Case report

Monitoring of therapeutic efficacy in a patient with RS₃PE syndrome by serologic variables and radiographic methods

Shin-ya Kawashiri¹, Michiko Nakano¹, Atsushi Kawakami¹, and Katsumi Eguchi¹

¹Unit of Translational Medicine, Department of Immunology and Rheumatology, Graduate School of Biomedical Sciences, Nagasaki University, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan

Address for correspondence and reprint requests:

Prof. Katsumi Eguchi, M.D., Ph.D.

Unit of Translational Medicine,

Department of Immunology and Rheumatology,

Graduate School of Biomedical Sciences, Nagasaki University,

1-7-1 Sakamoto, Nagasaki 852-8501, Japan

Phone: + 81-95-819-7266

Fax: 81-95-849-7270

e-mail: eguchi@net.nagasaki-u.ac.jp

Abstract

We experienced a typical patient with remitting seronegative symmetrical synovitis with pitting edema (RS₃PE) syndrome and describe here a successful clinical course monitored by serologic variables and radiographic methods. — Serum levels of interleukin-6 (IL-6), vascular endothelial growth factor (VEGF), matrix metalloproteinase-3 (MMP-3), and serum amyloid A (SAA) were remarkably elevated. Accumulation of inflammatory cells into the multiple joints was found by Gallium-67 scintigraphy. Multiple and symmetrical tenosynovitis with hypervascularity in the presence of subcutaneous edema of the hands and feet were determined by magnetic resonance imaging (MRI) and ultrasonography. These serologic and radiographic abnormalities immediately improved after treatment with a low-dose steroid. Our present case supports a previous observation that synovial tissue is a major inflammatory source of RS₃PE syndrome. IL-6 (and VEGF), probably produced from the synovial tissues, are considered to be essential factors in the development of RS₃PE syndrome.

Key words

Remitting seronegative symmetrical synovitis with pitting edema (RS₃PE) syndrome, VEGF, IL-6, Ga-67 scintigraphy, MRI, ultrasonography

Introduction

Remitting seronegative symmetrical synovitis with pitting edema (RS₃PE) syndrome is a rare inflammatory disease, first described by McCarty and colleagues in 1985 [1]. This syndrome is characterized by elderly patient status, acute onset, symmetrical synovitis, pitting edema of the dorsum of the hands and feet, seronegativity for rheumatoid factor (RF), and an excellent prognosis with low-dose corticosteroid therapy [2]. We previously reported that the serum level of vascular endothelial growth factor (VEGF) was markedly elevated in patients with RS₃PE syndrome [3]. As diagnostic imaging tools, magnetic resonance imaging (MRI), ultrasonography (USG), and Gallium (Ga)-67 scintigraphy are useful for the detection of inflammatory sites [4-8].

Based on this case report, we suggest that the synovial tissues rich in humoral factors of IL-6, VEGF, and matrix metalloproteinase-3 (MMP-3) are principal in the development of RS₃PE syndrome.

Case report

A 59-year-old Japanese woman was admitted to our hospital because of polyarthralgia, edema of the dorsum of the bilateral hands and feet, and high fever on 23 August 2008. A physical examination showed remarkable symmetrical pitting edema of the dorsum of the hands and feet, and tenderness and warmth of joints of the bilateral shoulders, elbows, wrists, and knees. Biochemical and serological data are shown in Table 1. The blood count showed anemia. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were increased. RF and anti-cyclic citrullinated peptide antibodies (anti-CCP Ab) were negative. The serum levels of interleukin-6 (IL-6), VEGF, MMP-3, and serum amyloid A (SAA) were markedly elevated. Bone erosion was not found by plain radiography. Ga-67 scintigraphy (Figure 1A) showed symmetrically multiple increased uptakes in the joints of the extremities. Dynamic MRI (Figure 1B) detected synovitis of the wrists, metacarpophalangeal joints, and proximal interphalangeal joints, tenovitis of extensor and flexor tendons, and diffuse subcutaneous edema in the bilateral hands. USG of the hands and feet (Figure 1C) also detected synovitis, tenosynovitis, and subcutaneous edema of the dorsum.

The patient was diagnosed with RS3PE syndrome fulfilling the following criteria [2]: (1) bilateral pitting edema of the hands, (2) sudden onset of polyarthritis, (3) age > 50 years, (4) seronegativity for RF. On 29 August 2009, treatment with oral prednisolone 15 mg daily was initiated. After the initiation of treatment, symptoms including fever, edema of the extremities, and arthralgia promptly improved. Serologic variables were remarkably improved beginning 2 weeks after treatment (Table 2). Tenosynovitis and subcutaneous edema in MRI and USG had almost disappeared at one month after the initiation of treatment, although a slight elevation of MMP-3 and SAA continued. We succeeded in tapering the dose of prednisolone without any recurrence.

Discussion

We previously reported synovial hypervascularity and subcutaneous edema in dynamic MRI with a remarkable increment of serum VEGF in patients with RS₃PE syndrome [3]. After treatment, MRI abnormalities and high serum VEGF rapidly decreased [3]. We had discussed that both synovial hypervascularity and increment of vascular permeability may be facilitated by VEGF [3]. We have investigated this hypothesis more intensely in the present case by serologic variables and radiographic methods. These abnormalities have been reported previously [3-9]; however, this is a first report of a patient showing recovery of all these parameters at once after treatment. In vitro studies have revealed that IL-6 induces the production of VEGF [10], MMP-3 [11], and SAA [12]. Since IL-6 concentration in synovial fluid of RS₃PE syndrome is much higher than in serum [9], IL-6, probably produced from the synovial tissues, may facilitate the pathologic status of RS₃PE syndrome via VEGF and MMP-3.

Ga-67 scintigraphy allows the detection of the distribution of systemic synovitis, whereas MRI and USG are useful to show the local inflammatory process precisely. As expected, intense accumulation of synovial inflammatory cells with hypervascularity in the presence of subcutaneous edema and tenosynovitis was determined in our case, which may have been driven by IL-6, VEGF, MMP-3 and was clearly improved by traditional low-dose steroid.

The findings in our present case support a previous observation that synovial tissues are a major inflammatory source of RS₃PE syndrome. Both serologic and radiographic methods are quite beneficial to monitor the disease activity of RS₃PE syndrome.

References

- [1] McCarty DJ, O'Duffy JD, Pearson L, Hunter JB. Remitting seronegative symmetrical synovitis with pitting edema. RS3PE syndrome. JAMA 1985; 25: 2763-7.
- [2] Olivé A, del Blanco J, Pons M, Vaquero M, Tena X. The clinical spectrum of remitting seronegative symmetrical synovitis with pitting edema. The Catalán Group for the Study of RS3PE. J Rheumatol 1997; 24: 333-6.
- [3] Arima K, Origuchi T, Tamai M, Iwanaga N, Izumi Y, Huang M, et al. RS3PE syndrome presenting as vascular endothelial growth factor associated disorder. Ann Rheum Dis 2005; 64: 1653-5.
- [4] Unlu Z, Orguc S, Ovali GY, Tarhan S, Dayan I, Angin A. Magnetic resonance imaging findings in a case of remitting seronegative symmetrical synovitis with pitting edema. Clin Rheumatol 2005; 64: 48-51.
- [5] Cantini F, Salvarani C, Olivieri I, Barozzi L, Macchioni L, Niccoli L, et al. Remitting seronegative symmetrical synovitis with pitting oedema (RS3PE) syndrome: a prospective follow up and magnetic resonance imaging study. Ann Rheum Dis 1999 Apr; 58: 230-6.
- [6] Agarwal V, Dabra AK, Kaur R, Sachdev A, Singh R. Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome: ultrasonography as a diagnostic tool. Clin Rheumatol 2005; 24: 476-9.
- [7] Klauser A, Frauscher F, Halpern EJ, Mur E, Springer P, Judmaier W, et al. Remitting seronegative symmetrical synovitis with pitting edema of the hands: ultrasound, color doppler ultrasound, and magnetic resonance imaging findings. Arthritis Rheum 2005; 53: 226-33.
- [8] Takeguchi T, Sugawara Y, Kikuchi K, Miki H, Mochizuki T, Ikezoe J, et al. Remitting seronegative symmetric synovitis with pitting edema: scintigraphic and magnetic resonance imaging findings. Clin Nucl Med 2003; 28: 766-8.
- [9] Oide T, Ohara S, Oguchi K, Maruyama M, Yazawa M, Inoue K, et al. Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome in Nagano, Japan: clinical, radiological, and cytokine studies of 13 patients. Clin Exp Rheumatol 2004; 22: 91-8.
- [10] Nakahara H, Song J, Sugimoto M, Hagihara K, Kishimoto T, Yoshizaki K, et al. Anti-interleukin-6 receptor antibody therapy reduces vascular endothelial growth factor production in rheumatoid arthritis. Arthritis Rheum 2003; 48: 1521-9.
- [11] Fuchs S, Skwara A, Bloch M, Dankbar B. Differential induction and regulation of matrix metalloproteinases in osteoarthritic tissue and fluid synovial fibroblasts. Osteoarthritis Cartilage 2004; 12: 409-18.
- [12] Castell JV, Gómez-Lechón MJ, David M, Hirano T, Kishimoto T, Heinrich PC. Recombinant human interleukin-6 (IL-6/BSF-2/HSF) regulates the synthesis of acute phase proteins in human hepatocytes. FEBS Lett 1988; 232: 347-50.

Figure Legend**Figure 1**

Ga-67 scintigraphy (A) showed symmetrically multiple increased uptakes in the joints of the extremities. Dynamic MRI (B) detected synovitis of the wrists, metacarpophalangeal joints, and proximal interphalangeal joints, and tenovitis of the extensor and flexor tendons in the bilateral hands. USG of the hands and feet (C) also detected synovitis and subcutaneous edema of the dorsum.

Abbreviations

anti-CCP Ab: anti-cyclic citrullinated peptide antibodies

CRP: C-reactive protein

ESR: erythrocyte sedimentation rate

Ga: Gallium

MMP-3: matrix metalloproteinase

MRI: magnetic resonance imaging

IL-6: interleukin-6

PSL: prednisolone

RF: rheumatoid factor

RS3PE: remitting seronegative symmetrical synovitis with pitting edema

SAA: serum amyloid A

TNF: tumor necrosis factor

USG: ultrasonography

VEGF: vascular endothelial growth factor

Table 1. Biochemical and serological evaluation

Laboratory test	Result	Laboratory test	Result
Urine glucose	Negative	Antinuclear antibodies	1:160 (homogenous pattern)
Urine protein	Negative	Rheumatoid factor	Negative
Urine urobilinogen	Negative	Anti-CCP	<4.5 U/ml
White cell count	7,200/mm ³	Serum MMP-3	1,274.4 ng/ml
Hemoglobin	9.5 g/dl	Serum amyloid A	2,190 µg/ml
Platelets	451,000/mm ³	Serum VEGF	1,560 pg/ml
Sodium	134 mEq/l	soluble IL-2 receptor	861 U/ml
Potassium	3.6 mEq/l	IgA	343 mg/dl
Chloride	95 mEq/l	IgG	1,310 mg/dl
BUN	7.0 mg/dl	IgM	168 mg/dl
Creatinine	0.4 mg/dl	C3	122 mg/dl
Uric acid	2.4 mg/dl	C4	28.5 mg/dl
Total protein	6.5 g/dl	CH50	40.1 U/ml
Albumin	2.7 g/dl	Ferritin	606 ng/ml
Total cholesterol	134 g/dl	C-reactive protein	9.49 mg/dl
Triglyceride	84 g/dl	ESR	112.4 mm/hr
AST	17 IU/l	Free thyroxine	1.56 ng/ml
ALT	27 IU/l	TSH	1.37 µU/ml
LDH	155 IU/l	HLA-B7	positive
γGTP	13IU/l		
ALP	266 IU/l		
creatine kinase	17 IU/l		
Aldolase	6.2 IU/l		

Table 2. Serologic variables at various points

Laboratory test	August 23	September 4	October 30
Serum VEGF (pg/ml)	2,190	476	510
Serum IL-6 (pg/ml)	125	5.0	2.5
Serum TNF-alpha (pg/ml)	1.4	1.5	1.1
Serum MMP-3 (ng/ml)	1274.4	164	143.8
SAA (µg/ml)	2,190	154	45.5
CRP (mg/dl)	9.49	1.02	0.04
ESR (mm/hr)	112.4	71.2	25

Normal concentrations of serum MMP-3, and SAA are 17.3-59.7 ng/ml and <8 µg/ml, respectively.

Figure 1