Case report

Ankylosing spondylitis presenting with enthesitis at an uncommon site and fever of unknown origin

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SUMMARY

A 58-year-old man presented with a 2-month history of arthralgia and bilateral temporal region pain, and a 1-month history of fever. He had had refractory neck pain since his 20s. Reduced cervical and lumbar mobility was observed. Radiographs of cervical and thoracic vertebrae disclosed syndesmophytes. Pelvic radiographs showed sclerosis in the right sacroiliac joint and ankylosis in the left sacroiliac joint. MRI with contrast enhancement showed enthesitis in the upper extremities and enhancement in the bilateral temporal muscle, which indicated enthesitis of temporal muscle. He was diagnosed with ankylosing spondylitis based on the limitation in mobility of the lumbar spine and radiographic findings. To the best of our knowledge, this is the first report describing enthesitis of the temporal muscle. This case highlights that ankylosing spondylitis can be accompanied with enthesitis at the temporal muscle and fever of unknown origin at the initial presentation.

BACKGROUND

Ankylosing spondylitis (AS) is one form of axial spondyloarthritis (SpA) which is a chronic inflammatory disorder characterised by inflammation of the vertebral and sacroiliac joints.[1] The major clinical feature of AS is chronic back pain, and AS can involve the cervical, thoracic, lumbar spine and pelvis, and/or extra-axial joints such as shoulders, wrists, hip joints, knees, ankles or sternoclaviculars.[2] Enthesitis is thought to be a clinical hallmark of SpA. It occurs frequently at the lower extremities compared with the upper extremities, and enthesitis in the heel is the most frequent.[3] To the best of our knowledge, temporal muscle enthesitis has not been previously described in the literature.

AS can present miscellaneous extra-articular symptoms including uveitis or inflammatory bowel disease.[4] On the other hand, fever is rarely associated with AS, and AS presenting as fever of unknown origin (FUO) would be atypical.[5–7]

Herein, we present a case of AS with enthesitis at the temporal muscle and fever of unknown origin.

CASE PRESENTATION

A 58-year-old Japanese man was referred to our department complaining of a 2-month history of arthralgia of the extremities accompanied with malaise, morning stiffness, bilateral temporal region pain and a 1-month history of fever exceeding 38°C. Before admission to our department, he was administered several antibiotics (amoxicillin, cefcapene pivoxil, ceftriaxone, meropenem and vancomycin), but his symptoms did not improve. He received insulin therapy for type 2 diabetes mellitus. He had chronic hepatitis C infection and had been treated with ledipasvir/sofosbuvir 2 years before, maintaining a sustained antiviral response. He denied myalgia, jaw claudication, visual disturbance or a preceding episode of urethritis or diarrhoea. He did report that he had had refractory neck pain since his 20s and impaired range of motion in the neck and lumbar spine. His occupation was housing renovation.

On admission, he was not in acute distress. Physical examination revealed body temperature 38.2°C, blood pressure 128/74 mmHg and pulse rate 80 per minute. No skin rash was observed systemically. Tenderness of the scalp to touch was not noted. However, the temporal muscles were tender bilaterally. Tenderness in the biceps branchii tendons and triceps branchii tendons was noted, but no swelling or local heat was observed. Hip joints and the Achilles tendon were not involved. No arthritis was noted. The mobility of his cervical and lumbar spine was extremely limited, and he could hardly rotate his head. Occiput-to-wall test was positive, and Schober test showed reduced lumbar mobility (10 cm in standing position changing to only 11 cm with lumbar flexion).

INVESTIGATIONS

Laboratory values were as follows: leucocyte count 4000/μL, haemoglobin 10.2 g/dL, platelet count 274000/μL, aspartate aminotransferase 42 U/L, alanine aminotransferase 44 U/L, creatinine 0.74 mg/dL, C-reactive protein 7.56 mg/dL and ferritin 632 ng/mL. Erythrocyte sedimentation ratio was 122 mm/hour. Rheumatoid factor, anti-cyclic citrullinated peptide antibody, antinuclear antibodies, myeloperoxidase-antineutrophil cytoplasmic antibody and proteinase 3-antineutrophil cytoplasmic antibody were all negative. The human leucocyte antigens (HLA) A24, B37 and B60 were positive. Urinalysis showed no glucose, protein, blood or leucocytes. Three sets of blood culture collected during the first week of admission yielded no organisms. Echocardiography showed no vegetation.

Chest radiograph showed abnormal ossification bridges connecting successive thoracic vertebral bodies (figure 1A). Radiographs of cervical and thoracic vertebrae in lateral view demonstrated a syndesmophyte at C4/5 (figure 1B) and multiple

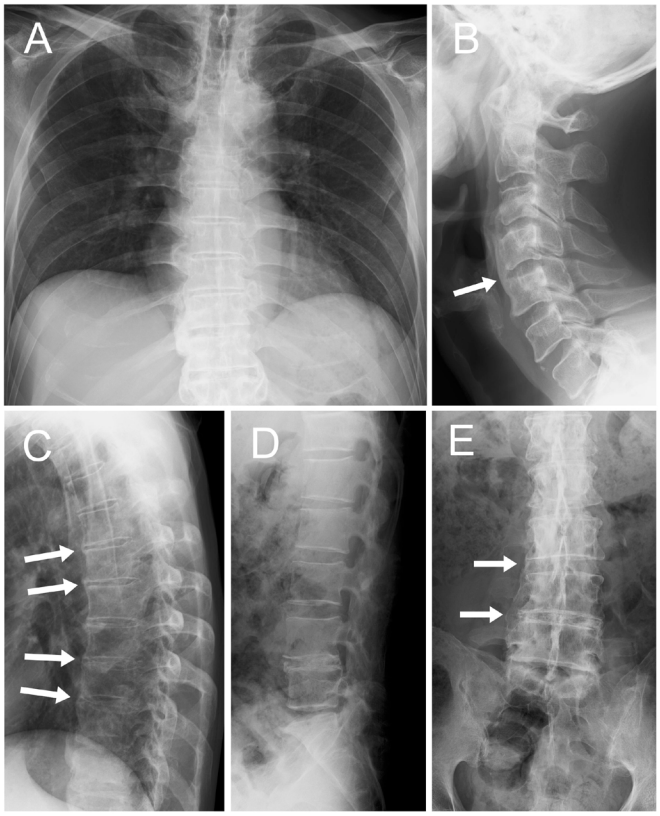

Figure 1 Chest radiograph showed ossification bridges connecting successive thoracic vertebral bodies (A). Radiographs of cervical and thoracic vertebrae in lateral view disclosed a syndesmophyte at C4/C5 (B, arrow) and multiple syndesmophytes in thoracic vertebrae (C, arrows). There were no syndesmophytes in lateral view of lumbar radiograph (D), but some syndesmophytes were observed in the anteroposterior view (E, arrows).

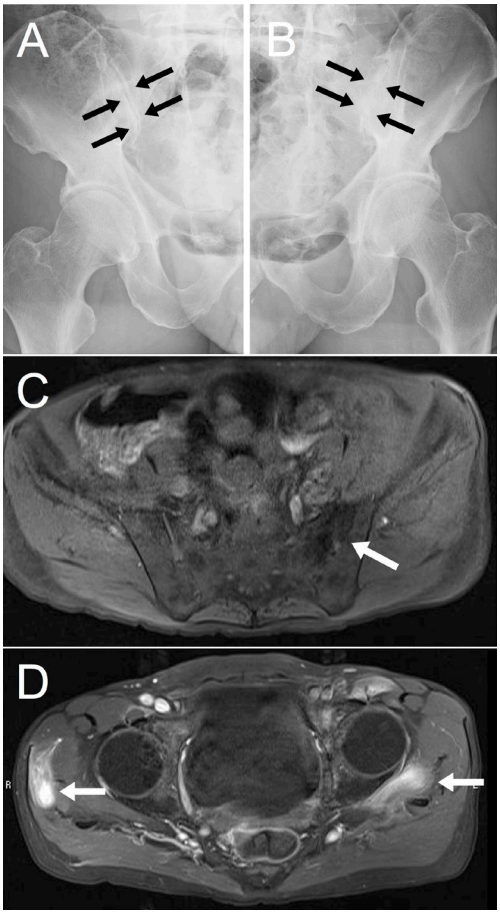

Figure 2 Radiographs of the sacroiliac joint in oblique view showed sclerosis in the right sacroiliac joint (A, arrows) and ankylosis in the left sacroiliac joint (B, arrows). On pelvic MRI, T1-weighted fat-suppressed images revealed hypointense lesions in the left sacroiliac joint (C, arrow), which were interpreted as ankyloses. T1-weighted fat-suppressed images with gadolinium contrast showed abnormal enhancement in the tendons of the right gluteus medius and left gluteus minimus (D, arrows).

syndesmophytes in thoracic vertebrae (figure 1C) respectively. There were no obvious signs of syndesmophyte in the lateral view of lumbar radiograph (figure 1D), but some syndesmophytes were observed in the anteroposterior view (figure 1E). Oblique views of a radiograph of the sacroiliac joint showed sclerosis in the right sacroiliac joint (figure 2A) and ankylosis in the left sacroiliac joint (figure 2B). On pelvic MRI, there was no abnormal fluid accumulation in the sacroiliac joint or pelvic bone oedema. However, T1-weighted fat-suppressed images revealed hypointense lesions in the left sacroiliac joint (figure 2C), which was interpreted as ankylosis by our radiologist, and T1-weighted fat-suppressed images with gadolinium contrast showed abnormal enhancement in the tendons of the right gluteus medius and left gluteus minimus (figure 2D). MRI showed enthesitis of the bilateral biceps branchii muscles (figure 3A, B and C), triceps branchii muscles, deltoid muscles and subscapularis muscles. On further examination of temporal region pain, the head MRI disclosed bilateral contrast enhancement at his temporal region, which indicates the enthesitis of temporal muscles (figure 4A and B), and no abnormality in the temporal artery.

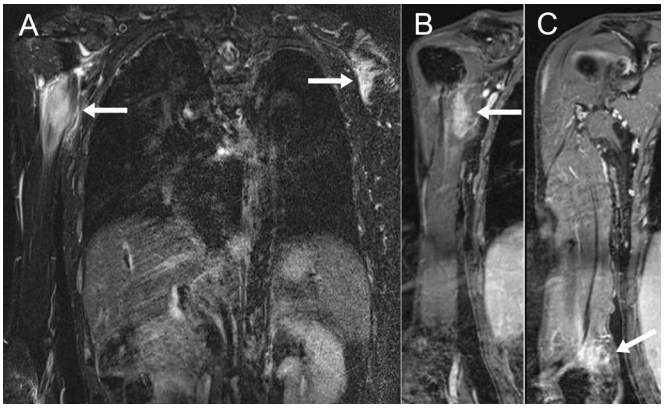

Figure 3 MRI showed enthesitis of the bilateral biceps branchii muscles (A, B and C, arrows).

DIFFERENTIAL DIAGNOSIS

Arthralgia of the upper extremities with fever and temporal region pain suggested the differential diagnosis of polymyalgia rheumatica with giant cell arteritis (GCA). To rule out GCA, a biopsy of the bilateral temporal artery was performed, but the results were negative for vasculitis.

His findings fulfilled modified New York criteria, limitation in mobility of lumbar spine plus radiographic observations. He was

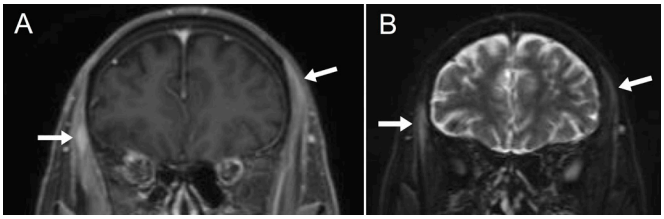

Figure 4 Head MRI disclosed bilateral contrast enhancement at the temporal region, which indicates enthesitis of the temporal muscles (A and B, arrows).

diagnosed with AS associated with enthesitis in temporal muscle and fever.

TREATMENT

The effect of non-steroidal anti-inflammatory drugs was insufficient. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was 6. He was started on infliximab (5 mg/kg, every 6 weeks).

OUTCOME AND FOLLOW-UP

His fever declined, and enthesitis in the upper extremities and temporal muscle resolved. The limitation in mobility of his cervical and lumbar spine partially resolved. Two-year follow-up after the diagnosis, he is now being treated by his primary physician.

DISCUSSION

Enthesitis is an inflammation at the enthesis, which includes several anatomical structures such as attachment of tendon, ligament, fascia and joint capsule to the bone. Enthesitis, especially when manifested as extra-articular enthesitis like inflammation at a tendon is thought to be a clinical hallmark of SpA,[3] and also to be an indicator of disease activity, and was adopted in the fourth question of the BASDAI.[8]

Clinical assessment of enthesitis is important, although physical examination lacks both sensitivity and specificity as compared with imaging techniques. In recent years, MRI and ultrasound, especially power Doppler ultrasound, are playing an increasingly important role in diagnostic imaging.[9] The typical MRI findings of SpA enthesitis are characterised by perientheseal bone marrow oedema and inflammatory changes of soft tissue outside the joint capsule.

Enthesitis tends to occur in the lower extremities in patients with AS.[3] On the other hand, enthesitis in the upper limbs is infrequent. It is unclear why enthesitis is more common in the lower limbs than in the upper limbs, though the length, anatomy and higher mechanical force at work at the lower extremities have been surmised to be underlying reasons.[9] In this case, the MRI showed enthesitis in the upper limbs. Moreover, tenderness of the bilateral temporal regions together with contrast enhancement of the temporal muscles on MRI indicated the existence of temporal muscle enthesitis. In 1987, Mander *et al* proposed the Mander enthesis index (MEI) to investigate enthesitis in AS patients.[10] Although the MEI lists 66 entheses in the whole body, the temporal regions are not included in this list. To the best of our knowledge, this is the first report describing enthesitis of temporal muscle.

Genetic factor has an important role in the diagnosis of SpA. In this case, HLA-A24, B37 and B60 were positive. Although HLA-B27 gene has the strongest association with AS, there are some reports about the interaction between HLA-B60 and AS.[11 12] In 1996, Brown *et al* reported that the phenotype frequency of HLA-B60 in HLA-B27 negative AS patients was significantly higher than in HLA-B27 negative controls (19% vs 6.2%, respectively).[11] Also, Wei *et al* compared the HLA class I gene in Taiwanese Chinese HLA-B27 negative AS patients with in HLA-B27 negative donors.[12] Of HLA-B alleles, only B60 and B61 significantly increased susceptibility to AS (38.0%: HLA-B27 negative and B60 positive donors vs 63.4%: HLA-B27 negative and B60 positive AS patients). Although the phenotype frequency is different between the races and regions, HLA-B60 may have an independent susceptibility for AS. Our patient was negative for HLA-B27, but his genetic subtypes of HLA might be reasonable for the diagnosis of AS.

Patients with AS experience disease flares in their long life. Disease flare is divided into two types: localised flare and generalised flare, and fever, sweat or extreme pain is recognised as the symptoms of a generalised flare.[13]Generalised flare is rare, whereas localised flare is frequent. In this case, the patient presented fever over 38°C, malaise and severe enthesitis, all of which were consistent with generalised flare. AS is a chronic inflammatory disorder, and most patients experiencing generalised flare have already been diagnosed with AS. Thus, AS presenting as FUO is rare,[5–7] and difficult to diagnose for primary care physicians. In one prospective study on the causes of FUO in Turkey, only one of 87 (1.2%) patients with FUO was diagnosed with AS.[6] Byun *et al* reported 26 febrile SpA patients with fever as the initial manifestation comprising four AS patients, and the proportion of patients who consulted a rheumatologist first was significantly lower in febrile SpA patients than in afebrile SpA patients (7.7% vs 59.0%).[7] In this case, the clue to the diagnosis of AS was the patient's past history especially refractory neck pain and disturbed range of motion in his neck and lumbar spine since his 20s. In the diagnostic approach to FUO, attention to past history or symptoms is also very important.

Learning points

- Ankylosing spondylitis can present with enthesitis at an uncommon site, including temporal muscles.
- Enthesitis of upper extremities and temporal muscles can mimic the clinical manifestations of polymyalgia rheumatica with giant cell arteritis.
- The precise recognition of the affected structures is very important in the assessment of myalgia and arthralgia for the correct diagnosis.
- In the diagnostic approach to fever of unknown origin, attention should be paid to not only the present illness or signs, but also past history or symptoms.

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REFERENCES

1 Taurog JD, Chhabra A, Colbert RA. Ankylosing spondylitis and axial spondyloarthritis. *N Engl J Med* 2016;374:2563–74.
2 Sampaio-Barros PD, Bertolo MB, Kraemer MH, *et al*. Primary ankylosing spondylitis: patterns of disease in a Brazilian population of 147 patients. *J Rheumatol* 2001;28:560–5.

3 D'Agostino MA, Olivieri I. Enthesitis. *Best Pract Res Clin Rheumatol* 2006;20:473–86.
4 Stolwijk C, van Tubergen A, Castillo-Ortiz JD, *et al*. Prevalence of extra-articular manifestations in patients with ankylosing spondylitis: a systematic review and meta-analysis. *Ann Rheum Dis* 2015;74:65–73.
5 Kinsella P, Ebringer R, Hooker J, *et al*. Ankylosing spondylitis presenting as PUO. *Br Med J* 1978;2:19–20.
6 Saltoglu N, Tasova Y, Midikli D, *et al*. Fever of unknown origin in Turkey: evaluation of 87 cases during a nine-year-period of study. *J Infect* 2004;48:81–5.
7 Byun SJ, Bae WH, Jung SM, *et al*. Fever as an initial manifestation of spondyloarthritis: a retrospective study. *PLoS One* 2017;12:e0184323.
8 Garrett S, Jenkinson T, Kennedy LG, *et al*. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol* 1994;21:2286–91.
9 Kehl AS, Corr M, Weisman MH. Review: enthesitis: new insights into pathogenesis, diagnostic modalities, and treatment. *Arthritis Rheumatol* 2016;68:312–22.
10 Mander M, Simpson JM, McLellan A, *et al*. Studies with an enthesis index as a method of clinical assessment in ankylosing spondylitis. *Ann Rheum Dis* 1987;46:197–202.
11 Brown MA, Pile KD, Kennedy LG, *et al*. HLA class I associations of ankylosing spondylitis in the white population in the United Kingdom. *Ann Rheum Dis* 1996;55:268–70.
12 Wei JC, Tsai WC, Lin HS, *et al*. HLA-B60 and B61 are strongly associated with ankylosing spondylitis in HLA-B27-negative Taiwan Chinese patients. *Rheumatology* 2004;43:839–42.
13 Brophy S, Calin A. Definition of disease flare in ankylosing spondylitis: the patients' perspective. *J Rheumatol* 2002;29:954–8.