RHEUMATOLOGY

Letter to the Editor (Case Report)

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Synovitis acne pustulosis hyperostosis osteitis (SAPHO) – paradoxical reactions and different responses to tumour necrosis factor inhibitors

Rheumatology key message

- Certolizumab pegol may be efficacious for patients with SAPHO refractory to other TNF inhibitors.

Sir,Synovitis acne pustulosis hyperostosis osteitis (SAPHO) is a syndrome within the spectrum of auto-inflammatory disease with osteoarticular and cutaneous inflammation. Manifestations can include anterior chest wall pain, axial arthropathy, acne and pustulosis. Treatment options include TNF inhibitors (TNFi).

A 29-year-old woman presented with a pruritic palmar rash consisting of scaly plaques and pustules (Fig. 1A). Her history was notable for 6 years of severe, episodic pain and stiffness in the neck, low back and knees with unremarkable radiographic evaluation and a lack of benefit from conservative measures. Her family history was negative for inflammatory conditions. She was started on high potency topical steroids, but after 9 months the rash worsened to involving the plantar surface. She was diagnosed with palmoplantar pustular psoriasis and started on MTX, which she discontinued due to intolerance.

She subsequently started adalimumab with an initial response that was followed by the eruption of new plaques on the scalp and extremities, with worsening palmar plaques and erosive plantar pustulosis (Fig. 1B). She was switched to etanercept. After 1 month of therapy, she noted worsening arthralgia, along with new plaques. She was evaluated by rheumatology for suspected PsA. She did not have synovitis or dactylitis on examination, and sacroiliac radiographs were normal. HLA B-27 and RF were negative. Etanercept was discontinued with a plan to initiate ustekinumab, but the patient was unable to receive it for financial reasons.

She presented 2 weeks later with severe neck pain in the absence of constitutional, infectious or focal neurological symptoms. She was admitted for infectious evaluation after a cervical MRI showed C5–6 spondylodiscitis and C4–7 anterior bridging syndesmophytes. She was afebrile with normal vital signs. Musculoskeletal examination was notable for tenderness at multiple costochondral junctions, lateral ribs and restricted motion of the cervical spine. CRP was elevated (44.2 mg/l), though ESR was normal (5 mm/h). Blood cultures were negative. Bone scintigraphy showed increased uptake at multiple costochondral junctions and the manubriosternal junction (Fig. 1C).

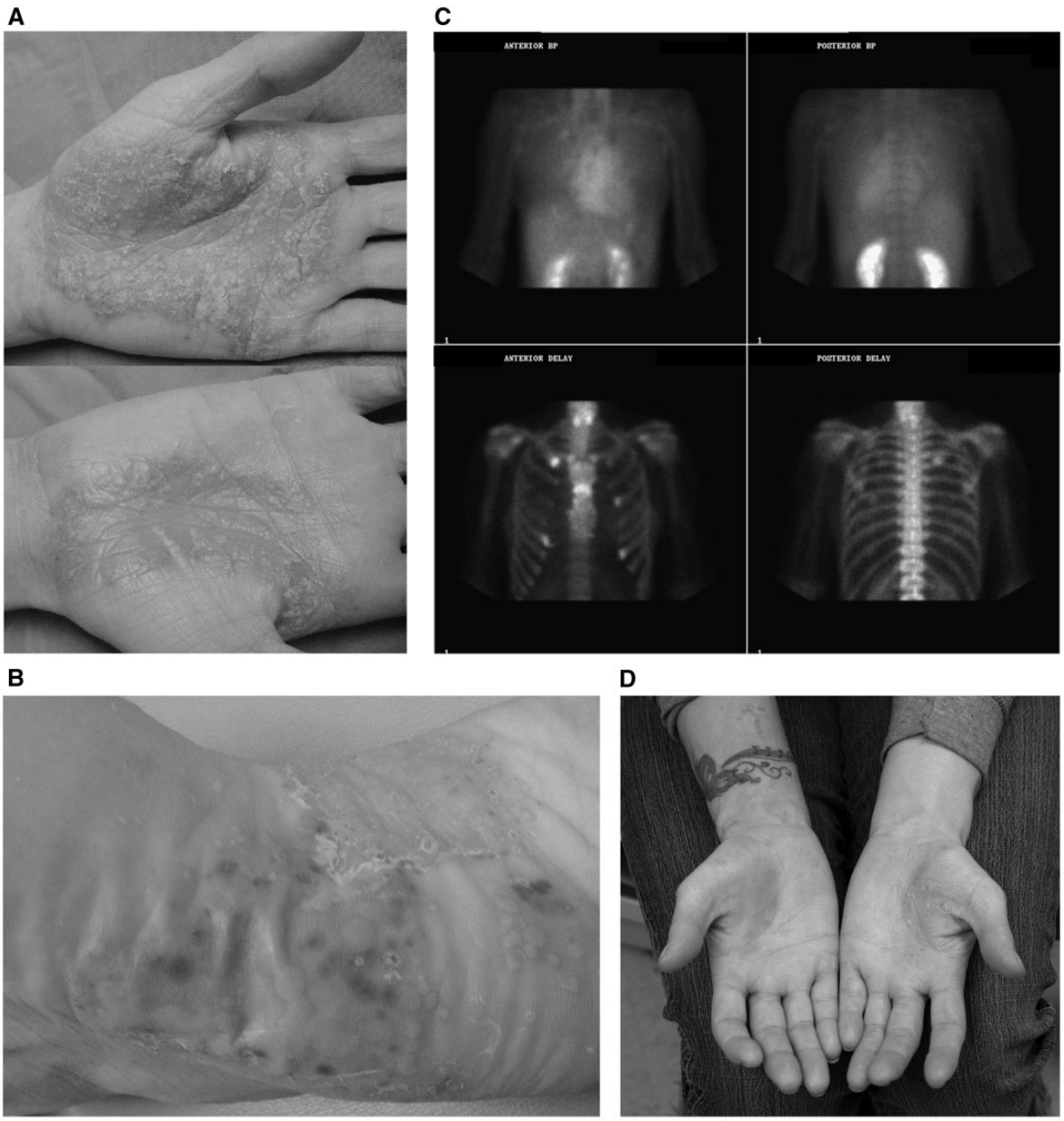
With findings of pustulosis, arthritis, hyperostosis and osteitis, the patient was diagnosed with SAPHO. Bone biopsy was deferred as there was decreased suspicion for septic arthritis or osteomyelitis. The patient was started on certolizumab pegol, with near complete resolution of skin lesions and neck and chest wall pain after 6 months of therapy. The CRP also normalized. However, treatment was interrupted for 2 years when the patient self-discontinued certolizumab pegol. Upon return to care, she presented with recurrent palmar lesions and arthralgia. She resumed certolizumab pegol with a similar good response after 6 months of therapy (Fig. 1D).

SAPHO is a rare condition comprising a characteristic constellation of findings involving the bones, skin and joints. It may mimic other rheumatological and dermatological conditions as well as infectious aetiologies. While some bony changes may be identified on plain film, MRI and radionuclide bone scintigraphy can localize and differentiate active inflammatory lesions. Bone biopsy of lytic lesions may be undertaken to exclude infectious or malignant aetiologies, although this procedure may be deferred if there is low suspicion for such alternative causes, as in our patient [1].

More frequently, TNFi have been utilized for SAPHO, particularly in individuals with disease refractory to more conservative measures such as NSAIDs, antibiotics, bisphosphonates and DMARDs. A case series of SAPHO patients treated with the TNFi infliximab, etanercept and adalimumab demonstrated complete remission of bone, skin and joint symptoms in the majority [2–4]. Some individuals, like our patient after starting adalimumab, developed or had paradoxical worsening of psoriatic skin lesions after starting TNFi [2, 5]. Additionally, our patient had persistent musculoskeletal and cutaneous symptoms on etanercept, but may have had benefit for cervical spine inflammation since she noticed worsened neck pain upon discontinuation of etanercept.

Kamata and Minota [6] described a patient with SAPHO whose disease responded to certolizumab pegol as a first line agent. We present the first description of a patient with inadequate response to multiple TNFi who had significant improvement on certolizumab pegol. The different molecular structures of the TNFi agents may account for the variation in response. Certolizumab pegol consists of polyethylene glycol bound to the Fab fragment of an anti-TNF mAb, whereas infliximab, adalimumab and golimumab are full monoclonal antibodies. Etanercept is a fusion protein of the Fc region of IgG1 to the extracellular domain of type II TNF receptor that blocks activities of both TNF and lymphotoxin. A greater concentration of certolizumab pegol distributes into inflamed joints and for a

Fig. 1 Clinical manifestations of SAPHO in our patient



(**A**) Palmar pustulosis prior treatment with adalimumab. (**B**) Worsened plantar pustulosis following treatment with adalimumab. (**C**) Bone scintigraphy demonstrating increased uptake at multiple costochondral junctions and the manubriosternal junction following failed treatment with adalimumab and etanercept. (**D**) Resolution of recurrent palmar lesions after re-initiation of certolizumab pegol following a 2-year period of treatment discontinuation.

longer duration of exposure as compared with either infliximab or adalimumab. This, and the comparatively smaller size of the certolizumab pegol molecule, may also allow for better distribution to skin and bone lesions [7]. These factors may account for our patient's different responses to the biologic agents with which she was treated.

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