

## Paraneoplastic remitting seronegative symmetrical synovitis with pitting edema

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### ABSTRACT

*Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) is a syndrome that may be associated with many conditions, including malignancy. Three further cases of paraneoplastic RS3PE are described and the literature is reviewed. Paraneoplastic RS3PE is more frequently associated with solid tumors, in particular adenocarcinoma. The two clinical characteristics suggestive of paraneoplastic RS3PE are systemic sign/symptoms and the poor response to corticosteroid therapy.*

Rheumatologic disorders, together with hematologic and neuromuscular manifestations, are the most frequent paraneoplastic syndromes (1). Carcinoma polyarthritides and Jaccoud's type arthropathy are well-known entities and they may be the initial manifestations of breast and lung cancers (2, 3). In the last few years several reports have described patients with distal extremity swelling with pitting edema as the first manifestation of hematological and solid malignancies (4-14).

A similar clinical finding has been reported in different rheumatic conditions including remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome (12), polymyalgia rheumatica (13), late onset rheumatoid arthritis (14), ankylosing spondylitis (15), late onset spondylarthropathies

(16), psoriatic arthritis (17), acute sarcoidosis (18), chondrocalcinosis (19) and polyarteritis nodosa (20). In most of these conditions, magnetic resonance imaging (MRI) has confirmed the clinical impression of a predominant tenosynovial involvement (17, 18, 21-24).

*Patient 1.* A 46-year old man presented with a 2-month history of pain and swelling in the left ankle and foot. Impressive swelling with pitting edema of the ankle and dorsum of the left foot was present (Fig. 1). Edema was distributed along the course of the peroneal, tibialis and extensor tendons. The clinical examination was otherwise normal. Laboratory investigations revealed a erythrocyte sedimentation rate (ESR) of 48 mm/hr, C-reactive protein (CRP) 2.6 mg/dl, and normal results for the other routine assays.

Rheumatoid factor and fluorescent antinuclear antibodies (ANA) were negative. Radiographs of the chest and pelvis were normal and x-rays of the left ankle and foot demonstrated only soft tissue swelling. Left ankle ultrasonography showed tenosynovitis of the peroneal, tibialis and extensor tendons. The patient was treated with prednisone 12.5 mg/day and indomethacin 150 mg/day for two months with only a slight improvement of the edema. During this time he began to complain of constipation associated with 3 episodes of rectal bleeding. Colonoscopy and histologic findings demonstrated the presence of sigmoid adenocarcinoma. After surgical resection, the distal edema gradually subsided over the following 10 days.

*Patient 2.* A 59-year old man presented with pain and stiffness in the shoulder and pelvic girdles associated with synovitis of the right



**Fig. 1.** Soft tissue swelling of malleolar and perimalleolar areas with pitting edema of the dorsum of the left foot in patient 1.

knee and distal extremity swelling with pitting edema of both hands. His ESR was 84 mm/hr; the remainder of the laboratory investigations were normal. Rheumatoid factor and ANA were absent. Radiographs of the chest and pelvis and abdominal ultrasonography were normal. Hand MRI showed impressive soft tissue swelling and fluid accumulation along the tenosynovial sheaths of the extensor and flexor tendons (Fig. 2). The patient was given prednisone 12.5 mg/die without any response. The dosage was progressively increased to 25 mg/day with only a slight reduction of the proximal symptoms and distal edema. Prednisone therapy was continued and 2 months later the patient returned because of the sudden onset of lumbar pain. Radiographs demonstrated a fracture of the L5 vertebral body. His ESR was 91 mm/hr.

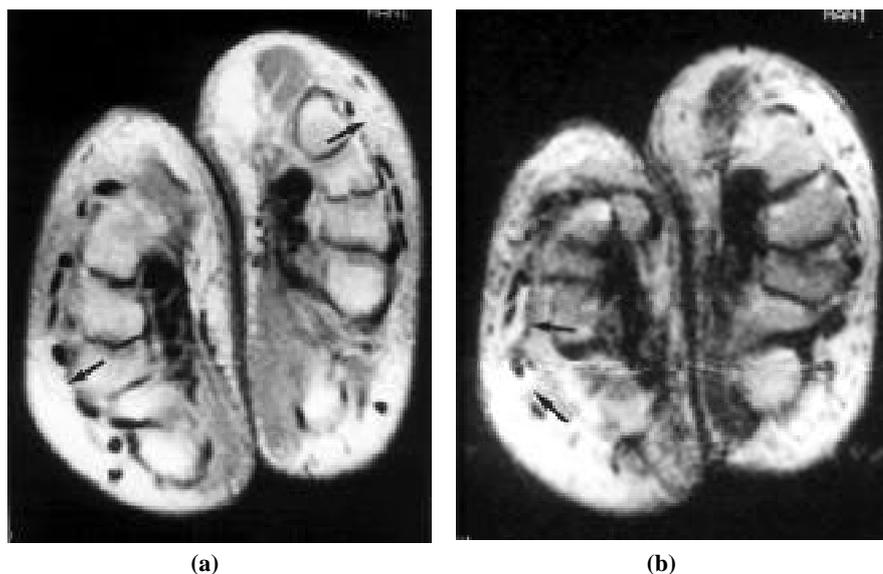
Lumbar computed tomography (CT) showed an osteolytic lesion of the L5 vertebral body. Radionuclide scanning detected multiple bone metastases. CT of the chest, abdomen and pelvis showed enlargement of the mediastinic, abdominal and retroperitoneal lymph nodes. A CT-guided biopsy from an osteolytic lesion of the pelvis demonstrated findings consistent with a diagnosis of undifferentiated carcinoma. The primary site of the cancer remained undefined and the patient died 2 months later.

**Patient 3.** A 78-year man presented with distal swelling and pitting edema of both hands of one month's duration. He denied a smoking habit and his medical history was negative for relevant diseases. Physical examination revealed only impressive swelling with pitting edema involving both wrists and hand dorsa and wheezing in the middle field of the right lung on chest auscultation.

Blood samples showed ESR 98 mm/hr, CRP 1.8 mg/dl, and lactate dehydrogenase 524 U/L (n.v.: 208 - 378 U/L). Rheumatoid factor and ANA were negative.

Hand radiographs showed only soft tissue swelling. Chest x-rays demonstrated a right parahilar nodule 4 x 3 cm in size. CT scans also demonstrated the presence of enlarged mediastinal lymph nodes and liver metastasis. CT-guided biopsy of the lung mass allowed a diagnosis of undifferentiated carcinoma. The patient was given prednisone at a dose of 50 mg/day without any improvement of the inflammatory distal swelling and edema. One month later he died.

The clinical picture of remitting seronegative symmetrical synovitis with pitting edema may be observed in different rheumatic conditions (15-25). Moreover, this feature has been reported as paraneoplastic syndrome (4-14). To date, 17 pa-



**Fig. 2.** Hand MRIs in patient 2. (A) Axial proton density section through the midpoint of the palm shows marked subcutaneous edema (arrows). (B) Axial T2 weighted section through the midpoint of the palm shows fluid collection in the extensor synovial sheaths (arrows).

tients in addition to the 3 described in the present review have been reported (Table I). In all of these patients RS3PE was an indirect manifestation of the tumor and started shortly before or after the malignancy.

In 12 out of 20 cases distal extremity swelling with pitting edema was the initial symptom and preceded the diagnosis of malignancy with a median interval of 2 months (range: 1 - 12 months). In 4 patients this feature was concomitant with the diagnosis of cancer, in 2 patients it was subsequent, and in 2 cases the temporal relationship was not specified. In 15/20 (75%) patients the malignancy was solid and in 73% the histological type was adenocarcinoma. The prostate, stomach and colon were the organs most frequently involved. In the remaining 5 patients the associated malignancy was a non-Hodgkin's lymphoma (4 cases) or chronic lymphoid leukaemia (1 case).

Furthermore, myelodysplastic syndrome (not included in Table I), which may be considered a pre-neoplastic condition, has been reported in patients with RS3PE syndrome (6).

In almost all the patients (19/20) distal swelling with pitting edema involved both hands symmetrically, and in 7 cases both feet were also involved. Among our three cases there was one with unilateral foot involvement. The inclusion of pa-

tients with only unilateral or lower extremity involvement may increase the frequency of this paraneoplastic condition. All of the cases published to date meet the clinical requirements of McCarty for RS3PE syndrome. The authors of these reports empirically selected only those patients with symmetrical upper limb involvement, while the spectrum of this condition also includes patients with unilateral findings (26, 28, 29).

Two clinical characteristics suggestive of paraneoplastic RS3PE are systemic signs/symptoms (fever, anorexia, weight loss) and the poor response to corticosteroid therapy. In the isolated form of RS3PE syndrome, not associated with other rheumatic conditions, systemic signs/symptoms are present only in 9% of the patients (26), in contrast to 10/20 (50%) of those reported patients with the paraneoplastic form.

Resistance to steroid therapy is another characteristic that should alert the clinician to the possibility of a malignancy, because pure RS3PE syndrome promptly remits after a short course of steroid treatment. The majority (19/20) of patients with paraneoplastic RS3PE were treated with prednisone or its equivalent at a dose of 10 - 20 mg/day in 15 patients and 40 - 50 mg/day in 4 patients. Of these 11 (58%) responded incompletely or not at all, independently of the prednisone dose employed. Three of the 7 patients

Table I. Reported cases of malignancy associated RS3PE syndrome.

Reference	No. of pts.	Sex/age (yrs.)	Interval between RS3PE onset and diagnosis of malign.	Type of malignancy	Site of pitting edema	Systemic signs/symptoms*	Response of RS3PE to corticosteroids	Response of RS3PE to cancer therapy
Roldan <i>et al.</i> 1993 (4)	1	F/63	5 months before	Non-Hodgkin lymphoma	Both hands and feet	No	Absent	Chemotherapy
Olivo <i>et al.</i> 1997 (5)	1	F/76	2 months before	Endometrial adenocarcinoma	Both hands and feet	No	Poor	Hysterectomy
Olivè <i>et al.</i> 1997 (6)	2	NR	NR	T lymphoma	Both hands	Not evaluable	Poor	NR
Tada <i>et al.</i> 1997 (7)	1	F/80	7 days after	Gastric adenocarcinoma	Both hands and feet	No	Not evaluable	Gastric resection
Cantini <i>et al.</i> 1998 (8)	1	M/75	2 months before	Pancreatic carcinoma	Both hands	Yes	Not evaluable	Pancreas resection
Goldenberg <i>et al.</i> 1998 (9)	1	F/60	16 months after	Non-Hodgkin lymphoma	Both hands	Yes	Absent	Chemotherapy
Sibilia <i>et al.</i> 1999 (10)	6	M/74 M/72 M/78 M/72 M/75 M/73	2 months before Concurrent 2 months before 1 month before Concurrent 2 1/2 mos. before	Prostatic adenocarcinoma Prostatic adenocarcinoma Prostatic adenocarcinoma Prostatic adenocarcinoma Undiff. gastric carcinoma Adenocarcinoma of colon	Both hands Both hands Both hands and feet Both hands Both hands Both hands and feet	Yes Yes Yes Yes Yes Yes	Poor Complete Complete Complete Partial Complete	Resistant to hormone therapy Hormone therapy Hormone therapy Hormone therapy Gastrectomy & chemother. Not evaluable
Nakashima <i>et al.</i> 1999 (11)	1	M/69	Concurrent	Hepatocellular carcinoma	Both hands and feet	No	Complete	Not evaluable
Dudler <i>et al.</i> 1999 (12)	1	M/78	8 months before	Prostatic adenocarcinoma	Both hands	No	Complete	Not evaluable
Ethiopia <i>et al.</i> 1999 (13)	1	F/82	2 months before	Gastric adenocarcinoma	Both hands	Yes	Poor	Not evaluable
Cobeta-Garcia <i>et al.</i> 1999 (14)	1	M/72	12 months before	Chronic lymphoid leukaemia	Both hands and feet	Yes	Complete	Not evaluable
Present study	3	M/46 M/59 M/78	4 months before 2 months before Concurrent	Adenocarcinoma of colon Undifferentiated carcinoma Undifferentiated lung carcinoma	Left foot Both hands Both hands	No No No	Poor Poor Absent	Colectomy Not evaluable Not evaluable

\* At least one of the followings: fever, anorexia, weight loss.

who had a complete response were also receiving hormone therapy for prostatic cancer. Therefore, the efficacy of steroid treatment should be questioned.

The response to surgical resection of the tumor or to chemotherapy was evaluable in 11/20 (55%). 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 (20, 21, 24-27) hand MRI showed in our second patient a predominant involvement of the tenosynovial extensor sheaths, suggesting that the tenosynovial membranes represent the anatomical target of the paraneoplastic process.

In conclusion, distal extremity swelling with pitting edema may represent a musculoskeletal manifestation of malignancies. This possibility should be considered in the absence of other associated rheumatic conditions, and in the presence of systemic signs/symptoms and resistance to corticosteroid therapy. Awareness that RS3PE syndrome may represent a paraneoplastic condition will help to facilitate the diagnosis in patients with this clinical feature.

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