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Myelodysplastic Syndrome Precedes the Onset of Remitting Seronegative Symmetrical Synovitis with Pitting Edema (RS3PE) Syndrome

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Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome is characterized by symmetrical synovitis predominantly involving the wrists, and is associated with marked pitting edema of the dorsum of the hands. Although the etiology of RS3PE syndrome is still unknown, several putative associations with malignancies and hematological disorders have been reported. Myelodysplastic syndrome (MDS) is characterized by infective hematopoiesis with possible transformation to leukemia; however, an association between RS3PE syndrome and MDS has been rarely reported. Here, we describe a 67-year-old man with MDS with refractory anemia who developed RS3PE syndrome 3 months after the diagnosis of MDS. The patient presented with polyarthritis with pitting edema at the dorsum of the hands, the elevated serum levels of C-reactive protein and a proinflammatory cytokine, interleukin-6, and the elevated plasma levels of vascular endothelial growth factor (VEGF). VEGF has been shown to be involved in the pathogenesis of RS3PE syndrome. Treatment with low doses of corticosteroids resulted in the regression of polyarthritis and pitting edema of the dorsum of the hands, as well as a reduction in the elevated levels of plasma VEGF. Partial resolution of refractory anemia was also observed with steroid therapy. In summary, RS3PE syndrome developed shortly after MDS was identified in this patient. The sequence of clinical events suggests that MDS-mediated immunological abnormalities including inflammatory cytokine induction may be responsible for the association between MDS and RS3PE syndrome. Patients with RS3PE syndrome should be screened for hematological disorders that promote proinflammatory mediators.

Keywords: corticosteroid; interleukin-6; myelodysplastic syndrome; remitting seronegative symmetrical synovitis with pitting edema syndrome; vascular endothelial growth factor
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Introduction

Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) is characterized by symmetrical synovitis predominantly involving the hands with pitting edema of the dorsum of the hands (Schaeverbeke et al. 1995). Patients have been found to respond well to low dose corticosteroids and to remain in remission (Paira et al. 2002). Previous reports indicated that RS3PE syndrome could be a paraneoplastic syndrome, including of hematological disorders (Goldenberg et al. 1998; Cantini et al. 1999; Cobeta-Garcia et al. 1999). Myelodysplastic syndrome (MDS) comprises a spectrum of pathologically and cytogenetically distinct bone marrow disorders associated with peripheral blood cytopenia (Fenaux 2004). Patients with MDS have often been found to have rheumatic conditions, including vasculitis, lupus-like syndrome, rheumatoid arthritis and polymyalgia rheumatic (Castro et al. 1991; Kuzmich et al. 1994). Manganelli et al. (2001) reported the patients with RS3PE syndrome, which was associated with an underlying hematological disorder, MDS. This report describes a patient with RS3PE associated with MDS.

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Case Presentaion

A 67-year-old man with a 1-month history of pain and swelling of both wrists and metacarpophalangeal (MP) joints was admitted to our hospital for further examination. Three months prior to admission, the patient had been found to have moderate anemia based on hematological findings. A bone marrow biopsy revealed compartmentalization of the hematopoietic lineages, dysplastic megakaryocytes and myeloid lineage cells with dyserythropoiesis (Fig. 1). No ringed sideroblast was detected and total blasts constituted fewer than 10% of bone marrow nucleated cells. Analysis of banded chromosomes revealed a deletion of chromosome 1 (Fig. 2). These findings were consistent with MDS, refractory anemia subtype according to WHO classification criteria for MDS (Vardiman et al. 2002). Two months later, he experienced a sudden onset of swelling and tenderness of the wrists, MP joints and shoulders, as well as diffuse pitting edema over the hands.

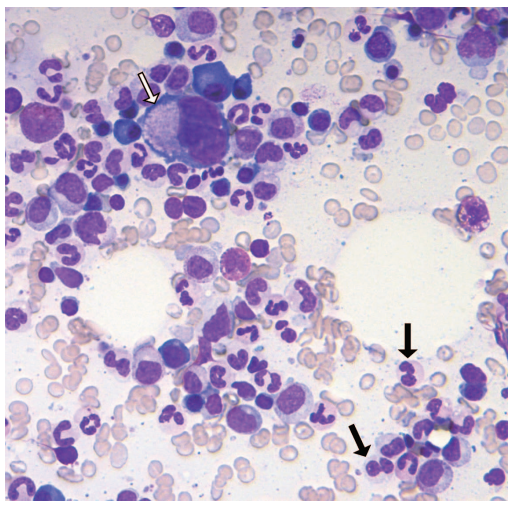

Fig. 1. Bone marrow aspirate smear from the present patient. Closed arrows point toward hypogranulation of pseudo-Pelger-Huët neutrophils. Open arrow point abnormal megakaryocytes with dispersed nuclear lobes and abnormal distribution of cytoplasmic granules. (May-Giemsa stain)

Physical examinations showed swelling and tenderness of both wrists and MP joints, with pitting edema of the wrist and dorsum of both hands (Fig. 3). There was no evidence of lymphadenopathy or hepatosplenomegaly. Laboratory data showed anemia; hemoglobin 8.3 g/dl; mean corpuscular volume, 87.6 μm^3; and white blood cells 7,300 /mm^3. Other laboratory assays revealed an erythrocyte sedimentation rate (ESR) of 107 mm/h and a C-reactive protein (CRP) concentration of 6.57 mg/dl. Tests for antinuclear antibody (ANA), rheumatoid factor and anti-cyclic citrullinated peptide antibody (Anti-CCP Ab) were negative. Renal and liver function tests were within normal limits (Table 1). X-ray of hands showed a soft tissue swelling and there was no bone erosion (Fig. 4). However, fat suppressed MRI of the hands showed prominent inflammatory changes around the synovium with extensive extracapsular soft tissue edema (Fig. 5). The patient was also screened and investigated for associated malignancy. Computed tomography (CT) of the thorax/abdomen, and gastrointesti-

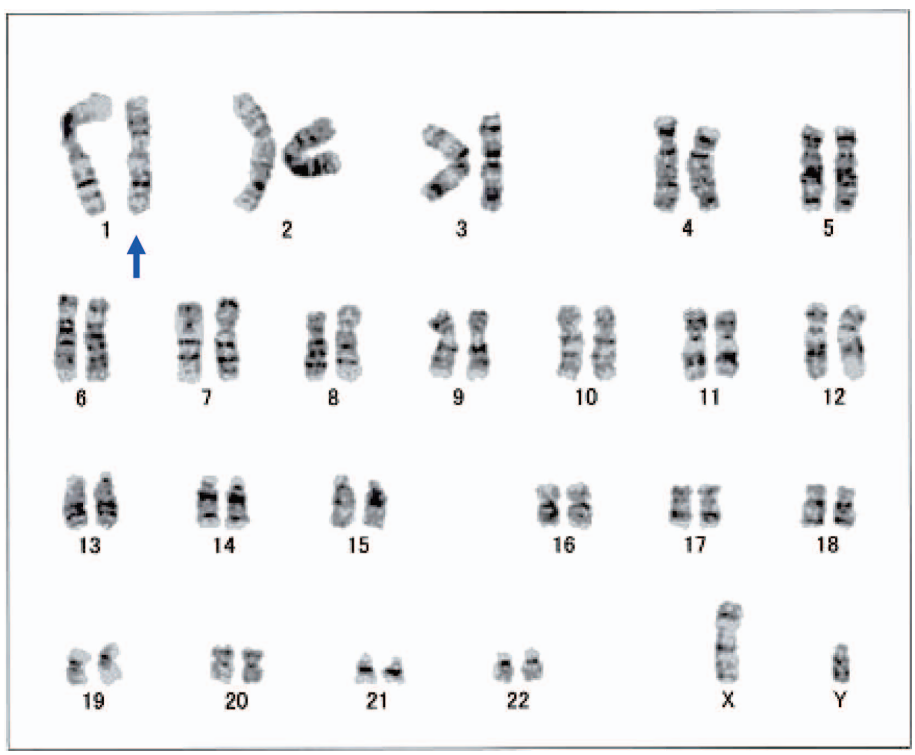

Fig. 2. G-banded karyotypes of bone marrow cells showing chromosome defect in proband; 46XY, del (1).

nal/colonic fiberscopy were normal. The patient was diagnosed with RS3PE and treated with prednisolone 15 mg/day, to which he responded extremely well. Follow up two weeks later on a tapering dose of prednisolone showed complete resolution of signs and symptoms without flare-ups. Prior to steroid treatment, the serum concentrations of interleukin-6 (IL-6) and plasma concentrations of vascular endothelial growth factor (VEGF) were elevated in this patient (IL-6 42.6 pg/ml; normal range < 4.0 pg/ml; VEGF 212 pg/ml; normal range < 55 pg/ml). Following steroid treatment, the elevated levels of IL-6 and VEGF were declined, in parallel with the resolution of joint swelling and pitting edema. Partial resolution of refractory anemia

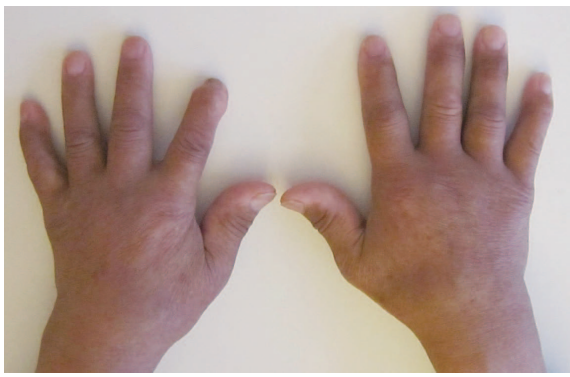

Fig. 3. Diffuse swelling of the hands with pitting edema.

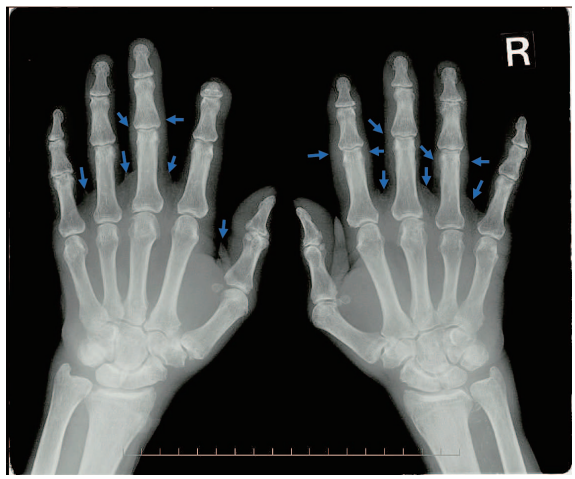

Fig. 4. X-ray of hands showing a soft tissue swelling.

Table 1. Laboratory findings on admission.

Peripheral blood		Serological tests	
Red blood cells	$282 \times 10^4/\mu l$	C-reactive protein	6.57 mg/dl (< 0.30)
Hemoglobin	8.3 mg/dl	Erythrocyte sedimentation rate	107 mm/hr
MCV	87.6	IgG	2,440 mg/dl (900-2,000)
White blood cells	7,300/μl	C3	171 mg/dl (86-160)
Neutrophil	70.7%	C4	40 mg/dl (17-45)
Monocyte	8.4%	Rheumatoid factor	(−)
Lymphocyte	20.0%	Anti-nuclear Ab	< 40
Eosinophil	0.8%	PR-3-ANCA	< 1.0 U/ml (< 3.5)
Basophil	0.1%	MPO-ANCA	< 1.0 U/ml (< 3.5)
Platlet	$26.0 \times 10^4/\mu l$	MMP-3	167 ng/ml (36.9-121)
Blood chemistry		Anti-CCP Ab	< 0.6 U/ml (< 4.5)
Total protein	7.2 g/dl	sIL-2R	709 U/ml (14-519)
Total bilirubin	0.7 mg/dl	Virological test	
Glutamic-oxaloacetic transaminase	21 IU/l (7-33)	HCV-Ab	(−)
Glutamic-pyruvic transaminase	22 IU/l (5-30)	HBsAg	(−)
Lactate dehydrogenase	134 IU/l (260-480)	Urinalysis	
Alkaline phosphatase	879 IU/l (80-250)	Protein	(−)
Creatinine kinase	11 IU/l (60-160)	Sugar	(−)
Total cholesterol	189 mg/dl	Occult blood	(−)
Blood urea nitrogen	22.3 mg/dl	Sediment	(−)
Creatinine	0.2 mg/dl		
Alb	2.5 g/dl		
Na	135 mEq/l		
K	4.0 mEq/l		
Cl	100 mEq/l		

HBsAg, hepatitis B surface antigen; Anti-CCP Ab, anti-cyclic citrullinated peptide antibody; HCV, hepatitic C virus; MCV, mean corpuscular volume; MMP-3, matrix metalloproteinase-3; MPO-ANCA, myeloperoxidase-anti-neutrophil cytoplasmic antibody; PR-3-ANCA, proteinase 3-anti-neutrophil cytoplasmic antibody; sIL-2R, soluble interleukin-2 receptor.

was also observed by steroid therapy (Fig. 6).

Discussion

Our patient exhibited the clinical and laboratory features of RS3PE syndrome (McCarty et al. 1985), including bilateral pitting edema of the hands and sudden onset of polyarthritis, 3 months after being diagnosed with MDS. The clinical features of RS3PE syndrome suggest a paraneoplastic syndrome that includes hematological disorders (Goldenberg et al. 1998; Cantini et al. 1999; Cobeta-Garcia et al. 1999). The musculoskeletal symptoms seen in RS3PE syndrome may be manifestations secondary to malignancy or hematological disorders (Cantini et al. 1999). In our patient, RS3PE syndrome may have been accompanied by a pre-existing hematological disorder, MDS, which may be considered a pre-neoplastic condition. MDS in this patient may have contributed to the induction of proinflammatory cytokines, as well as to the development of RS3PE.

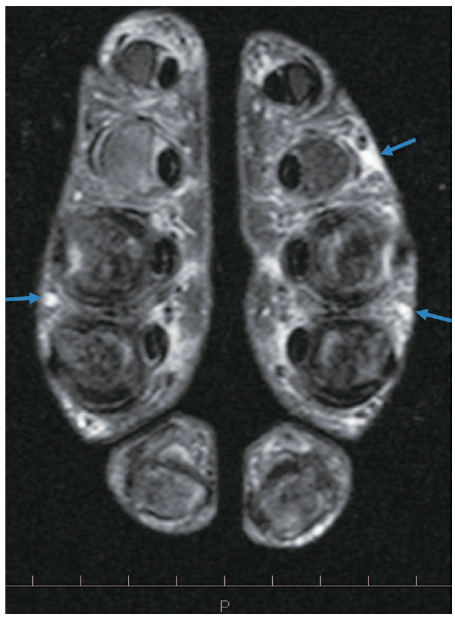

Fig. 5. Fat suppressed MRI of the hands.
Axial T2 weighted scan through the midpoint of the palm shows inflammatory changes outside the synovial compartments with extra capsular soft tissue edema.

The pathogenesis of RS3PE syndrome is still unclear. However, high levels of inflammatory cytokines are thought to contribute to active synovitis in RS3PE syndrome (Yao et al. 2010). High serum concentrations of VEGF have been reported in patients with RS3PE syndrome, suggesting that RS3PE syndrome could be classified as a VEGF-associated disorder (Arima et al. 2005). Indeed, plasma levels of VEGF in our patient were significantly elevated at the diagnosis of RS3PE. Furthermore, steroid treatment of our patient normalized the concentrations of VEGF and IL-6 as well as resulting in the complete regression of the clinical symptoms of RS3PE. VEGF production may be more important and may contribute to polyarthritis/polysynovitis and subcutaneous pitting edema of the extremities by inducing vascular permeability. Additionally, RS3PE in Japanese patients has been associated with a marked inflammatory response, including elevated IL-6 activity (Oide et al. 2004). The substantial elevation in VEGF and IL-6 levels and their reduction in parallel to clinical improvement after corticosteroid treatment suggest the involvement of these cytokines in RS3PE.

MDS is a group of disorders characterized by ineffective hematopoiesis. Hematopoietic precursors in these patients reduce survival, due to enhanced angiogenesis and

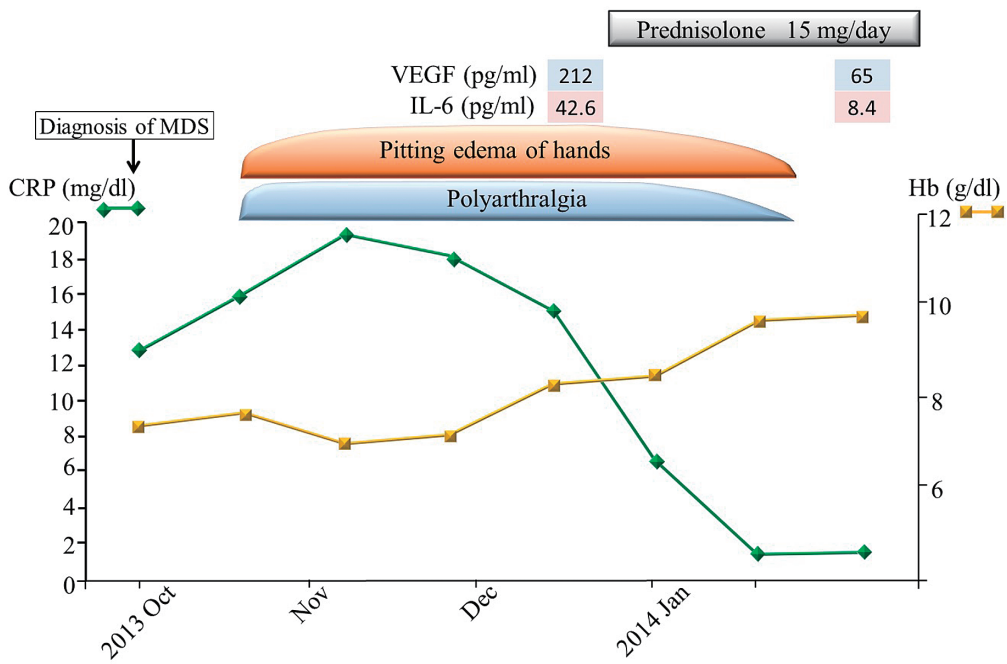

Fig. 6. Clinical course of the present case.

the induction of inhibitory or inflammatory cytokines (Sekeres and List 2006). In particular, VEGF not only promotes medullary neovascularization but also stimulates myeloblast clonal expansion and ineffective hematopoiesis (Allampallam et al. 2002).

Plasma VEGF concentrations were shown to be significantly higher in patients with MDS (median 34.41 pg/ml, range 22.45-408.67 pg/ml) than in normal controls (median 27.30 pg/ml, range 23.17-91.50 pg/ml) (Aguayo et al. 2002). Moreover, increased serum concentrations of inflammatory cytokines have been observed in MDS (Calado 2011). For example, IL-6, which is undetectable in the serum of healthy subjects, was present at concentrations higher than 3 pg/ml in 36 of 45 patients with MDS (Herold et al. 1992). Recently, MDS was found to be associated with symptoms similar to those of Behçet's disease, especially in patients with trisomy 8 (Ahn et al. 2008). Furthermore, this cytogenetic abnormality in patients with MDS may be involved in immunity and in the expression of proinflammatory genes, including IL-6 and monocyte chemotactic protein-1 (MCP-1), and the expression of adhesion molecules. These findings suggest that autoimmune complications associated with MDS result from immunological derangements in this disease. RS3PE has been reported in patients with hematological malignancies, including acute myeloid leukemia, chronic lymphocytic leukemia and MDS (Goldenberg et al. 1998; Cantini et al. 1999; Cobeta-Garcia et al. 1999). A retrospective study of 27 patients with RS3PE syndrome found that two had T cell lymphoma and one had MDS (Olivé et al. 1997). These findings have suggested a relationship between hematologic stem cell dysfunction in MDS and associated immunological abnormalities. Thus, a hematological disorder, MDS, may have triggered immunological abnormalities by inducing inflammatory cytokines, contributing to the occurrence of RS3PE syndrome in our patient. Steroid therapy was apparently effective by regulating these cytokines.

Although MDS with erythroid hypoplasia is usually resistant to steroids, the efficacy of steroids has been reported in several patients with MDS (García-Suárez et al. 1998). In patients with immunological disorders associated with MDS, autoimmune or inflammatory processes may modify the clinical course of MDS.

In conclusion, we have described RS3PE in a patient with MDS, suggesting that RS3PE syndrome does not necessarily develop in patients with a malignant disease. Patients with RS3PE syndrome should be screened for hematological disorders that promote proinflammatory mediators.

Acknowledgments

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Conflict of Interest

The authors declare no conflict of interest.

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