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Successful treatment of juvenile-onset HLA-B27-associated severe and refractory heel enthesitis with adalimumab documented by magnetic resonance imaging

Sir, Severe and therapy-resistant heel enthesitis is a challenging and complicated problem in the spondyloarthritis (SpA) field [1]. Recently D’Agostino et al. [2] have successfully treated with infliximab two patients suffering from long-standing refractory HLA-B27-associated heel enthesitis. They have documented the response to the therapy by using ultrasonography. We have treated a similar patient with adalimumab and documented the positive results by magnetic resonance imaging (MRI).

The patient was a 16-yr-old HLA-B27-positive boy. His disease began 9 months before with pain at insertion of the left Achilles tendon. Subsequently, there was the involvement of the insertion of the left plantar fascia. Pain did not respond to adequate trials (3 months at full doses) of nimesulide and diclofenac. The patient stopped all physical and sport activity due to the severity of his heel pain. His medical history did not reveal any other clinical manifestation of the HLA-B27-associated disease.

Physical examination showed pain at the insertion of the left Achilles tendon and plantar fascia. The level of pain on a 100-point VAS was 83.

Pelvic and foot radiographs were normal. MRI of the left foot showed a slight swelling of the insertion of the left Achilles tendon and plantar fascia and a distension of the retrocalcaneal bursa by fluid collection together with a diffuse bone oedema of the left calcaneus (Fig. 1A). Laboratory evaluation showed a C-reactive protein (CRP) level of 29.9 mg/l (normal <5).

Considering the severity of the situation, we decided to treat the patient with adalimumab at a dose of 40 mg fortnightly after obtaining his parents’ written, informed consent. The day after the first subcutaneous injection, pain in the heel disappeared completely. CRP normalized after 15 days. MRI obtained 25 days (Fig. 1B) and 50 days (Fig. 1C) after the beginning of therapy showed a marked progressive improvement of the oedema. Two months after the start of therapy we had to decide whether to give more importance to the clinical situation (the patient had no pain) or the persistence of the MRI findings. We decided to continue with adalimumab until a marked improvement of the MRI findings. This happened after 5 months from the beginning of the therapy (Fig. 1D), when we stopped the drug. The disease remained in remission in the following 15 months. New MRIs obtained after 3 (Fig. 1E) and 8 months (Fig. 1F) from the end of adalimumab therapy documented a further improvement of the bone oedema.

Our patient suffered from undifferentiated SpA (uSpA) starting and evolving with isolated severe and refractory peripheral enthesitis [3]. Amor et al. [1] consider enthesitis refractory to therapy only when it persisted for more than 2 yrs despite conventional treatment including NSAIDs, steroid injections, sulphasalazine, methotrexate and radiotherapy. Braun and Sieper [4] have recently suggested that six months is a sufficient period to try every conventional treatment. In the past, we would have treated the present patient with steroid injections. We did not because MRI showed a diffuse oedema of all the calcaneus that should probably have not responded to steroids injected only near the insertion of the plantar fascia and into the retrocalcaneal bursa. After the failure of the local therapy, we would have treated him with sulphasalazine and, in case of insufficient response, we would have added methotrexate. These therapies need time to be effective, and we did not want our patient to continue to have pain for another 3 or 4 months. On the other hand, the efficacy of these
drugs on peripheral enthesitis relies only on studies of a limited
numbers of cases. So, we decided start anti-tumour necrosis
factor-α (TNFα) therapy, which has been shown to ameliorate
the bone oedema due to enthesitis, which is visible on MRI both in
the spine as well as in the limbs [5,6]. Recently D’Agostino et al. [2]
have successfully treated two patients with B27-associated
refractory heel enthesitis with infliximab. They have monitored
the regression of enthesitis by using ultrasonography coupled with
power Doppler ultrasound. This examination assesses entheseal
inflammation by measuring increased blood flow due to
neovascularization. We have treated our patient with adalimum-
bab, which a recent open study has demonstrated to be useful
in SpA [7]. We have monitored the regression of enthesitis using
MRI. If we had used power Doppler ultrasound, we would have
missed the diffuse bone oedema of the calcaneus. Waiting for
a marked improvement of the bone oedema was crucial
for interrupting the therapy without having the recurrence of
the clinical symptoms of enthesitis. The role of MRI and
ultrasound in monitoring the response to therapy of enthesitis
should be the objective of future studies. Probably both should be
performed.

In conclusion, our experience suggests that a short course of
anti-TNFα therapy can cure severe and resistant HLA-B27-
associated enthesitis and that MRI can be useful in deciding when
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FIG. 1. Sagittal STIR (short tau inversion recovery) T2-weighted sequences of the left Achilles tendon. (A) Imaging obtained the day before
the beginning of adalimumab therapy, showing a diffuse oedema of the calcaneus (arrowheads) together with swelling of Achilles
tendon (open arrow) and distension of the retrocalcaneal bursa by fluid collection (solid arrow). The following images were obtained
1 month (B), two months (C), 5 months (D), 8 months (E) and 12 months (F) after the beginning of therapy, which was interrupted at the
fifth month, after observing the (D) imaging. A progressive improvement of MRI findings is evident. After 12 months (F), only a milder
distension of the retrocalcaneal bursa is present.
were not detectable.

positive whereas anti-nuclear and anti-dsDNA antibody levels and methotrexate. Rheumatoid factor was always strongly 

patients treated with the fully human anti-TNF-

etanercept [1, 2]. This complication of clinically manifest SLE 

Th1-driven inflammatory response in this patient.

adalimumab and provides data that indicate the involvement of a 

tumour necrosis factor-

described for rheumatoid arthritis (RA) patients treated with the 

clinical response. Gradually the clinical response waned; the effect 

(followed by 'Th2' cell responses [IL-4, IL-10] with persistent antibody levels [4]. Based on serum protein levels of 

patients with SLE, in particular, those who suffer from active 

disease, several studies have suggested the involvement of 

cytokines that induce Th1 responses [migration inhibitory factor 

(MIF), IL-12, IL-18] as well as Th1 activity itself (IFNγ, IL-2, 

IL-17) [5–7]. Along with the presence of this type of immune 

response, Th2 cell activity (IL-4) as well as IL-10 levels have been 

found to be increased and were found to correlate with markers 

of inflammation such as anti-dsDNA [6, 7].

To understand the anti-TNF-α-induced SLE immunopathol-

ogy, serum cytokine levels were assessed in retrospect which could 

explain the development of this clinical finding. Interestingly, 

associated with a rise in ESR, adalimumab treatment strongly 

increased cytokines indicative of Th1 activity in contrast to 

‘anti-inflammatory’ and Th2-associated cytokines, which were not significantly changed (Fig. 1C and D). In RA patients, the increase of systemic Th1 activity upon anti-TNF-α treatment can occur due to re-entry of inflammatory cells from the site of 

inflammation (joints) into the circulation or due to repression of 

TNF-α-inhibited Th1 activity [8, 9]. However, this is usually 

associated with decreased inflammation as indicated by decreased C-reactive protein (CRP) and ESR. In the presented patient, the development of skin inflammation and increased antibody levels could explain a rise in markers of inflammation such as ESR.

In contrast to the induction of autoantibodies, the clinical 

presentation of (biopsy-confirmed) active SLE upon adalimumab 

therapy is rarely, if at all, reported. As far as we know, this is the first article describing the biopsy-confirmed development of 

clinical SLE upon adalimumab treatment following infliximab 

therapy. Since infliximab treatment had already induced high 

anti-dsDNA levels, adalimumab treatment seems to have boosted the infliximab-induced mechanisms that were accompanied by pro-inflammatory activity. Finally, this may develop into the 

clinical presentation of SLE. Therefore caution may have to be 

taken when anti-dsDNA antibodies are present at the start of 

conversion therapy.

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