Transient Regional Migratory Osteoporosis in the Ankle and Foot: A case series and literature review

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Transient regional migratory osteoporosis (TRMO) is a rare self-limited syndrome characterized by sudden onset of joint pain, followed by focal osteopenia after a few weeks, with spontaneous recovery. We report six cases of TRMO seen in foot and ankle clinic together with a review of the literature.

Key words: Transient regional migratory osteoporosis, magnetic resonance imaging, reflex sympathetic dystrophy.

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Case 1

A 45 year-old male presented with right foot and ankle pain in January 2003. He had no recollection of injury to the foot. Clinically, the ankle was warm, swollen and painful to move. Laboratory studies revealed a normal white cell count and CRP level; the erythrocyte sedimentation rate was moderately elevated at 39. Plain radiographs revealed patchy osteoporosis about the ankle. The initial impression was that this was possibly due to a stress fracture and a Magnetic Resonance Imaging (MRI) scan was ordered on the basis of which a diagnosis of reflex sympathetic dystrophy (RSD) was made and he was referred to a pain clinic. He failed to respond to two guanethidine blocks. Several months later, he developed severe pain in his left hip.

Clinically, movements at the left hip were painfully restricted. Plain radiographs of the left hip showed evidence of patchy osteoporosis. MR scans of the hips showed an oedema-like pattern in the bone of the left upper femur. A bone scan showed marked increased uptake of isotope at the right ankle and throughout the right tarsal region but excluding the right calcaneum.

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There was also marked increased uptake of isotope within the left femoral head and less marked increased uptake throughout the left femoral neck and trochanteric region. A biopsy of the right ankle to exclude sinister pathology showed evidence of mild chronic synovitis with no evidence of granuloma formation. At this stage a diagnosis of tuberculosis was considered despite the negative culture and the absence of granuloma formation on biopsy. He was commenced on anti-TB treatment as he had a Heaf test which was strongly positive. A few months later he started to get discomfort in the right knee. At this stage, the right foot and the left hip had improved considerably. Clinically, the right knee was warm and swollen with restricted range of motion. He was mobilizing with crutches at this stage. MR imaging of the right knee performed in September 2003 showed a prominent oedema like pattern in the distal femur, particularly affecting the lateral femoral condyle. There was a small joint effusion, but the appearances did not suggest synovial hypertrophy or soft tissue swelling. Review of all the plain radiographs, the bone and MR scans finally led to the diagnosis of TRMO. In December 2003 he complained of discomfort in the left knee. MR images of the left knee were however normal. Repeat MR images of the ankle showed that it had virtually returned to normal and that there was no lasting damage to the ankle joint.

Case 2

A 53 year-old white female was referred with left ankle and hind foot pain from October 2002. The symptoms were of insidious onset. Plain radiographs of the ankle and hind foot at that stage were unremarkable. (Fig 1) Her symptoms continued to deteriorate over the next 6 months. Physical examination revealed some discoloration of the foot and ankle. There was a small joint effusion about the ankle. Weight bearing was uncomfortable and ankle movements were painful. Laboratory findings were unremarkable. Plain radiographs of the foot and ankle revealed gross osteopenia. (Fig 2) Bone scintigraphy confirmed marked increase in uptake about the foot and ankle (Fig 3). MR imaging of the ankle revealed minor effusion in the ankle and subtalar joints. T1-weighted images revealed low subarticular signals and low signal in the talus and anterior part of the os calcis. The patchy bone marrow signals were reported to be consistent with a diagnosis of RSD or TRMO. Over the next six months the ankle pain settled with physiotherapy, partial weight-bearing and oral analgesia. Eighteen months after the initial presentation, she started developing moderate pain in the ipsilateral knee. Physical examination revealed minor effusion. Plain radiographs and laboratory findings were unremarkable. MR imaging of the knee revealed joint effusion and a diffuse bone marrow oedema pattern consistent with TRMO.
Figure 3 Radioisotope bone scan showing increased uptake in the talar dome and head, and midfoot.

Case 3

A 60 year-old male was referred to our unit with a diagnosis of septic arthritis of the left ankle. He gave a 7-month history of pain and swelling of the ankle. The symptoms were of insidious onset. Physical examination revealed a diffuse swelling about the ankle particularly and increased local warmth. Plain radiographs and laboratory investigations were within normal limits. MR imaging revealed marrow oedema in the talar head, the talar dome and within the anterior aspect of the tibial plafond. (Fig 4) There was soft tissue swelling with effusions in the ankle, subtalar and talonavicular joints. The symptoms resolved considerably over the next six months, although he had residual ankle discomfort.

Figure 4 A curvilinear area of increased signal (arrowed) parallels the articular surface of the talar dome on a coronal T2-weighted STIR image. Note the oedema in the talar body with increased fluid in the sinus tarsi with surrounding soft-tissue oedema.

Case 4

A 34 year-old male was referred with a six-month non-specific hind/midfoot pain following a twisting injury. He was found to be hyperalgesic, with no other signs of chronic regional pain syndrome (CRPS). Physical examination revealed diffuse swelling about the foot and ankle with some tenderness. Laboratory findings were unremarkable. Bone scintigraphy demonstrated increased uptake in the hind/midfoot as well as the left hip. Plain radiographs of the hip revealed an almost healed transcervical femoral neck fracture. MR imaging again showed extensive high signal changes in the hind foot. By this stage he had developed a stress fracture of the 4th metatarsal. The symptoms resolved slowly over 12 months with symptomatic treatment. He is now back at work.

Case 5

A 60 year-old white male was referred for a second opinion. He had been diagnosed with osteomyelitis of the talus. He gave a 9 month history of right hind foot pain. The symptoms were of insidious onset. Plain radiographs revealed generalized osteopenia, with an apparent lytic lesion in the talar neck. Laboratory findings were normal. Bone scintigraphy revealed increased uptake in the hind/midfoot. Labeled white cell scan was negative. MR imaging demonstrated extensive high signal changes and a diagnosis of regional migratory osteoporosis was made by the radiologist. The symptoms resolved slowly. He returned a year later with similar symptoms on the left foot. MR imaging at that stage showed complete resolution on the right. The symptoms eventually settled on both sides at six month follow-up with supportive treatment.

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Table 1 Comparison of the cases.

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age</th>
<th>History of injury</th>
<th>Initial diagnosis</th>
<th>Positive imaging findings</th>
<th>Results of inflammatory serum markers</th>
<th>Management</th>
<th>Time to recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>45y</td>
<td>No</td>
<td>Stress fracture, RSD</td>
<td>Xray, bone scan, MR</td>
<td>Mildly raised ESR</td>
<td>Conservative</td>
<td>10-15 months</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>53y</td>
<td>No</td>
<td>RSD, TRMO</td>
<td>Xray, bone scan, MR</td>
<td>Normal limits</td>
<td>Conservative</td>
<td>18 months</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>60y</td>
<td>No</td>
<td>Septic arthritis</td>
<td>MR</td>
<td>Normal limits</td>
<td>Conservative</td>
<td>6-9 months</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>34y</td>
<td>Yes</td>
<td>RSD</td>
<td>Xray, bone scan, MR</td>
<td>Normal limits</td>
<td>Conservative</td>
<td>12 months</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>60y</td>
<td>No</td>
<td>Osteomyelitis</td>
<td>Xray, MR</td>
<td>Normal limits</td>
<td>Conservative</td>
<td>24 months</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>41y</td>
<td>Yes</td>
<td>Avascular necrosis</td>
<td>Xray, bone scan, MR</td>
<td>Normal limits</td>
<td>Conservative</td>
<td>&gt;18 months</td>
</tr>
</tbody>
</table>

Case 6

A 41 year-old white female was referred for a second opinion on a diagnosis of avascular necrosis of the talus. She gave a 6 month history of generalized hind foot pain following a minor twisting injury. Physical examination and laboratory findings were unremarkable. Plain radiographs revealed osteopenia affecting the calcaneus and the talus. Bone scintigraphy revealed increased uptake in the talus, os calcis and the cuboid. MR imaging demonstrated extensive high signal changes suggestive of TRMO. She was treated symptomatically. At follow-up 12 months from our initial review she continues to have pain and increased sensitivity. (Table 1)

Discussion

Transient Osteoporosis (TO) is a rare self-limited syndrome characterized by sudden onset of joint pain, followed by focal osteopenia after few weeks, with spontaneous recovery. This was first described by Revault, et al., as a distinct clinical syndrome in French literature and was thought to be due to neurotropic changes, possibly secondary to minor trauma. The first report of this disorder in the English literature was by Curtis and Kincaid in 1959. They described three women who developed hip pain and osteopenia in the last trimester of pregnancy. The symptoms and radiographic changes disappeared spontaneously after several months. Although this was the original description of the phenomenon, none of our cases included pregnant women. By 1968, Lequesne coined the term – transient osteoporosis of the hip. Subsequent reports described similar clinical and radiographic patterns in other locations such as the knee and ankle.
TO may present one episode affecting only one joint or recurrent episodes that may affect multiple joints. Multiple joints may be involved in as much as 40% of patients and when this occurs the condition is referred to as transient regional migratory osteoporosis or TRMO.6

The aetiology of TRMO remains unclear. Curtis and Kincaid 2 proposed a neurogenic compression hypothesis suggesting that TOH in pregnant women may be determined by a mechanical compression of the obturator nerve. Rosen7, Arinstein8, Bray, et al.,9 suggested an impairment of venous return and local hyperaemia. Lequesne3 advocated that TO is caused by non-traumatic form of RSD, a theory supported by Doury.10 However, TO lacks the vascular and cutaneous changes characteristic of RSD. McCord, et al.,11 reported electromyography (EMG) abnormalities in TRMO, which they associated with the commonly seen muscular atrophies. McCord documented denervation patterns coincident in location and time with TRMO attacks. However other reports12,13 have suggested normal EMG and nerve conduction studies. One of the likely explanations for the pathogenesis of TO is perhaps that proposed by Frost14 and others.15,16 He stated that under noxious tissue stimuli, the ordinary biological processes, including blood flow, cell metabolism and turnover and also tissue modelling and remodelling, might be greatly accelerated, called the Regional Acceleratory Phenomenon (RAP). In his opinion a prolonged or exaggerated RAP in which a large number of bone turnover foci are activated, is the cause of TO. It has been hypothesized that symptoms may be related to bone marrow edema demonstrated at MRI and to a transitory regional arterial hyperflow observed at the early scintigraphic analysis.7,17 Bone tissue microdamage is the most frequent noxious stimulus that provokes RAP and bone tissue micro fracture is the main consequence. Several elements support this hypothesis. The repeatedly observed histological findings in patients with TO showing mild inflammatory changes and osteoporosis, associated with an elevated bone turnover with increased bone resorption and reactive bone formation18,19,20 are a good description of ongoing TRMO.

The timing of the episodes of TO, with an abrupt onset, an acute phase of one or two months, a steady – state period and a final partial and delayed recovery resembles the course of RAP.21 The intense focal osteoporosis and the following partial bone resorption which occurs even in the absence of loading is in accordance with the temporarily increased remodeling space described in the case of RAP.14,21

In TRMO, diagnosis is challenging. In virtually all cases the pain gradually improves and the clinical and radiographic findings resolve in 6-12 months.22 Although instances lasting eighteen to twenty-four months have been noted, our cases illustrate two examples of TRMO lasting for 24 months and more. This has not been widely reported previously in the literature. Repeat attacks at adjacent sites are characteristic. Several regions may be affected sequentially or the episodes may overlap.23,24 Usually all the attacks occur within 1-3 years but episodes occurring 11 – 13 years apart have been reported.8 Occasionally the phenomenon of RMO can recur within the same joint. There are few reports of RMO affecting different regions of the same joint and in the knee there are reports of TRMO migrating from the lateral femoral condyle to the medial and vice versa.4,25

The condition is distinguished by its episodic migratory nature. No permanent joint damage results from these acute recurrent episodes.

A painful joint with localized demineralization is suspicious of an inflammatory or neoplastic disease process. The differential diagnosis must include inflammatory arthritis as rheumatoid arthritis, infectious arthritis, osteoarthritis and crystal arthropathy.8,16,26 Other diagnosis to be considered includes primary bone tumors, osteomyelitis, tuberculous arthritis, multiple myeloma and metabolic bone disease. Synovial chondromatosis of the hip may mimic TO, but the course is long and irreversible. The history, normal laboratory findings and characteristic imaging usually differentiates TRMO. It is often difficult to differentiate from RSD in the early stages. In RSD, there is often a history of trauma or surgery.

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Cardinal symptoms are diffuse burning pain in the affected region, sensory disturbances of hypo or hyperaesthesia, trophic changes of discoloration, swelling and thickening, alteration in the skin temperature, autonomic regulation and motor disturbance. In the early stages avascular necrosis (AVN) should be ruled out. A long self-limited course, recurrence in other joints and the imaging characteristics help to differentiate AVN from TO. In the early stages the two conditions can be difficult to differentiate, but typically in AVN the pain is present at rest, the limp and antalgic gait are late findings and the functional disability is proportional to the pain level. A prolonged and reversible clinical course, normal laboratory findings, negative cultures and characteristic radiographic findings should lead one to consider RMO after excluding the more common rheumatic diseases and especially infectious arthritis. Vigilance is however required since two authors report cases resembling RMO prior to recognizing tuberculous infection. Case 1 illustrates an example where a diagnosis of TB was made before bone biopsies returned as negative for the infection. Tannenbaum, et al., described that in two of their four cases the initial diagnosis was that of septic arthritis even though the patients were afebrile and constitutionally well. Three of our cases had an initial diagnosis with an infective cause for their symptoms (osteomyelitis, TB, septic arthritis) despite the patients being systemically well on presentation. Apart from slightly elevated ESR counts, the laboratory tests came back as normal in each case.

Diagnostic imaging can be challenging also. Little information is available on the quantitative assessment of systemic or local osteoporosis. Recently a precise assessment of the bone mass by quantitative methods has been reported at the lumbar spine in a case of TRMO and also at both hips and the lumbar spine in a case of transient osteoporosis of the hip in pregnancy (TOH). In both cases the appraisal of bone loss in sites other than the symptomatic site aroused suspicion of a wider systemic involvement, which has been suggested in recent literature. Due to the rarity of the disease and the unpredictability of the episodes, there is only a limited amount of quantitative data about the degree and extent of bone loss. Trevisan, et al., using bone densitometry assessment noted that in four of five acute episodes the decrease in bone mass was greater than 30%. In one episode the decrease in bone mineral content at the involved site was > 75%. With such an extreme decrease in bone mass it is not surprising that fractures have been reported as a complication of acute phase of bone loss in TRMO. Case 4 illustrates an example of fracture of the hip (transcervical) occurring as a complication of TRMO. During the acute episode, the bone loss may not be confined to the affected joint but involved the whole lower limb to a greater degree at sites with a predominantly trabecular pattern. The clinical subsidence of the acute phase was accompanied by an increase in the bone mineral density. Case 6 illustrates a patient initially diagnosed with AVN of the talus, then later diagnosed with TRMO on the basis of MRI findings. X-ray appearance of AVN rarely shows diffuse osteopenia and the classical appearance of AVN is a mottled radiolucent area surrounded by an area of sclerosis. Plain radiographs are not useful in the early stages as changes in TO may appear only four to eight weeks after the onset. The increased uptake is usually less intense in AVN and more limited to the femoral head. MR imaging is a useful tool to differentiate between the two conditions. In AVN a focal non-homogenous, segmental and well-demarcated lesion in the anterosuperior subchondral region of the femoral head is the classical appearance. T2-weighted images may demonstrate the double line sign pathognomonic of AVN.

Treatment modalities are difficult to assess because the condition is self-limiting. Several reports note favourable results with NSAIDs and glucocorticoids. However several authors found that with glucocorticoids there was no relief of joint pain or alteration of the disease course. Clinical and radiographic improvement has been noted with calcitonin, although not universally.
Antituberculous drugs have failed\textsuperscript{40}, as have attempts at sympathetic blockade.\textsuperscript{37,40} Several authors have recommended a conservative, symptomatic approach with protection against full weight bearing. Traumatic fractures of the femoral neck and stress fractures have been infrequently reported in patients with TO.\textsuperscript{41,42} Some authors have advocated the use of intravenous pamidronate treatment as potential therapy for the condition.\textsuperscript{35,43} We advocate the approach of mild analgesia with protected weight bearing and physiotherapy designed to enhance muscle function and prevent immobilization. In all our cases symptoms improved only with supportive measures.

**Conclusion**

Case descriptions of TRMO are not always consistent as TRMO is a rare phenomenon and a diagnosis usually made only after other inflammatory and neoplastic causes have been excluded. We highlight the potential problems in establishing the diagnosis due to its unclear etiology and clinical presentation. By presenting a large series of this condition affecting the foot and ankle, we propose that early bone scan and MR imaging should be considered in patients presenting with vague arthralgic symptoms in the presence of a lack of other constitutional symptoms.

**References**

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