

DIFFUSE LARGE B CELL LYMPHOMA OF THE FOOT IN A PATIENT WITH RHEUMATOID ARTHRITIS

Anna Litwic,¹ Madeleine Sampson,² Vipul Foria,³ *Elaine Dennison¹

1. MRC Lifecourse Epidemiology Unit, Rheumatology Department, University Hospital Southampton NHS Foundation Trust, Southampton, UK

2. Radiology Department, University Hospital Southampton NHS Foundation Trust, Southampton, UK

3. Histopathology Department, University Hospital Southampton NHS Foundation Trust, Southampton, UK

*Correspondence to emd@mrc.soton.ac.uk

Disclosure: The authors have declared no conflicts of interest.

Received: 16.03.15 **Accepted:** 27.04.15

Citation: EMJ Rheumatol. 2015;2[1]:84-88.

ABSTRACT

Patients with rheumatoid arthritis (RA) have an increased risk of developing malignant lymphomas, especially non-Hodgkin's lymphoma (NHL). However, primary lymphoma in a joint is rare. Here we report a case of a 68-year-old man with a background of RA who presented with a 1-year history of pain and swelling in his right ankle. Initial imaging results comprised of X-ray and magnetic resonance imaging were inconclusive. Ultrasound scan of the right foot revealed a very large vascular mass with grossly eroded tarsal bones, and a biopsy confirmed the diagnosis of diffuse large B cell lymphoma. Involvement of lymphoma of ankle/foot joints is very rare: to our knowledge this is the first case of a primary diffuse large B cell lymphoma of the joints of the mid and hind foot with underlying bone destruction in a patient with a background of RA. This case is important because it highlights that malignancy should be suspected in every patient with a background of RA and unusual characteristics before assuming a diagnosis of flare of RA. This is important because early diagnosis of NHL can contribute to improved outcome.

Keywords: Rheumatoid arthritis, lymphoma, joint, malignancy.

BACKGROUND

We present a case of a 68-year-old man with a background of longstanding seropositive rheumatoid arthritis (RA), who presented with a 1-year history of pain and swelling in his right ankle. Plain radiographs were unremarkable and magnetic resonance imaging (MRI) findings were inconclusive. Ultrasound (US) scan of the right foot revealed a very large vascular mass with grossly eroded tarsal bones and a biopsy confirmed the diagnosis of diffuse large B cell lymphoma (DLBCL). RA has been associated with malignancy, including haematological disease, but joint-based lymphomas are very rarely reported. This case is important because it highlights that malignancy should be suspected in every patient with a background of RA and unusual characteristics before assuming a diagnosis of flare of RA. This is important because early diagnosis of

non-Hodgkin's lymphoma (NHL) can contribute to improved outcome.

CASE PRESENTATION

A 68-year-old Caucasian male with a background of longstanding seropositive, erosive RA presented with a 2-month history of pain and swelling in his right ankle. He reported that there had been two preceding episodes of pain and swelling in the same joint during the previous year; both had lasted a few days and resolved spontaneously. There had been no history of trauma. He reported no problems with his other joints. He reported no symptoms suggestive of systemic disease; specifically, he denied fever, significant weight loss, and reported no history of longstanding night sweats. Past medical history was remarkable for asthma and osteoporosis. There was no personal history of hepatitis or tuberculosis, and no family history of

haematological malignancy. The patient was an ex-smoker who drank minimal alcohol socially. His RA was well controlled on methotrexate (MTX) 15 mg weekly and folic acid 5 mg weekly, and his other medications included an oral bisphosphonate, calcium and vitamin D supplements, and inhalers. He had required one course of oral steroids per year for exacerbations of asthma. He had seropositive (rheumatoid factor-positive) RA. Upon clinical examination, his right ankle was swollen and tender. There was no evidence of synovitis in any other peripheral joints. Lymphadenopathy, hepatomegaly, and splenomegaly were not found.

INVESTIGATIONS

The patient was initially investigated with blood tests and imaging in the form of radiographs and subsequent MRI. The blood test results, including full blood count and renal and liver profiles, were unremarkable apart from mildly elevated inflammatory markers (erythrocyte sedimentation rate: 22; C-reactive protein: 25). Plain radiographs of the right ankle and foot indicated a pathological process, with an initial suspicion of avascular necrosis of the navicular bone (Figure 1A). Further investigations of the right foot with MRI revealed bone marrow changes involving the talus, navicular, cuneiforms, cuboid, and the base of the fourth metatarsal with associated soft tissue component in the medial aspect of the mid/hind foot junction (Figure 1B). There was no effusion or evidence of erosions.

The differential diagnosis for these appearances was wide, including changes due to RA, infection, neuropathic joint, and tumour. Chest radiograph showed airway disease-associated changes only, with a stable appearance for 4 years. At this time, support of the foot with an Aircast® boot and follow-up was arranged, but no biopsy was undertaken. However, at follow-up 4 months later, the pain and swelling of the right foot had gradually worsened, warranting further investigations. Worryingly, new symptoms included weight loss, lethargy, and reduced appetite. There was no fever or night sweats. Upon examination there was a palpable right inguinal lymph node, but no hepatosplenomegaly, and the patient had developed a superficial ulcer on the right foot, a swab from which grew *Staphylococcus aureus* and which required treatment with antibiotics. In view of the clinical deterioration, US scan of the right

ankle/foot and US-guided biopsy was arranged. The US scan of the right foot revealed a very large vascular mass that extended all the way around the tendons and involved the ankle and hind-foot joints, with grossly eroded tarsal bones (Figure 1C and Figure 1D).

HISTOLOGY

The biopsy showed infiltration by pleomorphic lymphocytes that were positive for CD20 and CD79a, which confirmed a B cell lineage (Figure 1E, Figure 1F). The atypical cells were also positive for CD23, BCL-2, and BCL-6. The proliferation fraction, as assessed by Ki-67 staining, was high (40-50%) (Figure 1G). The morphological and immunohistochemical findings supported a diagnosis of DLBCL.

TREATMENT

Urgent hospital admission was arranged and the patient was referred to the oncology team. Blood tests revealed hypercalcaemia (Ca [adjusted]: 3.22 mmol/l) and new renal impairment (urea: 8.0 mmol/l; creatinine: 140 µmol/l). A staging computed tomography scan of the neck, chest, abdomen, and pelvis revealed a large (88 × 54 mm) right inguinal nodal mass and a 12 mm external iliac node. A bone-marrow biopsy showed no evidence of involvement with NHL. A course of chemotherapy was initiated and the patient began a regimen of cyclophosphamide, doxorubicin, vincristine, prednisolone, and rituximab; MTX was stopped at the time of chemotherapy. After completion of six cycles of chemotherapy with good partial response, the patient underwent radical consolidation radiotherapy. At follow-up, his ankle remained mildly swollen and painful, but the patient was well and in remission from his lymphoma.

DISCUSSION

RA has been associated with malignancy, including haematological disease, but joint-based lymphomas are very rarely reported, with only seven reports in the global case-report literature.¹⁻⁷ The musculoskeletal system is affected in up to 25% of patients diagnosed with NHL, although true articular signs such as joint swelling are less frequent and have been reported only rarely at the onset of NHL.⁸ DLBCL represents the most frequent type of lymphoma and accounts for

approximately 25% of all NHL in the developed world. In the whole of Europe, the incidence is approximately 4.92 cases per 100,000 persons per year. Similar to most other NHLs, there is a male predominance, but it is less pronounced than for other subtypes of haematological malignancy.

In a recent report from the Haematological Malignancy Research Network, the male/female DLBCL sex ratio was 1.13 (95% confidence interval [CI]: 1.01-1.26).⁹ Incidence increases with age and the median age at presentation is 70.4 years for patients as a whole.⁹

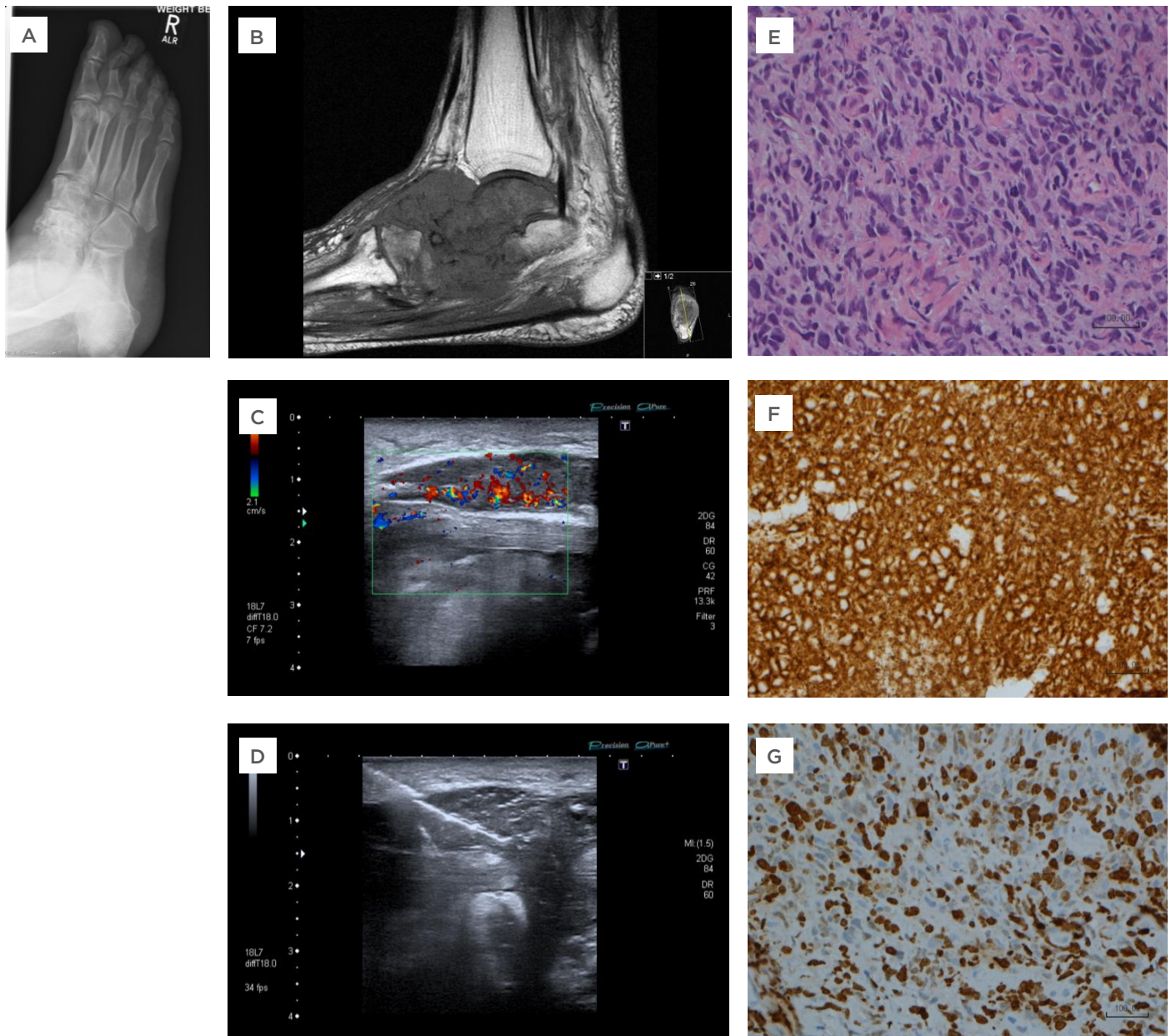


Figure 1: Radiology and histopathology images.

(A) Oblique radiograph of the right foot showing sclerosis and erosion of the talus, navicular, and medial cuneiform bones with soft tissue swelling. (B) Sagittally oriented image on 1.5 T Siemens Symphony magnetic resonance imaging scanner on T1 weighting showing the extent of the soft tissue mass invading the talus, navicular, calcaneum, and cuboid bones and crossing the sinus tarsi. (C and D) High-resolution ultrasound image with colour Doppler using a Toshiba 17 MHz linear probe showing extensive, highly vascular soft tissue enveloping the tibialis posterior tendon; and image demonstrating the ultrasound-guided needle biopsy passing into the soft tissue mass. (E) Foot-mass biopsy showing diffuse infiltrate of large cells with mitotic activity. (F) Tumour cells showing strong staining of CD20. (G) Ki-67 stain showing high proliferation fraction.

Patients with DLBCL typically present with a mass that has a rapid growth rate and which causes symptoms when it infiltrates tissues or obstructs organs (most commonly nodal enlargement in the neck or abdomen or, in the case of primary mediastinal large B cell lymphoma, the mediastinum) but it may present as a mass lesion anywhere in the body. However, DLBCL may present with only joint pain or swelling, even in the presence of normal haematological findings. If the primary presentation manifests as arthritis, the most common site of involvement is the knee.^{1,2,10-12} Other reported sites have been the shoulder, elbow, metacarpophalangeal and sternoclavicular joint, and as a polyarticular presentation, and these often mimic inflammatory arthritis.^{6-8,13-17} Several other reports have identified the involvement of lymphoma of the ankle/foot joints, but not specifically in patients with known RA.¹⁷⁻²² The only other reported case involving lymphoma of the ankle/foot joints in a patient with RA demonstrated a primary tumour of the synovium without bony involvement.²³

To the best of our knowledge this is the first case of a primary DLBCL of the joints of the mid and hind foot with underlying bone destruction in a patient with a background of RA. However, the association between RA and lymphoma has been well documented. Lymphoproliferative disorders occur with increased frequency in patients with RA: incidence and mortality rates due to leukaemia or lymphoma are approximately 2-fold higher than expected. The results of a meta-analysis suggest that RA patients have an approximately 2-fold increase in lymphoma risk compared with the general population (standardised incidence ratio: 2.08, 95% CI: 1.80-2.39).²⁴ Lymphoma incidence increases as active RA persists, and correlates with the severity of disease activity.²⁵ A recent review shows that aggressive B cell lymphomas, particularly the DLBCL as seen in the present case, are more strongly associated with autoimmune rheumatic diseases than more indolent lymphomas.²⁶ Although the presence of NHL is less strongly

associated with RA than with Sjögren's syndrome and systemic lupus erythematosus, a 28-fold increased risk of NHL in patients with RA has been reported in severe destructive RA.²⁶

The main pathophysiological mechanisms of NHL are B cell hyperactivity and chronic inflammation.²⁶ In RA, the rheumatic disease itself appears to have a larger effect on the development of lymphoma than its therapy.²⁵ However, there remains uncertainty as to the causative factor of RA-associated lymphoma. It remains possible that drugs used to treat the disease through alteration of immune function and immunological surveillance may contribute to the risk. This concern has been applied to medications such as azathioprine, MTX, and anti-tumour necrosis factor alpha therapy.²⁷ In addition, discontinuation of MTX has been followed by disappearance of lymphoma in some patients.²⁷ In a meta-analysis investigating the risk of lymphoma development in autoimmune diseases, the subgroup analyses for the studies using cytotoxic drugs, including MTX, show that the random effects standardised incidence rate for NHL in RA was 5.1 (95% CI: 0.9-28.6).²⁸

The case of our patient represents a diagnostic challenge not only because of the rarity of the condition but also due to the presentation of the disease without symptoms usually associated with a malignant condition. The presence of a monoarthritis in a patient with known RA can suggest several alternative diagnoses, such as monoarticular flare of RA, pigmented villonodular synovitis, and synovial chondromatosis. Moreover, several non-rheumatological diseases can present with musculoskeletal involvement coexisting with RA, especially infection and malignancy. Both need to be excluded early in the course of the disease in order to avoid errors in diagnosis, inappropriate treatment, and possible serious complications. In conclusion, malignancy must be suspected in every patient with a history of RA and unusual characteristics before assuming a diagnosis of flare of RA.

REFERENCES

1. Visser J et al. Non-Hodgkin's lymphoma of the synovium discovered in total knee arthroplasty: a case report. *BMC Res Notes*. 2012;5:449.
2. Chim CS et al. EBV-associated synovial lymphoma in a chronically inflamed joint in rheumatoid arthritis receiving prolonged methotrexate treatment. *Haematologica*. 2006;91(8 Suppl):ECR31.
3. George DA et al. Large B cell lymphoma of the subtalar and talonavicular joint synovium. *BMJ Case Rep*. 2013;doi:10.1136/bcr-2012-007683.
4. De Angelis F et al. Atypical presentation of anaplastic large T-cell

- lymphoma mimicking an articular relapse of rheumatoid arthritis in a patient treated with etanercept. A case report and literature review. *Leuk Res.* 2012;36(9):e199-201.
5. Gordon MJ et al. Lymphoma of the hands in a patient with rheumatoid arthritis: case report. *J Hand Surg Am.* 2014;39(4):728-31.
6. Kennedy JW et al. An unusual presentation of methotrexate-induced B-cell lymphoma of the metacarpophalangeal joint: a case report and literature review. *J Hand Surg Am.* 2006;31(7):1193-6.
7. Arredondo J et al. Non-Hodgkin's lymphoma as an unexpected diagnosis in a shoulder arthroplasty. *J Arthroplasty.* 1999;14(1):108-11.
8. Dorfman HD et al. Non-Hodgkin's lymphoma of the synovium simulating rheumatoid arthritis. *Arthritis Rheum.* 1987;30(2):155-61.
9. Smith A et al. Incidence of haematological malignancy by subtype: a report from the Haematological Malignancy Research Network. *Br J Cancer.* 2011;105(11):1684-92.
10. Jamieson KA et al. Synovial presentation of non-Hodgkin's lymphoma. *Br J Radiol.* 1998;71(849):980-2.
11. Khan SY, Hutchinson DG. Primary synovial non-Hodgkin's lymphoma in association with ankylosing spondylitis. *Rheumatology (Oxford).* 2004;43(3):391.
12. Haase KK et al. Non-Hodgkin's lymphoma presenting as knee monoarthritis with a popliteal cyst. *J Rheumatol.* 1990;17(9):1252-4.
13. Jawa A et al. Primary intra-articular non-Hodgkin's lymphoma of the elbow. A case report. *J Bone Joint Surg Am.* 2006;88(12):2730-4.
14. Neri R et al. Case report. Elbow monoarthritis revealing B cell non-Hodgkin's lymphoma. *Clin Rheumatol.* 2013;32 Suppl 1:S111-4.
15. Adunsky A et al. Malignant lymphoma presenting as sternoclavicular joint arthritis. *Arthritis Rheum.* 1980;23(11):1330-1.
16. Birlik M et al. Articular, B-cell, non-Hodgkin's lymphoma mimicking rheumatoid arthritis: synovial involvement in a small hand joint. *Rheum Int.* 2004;24(3):169-72.
17. Menon N, Madhok R. Symmetrical polyarthritis is not always rheumatoid. *Ann Rheum Dis.* 1994;53(10):631-2.
18. Gokdemir G et al. Primary cutaneous diffuse large B-cell lymphoma of the leg, with an atypical clinical picture of verrucous plaques associated with stasis dermatitis. *Clin Exp Dermatol.* 2010;35(3):e87-9.
19. Ramanujam CL et al. Cutaneous non-Hodgkin's lymphoma of the foot: a rare case report. *J Foot Ankle Surg.* 2009;48(5):581-4.
20. Singh DP et al. Primary lymphoma of the bones of the foot: management of two cases. *Foot Ankle.* 1991;11(5):314-6.
21. Nickisch F et al. Primary malignant non-Hodgkin lymphoma of the talus: a case report. *Foot Ankle Int.* 2005;26(7):568-71.
22. Mendeszoon MJ, Wire KR. Diffuse large B-cell lymphoma of the ankle: a case study of surgical intervention and outcome. *J Am Podiatr Med Assoc.* 2010;100(6):505-10.
23. Blume P et al. Case report and review of primary bone diffuse large B-cell lymphoma involving the calcaneus. *J Foot Ankle Surg.* 2013;52(5):666-72.
24. Smitten AL et al. Meta-analysis of the incidence of malignancy in adult patients with rheumatoid arthritis. *Arthritis Res Ther.* 2008;10(2):R45.
25. Baecklund E et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. *Arthritis Rheum.* 2006;54(3):692-701.
26. Dias C, Isenberg DA. Susceptibility of patients with rheumatic diseases to B-cell non-Hodgkin lymphoma. *Nat Rev Rheumatol.* 2011;7(6):360-8.
27. Wolfe F, Michaud K. Lymphoma in rheumatoid arthritis: the effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients. *Arthritis Rheum.* 2004;50(6):1740-51.
28. Zintzaras E et al. The risk of lymphoma development in autoimmune diseases: a meta-analysis. *Arch Intern Med.* 2005;165(20):2337-44 .