Case 11

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A Critical Evaluation of the Role of Ultrasound in the Diagnosis and Treatment of Morton's Neuroma: A Case Study

Introduction

Morton's neuroma (MN) was first described by Thomas Morton in 1876 and is a benign thickening of a plantar interdigital nerve between the metatarsal heads (McNally, 2014) (see Appendix 1). It is also known as "Morton's metatarsalgia, Morton's entrapment, interdigital neuroma, intermetatarsal neuroma and interdigital nerve compression syndrome" (National Institute for Health and Care Excellence (NICE), 2016, para. 1). It is not a true neuroma however, as it is a degenerative rather than proliferative process, thought to occur due to compression from biomechanical overloading, deformity and/or calf muscle tightness (Gougoulias, Lampridis and Sakellariou, 2019; Santos, Morrison and Coda, 2018). This causes perineural fibrosis and axonal degeneration, with the third webspace most commonly affected (Bianchi and Martinoli, 2015). It is 4-15 times more prevalent in women and this is likely related to wearing high heels which increase pressure in the forefoot (NICE, 2016, para. 3). Patients typically present with burning pain and paraesthesia in the affected webspace and may describe the sensation of walking on a pebble (Pomeroy, Wilton and Anthony, 2015). Conservative treatments such as activity and footwear modification, nonsteroidal anti-inflammatory medications and plantar orthoses are recommended initially and if unsuccessful orthopaedic referral advised (NICE, 2016, para. 5). This case study provides an example, and critical evaluation, of the role of diagnostic ultrasound and ultrasound guided corticosteroid injections (USG-CSI) in a patient with MN who was referred to orthopaedic outpatients (OOPD) with symptom relapse following conservative treatment and a landmark guided (blind) corticosteroid injection (CSI) in the community.

Clinical Presentation

A 35 year old female (Patient A) was referred by Podiatry to the OOPD at XXX National Health Service (NHS) Trust in January 2020 for assessment of persistent right metatarsalgia. The referral detailed a 3 year history of a burning sensation in the right forefoot on weight bearing (WB) with toe numbness. Tight footwear and driving exacerbated her symptoms. Patient A works as a cleaner, is a non-smoker, is not overweight and has no pre-existing health

conditions. In March 2019, an ultrasound scan of her right foot was performed elsewhere which reported intermetatarsal bursitis in the third webspace. Following, orthoses and footwear advice, a blind CSI into the third webspace was performed by a Podiatrist in April 2019, with symptomatic relief for 4-5 months. However, her symptoms had since reoccurred resulting in the onward referral.

The Orthopaedic Surgeon conducted a physical examination of Patient A's feet and reported symmetrical appearances, with irritable second and third right webspaces on the webspace tenderness test (pain elicited when examiners thumb is pushed into the webspace). A positive Mulders click was also noted in the third webspace (a painful, palpable click on lateral compression of the forefoot). WB plain film radiographs (x-rays) were unremarkable (see Appendix 2, Figures 1, 2 and 3) and in view of the symptoms, clinical findings and previous ultrasound, a repeat ultrasound was requested, along with an USG-CSI, to clarify the diagnosis as a MN was suspected.

The Role of Diagnostic Imaging in the Diagnosis of MN

Due to the wide range of differential diagnoses for metatarsalgia, x-rays are recommended as a first line investigation to assess bony anatomy and exclude pathologies such as stress fracture or arthropathy as a cause (Di Caprio *et al.* 2018; Gougoulias, Lampridis and Sakellariou, 2019). Evaluation should include foot and ankle views, performed WB where possible to provide biomechanical information (Ho, Lui and Tam, 2015). However, whilst these are inexpensive, ultrasound is superior for assessing soft tissues and is advised if no x-ray abnormality is detected and/or clinical findings are equivocal, as with Patient A. Whilst, her presenting symptoms and clinical examination were highly suggestive of MN, ultrasound was necessary to confirm the diagnosis due to the history and fact multiple webspaces were symptomatic (Gougoulias, Lampridis and Sakellariou 2019; Santiago *et al.* 2018).

A Canon Aplio i800 ultrasound machine and 4-14MHz linear array probe demonstrated MN in the second and third webspaces of the right foot with associated intermetatarsal bursae. In longitudinal section MN appear as a fusiform, elongated hypoechoic lesion, situated in the webspace just proximal to the metatarsal heads (See Appendix 3, Figures 1 and 2). In transverse section they appear as a round hypoechoic lesion in the webspace just proximal to the metatarsal heads. Visualisation of the MN's was improved with lateral compression of the forefoot using the free hand, resulting in plantar displacement of the MN's between the

metatarsal heads (sonographic Mulder's sign) (Bianchi and Martinoli) (See Appendix 2 Figures 3 and 4). In addition, the lesions were partially compressible, aiding differentiation from intermetatarsal bursitis alone, which usually efface completely.

MN is a common cause of metatarsalgia and should always be in the differential diagnosis (Adams, 2010). Clinical examination is highly accurate for MN (as with Patient A), with research demonstrating a 96% sensitivity for the webspace tenderness test and 61-98% sensitivity for Mulder's click (Di Caprio *et al.* 2018; Mahadevan *et al.* 2015). However, ultrasound is useful to confirm the diagnosis, determine the site and size of MN, detect MN and exclude other causes of symptoms. Therefore, it can prevent patients from unnecessary invasive treatments for an incorrect diagnosis (Lee *et al.* 2007). Furthermore, ultrasound is cost effective, quick, radiation free, readily available, portable, dynamic, can guide treatments and has no known contraindications. Nevertheless, despite its excellent visualisation of soft tissues, detection of small MN's is challenging and extremely operator dependent with a long learning curve (Ata, Onat and Ozcakar, 2016).

The alternative, Magnetic Resonance Imaging (MRI), has superior soft tissue contrast and can examine larger areas. However, it is not routinely performed for suspected MN at our NHS Trust due to its cost, contraindications, long acquisition times and lack of availability. In addition, a metanalysis by Xu *et al.* (2015) comparing sensitivity and specificity of Ultrasound and MRI for MN, with surgery as a reference standard, found similar sensitivity values for both modalities (Ultrasound 0.90, MRI 0.93) and a higher specificity for ultrasound (0.88 versus 0.68 for MRI) indicating better overall diagnostic accuracy for ultrasound. Conversely, in a similar metanalysis by Bignotti *et al.* (2015), whilst similar results were noted for sensitivity (Ultrasound 0.90, MRI 0.9), MRI was more specific (1.00 versus 0.854) resulting in the opposite conclusion. This suggests that the most accurate modality remains unclear with multiple factors that make comparison difficult; accuracy of ultrasound depends on operator experience, size of studied MN may impact on detection rates and false positive/true negative rates could not be calculated as not all patients went on to surgery. In the context of the existing evidence and its limitations, ultrasound has thus far prevailed as the preferable examination due to its previously detailed inherent advantages. Nevertheless, MRI does have a limited role for atypical cases or those with a markedly restricted webspace preventing adequate ultrasound assessment (Bianchi & Martinoli, 2015). Regardless of which is utilised though, findings must

be interpreted in conjunction with clinical assessment as detection of asymptomatic MN's is common (Di Caprio *et al.* 2018).

The Role of Ultrasound in the Treatment of MN

Following diagnostic ultrasound Patient A was verbally consented through a process of shared decision making (SDM) for an USG-CSI with local anaethesthic (LA). SDM "involves healthcare professionals and patients working together to make choices about medicines based on clinical evidence and the patients informed preferences about what they hope to gain from the treatment" (NICE, 2019, p. 1). This is a legal requirement which ensures patients understand the risks of the proposed treatment and alternatives (NICE, 2019). Consequently, information was provided to Patient A on the risks of the procedure including: allergic reaction, infection, steroid flare, skin changes, depigmentation and poor therapeutic response (Netto *et al.* 2018). No cautions or contraindications were identified during discussion. In view of the current novel coronavirus (2019-nCoV) pandemic, information was also given on the potential risks of receiving corticosteroids if incubating the virus. Currently, the impact of corticosteroids in this situation remains unknown, with limited research available. Previously, corticosteroids have been associated with adverse effects such as delayed viral clearance when used on patients with Middle East Respiratory Syndrome coronavirus and severe acute respiratory syndrome coronavirus (Russell, Miller and Baillie, 2020). Likewise a small study of 2019-nCoV reported that corticosteroids increased the severity of the virus (Zha *et al.* 2020). However, these studies were not undertaken in the context of the low doses used for musculoskeletal injections and consequently a risk/benefit approach is advised for these on an individual basis (British Society for Rheumatology (BSR) *et al.* 2020). During the initial wave of the pandemic all non-urgent surgery was cancelled at our NHS Trust with only limited lists operating now. Currently, it's unknown when full operating capacity will resume. Given Patient A's symptoms, failed conservative treatment, previous relief with CSI, the waiting times and risks of surgery, an USGI-CSI was deemed appropriate and patient A agreed. In addition, in accordance with local protocol (see Appendix 4), patient A was not deemed vulnerable to 2019-nCoV so no shielding or test was needed prior to proceeding.

USG-CSI Technique

Patient A was positioned supine on the ultrasound couch with her legs extended. The operator wore personal protective equipment in accordance with local 2019nCoV infection control policies and Public Health England guidance (2020) and aseptic technique was used. The 4-14 MHz linear array ultrasound probe was placed in long axis on the plantar aspect of the second and third webspaces whilst 0.5ml 1% lidocaine (LA) was injected subcutaneously, and around, each MN in turn. Two 25 gauge orange needles were used (one for each webspace) and inserted using a dorsal in-plane approach (see Appendix 5). Once LA injection was complete and the needles abutted the MN's, 20mg (0.5ml) of Methylprednisolone (CSI) was injected around each MN (see Appendix 6). There were no complications and Patient A reported an immediate absence of her usual pain. A pain diary was issued to document injection response and she was advised to rest for 48 hours and use ice and analgesia to manage any post injection flare symptoms. At time of writing, the pain diary had not been returned so no information on longer term outcomes is currently available.

A dorsal needle approach was chosen as the skin is thinner in this area resulting in improved disinfection, patient tolerance, and a reduced risk of plantar fat pad atrophy (Netto *et al.* 2018). Skin changes such as subcutaneous fat atrophy are a risk of CSI and can cause pain and affect gait. Methylprednisolone was administered rather than Triamcinolone Acetonide (TA) as the risk of this is lower with this corticosteroid, despite its similar potency (McNally, 2014). Lidocaine was used as a LA as it has a faster onset than bupivacaine, providing immediate pain relief and diagnostic information on if the MN is the pain generator. In addition, 1% strength was used as higher strengths are associated with chondrocyte toxicity (Murakami, 2015). Use of LA prior to CSI enabled the needle positions to be confirmed as visualisation was challenging due to the thin needle used chosen to minimise discomfort. Total volume of fluid administered to each webspace was limited to 1ml to reduce the risk of extravasation complications (Netto *et al.* 2018).

The Role of Injection Therapy

LA and CSI is the most commonly used interventional non-operative treatment for MN (Gougoulias, Lampridis and Sakellariou, 2019). Whilst LA alone provides diagnostic information, addition of corticosteroid is thought to provide longer symptomatic relief by reducing the surrounding inflammatory response (Bianchi and Martinoli, 2015). Compared with orthoses, CSI produced better outcomes for MN with patient satisfaction significantly better ($p<0.01$) at 1, 6 and 12 months (Saygi *et al.* 2005). This study was subject to bias though

as patients could not be blinded to their treatment and the sample was small (n=82) limiting external validity. However, a further study also found significantly improved outcomes (p=0.02) at 3 months following LA and CSI, when compared with LA alone, further indicating CSI can improve MN symptoms (Thomson *et al.* 2013). Furthermore, this was a methodologically superior randomised controlled trial (RCT) with enough power to generalise results. Unfortunately though this study could not maintain blinding beyond 3 months and consequently the long term efficacy of CSI remains unestablished. Nevertheless, LA and CSI can confirm the diagnosis, improve symptoms, guide further treatment, and delay or avoid surgery (Di Caprio *et al.* 2018; Netto *et al.* 2018). For example, in a study evaluating a staged treatment programme of conservative measures followed by LA and CSI, followed by surgery, 79% (n = 91) of patients avoided surgical treatment (Bennett *et al.* 1995). This has clear patient benefits given that risks of surgery for MN include abscess, haematoma, stump neuroma, hammertoe and keloid scar formation (Masala *et al.* 2017).

Evidence for USG-CSI Therapy

USG-CSI for Patient A enabled the administration of the LA and corticosteroid to be visualised in real time ensuring it reached the MN's. As discussed earlier, accurate LA injection is a valuable part of the diagnostic pathway (particularly in the context of a limited response to blind injection), as surgical decisions may depend on response (McNally. 2014). USG-CSI is also thought to reduce procedural and post procedural pain as trauma to the area is minimised as a result of being able to see the needle (Murakami, 2015). However, whilst there is no doubt that ultrasound guidance improves injection accuracy, with acromioclavicular joint injections demonstrating 100% accuracy for USG-CSI versus 40% accuracy for blind injections (no study on injection accuracy specific to MN could be identified), the impact on efficacy remains unclear given the systemic effect of CSI (Peck *et* al, 2010 in Malanga, Axtman and Mautner, 2014). A double blinded RCT comparing USG-CSI with blind injections for 36 patients with MN found that whilst both patient groups mean visual analogue scores (VAS) improved significantly, there was no statistical differences between them at any review point, indicating no increased efficacy with USG-CSI (Mahadevan *et al.* 2016). However, improvement in Manchester Oxford Foot Questionnaire Index and patient satisfaction information favoured USG-CSI in the short term (3 months) almost reaching statistical significance (p = 0.059 and p=0.066), a result which may have been different with a larger sample size. In comparison, a similar study by Santiago *et al.* (2018), with a larger sample of 56 patients, demonstrated improved VAS and Manchester Foot Pain and Disability Scores in both groups, but the USG-

CSI group showed significantly better improvements at follow up intervals of 45 days, 2 months and 3 months. Both groups were randomly assigned with no differences in mean age or neuroma size. Consequently, these results suggest USG-CSI does improve efficacy with further advantages noted of fewer cases of skin depigmentation (one versus 5 in the blind group) and significantly fewer repeat injections (2.1 ± 0.1 versus 2.7 ± 0.2, $p = 0.01$). However, given that in both studies the blind injection groups still showed symptomatic improvement, it could be argued the additional cost of USG-CSI is unjustified. However, at our NHS trust, many patients receive USG-CSI as an adjunct to diagnostic ultrasound limiting additional costs. In addition, improved accuracy arguably has the potential to reduce long term costs through improved patient outcomes.

Alternative Treatments to USG-CSI Therapy

Currently alternative treatments to USG-CSI for MN in the United Kingdom consist of ultrasound guided alcohol injections or surgery (neurectomy or nerve decompression) (NICE, 2016). Alcohol injections are a form of chemical neurolysis which cause dehydration and necrosis of the MN, however this is associated with pain, bruising, numbness and soft tissue necrosis (Netto *et al.* 2018). In addition, it requires multiple sessions (up to 6) making it more time consuming and expensive than USG-CSI (Goldin & Shiple, 2014). Nevertheless, a systematic review of 11 studies investigating this treatment found it is relatively safe (with only some reports of short term adverse effects) and demonstrated evidence of symptomatic improvement (Santos, Morrison and Coda, 2018). However, all 11 studies lacked methodological rigour with no RCT identified, only case series, providing low level evidence at high risk of bias. Comparison between studies was difficult due to differences in injection methodology, with variations in numbers of injections given, alcohol concentrations used, injection intervals, follow up intervals and outcome measures. Consequently, further higher quality research is needed to establish conclusions on this treatment and as a result it is not offered at our NHS Trust.

Another treatment with potential is ultrasound guided radiofrequency ablation (RFA) which currently can only be used if specific clinical governance arrangements exist (NICE, 2015). This is a minimally invasive, percutaneous alternative to surgery which uses a radiofrequency probe attached to a generator to deliver pulses of thermal energy into the webspace causing thermal ablation of the MN (NICE, 2015). This demonstrated promising results in a study of 22 MN with significant improvements in VAS at 8 weeks ($p=<0.001$) and 8 months ($p=<0.008$) and no significant adverse effects (Shah *et al.* 2019). Similarly, 3 studies identified in a review

by Matthews *et al.* (2019) also demonstrated favourable results after a mean follow up of 7 months. However, again all of these studies were low quality (uncontrolled pre/post study designs) with RCT's needed to establish conclusions. This is also true of a study by Climent *et al.* (2013) of botox injections for MN which demonstrated symptomatic improvement in 70.6% patients at 3 months after a single injection, and two studies on cryoneurolysis (freezing the nerve using an ultrasound or MRI guided probe) which was successful after a mean review period of 11.4 months (Cazzato *et al.* 2016; Friedman, Richman and Adler, 2013). Whilst these treatments show promise, the low number of studies and lack of high quality evidence means they are not currently offered within the NHS.

Surgery is offered at our NHS Trust as a last resort following the use of an USGI- CSI with LA. This is because the success rate for neurectomy rarely exceeds 80% and there is a high rate of complications; 25% for neurectomy and 7% for neurolysis (Masala *et al,* 2017, Santiago *et al.* 2018). Consequently, confirming the diagnosis and webspace with USG-CSI prior to operating is crucial for ensuring the highest chance of success. Given that the LA resulted in an immediate resolution of Patient A's symptoms she may be offered surgery in the future should her symptoms persist post USG-CSI.

Conclusion

MN is a common cause of metatarsalgia which has a marked female predilection, as was the case with Patient A (NICE, 2016). Although clinical examination is highly sensitive for MN, x-rays and ultrasound help exclude other causes of pain, with MRI reserved for difficult/ atypical cases (Di Caprio *et al*, 2018; Mahadevan *et al.* 2015). Injection of LA and corticosteroid improves symptoms when compared with orthoses and LA alone and can delay/ avoid the need for surgery (Bennett *et al*. 1995; Saygi *et al.* 2005; Thomson *et al.* 2013). The use of USG-CSI improves accuracy of the procedure, with potential advantages including less procedural and post-procedural pain, fewer adverse effects and fewer repeat injections; although effect on efficacy remains unclear (Mahadevan *et al.* 2016; Murakami, 2015; Santiago *et al.* 2018). In addition, CSI is the only non-surgical invasive treatment that has shown efficacy in a RCT (Thomson *et al.* 2013). Whilst alternative non-surgical invasive treatments show promise, further higher quality research is needed to establish conclusions on their efficacy. It is possible however, that ultrasound may have a wider role in future treatment as a means of guiding these procedures. Most importantly though, no treatment should be undertaken without informed consent and shared decision making, a discussion which requires

additional risk/benefit analysis due to the 2019-nCoV pandemic. However, this is only one of many safety considerations with careful thought also given to medication used, needle approach and risk of adverse effects.

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Appendix 1 –Anatomical Illustration of MN

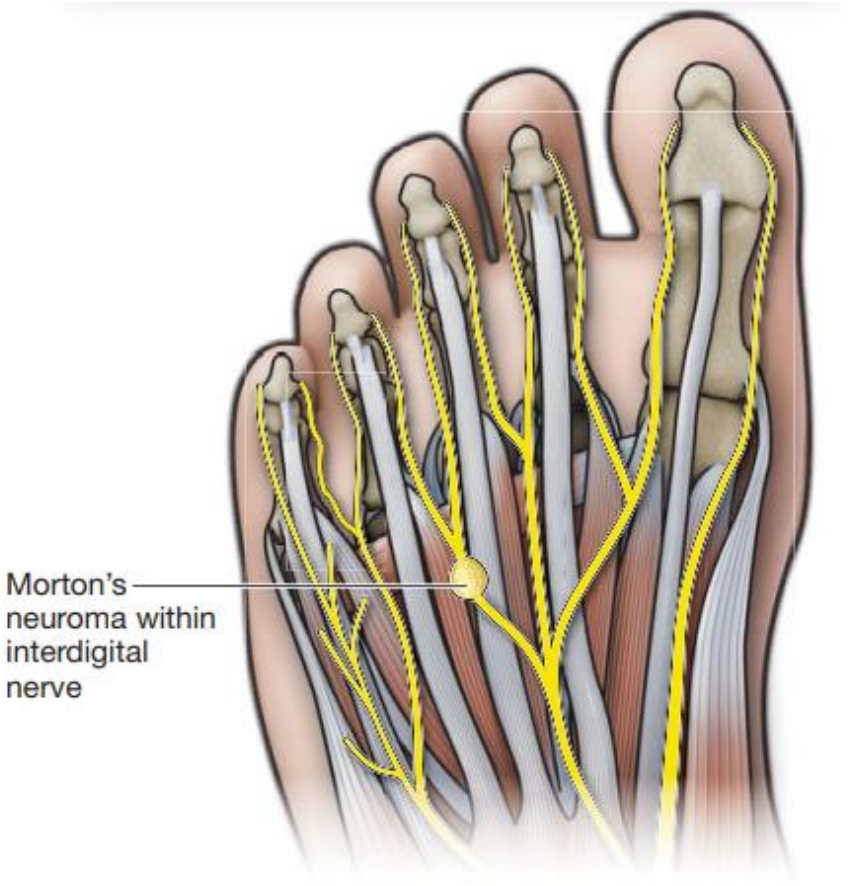
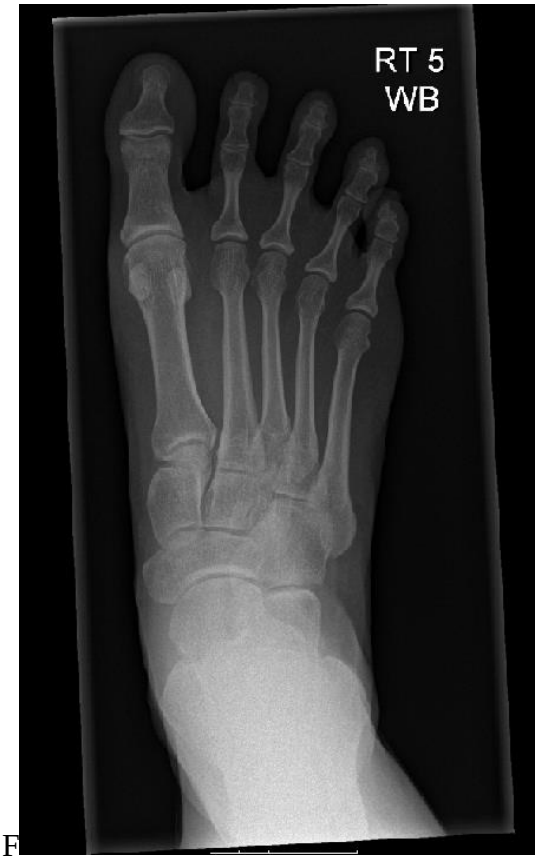


Figure 1: Illustration demonstrating location of a MN, between the metatarsophalangeal joints, in this case the 3rd and 4th (3rd webspace), as this is the most commonly affected (Goldin and Shiple, 2014, p. 413, fig. 102-1.

Appendix 2 – Plain Film Radiographs of Patient A's Right Foot



F

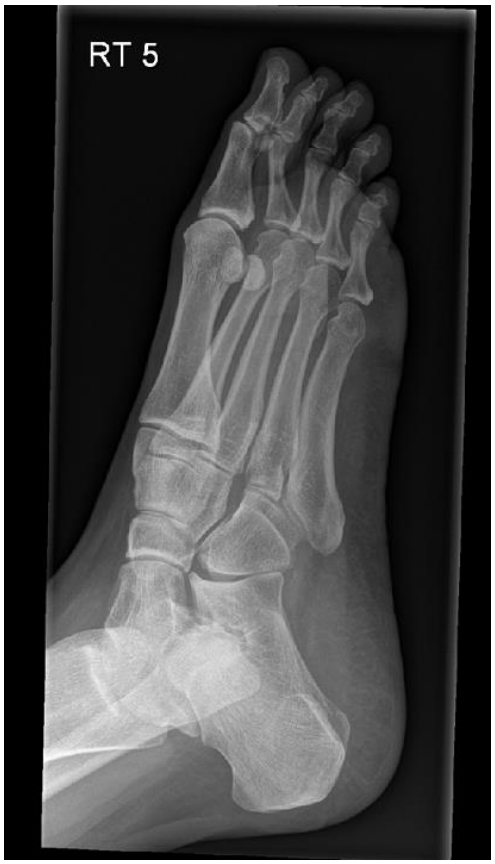


Figure 1: WB Dorsoplantar Projection

Figure 2: Dorsoplantar Oblique Projection

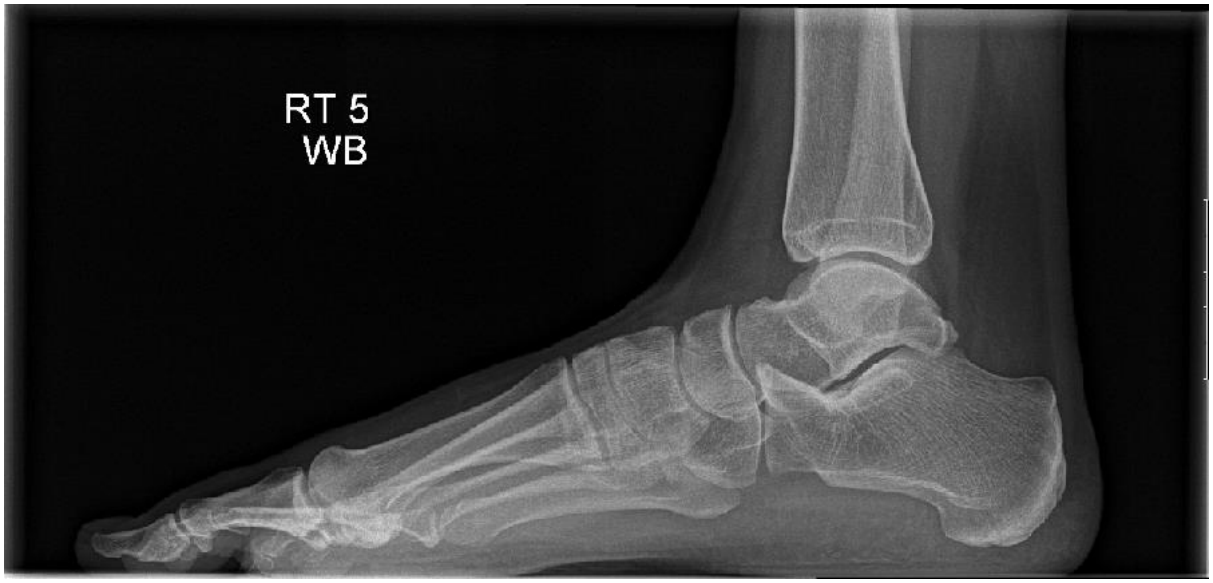


Figure 3: WB Lateral Ankle Projection

Appendix 3 – Diagnostic Ultrasound Images of Patient A's Right Forefoot

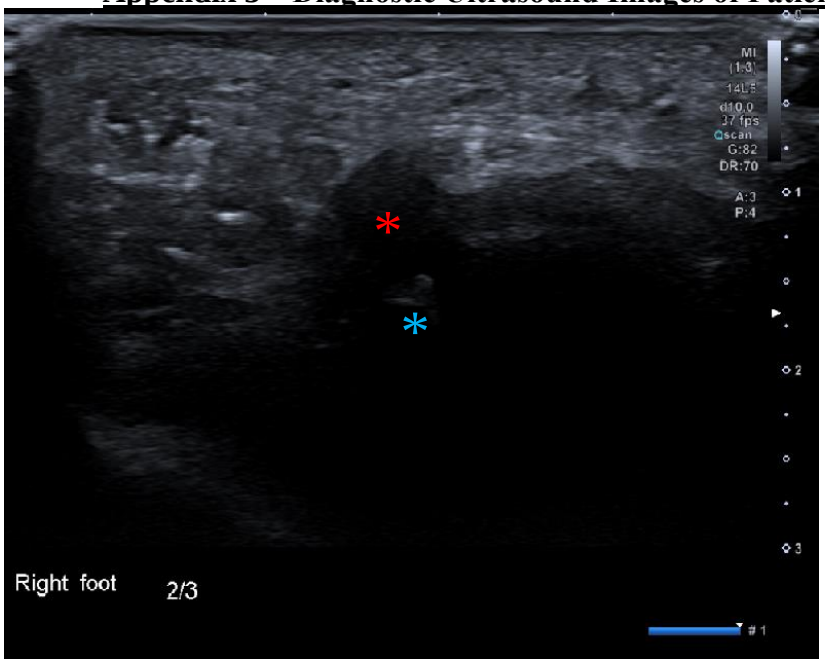


Figure 1: Longitudinal section of the 2nd webspace demonstrating a MN and associated intermetatarsal bursa. Image obtained with the transducer in a sagittal plane on the plantar aspect of the foot, parallel to the metatarsal heads. * indicates MN, * indicates associated intermetatarsal bursa.

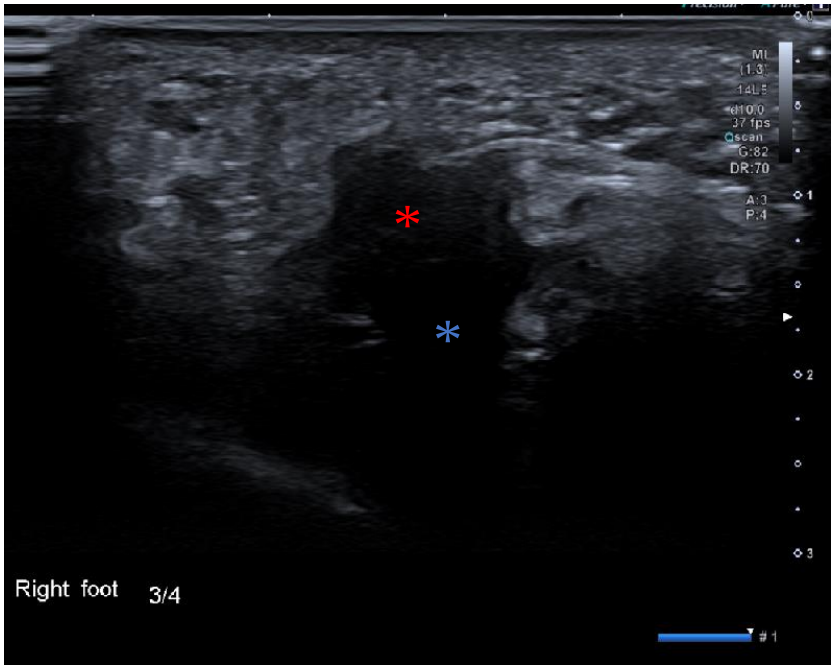


Figure 2: Longitudinal section of the 3rd webspace demonstrating a MN and associated intermetatarsal bursa. Image obtained with the transducer in a sagittal plane on the plantar aspect of the foot, parallel to the metatarsal heads. * indicates MN, * indicates associated intermetatarsal bursa.

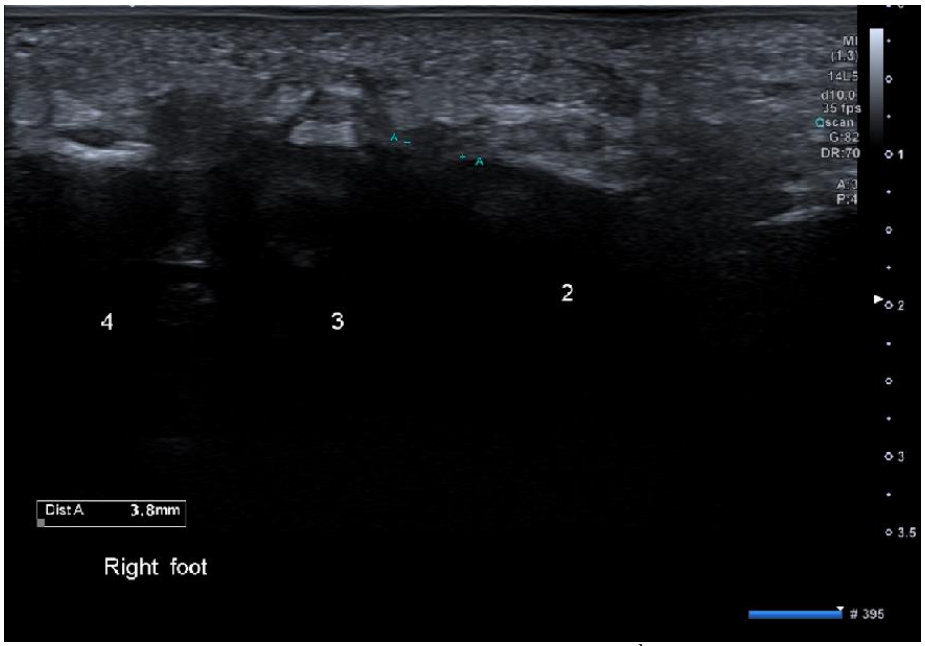


Figure 3: Transverse section of the MN in the 2nd webspace with callipers indicating outline and size. Image obtained with the transducer positioned on the plantar aspect of the foot, axial to the metatarsal heads, with lateral compression of the forefoot applied using the free hand to improve visualisation.

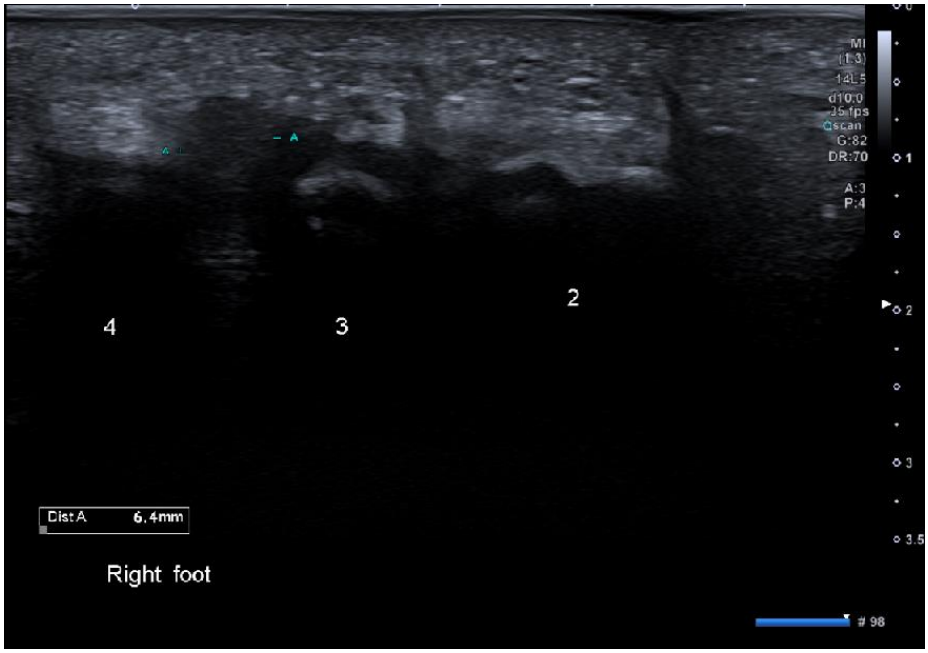


Figure 4: Transverse section of the MN in the 3rd webspace with callipers indicating outline and size. Image obtained with the transducer positioned on the plantar aspect of the foot, axial to the metatarsal heads, with lateral compression of the forefoot applied using the free hand to improve visualisation.

Appendix 4 – Local Protocol for CSI during 2019nCoV Pandemic

Current or deferred referral for Ultrasound (USS) +/- CSI

Patient invited for diagnostic USS

Patient defers, e.g. shielding

Appropriate IF:-
there is active synovitis, OR

severe symptoms and no remaining options (had trial of conservative management and continuing)

If CSI not appropriate.
STOP

OR Therapeutic arthrogram referral
OR USG-CSI without prior diagnostic

OR 14 days self-isolation

Therapeutic arthrogram/ USG-CSI
(same Radiologist as Diagnostic appt, vulnerable patients at start of list)

Normal post injection advice	**Post injection 5-10 days self-isolation suggested for vulnerable**

Appendix 5 - USG-CSI Technique

Figure 1: Example of dorsal, in-plane approach used for USG-CSI of both the 2nd and 3rd webspaces. The ultrasound probe was positioned in long axis on the plantar aspect of the right forefoot, in the appropriate webspace, at the level of the metatarsophalangeal joint. The 25 gauge orange needles were inserted through the dorsal aspect of the 2nd and 3rd webspaces in turn, a distal to proximal direction, towards the MN's, keeping the needle as close to parallel with the probe as possible ("in-plane") (Goldin and Shiple, 2014, p. 416, fig. 102-80).

Appendix 6 - Post USG-CSI Ultrasound Image

Figure 1: Post USG-CSI ultrasound image of 3rd webspace demonstrating the injectate fluid surrounding the MN. Red arrow indicates approximate needle approach (same approach used for the 2nd webspace).