CONCISE REPORT

RS3PE syndrome presenting as vascular endothelial growth factor associated disorder

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Objectives: To characterise serum concentrations of various cytokines and detection by magnetic resonance imaging (MRI) of synovial hypervascularity in patients with remitting seronegative symmetrical synovitis with pitting oedema (RS3PE) syndrome before and after corticosteroid treatment.

Methods: Vascular endothelial growth factor₁₆₅ (VEGF₁₆₅), tumour necrosis factor α (TNF α), and interleukin 1 β (IL1 β) were measured by enzyme linked immunosorbent assay (ELISA) in serum samples from three patients with RS3PE syndrome. As controls, serum samples from 26 healthy volunteers, 12 patients with rheumatoid arthritis, 10 patients with systemic lupus erythematosus, 13 patients with polymyositis/dermatomyositis, 13 patients with vasculitis syndrome, and 6 patients with mixed connective tissue disease were also analysed. Synovial hypervascularity of patients with RS3PE syndrome was estimated by rate of enhancement (E-rate) in a dynamic MRI study.

Results: Serum concentrations of VEGF₁₆₅ (mean (SD) 2223.3 (156.3) pg/ml) were significantly higher in patients with active RS3PE syndrome than in controls before corticosteroid treatment. TNF α and IL1 β levels were similar in patients and controls. Synovial hypervascularity in affected joints and subcutaneous oedema decreased during corticosteroid treatment, in parallel with the fall in serum VEGF₁₆₅.

Conclusions: VEGF promotes synovial inflammation and vascular permeability in patients with RS3PE syndrome, suggesting that RS3PE can be classified as a VEGF associated disorder.

PATIENTS AND METHODS

Patients

Serum samples were obtained from three patients with typical manifestations of RS3PE syndrome. As controls, serum samples from 26 healthy volunteers, 12 patients with rheumatoid arthritis, 10 patients with systemic lupus erythematosus, 13 patients with polymyositis/dermatomyositis, 13 patients with vasculitis syndrome, and 6 patients with mixed connective tissue disease were analysed. Informed consent was obtained from each patient, and the study was approved by the Institutional Review Board of Nagasaki University.

Enzyme linked immunosorbent assay

Serum concentrations of VEGF₁₆₅ (major isoform of VEGF) as well as those of tumour necrosis factor- α (TNF α) and interleukin 1 β (IL1 β) in the above subjects were analysed by enzyme linked immunosorbent assay (ELISA; VEGF₁₆₅, R&D Systems, Inc, Minneapolis, MN, USA; TNF α , BioSource Europe SA, Nivelles Belgium; IL1 β , Amersham Biosciences, Buckinghamshire, UK).

Dynamic magnetic resonance imaging (MRI)

MRI of both wrists and finger joints was carried out simultaneously using a 1.5 T system (Sigma, GE Medical Systems, Milwaukee, WI, USA) with the use of an extremity coil. Coronal T₁ weighted spin echo (repetition time (TR) 450, echo delay time (TE) 13) and short time inversion recovery (STIR) (TR 3000, TE 12, T₁ 160) images were acquired. Dynamic study data were obtained at 4 second intervals for 150 seconds with fast spoiled gradient echo recalled (SPGR) sequences after intravenous injection of 0.1 mmol/kg of gadolinium-diethylenetriamine (Magnevist, Schering, Germany). Post-contrast, fat suppressed T₁ weighted images (TR 600, TE 13) were acquired in axial and coronal planes after completion of the dynamic study.

Images were evaluated for the presence or absence of synovitis in 15 joints in each wrist and finger joint—that is, distal radioulnar joint, radiocarpal joint, mid-carpal joint, 1st carpometacarpal joint, 2nd–5th carpometacarpal joints (together), 1st–5th metacarpophalangeal joints separately, and 1st–5th proximal interphalangeal joints separately. A dynamic curve was obtained by plotting signal intensity against time in a round region measuring approximately 2–3 mm placed on the site of maximum enhancement in the aforementioned 15 joints. The rate of enhancement (E-rate) was defined as the rate of increase in signal intensity over the

Abbreviations: E-rate, rate of enhancement; IL1 β , interleukin 1 β ; MRI, magnetic resonance imaging; RS3PE syndrome, remitting seronegative symmetrical synovitis with pitting oedema syndrome; STIR, short time inversion recovery; TE, echo delay time; TNF α , tumour necrosis factor α ; TR, repetition time; VEGF, vascular endothelial growth factor

Remitting seronegative symmetrical synovitis with pitting oedema (RS3PE) syndrome is a rare inflammatory arthritis, first described by McCarty and colleagues in 1985,¹ and is characterised by abrupt onset of marked dorsal swelling of both hands with pitting oedema. Because RS3PE syndrome is sometimes complicated by neoplastic conditions such as non-Hodgkin's lymphoma and solid tumours,^{2,3} it is speculated that some humoral factors facilitate the clinical manifestations in patients with RS3PE syndrome; however, the precise mechanisms remain to be elucidated.^{4,5}

Vascular endothelial growth factor (VEGF) enhances angiogenesis as well as vascular permeability, and is a candidate humoral factor responsible for tumour angiogenesis.⁶ We studied three patients with RS3PE syndrome, who showed markedly high serum concentrations of VEGF than patients with other connective tissue diseases, and studied whether VEGF contributes to synovitis and subcutaneous oedema in patients with RS3PE syndrome.

Table 1 Serum concentrations of VEGF-A, TNF α , and IL1 β in various connective tissue diseases

Connective tissue disease	VEGF-A (pg/ml)	TNF α (pg/ml)	IL1 β (pg/ml)
RS3PE syndrome (n=3)	2223.3 (156.3)*	26.3 (20.8)	0.67 (0.81)
RA (n=12)	711.0 (401.7)	19.9 (13.7)	0.61 (0.39)
SLE (n=10)	309.9 (140.6)	34.2 (19.4)	0.32 (0.16)
MCTD (n=6)	682.3 (575.0)	51.8 (27.7)	0.48 (0.39)
PM/DM (n=13)	324.2 (188.9)	22.6 (10.9)	0.32 (0.24)
Vasculitis syndrome (n=13)	736.1 (475.5)	27.3 (14.2)	0.90 (1.38)

RS3PE syndrome, remitting seronegative symmetrical synovitis with pitting oedema syndrome; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; MCTD, mixed connective tissue disease; PM/DM, polymyositis/dermatomyositis.

Data are mean (SD) of the indicated number of patients.

*p<0.0001 v other connective tissue diseases by Student's *t* test.

Table 2 Serum concentrations of VEGF₁₆₅ and E-rate of dynamic MRI during corticosteroid treatment

Patient No	VEGF ₁₆₅ (pg/ml)			E-rate		
	Before treatment	After treatment	Mean (SD) inhibition (%)	Before treatment	After treatment	Mean (SD) inhibition (%)
1	2341	393		19.6	10.9	
2	2283	605	60.9* (30.6)	15.4	10.7	31.5† (12.4)
3	2046	1516		9.7	7.8	

*p=0.037 and †p=0.024 v before corticosteroid treatment by Student's *t* test.

steep linear region of the curve and was used as a measure of hypervascularity of the tissue.

Statistical analysis

Data were expressed as mean (SD). Statistical analysis was performed using Student's *t* test. Values of p<0.05 were considered significant.

RESULTS

Serum concentrations of cytokines

Table 1 summarises the serum concentrations of the cytokines. As shown in table 1, no significant differences in TNF α and IL1 β serum concentrations were noted between RS3PE syndrome and other connective tissue diseases; however, markedly high serum VEGF₁₆₅ levels were found in patients with RS3PE syndrome. Because VEGF₁₆₅ serum concentrations in other connective tissue diseases were comparable with those found in previous reports,^{7,8} the high serum VEGF₁₆₅ was considered to be specific for RS3PE syndrome. TNF α and IL1 β were not detected in serum samples from healthy volunteers (data not shown), and serum concentrations of VEGF₁₆₅ in these subjects were also low (data not shown).

MRI in patients with RS3PE syndrome

Table 2 shows the mean E-rate of 30 joints (both wrists and finger joints) in three patients with RS3PE syndrome before and after 1 month of corticosteroid treatment. Synovial hypervascularity determined by the E-rate was reduced by corticosteroid treatment in all the three patients in parallel with the fall of serum VEGF (table 1). Subcutaneous oedema shown by a STIR image was also reduced after corticosteroid treatment in each patient with RS3PE syndrome (data not shown).

DISCUSSION

VEGF is a potent angiogenic,^{9,10} vasoactive,⁶ molecule which increases permeability,^{11,12} first described by Senger *et al* in 1983.¹³ They partially purified a factor secreted by

hepatocarcinoma cell lines that increased dye extravasations into the skin of guinea pigs. In addition, recent studies reported that serum VEGF concentrations, although not as high as RS3PE syndrome found in the present cases, correlate with disease activity in patients with inflammatory arthropathies such as rheumatoid arthritis.^{7,14}

The pathogenic mechanism of RS3PE syndrome is still unknown. As far as we know, this is the first report indicating that VEGF may contribute to the pathological changes seen in patients with RS3PE syndrome; both synovial hypervascularity (synovitis) and increment of vascular permeability (subcutaneous oedema) may be facilitated by VEGF in patients with RS3PE syndrome. Serum VEGF₁₆₅ levels were selectively high in active RS3PE syndrome as compared with other connective tissue diseases. This difference of serum VEGF₁₆₅ may be due to the difference of corticosteroid dosage among patient groups, and we cannot exclude the possibility at present that high serum VEGF₁₆₅ concentrations in RS3PE syndrome may be a consequence of in vitro platelet activation in serum.¹⁵ However, our consecutive analysis of VEGF₁₆₅ as well as MRI suggests that serum VEGF might be useful for the diagnosis and monitoring of disease activity in patients with RS3PE syndrome.

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