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Intermetatarsal bursitis as first disease manifestation in different rheumatological disorders and related MR-imaging findings

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Abstract

Metatarsalgia defined as pain at the plantar aspect of the forefoot. Intermetatarsal bursitis is considered one potential soft-tissue cause of metatarsalgia that is presumably under-estimated, under-investigated, and, consequently, often misdiagnosed. To assess the role of MRI in the elucidation of the cause of metatarsalgia in patients with different autoimmune disorders presenting primarily with this symptom and to present the accompanying clinical and radiological findings of intermetatarsal bursitis. Retrospective evaluation of the medical records of patients with different rheumatological conditions claiming primarily of pedal pains suggests metatarsalgia and who underwent, therefore, all magnetic resonance imaging between March 2010 and April 2018. Of them, six patients fulfilled these criteria and were diagnosed subsequently with intermetatarsal bursitis. Several underlying autoimmune conditions were diagnosed. All patients were clinically assessed by the squeeze test and radiologically investigated with MRI; three patients underwent additional sonography. All patients presented intermetatarsal bursitis as first disease manifestation. The number of involved bursae ranged from one to three on one side. The main MR findings were distension of the intermetatarsal bursa with increased signal intensity on T2-weighted and post-contrast fat saturation T1-weighted images. Most frequent locations were the second and third intermetatarsal spaces. The size of the intermetatarsal bursitis and its plantar extension were correlated in all patients. Intermetatarsal bursitis can potentially be the first manifestation of different rheumatological diseases. Awareness of this potential association as well as cognizance of its imaging findings can help for making a more accurate and prompt earlier diagnosis of the underlying disease changing also the therapeutic approach.

Keywords Intermetatarsal · Bursitis · Metatarsalgia · Squeeze test · Foot MRI

Introduction

Metatarsalgia is a common symptom in patients with rheumatological disorders, though it can occur also from many causes [1]. In the setting of, e.g., rheumatoid arthritis (RA), metatarsalgia generally is related to tendinitis of the flexor digitorum tendons or to arthritis of the metatarsophalangeal (MTP) joints, and can manifest symmetrically or asymmetrically [2]. However, other differential diagnoses exist and should be considered in this setting. The intermetatarsal bursitis (IMTP) is one of them, and notably, its incidence in RA patients seems to be high (up to 90%) according to prospective ultrasound studies [3, 4]. Thereby, only few patients are symptomatic and its occurrence is expected later in the course of the disease [4]. The MTP joints and the foot tendons can be involved also in other autoimmune disorders including systemic lupus erythematosus (SLE), systemic sclerosis (SSc), mixed collagenous diseases,

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psoriasis arthritis (PsA), etc. [5, 6]. However, in a first report on the prevalence of bursal inflammation in SLE-patients, Mukherjee found 100% involvement of intermetatarsal and submetatarsal bursae, however, without specifying if symptomatic or not [6]. Moreover, these authors did not differentiate between intermetatarsal and submetatarsal bursae which seem to be of different causes as the latter have no synovial lining [4]. In all other autoimmune disorders, the incidence of IMTP seems, however, to be rare as the specialty literature on this topic is scarce, whereas, in RA, MTP involvement is more common and frequently symmetrical; in the other mentioned diseases, it can occur isolated or be asymmetrical which makes differentiation from mimics like Morton's neuroma or intermetatarsal bursitis (IMTB) more challenging [7–10]. IMTB, on contrary, is more often isolated with only few cases experiencing multiple synchronous manifestations. As the clinical examination alone is not enough for making an accurate diagnosis, foot imaging, in particular MRI, is gaining an essential role in patients experiencing metatarsalgia. Hence, recognition of IMTB as an independent cause of metatarsalgia implies knowledge of its imaging features as well as awareness of the potential clinical setting for its occurrence. Moreover, MRI and ultrasound are the best imaging techniques, capable to detect and characterize IMTB and in particular to differentiate it from its mimics. Knowledge of local anatomy helps for correct diagnosis and exclusion of potential differentials. Awareness of the potential of developing IBMT as a first disease manifestation in autoimmune disorders other than RA is a prerequisite for an early diagnosis and its clinical relevance derives from the potential for primary targeted therapy (e.g., steroid infiltration) [11].

The purpose of this retrospective image analysis was twofold: to assess the role of MRI in the elucidation of the cause of metatarsalgia in patients with different autoimmune disorders presenting primarily with this symptom, and to demonstrate the imaging features of IMTB as documented by MRI and ultrasound and to address differences to its mimics.

Materials and methods

Patient series

This was a retrospective evaluation based on a patient data search for IMTB between March 2010 and April 2018. While reviewing the institute database, we searched for all patients presenting directly or being referred to our in-house ambulatory for suspicion of rheumatological or autoimmune disorder, thus identifying all new patients confirmed later with time as having suffering of one of these diseases. In the next step, a search for metatarsalgia as the first occurred symptom was done in all these patients. At our outpatient clinic, about 4600 patients with rheumatological/autoimmune diseases are taking care of yearly. About 10% of them are new cases.

The retrospective data analysis/institutional review board was approved by the ethic committee at our university and all patients gave their written consents. Six consecutive patients (all female; mean age 35.8 years; range 20–59 years,) with RA/SLE overlap syndrome ($n=1$), RA/Sjögren syndrome overlap syndrome ($n=1$), RA ($n=1$), psoriasis arthritis ($n=2$), and RA/spondyloarthritis were retrospectively analyzed for correlation of imaging and clinical findings.

MRI protocol and imaging analysis

Conventional MR imaging was performed on three 1.5 T MR units (Siemens Espree, Siemens Magnetom Avanto, Siemens Magnetom Aera, and one 3 T Siemens Magnetom Skyra, all Siemens Healthcare, Erlangen, Germany) with a protocol that included a minimum of axial non-contrast spin echo T1-weighted, coronal fat saturation time spin echo T2 (STIR)-weighted, as well as post-contrast fat saturation axial + coronal T1-weighted images. The T1-weighted spin echo sequences were performed using a TR = 555–731 ms and a TE = 11–14 ms. The STIR sequences were acquired using a TR = 4000–5560 ms, TE = 54–108 ms, and TI = 150 ms (1.5 T) and 200 ms (3 T). The post-gadolinium T1-weighted sequence was performed with parameters that were identical to non-enhanced T1-weighted sequences with fat saturation. Slice thickness varied among the sequences being 2–3 mm with 10% gap. Matrix size varied between 256 × 143 and 320 × 150. The field of view was adapted to the patient size (250–350 mm). Standard-dose contrast material was administered in all patients.

Two radiologists with 25 and 10 years' experience in MSK diagnosis retrospectively analyzed all MR images of the forefeet. MR signal characteristics were analyzed on both T1-weighted and T2-weighted images as well as on fat-saturated post-contrast T1w images. We registered the signal intensity and contrast enhancement in MTP joints as well as the number of IMTB. The signal intensity was classified normal vs. hypointense vs. hyperintense. Bone marrow edema was registered as well as teno-synovial abnormalities. We measured the size of IMTB in the coronal plane (mm) and the number and localization of involved IMTB. The distance of plantar extension of the IMTB below a plane joining the interior cortex of the nearby metatarsal bones has been correlated as an objective mean to investigate the plantar extension of the IMTB toward the corresponding neurovascular bundle (Fig. 1).

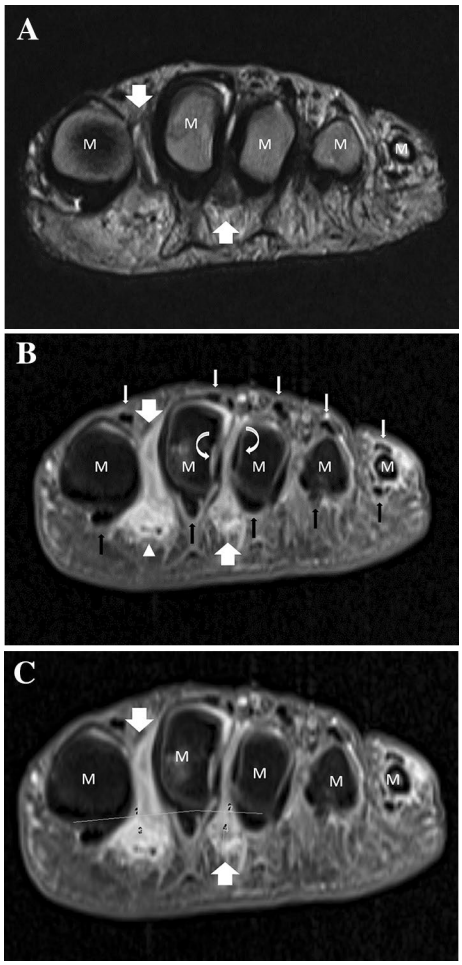

Fig. 1 Second case with rheumatoid arthritis/Sjögren Syndrome. Coronal MRI scan at the level of the metatarsal head (M) (**A**) T2 weighted images shows a fluid signal at the intermetatarsal spaces I, II (Thick arrows) between the metatarsal head (M) (**B**) Post contrast T1 fat saturation image shows a corresponding avid enhancement, in keeping with intermetatarsal bursitis (Thick arrows), Extensor tendons (White arrows), Flexor tendons (Black arrows), (Interosseous tendons (curved white arrows) and neurovascular bundle (Arrow head) (**C**) Post contrast T1 fat saturation image shows how to measure the distance of plantar extension of the intermetatarsal bursitis (Thick arrows) below a line joining the inferior cortex of the nearby metatarsal head

Ultrasound/doppler protocol and imaging analysis

Ultrasound was performed using an ESAOTE MyLab™ 70 X-Vision machine (Easote Biomedica Germany GmbH, Köln, Germany) with an LA 523 multi-frequency linear 4–13 MHz probe. B mode and Power Doppler were performed at each forefoot focusing on the metatarsal joints and the intermetatarsal spaces. The MTP joints were evaluated for synovitis and intra-articular effusion. Ultrasound abnormalities in the intermetatarsal spaces were evaluated by B mode or Power Doppler trying to identify intermetatarsal bursitis. One rheumatologist with 13 years' experience in ultrasound diagnostic of the joints carried out the ultrasound examination.

Results

Patients

Retrospective evaluation of the medical records between March 2010 and April 2018 identified six patients with different rheumatological conditions claiming primarily of pedal pains suggesting metatarsalgia who were diagnosed subsequently with IMTB. Considering the mean of newly diagnosed rheumatologic/autoimmune patients, the incidence of IMTB was about 0.16%.

The following underlying autoimmune conditions were diagnosed: RA/SLE overlap syndrome ($n=1$), RA/Sjögren overlap syndrome ($n=1$), RA ($n=1$), psoriasis arthritis ($n=2$), and RA/spondyloarthritis ($n=1$).

All patients were clinically assessed by the squeeze test and radiologically investigated with MRI; three patients underwent ultrasound examination additionally (Figs. 1, 2, 3).

Clinical findings

Patient 1: First symptoms occurred in September 2010: forefoot pain was followed by tender and swollen finger joints, wrists, knees, and ankle joints. She was diagnosed in March 2012 as RA (cyclic citrullinated peptide positive and rheumatoid factor negative) plus SLE [Anti-Ro (SSA)/La (SSB) positive] according to the 2010 revised criteria for RA [12].

Patient 2: First symptom consisted of forefoot pain followed by tender and swollen finger joints. She was diagnosed in October 2010 as RA (cyclic citrullinated peptide positive and rheumatoid factor negative) with secondary Sjögren Syndrome according to the 1987 American College of Rheumatology (ACR) criteria for RA.

Patient 3: First symptoms occurred in November 2012 consisting of forefoot pain and swelling of the second toe on both sides. She was diagnosed in November 2012 as psoriatic arthritis according to the 2006 ClASsification for Psoriatic Arthritis (CASPAR) criteria.

Patient 4: First symptoms occurred in November 2012 and presented as forefoot pain followed by tender and swollen proximal interphalangeal joints. She was diagnosed in April 2013 as rheumatoid arthritis (cyclic citrullinated peptide positive and rheumatoid factor negative) according to the 2010 revised criteria for RA.

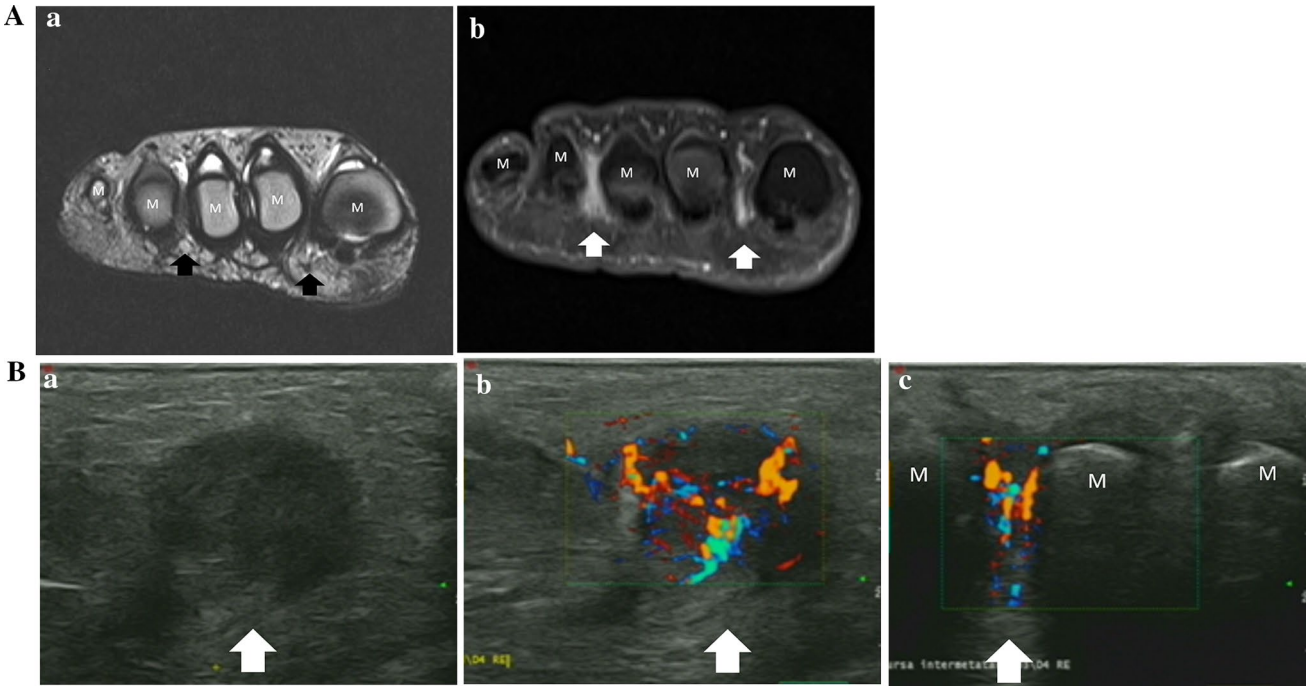

Fig. 2 **A** Fourth case with rheumatoid arthritis. Coronal MRI scan at the level of the metatarsal head (M) (*a*) T2 weighted images shows a iso- to slight hyperintense fluid signal at the first and third intermetatarsal spaces (Thick arrows) (*b*) Post contrast T1 fat saturation image shows a corresponding more evident avid enhancement, in keeping with intermetatarsal bursitis (Thick arrows). **B** Fourth case with rheumatoid arthritis. Ultrasound scan at the level of the metatarsal head (*a*) Sagittal image shows a hypoechoic mass at the intermetatarsal spaces III (Thick arrow) (*b*) a color doppler sagittal image shows a corresponding increased perfusion, in keeping with intermetatarsal bursitis (Thick arrow) (*c*) coronal color doppler image at the image at the intermetatarsal spaces III shows more anatomical delineation of the intermetatarsal space between the metatarsal head III, IV (M) and the depth of the plantar extension of the intermetatarsal bursitis (Thick arrow)

Patient 5: First symptoms are dated January 2018 and consisted of forefoot pain on both sides increasing with standing and during night. The patient has been suffering from plaque psoriasis for about 25 years. She was diagnosed with psoriatic arthritis in April 2018.

Patient 6: First symptoms are dated back in May 2014 consisting of forefoot pain in the right foot and later also in the left foot. She was initially misdiagnosed as Morton neuroma, respectively hemangioma. Later, she was diagnosed as seronegative RA according to the 2010 revised criteria for RA.

Imaging findings

MRI results are presented in Table 1.

We had a total of 13 IMTB involved in our patient's series. The most frequent localization was in the II ($n = 4$) and III ($n = 5$) intermetatarsal spaces. In five patients, bursitis was diagnosed unilateral, while one showed bilateral involvement. The right foot was involved more frequently ($n = 4$) than the left side ($n = 3$). In the fourth case, there was a non-continuous IMTB including spaces I and III (Fig. 2A). Mean bursal craniocaudal dimension was 17.7 mm (range 10–28 mm), whereas the mean transverse dimension was 6.6 mm (range 4–11 mm). The distance of plantar extension of the IMTB below a plane joining the inferior cortex of the nearby metatarsal bones has been measured and reached a maximum of 9 mm (Fig. 1).

Signal intensity on T2-weighted images ranged from slight to marked hyperintense, whereas, on T1w images, it showed hypointense appearance (Figs. 1, 2, 3). None of the adjacent MTP joints showed abnormalities compatible with arthritis at the time of IMTB diagnosis. On post-contrast fat saturation T1-weighted images, there was avid bursal enhancement in all IMTB (Figs. 1, 2, 3). No osseous edematous changes in the vicinity of the IMTB were present.

In the patient with RA/Sjögren syndrome, ultrasound-guided steroid infiltration has been carried out.

Ultrasound findings

Ultrasound was performed looking for the corresponding inflammatory changes as well as using power Doppler mode at each forefoot. The presence of associated joint

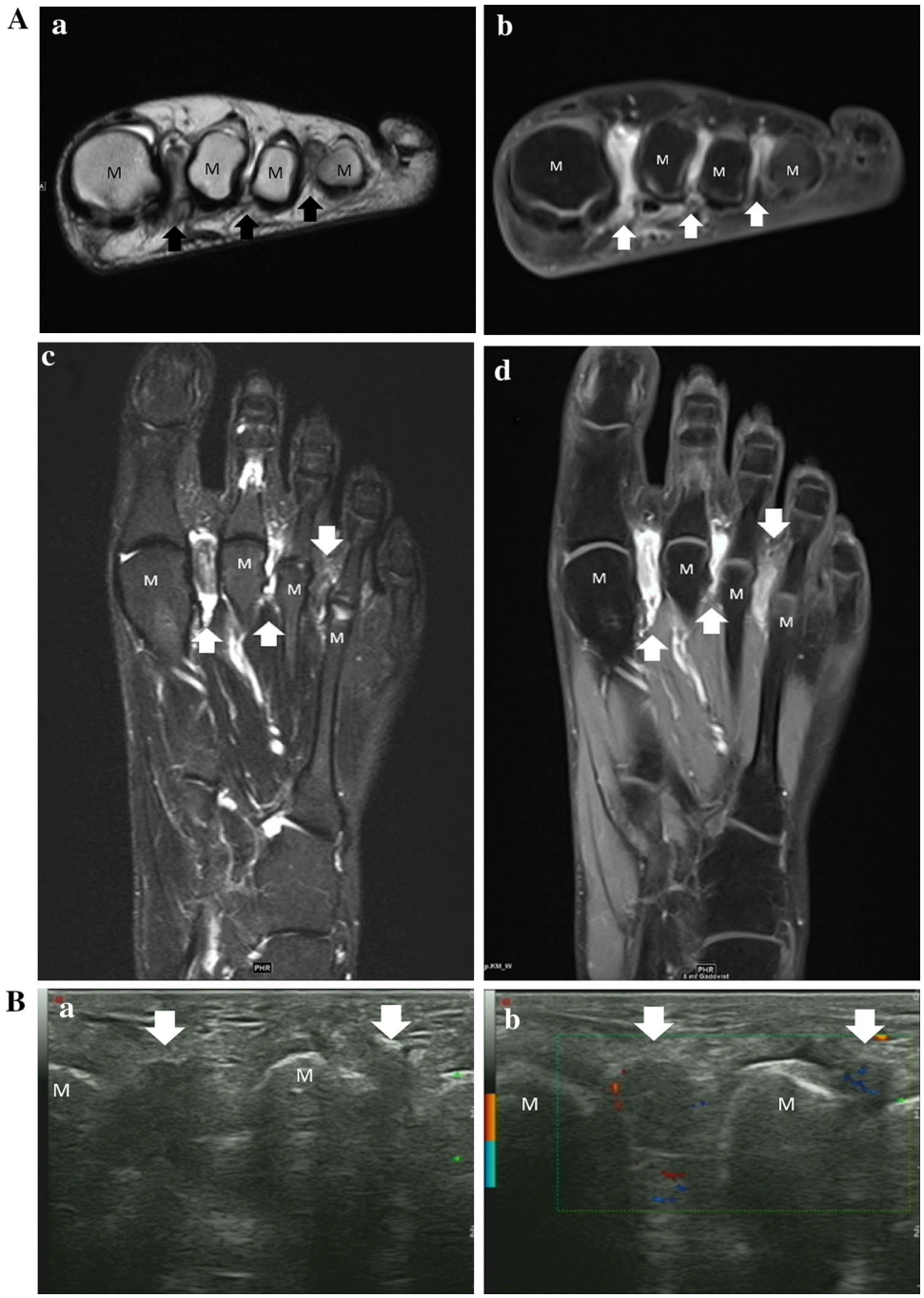

Fig. 3 **A** Sixth case with Rheumatoid arthritis/Spondyloarthritis (Left foot). Coronal and axial MRI scans at the level of the metatarsal head (M) (*a*) T2 weighted image shows a isointense to hyper-intense signal at the first, second and third intermetatarsal spaces (Thick arrows) (*b*) Post contrast T1 fat saturation image shows a corresponding more evident avid enhancement at first, second and third intermetatarsal spaces, in keeping with intermetatarsal bursitis (Thick arrows) (*c*) STIR image shows a hyper-intense signal at the first, second and to a lesser extent third intermetatarsal spaces (Thick arrows) (*d*) Post contrast T1 fat saturation image shows a corresponding more evident avid enhancement at first, second and third intermetatarsal spaces, in keeping with intermetatarsal bursitis (Thick arrows). **B** Sixth case with Rheumatoid arthritis/Spondyloarthritis (Left foot). Coronal ultrasound scan at the level of the metatarsal head (M) (*a*) shows a hypoechoic mass at the first and second intermetatarsal spaces (Thick arrows) (*b*) a color doppler image at the same level shows a increased perfusion at first and second intermetatarsal spaces, in keeping with intermetatarsal bursitis (Thick arrows)

abnormalities has been excluded as well, including, for example, the presence of synovitis (synovial thickening and increased power Doppler signals) or intra-articular effusion, to further delineate the possible causes of the metatarsalgia.

The IMTB was identified as a mass with hypoechogenicity at the level of the metatarsal head (Figs. 1, 2, 3). On power Doppler, the blood flow to the IMTB was assessed, which revealed an apparent regional increase in blood flow in all of the identified patients (Figs. 1, 2, 3). Anatomical details have been identified by ultrasound as well as the extent of extension below the plantar cortices of the metatarsals and the relations to the neurovascular bundles.

Discussion

Our patient series demonstrates the possibility of intermetatarsal bursitis as the first manifestation of different rheumatologic diseases presenting with metatarsalgia and typical MRI findings. Awareness of this rare pathology and

Table 1 Patient with intermetatarsal bursitis

Cases	Diagnosis	Age at diagnosis (year)	Gender	Metatarsal space (I to IV)	Size of bursitis (mm)	Plantar bursal extension (mm)	Side involved
1	Rheumatoid arthritis/systemic lupus erythematosus	24	Female	III	III = 16 × 7	5	Right
2	Rheumatoid arthritis/Sjögren syndrome	39	Female	I, II	I = 19 × 11 II = 18 × 9	I = 6 II = 7	Left
3	Psoriatic arthritis	50	Female	III	III = 14 × 6	5	Right
4	Rheumatoid arthritis	23	Female	I, III	I = 20 × 5 III = 16 × 5	I = 2 III = 4	Right
5	Psoriatic arthritis	59	Female	II	II = 20 × 8	6	Left
6	Rheumatoid arthritis/spondyloarthritis	20	Female	I, II, III	Left: I = 21 × 8 II = 16 × 4 III = 12 × 6	Left: I = 2 II = 4 III = None	Bilateral
				I, II, III	Right I = 21 × 6 II = 28 × 7 III = 11 × 4	Right I = 6 II = 9 III = None	

cognizance of its imaging findings helps for prompt diagnosis and should raise the suspicion of a potentially underlying rheumatological/autoimmune disorder.

In our cohort, an estimated incidence of IMTB as first manifestation of a rheumatological/autoimmune disease of 0.16% of the new cases at our institution was found. All patients became symptomatic by metatarsalgia which was frequently first misinterpreted as inappropriate mechanical stress to the joints or due to arthritis at MTP joints. Due to symptom persistence, all patients underwent clinical examination and later MRI ± ultrasound of the feet, and the diagnosis of IMTB was confirmed. Clinical and laboratory tests for exclusion/confirmation of an underlying rheumatological/autoimmune disorder were subsequently carried out. The few prospective studies assessing the incidence of IBMT in patients with RA and SLE indicated a much higher frequency of bursitis ranging from 80 to 100% [4, 6, 13]. However, these reports did not mentioned if their patients were symptomatic or not and also not in which stage of the disease which they were diagnosed. This discrepancy to our results is presumably due to more advanced disease stages examined in their cohorts. Moreover, all their patients are reported to have had synchronous joint involvement. Interestingly, Boutry et al. advised the addition of foot MRI scan when the evaluation of the hands did not help to identify early RA [14]. Cherry et al. considered IMTB to be both a prognostic indicator of foot-related instability and a sign of increased RA activity [15]. Hence, the isolated IBMT could be a potential herald of a threatening autoimmune disorder having, thus, prognostic relevance.

Interestingly, the number of involved IMTB varied throughout our series being mostly unilateral with one case showing bilateral involvement. The right foot was preferentially involved (five vs. one) which could represent increased stress for weight-bearing right foot in most patients. Most IMTB were localized in the second and the third intermetatarsal spaces. Significant differences in the size of the IMTB were present. Also of note was the uniformity with respect to signal intensity on T2-weighted images and post-contrast T1 fat saturation where all bursae presented with increased contrast to background. Therefore, the significance of painful IMTB should be differentiated from the incidentally diagnosed fluid-filled bursae that seem to be much more frequent in particular in RA, but lack prognostic value. Cherry et al. also doubted the clinical significance of forefoot bursae diagnosed by MRI as long as they are not clearly symptomatic [15]. Metatarsalgia can be clinically assessed by the squeeze test, which has been defined as pain produced upon lateral compression of the metacarpophalangeal or MTP joints with IMTB being one potential soft-tissue cause of it, most clinicians and radiologists are less aware of [16].

From an etiological point of view, causes of metatarsalgia vary including soft-tissue-related, i.e., Morton neuroma and IMTB, osseous causes, i.e., avascular necrosis or fractures, as well as joint-related conditions that can be important differential diagnosis in rheumatologic/autoimmune patients.

Anatomical delineation of the intermetatarsal space has been previously studied by Theumann et al. using MRI bursography [17]. These anatomical details play a major role in differentiation of the potential causes of metatarsalgia. The first intermetatarsal space was

described as a tendon sheath covering the adductor hallucis tendon [9, 17]. The second and third spaces share a common feature of inferior extension of the intermetatarsal space below the level of the DTML [7, 16–18]. In our patient series, we have suggested measuring the distance of plantar extension of the IMTB below a plane joining the interior cortex of the nearby metatarsal bones, which is easily done and is a definable criteria compared with other anatomical landmark that could be more difficult to delineate (Fig. 1). The measured inferior extension reached maximum of 9 mm. The middle two spaces share as well a common feature of being associated with higher incidence of Morton neuroma (MN). The increase incidence of the two entities might be the result of neural irritation produced by the distally extended IMTB [17, 19–21]. The presence of the MN and IMTB has been studied in asymptomatic volunteers using MRI scan, which has pointed toward a physiologic occurrence of the IMTB when the transverse diameter is 3 mm or less by Zanetti et al. [19].

MR imaging is a highly sensitive tool in the evaluation of the IMTB. The presence of fluid-equivalent hyperintense signal between the heads of the metatarsal bones in coronal plane is thereby the main imaging finding. The use of coronal planes for optimal delineation of anatomical landmarks including the DTML, as well as the interosseous tendons which represent together the normal boundaries of the intermetatarsal space is thereby essential [9]. MRI also enables visualization of the inferior intermetatarsal space lying underneath the DTML and superior to the superficial transverse metatarsal ligament that contains the neurovascular bundle [17]. Whereas T2-weighted sequences are helpful for detection of IMTB, the administration of contrast media is of paramount importance in detecting contrast enhancement which mostly reflects local inflammation and thus disease activity. Moreover, it helps also for detection of IMTB that contains minimal fluid or lacks fluid signal, resulting in an increased sensitivity of its detection (Fig. 2). MRI can help as well in the differentiation between two important cause of the metatarsalgia including Morton neuroma and the IMTB based on the distinct anatomical location below and above the above DTML, respectively. Morton neuroma consists of perineural fibrosis and nerve degeneration, which classically exhibits iso- or hypointense signal on T2-weighted images with moderate post-contrast enhancement, while IMTB shows a striking fluid signal with predominantly peripheral enhancement on post-contrast sequences [22].

Ultrasound examination is a good alternative to MRI for evaluation of metatarsalgia as described by Iagnocco et al. which resulted in IMTB in 20.5%, Morton neuroma in 15.2%, and effusion of the MTP joint in 11.7% [23]. Cohen et al. have studied the preoperative and the postoperative ultrasound appearance of ten patients with MN, and pointed on the heterogeneous hypoechoic character of masses representing the neuroma–bursal complex, which is much larger than the actual neuroma [24], which again emphasizes the relationship between the MN and IMTB.

MRI imaging not only serves as important imaging modality in diagnosing IMNB, but also helps in beneficial for excluding the presence of other forefoot entities that could result in metatarsalgia, which could be encountered and expected in patients with rheumatological conditions.

Study limitations include small sample size and lack of a control group for those having no metatarsalgia. Further analysis regarding the association of IMTB and early diagnosis of rheumatologic disorder could be better appreciated on prospective multicentric studies to include large sample size as well as screening of all new cases including those with no metatarsalgia by foot MRI/Doppler Ultrasound.

Conclusion

Metatarsalgia can be the first clinical findings in patients who are later classified as suffering from a rheumatological disorder. IMTB is one of the under-estimated, under-investigated, as well as often overlooked causes of the metatarsalgia that shows an association with different rheumatological conditions, especially in the early course of the disease process.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by OMA, TX, and MH. The first draft of the manuscript was written by OMA, TX, and MH, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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