range of motion through everyday activities and (iv) greater resilience of ankle cartilage due to differences in density, stiffness, water content and permeability [4]. Whether the evolutionary delay in development of the ankle in homo sapiens permitted these advantageous characteristics is uncertain.

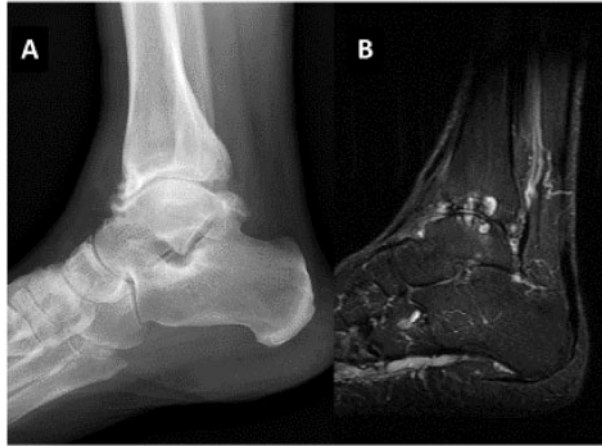
When OA of the ankle is reported to be secondary to a preceding arthritis, the conditions listed in a series of 390 patients with symptomatic end stage disease were RA, haemochromatosis, haemophilia, avascular necrosis of the talus and post infectious arthritis [8]. Among patients with genetic haemochromatosis (GH) an arthropathy resembling accelerated OA, with florid radiographic features, is well described [11]. Ankle arthropathy was found in 32–61% of GH patients attending secondary care centres and reported by 35% of GH patients responding to a questionnaire [12, 13]. A link between primary OA of the ankle, MCP 2/3 joint OA and the lesser H63D mutation in the high iron *HFE* gene has also been described [14]. MRI of the ankle of GH patients with arthropathy reveals more severe appearances compared with paired primary OA controls, with significantly higher scores for bone marrow lesion/cyst size and number, presence and extent of full thickness cartilage loss and osteophytes [15]. Imaging examples of haemochromatosis arthropathy of the ankle are shown in Fig 1.

Recurrent haemarthroses cause the arthropathy seen in haemophilia, with joint destruction as a consequence. Characteristically weight bearing lower limb large joints are affected, suggesting an aetiological combination of mechanical factors as well as the intrinsic clotting disorder, leading to specific joint bleeds. In haemophilia the ankle, as well as the knees and elbows, is a frequently involved joint [16] and in one series the most commonly affected joint [17].

Incident inflammatory arthritis

Monoarthritis (excluding crystal and septic causes)

In a Norwegian series of 347 patients with incident monoarthritis of <16 weeks duration and followed for 2 years [18], the ankle was involved in 16.7%, the second most commonly involved joint after the knee (49.3%). The outcome of ankle monoarthritis was resolution, degenerative disease or gout in 89.7% of cases, with 10.3% progressing to a chronic inflammatory rheumatic disease, either chronic spondyloarthritis (SpA) or undifferentiated arthritis (UA) and no cases developing RA or psoriatic arthritis (PsA). On multivariate analysis the odds ratio for developing any chronic inflammatory arthritis was 0.5 (0.2–1.2) for the ankle and 2.0 (1.0–4.2) for the wrist, compared with all other joints. In a Korean series of 171 patients with monoarthritis, the ankle was the affected joint in 18.7%, the third most commonly involved joint after the knee (24%) and wrist (22.8%). Progressive ankle monoarthritis occurred in

Fig. 1 Haemochromatosis arthropathy of the ankle

(A) Plain radiograph showing reduced tibio-talar joint space and marginal osteophyte formation. **(B)** T2 fat suppressed MRI showing periarticular marrow oedema and multiple distal tibia and talar dome subchondral cysts.

20/32 cases (62.5%) and multi variate analysis showed ankle monoarthritis to predict a final diagnosis of peripheral SpA, odds ratio 3.04, 1.13–8.19 [19]. In a French series of 50 patients presenting with <1 year of monoarthritis (excluding septic and crystal arthritis), the ankle was involved in 5 cases (10%) with 2 recovering fully, 2 developing SpA and 1 developing RA [20]. In a UK series of 25 cases of incident ankle monoarthritis, the initial diagnosis was UA in 48%, sarcoid 24% and SpA 12%. Persistent disease developed in 8 cases (32%), with 3 sarcoid, 2 RA, 1 SLE, 1 SpA and 1 UA [21].

Thus, the ankle, in these combined series of 593 patients presenting with a monoarthritis, is reported to be the affected joint in 10–18.7% of all cases. The outcome is reported to be resolution in many cases, possibly exaggerated if the initial diagnosis was not ankle arthritis but another cause of hind foot swelling such as traumatic tendon or ligament injury. In those with a persisting arthropathy the diagnostic pattern appears more likely to be SpA/UA or sarcoidosis. This is in contrast to RA; in a study of 102 patients with early RA of <1 year duration, ankle monoarthritis was the initial presentation in only 6% [22].

Oligo/polyarthritis

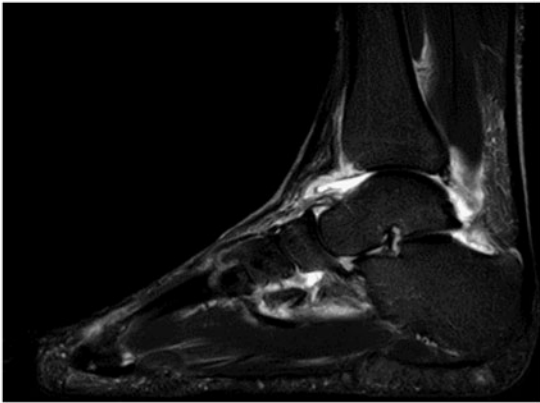
In a UK series of 324 cases of early inflammatory oligoarthritis of <3 months duration [21], the ankle was involved in 78 cases (24%). Bilateral ankle disease independently associated with acute sarcoid arthritis and unilateral ankle involvement was associated with a subsequent diagnosis of SpA. In those with an oligoarthritis and negative for RF and ACPA, ankle involvement was also associated with a diagnosis of sarcoid, SpA and UA. As in incident monoarthritis, a lack of association with RA was highlighted by the authors, so much so that they question whether ankle arthritis in an early oligoarthritis setting should be seen as a negative

scoring variable for RA. In a Norwegian series of 138 patients with oligoarthritis, the ankle was involved in 60 patients (43%) with a final diagnosis of UA in 25 (42%), reactive arthritis (ReA) in 18 (30%), and sarcoid in 15 (25%). Of all patients with oligoarthritis and a final diagnosis of UA or ReA, the ankle was involved in 40% and 39%, respectively [23]. In a series of 100 patients with ReA from Kosovo [24], the most frequent presentation was as an oligoarthritis. The ankle was the second most commonly affected joint, involved in 55% of all patients, higher in males (57.5% of 66 cases) than females (50% of 34 cases). In a French series of 220 patients with acute oligo or polyarthritis <1 year duration, 64 ankle joints were involved, not stated whether unilateral or bilateral, giving a prevalence between 14.5% and 29% [20].

Evaluation of joint distribution at RA presentation in two early arthritis cohorts from the Netherlands ($n=947$) and India ($n=947$) revealed the ankle to be recorded as swollen in 5–15% of cases, slightly more so in autoantibody negative cases in the Netherlands [25]. In a large series of 1000 RA patients from Sweden with established RA, median duration 10 years, 17% recalled involvement of the hindfoot/ankle at presentation [26]. In a study of 102 patients with early RA of <1 year duration, unilateral ankle involvement was reported in 23–25%, bilateral in 18% [27]. In a series of early RA ($n=61$) and early PsA ($n=33$) from UK and Italy, with <12 months disease duration, ankle involvement was reported in 40% with RA and 27% with PsA [28].

Thus, in these series of 462 patients presenting with incident oligo or polyarthritis, the ankle is reported to be affected in 24–43% of all cases. As with incident monoarthritis, the final diagnosis in those with persisting arthropathy appears more likely to be SpA/ReA, UA or sarcoidosis than RA or other conditions. In RA, ankle involvement at presentation is less prevalent,

Fig. 2 Sero-negative undifferentiated peripheral spondyloarthropathy of the ankle



Sagittal Short-T1 Inversion Recovery (STIR) MRI of the left ankle showing joint capsule thickening, synovitis and effusion of the tibio-talar joint extending into the posterior joint recess.

in series ranging from 5–25% with one exception reporting 40%. The MRI appearances of sero-negative undifferentiated inflammatory arthritis of the ankle are shown in Fig. 2.

Established inflammatory arthritides

Axial spondyloarthritis

In a Brazilian series of 147 patients with established ankylosing spondylitis [29], the ankles were the most frequently involved extra-axial joints, affected in 39.5% of cases, followed by hips (36.1%) and knees (29.3%). Ankle involvement was significantly more frequent among B27 positive cases (45.2% vs 18.8%) and in those with juvenile vs adult onset AS, occurring in 63.6% vs 35.2% of cases, respectively.

Peripheral spondyloarthritis with psoriasis

In a UK series of 87 patients with established PsA, with data available at two time points (baseline median disease duration 11 years, followed for a median 65 months) the prevalence of ankle arthritis was 10.3% rising at follow up to 26.4% [30]. In a separate UK series of 50 patients with established PsA, median disease duration 19.5 years, the ankle was involved in 30–39%, slightly less frequently in males and those without nail disease [31]. In a second series from the same author of 77 patients with late PsA from UK and Italy, ankle involvement was recorded in 38.5% [28].

Peripheral spondyloarthritis with inflammatory bowel disease

In a population-based inception cohort of 160 patients with IBD, mean disease duration 50 months, peripheral arthritis was found in 17 cases (10.6%) with the knee and

ankle being the most frequently affected joints in 9/17, 53% [32]. In a large UK hospital series of 1459 patients with IBD, median 10 years follow up, ankle joint arthropathy was recorded in 29–34% with ulcerative colitis and in 42–52% with Crohn's disease, in the setting of pauci and polyarticular patterns, respectively [33].

Thus, ankle involvement in established axial and peripheral spondyloarthritis is common affecting up to 63% of juvenile and 10–52% of adult cases, though the literature is remarkably sparse.

Rheumatoid arthritis

A study assessing the validity and reliability of joint counts (28 vs 66/68 joints) using data from 735 patients with established RA reports a prevalence of ankle joint swelling and pain between 60% and 65% [34]. In a Swedish cross-sectional clinic survey of 1000 RA patients with median disease duration 10 years, 52% had ankle or hindfoot disease [26]. In a series of late RA ($n=93$) from UK and Italy, ankle involvement was reported in 65% [28], and in the UK Early RA Study (ERAS) of 1237 patients, reduced ankle range of movement was found in 37% ever, during up to 25 years follow up [35]. From a postal questionnaire, returned by 585 UK RA patients with mean disease duration 12.7 years, 42.7% reported ankle pain at some stage in the course of their RA, and 30.6% reported ankle pain in the last month [36]. A Korean series of 2046 patients with established RA found a prevalence of ankle tenderness in 21% and ankle swelling in 17% [37].

Thus, while ankle involvement is unusual at disease onset in RA, it is reported in higher prevalence in established RA, in the range 37–65% with a lower report from Korea of 17–21%.

Connective tissue diseases

In SLE, arthralgia without evidence of synovitis is a common feature. In contrast, the typical non-erosive deforming arthropathy of Jaccoud is not, with most series indicating a prevalence <5%, focused mainly on the hands [38, 39]. When foot problems have been addressed, Jaccoud's arthropathy of the feet has been reported to rarely occur without hand involvement [40]. A postal survey of symptoms in 131 New Zealand SLE patients reported the hind foot or ankle to have ever been painful since SLE diagnosis in 30% and 32% of respondents, and painful in the last month in 19% and 13%, without independent clinical assessment or ascertainment of the relation to SLE itself as opposed to other biomechanical factors [41].

In SSc, arthralgia is commoner than arthritis; however, when synovitis occurs the MCP, PIP, wrists and ankles predominate. In the hind foot, care should be taken to distinguish ankle arthritis from tendon disease as tendonopathy, often with friction rubs, is a characteristic feature of SSc and the tibialis anterior, peroneal and Achilles tendons can all be affected [42].

Fig. 3 Septic arthritis of the ankle due to *Staphylococcus aureus* infection

Plain radiograph showing fuzziness of cortical margins of the distal tibia, fibula and both malleoli.

Septic arthritis

Bacterial infection

Bacterial sepsis can potentially affect any joint, though certain joints are more frequently involved than others, especially the knee, and the ankle is not exempt. In a Dutch study of 186 patients with bacterial septic arthritis, the ankle was the third most commonly affected joint, reported in 12% of cases, after knee (48%) and hip (21%) [43]. A prospective UK study of 75 patients with bacterial septic arthritis also found the knee (56%) and hip (16%) to be the most frequently affected joints, whereas the ankle was only involved in 1% of cases [44]. An example of the X-ray appearances of bacterial septic arthritis of the ankle are shown in Fig. 3.

A report of 25 cases of polyarticular bacterial septic arthritis, and review of 303 case reports in the literature, found the ankle to be affected in 24% of 25 cases, less frequently than the knee, elbow, shoulder, wrist and MCP/PIP joints. From the literature review of 303 polyarticular bacterial septic cases, the ankle was affected in 54 cases (18%) also less frequently than knee, elbow, shoulder and wrist [45]. In gonococcal disease, an acute oligoarthritic presentation including the ankle is recognized [46].

Viral infection

Viral arthritides are often polyarticular, involving small and large joints, non-erosive and transient [47]. The ankles are notably reported to be involved in Hepatitis B, C, chikungunya and HIV infections [47, 48]. A review from the literature of 63 patients with Hepatitis B related arthritis reports ankle involvement in 24% cases, the third most frequently affected joint after the proximal interphalangeal (82%) and knees (30%) [49]. In a prospective Colombian cohort of 500 confirmed cases of chikungunya infection, ankle pain was recorded in 87%, being the second commonest site of joint pain after the wrist [50]. In two series of patients with chikungunya

infection from India and Sri Lanka, the ankle was reported to be a site of arthralgia at disease onset in 11.39% and 33.7% cases, respectively [51].

HIV-associated arthritis/painful articular syndrome can occur at any stage of HIV illness, usually presenting as a self-limiting asymmetric oligoarthritis predominantly affecting knees, shoulders and ankles [52]. Of 21 cases reported in one centre, over half presented with an oligoarthritis involving knees and ankles. HIV is also associated with a high prevalence of peripheral SpA with predominant lower limb involvement including a high prevalence of ankle disease [52–54]. In a series of 27 HIV-positive patients presenting with PsA, the joint distribution at onset involved the knee and/or ankle in 90% in the context of psoriasis with an asymmetric lower limb dominant polyarthritis and enthesitis [55]. A series of 18 cases of ReA in HIV-positive patients reported ankle involvement in 27%, after knee (41%) and wrist (29%) [54]. The same authors report ankle involvement in 50% of nine cases of PsA in HIV-positive patients, and ankle involvement in 20% of cases with undifferentiated SpA and HIV.

Tuberculosis

Tuberculosis (TB) of the foot and ankle is rarely described, accounting for 1–4% of all cases of osteoarthritic TB [56]. A series of 74 patients with TB of the foot and ankle reported ankle involvement in 13 cases (17%) with a similar frequency involving the midtarsal and Lisfrancs joint [57].

Crystal arthritis

Gout is well known to have a predilection for affecting the first MTP, and potentially any other joint in the body. The ankle is frequently involved, with 50% of 354 patients with chronic gout reporting involvement of the ankle/foot (not great toe) in a historic UK series [58]. This is supported by findings in a series of 164 UK patients where the ankle is reported as the third most

frequently affected joint in acute gout, involving 12–15% cases, after the first MTP and mid-foot [59] and the most frequently affected joint, with the first MTP and knee, in a series from West Africa [60]. A contemporary review confirms the ankle as a frequent site of acute gouty arthritis [61].

Calcium pyrophosphate arthropathy is often found in the context of OA, irrespective of whether primary or post traumatic/inflammatory in origin. The knee and wrist are the most commonly affected joints [62], and although the ankle can be involved [63], it is less often cited, possibly reflecting the low prevalence of OA of this joint.

Charcot arthropathy

Charcot neuropathic arthropathy affects people with peripheral neuropathies and commonly affects the foot, reported in 0.1–0.9% of people with diabetes [64]. The mid foot is the most frequent site of pathology with the ankle much less frequently involved, reported with the subtalar joint in 10% of cases compared with tarso-metatarsal 40% and navicular/cuboid in 30% [65].

Peri-articular swelling

As advances in medicine bring more investigations into routine practice, the skill and value of clinical examination can be overshadowed in the diagnostic process [66, 67]. The hind foot is a particularly complex anatomical region where it can be difficult to distinguish ankle arthritis from sub talar disease, the former assessed with passive flexion and extension and the latter with inversion and eversion. Many non-articular conditions may also cause peri-articular swelling and/or a reduced range of hind foot flexion and extension. This can be due to periostosis, subcutaneous oedema, tender adipose tissue, panniculitis, tendon or ligament injury and dermatologic conditions such as cellulitis, lipodermatosclerosis and chronic leg ulcers (arthropathica ulcerosa) [68]. Historical reports in the literature are confounded by these clinical limitations. When necessary, ultrasound and other imaging techniques can be used to confirm the presence of ankle joint disease, as opposed to other causes of hind foot swelling, alongside thorough clinical examination and gait analysis, skills we risk losing [64].

Sarcoidosis

Acute sarcoid arthritis occurs in the context of Lofgren's syndrome, characterised classically in younger patients (<40 years) by the triad of erythema nodosum, bilateral hilar lymphadenopathy and migratory polyarthritis, sometimes with fever. Involvement of the ankle in acute sarcoid arthritis is almost universally reported [69]. However, this is a historical error of attribution, as the hind foot swelling of Lofgren's syndrome has been demonstrated on ultrasound to be more frequently due to deep subcutaneous oedema (panniculitis) or tenosynovitis, with no abnormal features in the ankle joint. Three

ultrasound studies have demonstrated this in 100 cases, with the majority not showing features of arthritis, instead just small effusions in 25%, and increased vascularity in only 5.6–7.5% [70–72]. MRI of five ankles from four patients with Lofgren's syndrome confirms this, with swelling located to the subcutaneous fat (panniculitis) and only small ankle joint effusions with no synovial thickening [73]. Thus, the cause of hind foot swelling in acute sarcoidosis due to Lofgren's syndrome is principally not due to ankle arthritis and any joint involvement is likely to be reactive. An example of the clinical and MRI appearances of the hind foot in Lofgren's syndrome is shown in Fig. 4.

Chronic sarcoid arthritis is much less frequent than Lofgren's and also said to commonly affect the ankles [69]. Reports in the literature are of mixed acute and chronic cases, with many resolving, making the attribution of arthritis to the ankle as opposed to periarticular panniculitis uncertain. Nevertheless, in one report of chronic sarcoid arthritis, the ankle was involved in all four cases [74], and it has been suggested that the presence of real ankle arthritis in Lofgren's syndrome is a risk factor for the development of chronic arthritis [72].

Hypertrophic pulmonary osteoarthropathy

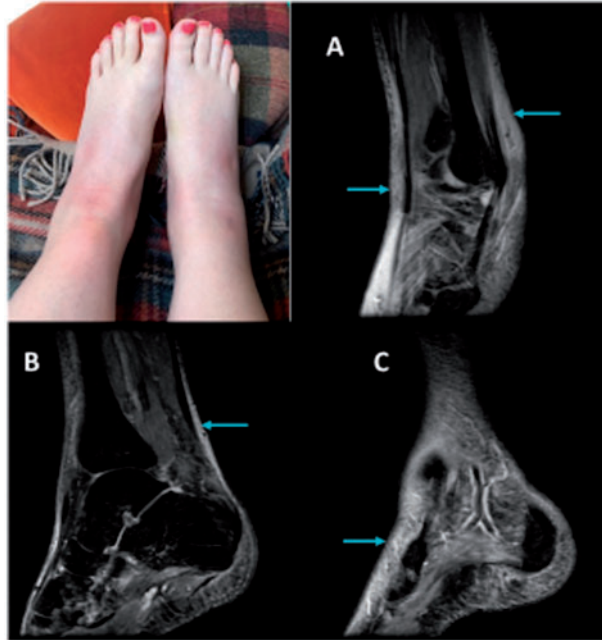
Hypertrophic osteoarthropathy is characterised by a triad of digital clubbing, periosteal reaction of long bones (periostosis) and pain or tenderness of the limbs, sometimes with non-inflammatory effusions of large joints [75]. The distal tibia and fibula are frequently involved, and radionuclide bone scan is the most sensitive imaging modality to detect this pathology. Multiple case series involving the hind feet are reported in the literature, some with ankle joint effusions mimicking reactive or other inflammatory arthritides [75, 76].

Tibialis posterior tendon dysfunction

This is a common cause of hind foot pain and swelling, particularly prevalent in women over 40 years. It may present with diffuse hind foot swelling and maximal tenderness posterior and inferior to the medial malleolus, along the course of the tendon [77]. Chronic cases are invariably associated with hindfoot valgus deformity and flatfoot, which can be easily appreciated by gait analysis, with visual inspection of the hind foot from behind.

Conclusions

This review has highlighted the diagnostic implications of ankle joint arthropathy across the spectrum of clinical rheumatologic practice, revealing this joint to be a useful signpost. It is structurally interesting, having evolved much later than the knee, with significant differences in cartilage properties and response to inflammatory cytokines. These properties may make the ankle less susceptible to the pathologic processes leading to some arthropathies; notably, rarely developing OA in the

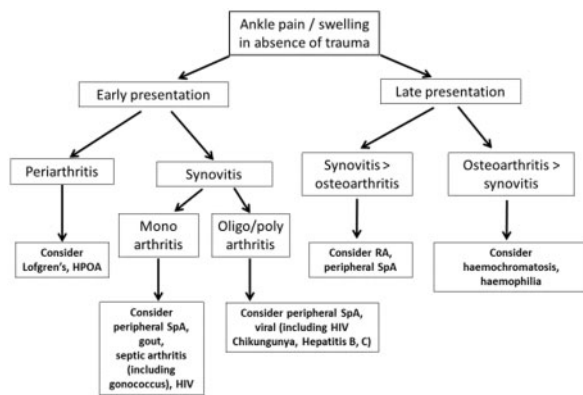
Fig. 4 Lofgren's syndrome clinical and MRI inversion recovery images

Images show (A) lateral, (B) midline and (C) medial sagittal sections of the hind foot with extensive subcutaneous enhancement (arrows) and no ankle joint disease.

TABLE 1 Prevalence of ankle arthritis in rheumatic diseases in individual case series

Condition	Prevalence of ankle involvement	Number of patients, number with ankle involvement	Author (reference)
Early RA	15%	1894, 284	Bergstra 2017 [25]
	17%	1000, 170	Grondal 2008 [26]
	25%	102, 25	Fleming 1976 [27]
	40%	61, 24	Helliwell 2000 [28]
Combined total	16.4%	3057, 503	
Established RA	65%	735, 478	Smolen 1995 [34]
	52%	1000, 520	Grondal 2008 [26]
	37%	1237, 458	Backhouse 2011 [35]
	65%	93, 60	Helliwell 2000 [28]
	17%	2046, 348	Lee 2019 [37]
Combined total	36%	5129, 1864	
Early PsA	27%	33	Helliwell 2000 [28]
Early ReA	55%	100, 55	Lahu 2015 [24]
	39%	46, 18	Kvien 1996 [23]
	50%	146, 73	
Combined total	39%	50, 19	Helliwell 1991 [31]
Established PsA	38.5%	77, 30	Helliwell 2000 [28]
	26%	87, 22	McHugh 2003 [30]
	33%	214, 71	
Combined total	39.5%	147	Sampaio-Barros 2001 [29]
Septic arthritis	18%	303, 55	Dubost 1993 [45]
	12%	186, 22	Kaandorp 1997 [43]
	1%	75, 1	Gupta 2001 [44]
	14%	564, 78	

Fig. 5 Algorithm of likely differential diagnosis when the ankle joint is affected in early and established arthritis



absence of trauma, and less commonly involved in early RA than peripheral SpA.

A summary of the information we have gathered is presented in [Table 1](#), and [Supplementary Table S1](#), available at *Rheumatology* online, and we propose an algorithm to help the diagnostic process ([Fig. 5](#)). As a signpost, the finding of OA of the ankle should prompt careful evaluation. If a traumatic cause cannot be established, and primary OA seems likely, this should be recognised as a rarity and trigger a search for other conditions, especially haemochromatosis. Ankle involvement in incident inflammatory arthritis is also a signpost. If it is a monoarticular presentation, then a crystal explanation points to gout rather than CPPD disease. In septic causes, ankle disease points to bacterial including gonococcus but not TB, and of the autoimmune arthropathies to UA or peripheral SpA rather than RA or CTD as a final diagnosis. If the presentation is acute oligo or polyarthritis then, as in monoarthritis, ankle disease points to UA or peripheral SpA rather than RA or CTD, and of septic causes to bacterial including gonococcal and viruses including chikungunya and HIV. Why the ankle is more likely to be affected early in peripheral SpA as opposed to RA or CTD arthropathies is unclear, but a useful clinical observation and signpost.

In established inflammatory arthritis, involvement of the ankle is more universal, with a similar prevalence in RA as axial and peripheral SpA and so in this context the presence of ankle disease is of less value to the diagnostic process.

A limitation of this article is that there are surprisingly few reports in the literature of individual joint distribution and prevalence in various rheumatic diseases. This is not a formal systematic review and some published data may have been overlooked. Many descriptions of classic arthropathies combine joint regions (e.g. 'foot', or 'knee and ankle') or report overall prevalence of peripheral arthropathy rather than providing individual joint level data. Furthermore, difficulties in clinical assessment

before the introduction of US and MRI make it likely that some historical reports of ankle arthritis were inaccurate if the pathology was not distinguishable from peri-articular causes of pain or swelling. Lofgren's syndrome exemplifies this, with ankle arthritis enshrined in medical literature as a classic feature, whereas US and MRI reveal that the cause of hind foot swelling is usually deep subcutaneous oedema and only rarely ankle arthritis. The time has come for textbooks to be re-written in this instance.

With the advent of artificial intelligence and its application to diagnostic medicine, it would be useful for new detailed reports of individual joint prevalence to be documented at various stages of rheumatic and musculoskeletal diseases. Accurate documentation of clinical signs can provide essential 'big data' to inform computer algorithms to support diagnosis, and enable subgroup classification. This has been applied to juvenile idiopathic arthritis, where detailed assessment of every joint resulted in the ability to model disease course and outcome based on seven presenting patterns of joint involvement [78].

Thorough clinical assessment, aided by imaging where necessary, remains central to good quality clinical practice. A potential weakness of telemedicine, which has become a necessity in the COVID-19 pandemic, will be an emphasis on imaging and laboratory assessments over examination findings [67, 68]. Furthermore, enshrinement of 28 joint counts in DAS28, Clinical Disease Activity Index (CDAI) and Simple Disease Activity Index (SDAI) composite scores in RA management contributes to a loss of emphasis on assessment of the distal lower limb in the mindset of the clinician. However, the recognition of clinical patterns is fundamental to making a diagnosis and the presence of ankle arthritis is especially valuable. The relative protection of the ankle from OA compared with the knee and hip, and its differential involvement in the auto-immune arthritides remain intriguing and under-investigated research questions. We believe the ankle joint is a useful signpost to differential diagnosis in clinical rheumatologic practice, and we should be encouraged to pay it particular attention.

Acknowledgements

The authors thank Dr Derek Svasti-Salee for MRI images of ankle synovitis ([Fig. 2](#)), Dr Vivian Ejundu for X-ray image of septic arthritis ([Fig. 3](#)) and Dr Brian Bourke for MRI images of Lofgren's syndrome ([Fig. 4](#)).

Funding: No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

Disclosure statement: The authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* online.

References

- 1 Brockett CL, Chapman GJ. Biomechanics of the ankle. *Orthop Trauma* 2016;30:232–8.
- 2 Frelat MA, Shaw CN, Sukhdeo S *et al*. Evolution of the hominin knee and ankle. *J Hum Evol* 2017;108:147–60.
- 3 Treppo S, Koepp H, Quan EC *et al*. Comparison of biomechanical and biochemical properties of cartilage from human knee and ankle pairs. *J Orthop Res* 2000; 18:739–48.
- 4 Cole AA, Kuettner KE. Molecular basis for differences between human joints. *Cell Mol Life Sci CMLS* 2002;59: 19–26.
- 5 Rogers J. Paleopathology of osteoarthritis. In: KD Brandt, M Doherty, LS Lohmander, eds. *Osteoarthritis*. Oxford: Oxford University Press, 1998; 62–69.
- 6 Cushnaghan J, Dieppe P. Study of 500 patients with limb joint osteoarthritis. I Analysis by age, sex, and distribution of symptomatic joint sites. *Ann Rheum Dis* 1991;50:8–13.
- 7 Peyron JG. The epidemiology of osteoarthritis. In: RW Moskowitz, DS Howell, VM Goldberg, HJ Mankin, eds. *Osteoarthritis diagnosis and treatment*. Philadelphia, PA: WB Saunders, 1984: 9–27.
- 8 Valderrabano V, Horisberger M, Russell I, Dougall H, Hintermann B. Etiology of ankle osteoarthritis. *Clin Orthop Relat Res* 2009;467:1800–6.
- 9 Saltzman CL, Salamon ML, Blanchard GM *et al*. Epidemiology of ankle arthritis. Report of a consecutive series of 639 patients from a tertiary orthopaedic center. *Iowa Orthop J* 2005;25:44–6.
- 10 Ritterman SA, Fellars TA, Digiovanni CW. Current thoughts on ankle arthritis. *Rhode Island Med J* 2013;96: 30–3.
- 11 Kiely PDW. Haemochromatosis arthropathy – a conundrum of the celtic curse. *J R Coll Physicians Edinb* 2018;48:233–8.
- 12 Sahinbegovic E, Dallos T, Aigner E *et al*. Musculoskeletal disease burden of hereditary haemochromatosis. *Arthritis Rheum* 2010;62:3792–8.
- 13 Richardson A, Prideaux A, Kiely PDW. Haemochromatosis: unexplained MCP or ankle arthropathy should prompt diagnostic tests; findings from two UK observational cohort studies. *Scand J Rheumatol* 2017;46:69–74.
- 14 Carroll GJ. Primary osteoarthritis in the ankle joint is associated with finger metacarpophalangeal osteoarthritis and the H63D mutation in the HFE gene: evidence for a haemochromatosis-like polyarticular osteoarthritis phenotype. *J Clin Rheumatol* 2006;12: 109–13.
- 15 Elstob A, Ejindu V, Heron C, Kiely PDW. Haemochromatosis arthropathy: MRI hindfoot characteristics; a case-control study. *Clin Rad* 2018;73: 323.e1-323–e8.
- 16 Madhok R, York J, Sturrock RD. Haemophilic arthritis. *Annals Rheum Dis* 1991;50:588–91.
- 17 Manco-Johnson MJ, Abshire TC, Shapiro AD *et al*. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med* 2007;357:535–44.
- 18 Norli ES, Brinkmann GH, Kvien TK *et al*. Joint distribution and 2-year outcome in 347 patients with monoarthritis of less than 16 weeks' duration. *Arthritis Care Res* 2020;72:705–10.
- 19 Jeong H, Kim AY, Yoon HJ *et al*. Clinical course and predictors of outcomes in patients with monoarthritis: a retrospective study of 171 cases. *Int J Rheum Dis* 2013; 17:502–10.
- 20 Binard A, Alassane S, Devauchelle-Pensec V *et al*. Outcome of early monoarthritis: a followup study. *J Rheumatol* 2007;34:2351–7.
- 21 Abhishek A, de Pablo P, Cader MZ *et al*. Diagnostic outcomes associated with ankle synovitis in early inflammatory arthritis: a cohort study. *Clin Exp Rheumatol* 2014;32:533–8.
- 22 Fleming A, Crown JM, Corbett M. Early rheumatoid disease. I. Onset. *Ann Rheum Dis* 1976;35: 357–60.
- 23 Kvien TK, Glennas A, Melby K. Prediction of diagnosis in acute and subacute oligoarthritis of unknown origin. *Br J Rheumatol* 1996;35:359–63.
- 24 Lahu A, Backa T, Ismaili J, Lahu V, Saiti V. Modes of presentation of reactive arthritis based on the affected joints. *Med Arh* 2015;69:42–5.
- 25 Bergstra SA, Chopra A, Saluja M *et al*. Evaluation of the joint distribution at disease presentation of patients with rheumatoid arthritis: a large study across continents. *RMD Open* 2017;3:e000568.
- 26 Grondal L, Tengstrand B, Nordmark B, Wretenberg P, Stark A. The foot: still the most important reason for walking incapacity in rheumatoid arthritis: distribution of symptomatic joints in 1000 RA patients. *Acta Orthop* 2008;79:257–61.
- 27 Fleming A, Benn RT, Corbett M, Wood PHN. Early rheumatoid disease. II. Patterns of joint involvement. *Ann Rheum Dis* 1976;35:361–4.
- 28 Helliwell PS, Hetthen J, Sokoll K *et al*. Joint symmetry in early and late rheumatoid and psoriatic arthritis. *Arthritis Rheum* 2000;43:865–71.
- 29 Sampaio-Barros PD, Bertolo MB, Kraemer MH, Neto JF, Samara AM. Primary ankylosing spondylitis: patterns of disease in a Brazilian population of 147 patients. *J Rheumatol* 2001;28:560–5.
- 30 McHugh NJ, Balachrishnan C, Jones SM. Progression of peripheral joint disease in psoriatic arthritis: a 5-yr prospective study. *Rheumatology* 2003;42:778–83.
- 31 Helliwell PS, Marchesoni A, Peters M, Barker M, Wright V. A re-evaluation of the osteoarticular manifestations of psoriasis. *Br J Rheumatol* 1991;30:339–45.

- 32 Salvarani C, Vlachonikolis IG, van der Heijde DM *et al*. Musculoskeletal manifestations in a population-based cohort of inflammatory bowel disease patients. *Scand J Gastroenterol* 2001;36:1307–13.
- 33 Orchard TR, Wordsworth BP, Jewell DP. Peripheral arthropathies in inflammatory bowel disease: their articular distribution and natural history. *Gut* 1998;42: 387–91.
- 34 Smolen JS, Breedveld FC, Eberl G *et al*. Validity and reliability of the twenty-eight-joint count for the assessment of rheumatoid arthritis activity. *Arthritis Rheum* 1995;38:38–43.
- 35 Backhouse MR, Keenan A-M, Hensor EMA *et al*. Use of conservative and surgical foot care in an inception cohort of patients with rheumatoid arthritis. *Rheumatology* 2011;50:1586–95.
- 36 Otter SJ, Lucas K, Springett K *et al*. Foot pain in rheumatoid arthritis prevalence, risk factors and management: an epidemiological study. *Clin Rheumatol* 2010;29:255–71.
- 37 Lee SW, Kim S-Y, Chang SH. Prevalence of feet and ankle arthritis and their impact on clinical indices in patients with rheumatoid arthritis: a cross-sectional study. *BMC Musculoskelet Disord* 2019;20:420.
- 38 Ball EMA, Bell AL. Lupus arthritis – do we have a clinically useful classification? *Rheumatology* 2012;51: 771–9.
- 39 Van Vugt RM, Derksen RHW, Kater L, Bijlsma JWJ. Deforming arthropathy or lupus and rhus hands in systemic lupus erythematosus. *Ann Rheum Dis* 1998;57: 540–4.
- 40 Mizutani W, Quismorio FP Jr. Lupus foot: deforming arthropathy of the feet in systemic lupus erythematosus. *J Rheumatol* 1984;11:80–2.
- 41 Otter S, Kumar S, Gow P *et al*. Patterns of foot complaints in systemic lupus erythematosus: a cross sectional survey. *J Foot Ankle Res* 2016;9:10.
- 42 Avouac J, Clements PJ, Khanna D, Furst DE, Allanore Y. Articular involvement in systemic sclerosis. *Rheumatology* 2012;51:1347–56.
- 43 Kaandorp CJE, Dinant HJ, van de Laar MAFJ *et al*. Incidence and source of native and prosthetic joint infection: a community based prospective survey. *Ann Rheum Dis* 1997;56:470–5.
- 44 Gupta MN, Sturrock RD, Field M. A prospective 2-year study of 75 patients with adult-onset septic arthritis. *Rheumatology* 2001;40:24–30.
- 45 Dubost J-J, Fis I, Denis P *et al*. Polyarticular septic arthritis. *Medicine* 1993;72:296–310.
- 46 Park L, Nelson SB, Turbett SE. Case 29-2017: a 59-year-old woman with pain and swelling in the right hand and ankles. *N Engl J Med* 2017;377:1189–95.
- 47 Marks M, Marks JL. Viral arthritis. *Clin Med* 2016;16: 129–34.
- 48 Pathak H, Mohan MC, Ravindran V. Chikungunya arthritis. *Clin Med* 2019;19:381–5.
- 49 Inman R. Rheumatic manifestations of Hepatitis B virus infection. *Semin Arthritis Rheum* 1982;11:406–20.
- 50 Chang AY, Encinales L, Porras A *et al*. Frequency of chronic joint pain following chikungunya virus infection. A Colombian cohort study. *Arthritis Rheum* 2018;70: 578–84.
- 51 Rodriguez-Morales AJ, Cardona-Ospina JA, Urbano-Garzon SF, Hurtado-Zapata JS. Prevalence of post-chikungunya infection chronic inflammatory arthritis: a systematic review and meta-analysis. *Arthritis Care Res* 2016;68:1849–58.
- 52 Adizie T, Moots RJ, Hodkinson B, French N, Adebajo AO. Inflammatory arthritis in HIV positive patients: a practical guide. *BMC Infect Dis* 2016;16:100.
- 53 Burke S, Healy J. Musculoskeletal manifestations of HIV infection. *Imaging* 2002;14:35–47.
- 54 Mody G, Parke F. Articular manifestations of HIV infection. *Best Pract Res Clin Rheumatol* 2003;17: 265–87.
- 55 Njobvu P, McGill P. Psoriatic arthritis and HIV infection in Zambia. *J Rheumatol* 2000;27:1699–702.
- 56 Müller F, Zellner M, Füchtmeier B. Treatment and outcome of destructive tuberculosis of the talus. *Foot Ankle Surg* 2015;21:e45–7.
- 57 Dhillon MS, Nagi ON. Tuberculosis of the foot and ankle. *Clin Orthop Relat Res* 2002;398:107–13.
- 58 Grahame R, Scott JT. Clinical survey of 354 patients with gout. *Ann Rheum Dis* 1970;29:461–8.
- 59 Roddy E, Zhang W, Doherty M. Are joints affected by gout also affected by osteoarthritis? *Ann Rheum Dis* 2007;66:1374–7.
- 60 Mijiyawa M. Gout in patients attending the rheumatology unit of Lomé hospital. *Rheumatology* 1995;34:843–6.
- 61 Roddy E. Revisiting the pathogenesis of podagra: why does gout target the foot? *J Foot Ankle Res* 2011;4:13.
- 62 Rosenthal AK, Ryan LM. Calcium pyrophosphate deposition disease. *N Engl J Med* 2016;374:2575–84.
- 63 Song JS, Lee YH, Kim SS, Park W. A case of calcium pyrophosphate dihydrate crystal deposition disease presenting as an acute polyarthritis. *J Korean Med Sci* 2002;17:423–5.
- 64 Harris A, Violand M. Charcot neuropathic osteoarthropathy (Charcot joint). *StatPearls [Internet]* Treasure Island FL: StatPearls Publishing;2020 Jan. <https://www.ncbi.nlm.nih.gov/books/NBK470164/>.
- 65 Papanas N, Maltezos E. Pathophysiology and classifications of the diabetic Charcot foot. *Diabet Foot Ankle* 2013;4:20872.
- 66 Elder A, Chi J, Ozdalga E, Kugler J, Verghese A. The road back to the bedside. *JAMA* 2020;323: 1672–3.
- 67 Ehrenstein B, Pongratz G, Fleck M, Hartung W. The ability of rheumatologists blinded to prior workup to diagnose rheumatoid arthritis only by clinical assessment: a cross-sectional study. *Rheumatology* 2018;57:1592–601.
- 68 Heliwell PS, Cheesbrough MJ. Arthropathica ulcerosa: a study of reduced ankle movement in association with chronic leg ulceration. *J Rheumatol* 1994;21: 1512–4.

- 69 Sweiss N, Patterson K, Sawaqed R *et al*. Rheumatologic manifestations of sarcoidosis. *Semin Respir Crit Care Med* 2010;31:463–73.
- 70 Goussault C, Albert J-D, Coiffier G *et al*. Ultrasound characterization of ankle involvement in Lofgren syndrome. *Joint Bone Spine* 2018;85:65–9.
- 71 Kellner H, Späthling S, Herzer P. Ultrasound findings in Lofgren's syndrome: is ankle swelling caused by arthritis, tenosynovitis or peri-arthritis? *J Rheumatol* 1992; 19:38–41.
- 72 Le Bras E, Ehrenstein B, Fleck M, Hartung W. Evaluation of ankle swelling due to Lofgren's syndrome: a pilot study using B-mode and power Doppler ultrasonography. *Arthritis Care Res* 2014;66: 318–22.
- 73 Anandacoomarasamy A, Peduto A, Howe G, Manolios N, Spencer D. Magnetic resonance imaging in Lofgren's syndrome: demonstration of peri-arthritis. *Clin Rheumatol* 2007;26:572–5.
- 74 Spilberg I, Siltzbach LE, McEwen C. The arthritis of sarcoidosis. *Arthritis Rheum* 1969;12:126–37.
- 75 Bozzao F, Bernardi S, Dore F, Zandonà L, Fischetti F. Hypertrophic osteoarthropathy mimicking a reactive arthritis: a case report and review of the literature. *BMC Musculoskelet Disord* 2018;19:145.
- 76 Armstrong DJ, McCausland EMA, Wright GD. Hypertrophic pulmonary osteoarthropathy (HPOA) (Pierre Marie-Bamberger syndrome): two cases presenting as an acute inflammatory arthritis. Description and review of the literature. *Rheumatol Int* 2007;27:399–402.
- 77 Kohls-Gatzoulis J, Angel JC, Singh D *et al*. Tibialis posterior dysfunction: a common and treatable cause of adult acquired flatfoot. *BMJ* 2004;329:1328–33.
- 78 Eng SWM, Aeschlimann FA, van Veenendaal M *et al*. Patterns of joint involvement in juvenile idiopathic arthritis and prediction of disease course: a prospective study with multilayer non-negative matrix factorization. *PLoS Med* 2019;16:e1002750.