RS3PE syndrome: An overview

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ABSTRACT
More than ten years ago McCarty et al. described the RS3PE syndrome based on their study of 23 patients. Numerous additional cases have since been reported. In addition to the isolated or “pure” type which probably forms part of the clinical spectrum of polymyalgia rheumatica, inflammatory swelling with pitting edema of the dorsum of the hands and/or feet can be observed in different inflammatory rheumatic diseases as well as in haematological and solid malignancies.

In 1985 and 1990, McCarty and co-workers described the case histories of 23 elderly patients with a very abrupt onset of a bilateral symmetrical synovitis involving predominantly the wrists, the carpal joints, the small hand joints, and the flexor digitorum sheaths that was accompanied by a marked dorsal swelling of the hands with pitting edema (“boxing-glove” hand) (1, 2). In the authors’ opinion, flexor tenosynovitis appeared to play a major role in the development of the edema. Pitting edema over the feet and pretilial areas and the involvement of foot joints, ankles, knees, hips, elbows and shoulders were also observed in some patients. Persistent rheumatoid factor seronegativity and elevated acute phase reactants were the rule. The edema was very sensitive to small doses of corticosteroids and the disease remained in remission after such therapy. Flexion contractures of the fingers, wrists and elbows often persisted indefinitely. Fifty-nine percent of the patients showed the HLA-B7 antigen versus 24% in the general population. The authors called this syndrome RS3PE (remitting, seronegative, symmetrical synovitis with pitting edema). Other authors have since reported additional cases (3-18). There are also reports of rare cases with unilateral hand involvement (19-21).

The remitting course and the absence of radiographic joint destruction differentiate RS3PE syndrome from rheumatoid arthritis (RA). In McCarty’s opinion the predominance in men, the infrequent presence of proximal limb girdle symptoms, the peripheral pitting edema and the association with the B7 antigen differentiate RS3PE syndrome from polymyalgia rheumatica (PMR) (1, 2, 20). However, as discussed in another paper in this supplement (23), our studies suggest that isolated RS3PE syndrome and PMR form part of the clinical spectrum of the same disease (18, 24). Hand and foot magnetic resonance imaging (MRI) showed that extensor tenosynovitis was the responsible lesion for the edema in the subcutaneous and peritendinous soft tissue of the dorsum in both conditions equally (18).

Remitting swelling with pitting edema of the dorsum of the hands and feet may be observed in several inflammatory rheumatic diseases (10, 14, 15, 17, 25). Recent studies have described distal pitting edema in late onset undifferentiated spondyloarthropathy (26-29). In these patients the swelling was usually unilateral and more frequent in the lower limbs. The asymmetric involvement, especially of the lower limbs, the presence of constitutional symptoms, the presence of other manifestations of spondyloarthropathy and the association with the B27 antigen differentiate late onset spondyloarthropathy from pure RS3PE syndrome (26, 28, 29). Dubost and Savezie have suggested that late onset spondyloarthropathy begins predominantly with oligoarthritis occurring together with pitting edema of the extremities (27). However, we have suggested that pitting edema is not always present and that the clinical spectrum of undifferentiated spondyloarthropathy is as broad in the elderly as it is in children and young and middle aged adults (29). Only 10 of our 23 consecutive patients with late onset undifferentiated spondyloarthropathy had peripheral arthritis. Three of these had a large pitting edema of the lower limbs. Moreover, synovitis with pitting edema may also occur after the age of 50 in patients with longstanding ankylosing spondylitis (13, 30).
Distal extremity swelling with pitting edema is frequently observed in psoriatic arthritis (25, 31-34). Two different forms may occur (23, 31). The first, and more rare form is due to impaired lymphatic drainage which can be demonstrated by lymphoscintigraphy. The lymphedema predominantly involves the upper limbs in an asymmetric pattern, does not follow the course of the tenosynovial membranes and is resistant to therapy. MRI shows the honeycomb appearance of subcutaneous edema without any involvement of the extensor synovial sheaths. The second form is much more frequent. The pitting edema, which is due to tenosynovitis, follows the course of the tenosynovial sheaths and goes into remission after a short period of corticosteroid therapy. MRI shows subcutaneous and peritendinous edema together with fluid collection in the extensor synovial sheaths. No lymphatic obstruction is visible on lymphoscintigraphy.

We recently performed a case-control study on the frequency of inflammatory distal pitting edema in psoriatic arthritis (34). Edema was recorded in 39 (21%) out of 183 patients with psoriatic arthritis and in 18 (4.9%) out of 366 controls. The lower limbs were more frequently affected asymmetrically. In 8 (20%) patients, inflammatory pitting edema was the first isolated symptom of psoriatic arthritis and in another 8 it was associated to other features of psoriatic arthritis at diagnosis.

The inflammatory pitting edema of the dorsum of the hands has also recently been reported in RA (17, 35). Cases of a firm non-pitting lymphedema, similar to that of psoriatic arthritis, have also been described (36, 37). Lymphoscintigraphy as well as lymphography showed changes in lymphatic drainage. Like in psoriatic arthritis this lymphedema does not respond to second line therapy or corticosteroids.

We have also observed remitting distal extremity swelling in acute sarcoidosis (38). This was the first manifestation in 5 (29%) of 17 consecutive patients with acute sarcoidosis seen in a 2-year period. The swelling and the pitting edema were most prominent over the dorsum of both feet and ankles. In perimalleolar areas the edema followed the course of the tibialis and peroneal tendons. MRI confirmed in 3 patients that a severe tenosynovitis of the peroneal, tibialis, and extensor tendons was the main lesion responsible for the edema in the subcutaneous and peritendinous ankle and foot soft tissues.

Recently, we examined 9 consecutive patients with Whipple’s disease (39). Eight had rheumatologic manifestations related to the disease. Of these, 5 had episodes of swelling with pitting edema over the dorsum of the hands and/or feet. Other inflammatory diseases in which remitting distal extremity swelling with pitting edema has been observed include: chondrocalcinosis, amyloid arthropathy, dermatomyositis, polyarteritis nodosa, systemic lupus erythematosus, mixed connective tissue disease, Sjögren syndrome and systemic sclerosis (7, 10, 11, 17, 22).

In the last few years several articles have reported patients with distal extremity swelling with pitting edema as the first manifestation of haematological and solid malignancies (14, 17, 40-50). We have recently observed 3 additional cases of paraneoplastic RS3PE and reviewed the literature (48). To date 20 cases have been reported. In 12 patients distal extremity swelling with pitting edema was the initial symptom and preceded the diagnosis of malignancy with a median interval of 2 months. In 4 patients this feature was concomitant with the diagnosis of cancer and in 2 it was subsequent. In 15 (75%) out of 20 the malignancy was solid and adenocarcinoma was the most frequent histological type. The prostate, stomach and colon were the most frequently involved organs. In the remaining 5 patients the associated malignancy was a non-Hodgkin lymphoma or chronic lymphoid leukemia. In almost all patients (19/20) distal swelling with pitting edema involved both hands symmetrically, and in 7 cases both feet as well. One of our 3 patients had unilateral foot involvement. The inclusion of patients with only unilateral or lower extremity involvement may increase the frequency of this paraneoplastic condition. The cases published up to now met the clinical requirements of McCarty for RS3PE syndrome. The authors of these reports empirically selected only patients with symmetrical upper limb involvement, while the spectrum of this condition also includes patients with unilateral findings. Two clinical characteristics suggestive of paraneoplastic RS3PE syndrome are the presence of systemic signs and symptoms such as fever, anorexia, weight loss, and a poor response to corticosteroids. Systemic symptoms were observed in about 50% of patients in contrast to 9% of the patients with isolated RS3PE syndrome. Nineteen of the 20 patients with paraneoplastic RS3PE syndrome were treated with corticosteroids. Of these 11 (58%) responded incompletely or not at all. Of the 5 patients showing a complete response 3 were also receiving hormone therapy for prostatic cancer. Therefore, the efficacy of corticosteroid treatment should be questioned. The response to surgical resection of the tumor or to chemotherapy was good in 11/20 (55%) patients. In all but one distal swelling with pitting edema rapidly remitted, confirming the paraneoplastic nature of the condition. As observed in the other forms of RS3PE syndrome, hand MRI showed a predominant involvement of the tenosynovial extensor sheaths in one of our patients, suggesting that the tenosynovial membranes represent the anatomical target of the paraneoplastic process.

In conclusion, inflammatory swelling with pitting edema is not specific and may be observed in different inflammatory rheumatic diseases and in patients suffering from malignancy. Our studies suggest that subcutaneous edema of the dorsum is attributable to a local alteration of capillary permeability secondary to extensor tenosynovitis.

References
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