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ORIGINAL ARTICLE

High serum matrix metalloproteinase 3 is characteristic of patients with paraneoplastic remitting seronegative symmetrical synovitis with pitting edema syndrome

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Abstract Recently, it was reported that remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome could be complicated with solid tumors. In a retrospective, multicenter study between October, 2003 and September, 2010, we investigated the characteristics of patients with paraneoplastic RS3PE syndrome who fulfilled following criteria: (1) bilateral pitting edema of hands or feet or both, (2) sudden onset of polyarthritis, and (3) age >50 years, (4) seronegativity for rheumatoid factor (RF). A total of 33 cases fulfilled the above criteria. Eight patients (seven men and one woman) developed cancer within 2 years of RS3PE syndrome onset. There was no significant difference between the neoplastic and nonneoplastic groups in the proportions of patients with fever, symmetrical polyarthritis, pitting edema, and good response to corticosteroids. Serum matrix metalloproteinase 3 (MMP-3) level (median 437.3 ng/ml) in the paraneoplastic RS3PE patients was significantly higher than that in patients without neoplasia (median 114.7 ng/ml) ($p < 0.05$). We found that high serum MMP-3 is characteristic of patients with paraneoplastic RS3PE syndrome.

Keywords Remitting seronegative symmetrical synovitis with pitting edema syndrome (RS3PE syndrome) · Matrix metalloproteinase 3 · Neoplasia

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Introduction

Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome was first described by McCarty and colleagues in 1985 [1]. Recently, it was reported that RS3PE syndrome is frequently complicated with malignancies [2, 3]. Sibilia et al. [3] reported six cases of RS3PE syndrome with solid tumors (four prostatic, one gastric, and one colic adenocarcinomas), all of which displayed elevated intetleukin-6 (IL-6) levels . It has been shown that proinflammatory cytokines, including IL-6, can be secreted by certain solid tumors, and the authors postulated that an underlying malignancy might have triggered RS3PE syndrome via an inflammatory process involving IL-6, resulting in high serum C-reactive protein (CRP) levels [3]. In addition to IL-6, we reported high serum concentrations of other humoral factors in patients with RS3PE syndrome, namely, vascular endothelial growth factor (VEGF) and matrix metalloproteinase 3 (MMP-3), which, respectively, account for synovial hypervascularity and inflammation in these patients [4, 5].

Several environmental factors, or infectious agents such as *Borrelia burgdorferi*, *Campylobacter jejuni* or *Helicobacter pylori* (*H. pylori*), have been identified as possibly being involved in the pathogenesis of RS3PE syndrome [6]. It was reported that among *H. pylori*-infected individuals, those with gastric cancer have significantly higher MMP-3 levels and that elevated MMP-3 levels may thus be able to predict gastric cancer in such individuals [7]. Considering that RS3PE syndrome may be classified as paraneoplastic syndrome [3], MMP-3 is considered a biomarker for these patients. In this regard, we sought to identify the characteristics of MMP-3 in patients with paraneoplastic RS3PE syndrome.

Patients and methods

Patients

A retrospective multicenter study was performed on patients with RS3PE syndrome fulfilling the following criteria: (1) bilateral pitting edema of hands or feet or both, (2) sudden onset of polyarthritis, (3) age >50 years, and (4) seronegativity for rheumatoid factor (RF). A total of 33 patients was diagnosed with RS3PE syndrome between October 2003 and September 2010, including nine who developed solid tumors. Eight of those nine patients developed cancer within 2 years from RS3PE syndrome onset; thus, we defined paraneoplastic RS3PE syndrome by an interval of <2 years between the cancer diagnosis and RS3PE syndrome. Clinical characteristics of patients with paraneoplastic RS3PE syndrome ($n = 8$) were compared with RS3PE syndrome patients without neoplasia ($n = 24$). The one patient in whom cancer occurred early was excluded from the analysis. Baseline variables included age, gender, duration from onset to diagnosis, initial prednisolone dosage, distribution of inflamed joints and edema, and laboratory data including MMP-3. Response to prednisolone and the relapse during treatment were also examined. Informed consent was obtained from each patient, and the study was approved by the Institutional Review Board of Nagasaki University.

Enzyme-linked immunosorbent assay (ELISA)

Serum concentrations of MMP-3 in the above individuals were analyzed by enzyme-linked immunosorbent assay (ELISA) (Daiichi Fine Chemical Co. Ltd, Takaoka, Japan), as previously described [8].

Statistical analysis

Clinical data are expressed as the number (%) of patients with the indicated characteristic. Statistical analysis was performed using the chi-square test of independence for sex, number of patients with relapse, fever, and antinuclear antibody (ANA) positivity. Data for age, WBC count, hemoglobin, platelets, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and MMP-3 levels are expressed as medians [standard deviations (SD)]; statistical analysis was performed using Mann–Whitney's U test. A p value <0.05 was considered to indicate statistical significance.

Results

Clinical characteristics of paraneoplastic RS3PE syndrome

The eight patients in the paraneoplastic group and the 24 patients in the nonneoplastic group were subjected to analysis (Table 1). Neoplasia developed within 2 years of RS3PE syndrome onset in eight patients (25.0%) who were designated as having paraneoplastic RS3PE syndrome. These patients were uniformly elderly, with a median age of 79 (73–87) years; seven (87.5%) were men. The ratio of male to female patients was significantly higher in the paraneoplastic group than in the nonneoplastic group. There was no significant difference between groups in the number of patients with fever, symmetrical polyarthritis, or pitting edema. All patients had a good response to prednisolone; however, a few patients relapsed. Rheumatoid factor and anti-citrullinated protein antibody (CCP Ab) antibody were all negative.

Serum MMP-3 is high in paraneoplastic RS3PE syndrome

There was a trend for serum CRP and ESR to be higher in paraneoplastic RS3PE patients than in nonneoplastic patients (Table 1). Serum MMP-3 concentration was examined, and notably, the median MMP-3 level (437.3 ng/ml) in paraneoplastic RS3PE patients was significantly higher than that in patients without neoplasia (114.7 ng/ml) ($p < 0.05$). In male patients, the median MMP-3 level (437.3 ng/ml) in the paraneoplastic group was significantly higher than that in nonneoplastic group (124.0 ng/ml) (Fig. 1). Although active RS3PE patients had extremely high serum levels of MMP-3, even in the non-neoplastic group, serum levels of MMP-3 in most nonneoplastic patients were around 100 ng/ml. In female patients, the median MMP-3 level in the paraneoplastic group was 114.35 ng/ml and that of one paraneoplastic RS3PE patient was 588.1 ng/ml (Table 2).

Discussion

The clinical and laboratory features of patients with RS3PE are similar to those reported earlier [1–5, 7–10]; however, we found that malignancies were often complicated with RS3PE syndrome patients in Japan. A predominance of male paraneoplastic RS3PE patients was found; however, their other clinical characteristics, except for MMP-3, were not markedly different from RS3PE patients without neoplasia. Although all our patients met the clinical requirements of McCarty for RS3PE syndrome, it was reported that the inclusion of patients with unilateral involvement or steroid resistance may increase the frequency of this paraneoplastic condition [11]. Systemic signs/symptoms (fever, anorexia, weight loss) have also been suggested as one clinical characteristics of paraneoplastic RS3PE syndrome. As serum MMP-3 levels are influenced by several factors, such as sex, corticosteroids, and renal function, we divided MMP-3 levels by sex and calculated the difference

Table 1 Comparison of clinical features of 32 remitting seronegative symmetrical synovitis with pitting edema (RS3PE) patients with/without neoplasia

Characteristic	Paraneoplastic group ($n = 8$)	Nonneoplastic group ($n = 24$)	*P* value
Age at diagnosis (years)	79 (73–87)	76 (59–89)	0.327
Sex (M:F)	7:1	10:14	0.024
Duration (from onset to diagnosis)	≤3 days: 0; ≤1 week: 1; ≤1 month: 5; >1 month: 2	≤3 days: 2; ≤1 week: 8; ≤1 month:3; >1 month: 11	
Initial prednisolone dose	5 mg/day: 2; 7.5 mg/day: 0; 10 mg/day: 0; 15 mg/day: 0; 20 mg/day: 5; 30 mg/day: 1	5 mg/day: 2; 7.5 mg/day: 2; 10 mg/day: 2; 15 mg/day: 8; 20 mg/day: 9; 30 mg/day: 1	
Response to prednisolone	All patients: good response	All patients: good response	
Relapse	1	2	0.726
Fever	4	15	0.533
Inflamed joints	Shoulder 3; elbow 3; wrist 9; MCP 5; PIP 7; knee 3; ankle 5; MTP 1	Shoulder 13; elbow 13; wrist 22; MCP 13; PIP 11; knee 7; ankle 22 MTP 8	
Pitting edema	Right hand 7; left hand 7; right foot 6; left foot 7	Right hand 21; left hand 20 right foot 25; left foot 15	
WBC (/mm^3)	6,500 (3,900–17,900)	8,600 (3,900–17,200)	0.157
Hemoglobin (mg/dl)	10.3 (9.2–12.5)	11.4 (7.2–18.3)	0.361
Platelet ($\times 10^4$/mm^3)	29.5 (16.3–46.3)	32.4 (14–85.1)	0.408
ESR (mm/h)	89.0 (55–108) ($n = 6$)	61.0 (9–132) ($n = 24$)	0.341
CRP (mg/dl)	10.59 (3.96–12.35)	5.01 (0.43–21.5)	0.117
ANA ($\geq$40×)	4	7	0.282
RF positive	0	0	
Anti-CCP Ab positive	0	0	
MMP-3 (ng/ml)	437.3 (107.9–761)	114.7 (41.3–2,973.7)	0.045

Data are presented number, unless otherwise indicated

WBC white blood cells, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *ANA* antinuclear antibodies, *RF* rheumatoid factor, *anti-CCP Ab* anti-citrullinated protein antibody, *MMP-3* matrix metalloproteinase 3, *MCP* metacarpophalangeal, *PIP* proximal interphalangeal, *MTP* metatarsophalangeal

P value refers to the differences between paraneoplastic and nonneoplastic groups

in serum MMP-3 levels between the paraneoplastic and nonneoplastic groups. Among male patients, MMP-3 concentrations of the paraneoplastic group were significantly higher than those of the nonneoplastic group; concentrations could not be compared in female patients because there was only one in the paraneoplastic RS3PE group. The influence of corticosteroids and renal function also could not be assessed, given the small sample size and retrospective nature of the study. Nevertheless, our results raised the question: Why was there such a significant difference in MMP-3 levels between paraneoplastic and nonneoplastic patients?

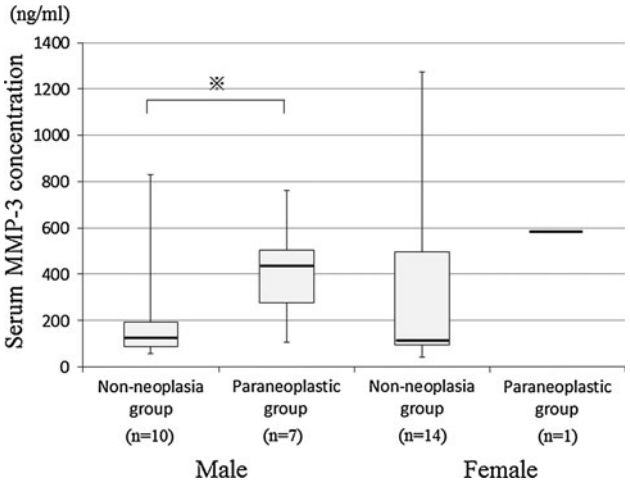

Fig. 1 Comparison of serum matrix metalloproteinase 3 (MMP-3) concentrations in remitting seronegative symmetrical synovitis with pitting edema (RS3PE) patients with/without neoplasia. The MMP-3 level in male patients is shown on the *left* and that in female patients on the *right*. The median MMP-3 level (437.3 ng/ml) in the male paraneoplastic RS3PE group was significantly higher than that in the nonneoplastic group (124.0 ng/ml) (※ $p < 0.05$). *Boxes* indicate interquartile values (25th–75th percentile); *lines* across the *boxes* indicate median values

It is well known that serum MMP-3 levels are increased in patients with active RA, psoriatic arthritis, and polymyalgia rheumatica (PMR) [12]. On the other hand, MMPs are a family of proteolytic enzymes involved in tumor invasion; several members of this family have been shown to be relevant to tumor prognosis [13]. It has been reported that colorectal tumors exhibit increased coexpression of MMP-3 and MMP-9 [14]. Inuzuka et al. [15] hypothesized that urokinase-type plasminogen activator (uPA) coexpressed with MMP-9 in colorectal cancers is responsible for activation of plasminogen to plasmin. Plasmin then activates pro-MMP-3 to MMP-3, which then activates pro-MMP-9, resulting in colorectal cancer progression. Elevated MMP-3 tissue levels have also been noted in some urologic carcinomas [16]. These data suggest that increased levels of MMP-3 might be associated with the progression or invasion of solid carcinoma. The expression of MMP-3

Table 2 Clinical features of eight patients with paraneoplastic remitting seronegative symmetrical synovitis with pitting edema (RS3PE)

Characteristics	1	2	3	4	5	6	7	8
Age at diagnosis (years)	80	81	73	78	74	79	83	87
Sex	M	M	M	F	M	M	M	M
Neoplasia	Lung	Prostate	Rectum	Breast	Stomach	Colon	Lung	Stomach
Duration (months)	0.8	2.3	1.5	4.5	1.7	1.2	13.2	1.0
Initial prednisolone dose (mg/day)	5	5	30	20	20	20	20	20
Response to prednisolone	Good	Good	Good	Good	Good	Good	Good	Good
Relapse	No	No	No	No	No	No	Yes	No
Fever	No	No	Yes	Yes	Yes	No	Yes	No
Arthritis	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pitting edema	Hands	Hands	Hands, feet	Hands, feet	Hands, feet	Feet	Hands, feet	Hands, feet
WBC (/mm^3)	8,230	7,410	17,900	7,000	6,500	5,800	3,900	6,100
Hb (mg/dl)	12.5	11.9	10.3	9.6	9.2	9.2	12.2	10.8
Platelet ($\times 10^4$/mm^3)	37.3	29.5	46.3	17.3	31.1	21	16.3	41.8
ESR (mm/h)	n.d.	55	108	n.d.	79.1	98	89	41
CRP (mg/dl)	10.59	6.37	12.35	11.09	11.3	8.7	3.96	10.69
RF	–	–	–	–	–	–	–	–
Anti-CCP Ab (U/ml)	1.6	1.2	1	0.6	n.d.	0.9	–	n.d.
ANA	<20×	20×	<20×	20×	40×	40×	320×	40×
MMP-3 (ng/ml)	107.9	457.9	437.3	588.1	761	425	130	550
Serum VEGF (pg/ml)	n.d.	n.d.	4.006.5	n.d.	2.010	n.d.	n.d.	n.d.

WBC white blood cells, Hb hemoglobin, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *ANA* antinuclear antibodies, *RF* rheumatoid factor, *anti-CCP Ab* anti-citrullinated protein antibody, *MMP-3* matrix metalloproteinase 3, *VEGF* vascular endothelial growth factor, *n.d.* not determined

was also reported in other cancers, such as breast, colon, and basal cell [14, 17, 18]. Fifteen (75%) of the 20 paraneoplastic RS3PE patients described by Cantini et al. [11] had prostatic, gastric, or colon carcinomas, and in 11 (73%) of them, the histological type was adenocarcinoma. Four of the remaining five patients had non-Hodgkin's lymphoma. In our paraneoplastic RS3PE syndrome patients, six who had alimentary tract, breast, or prostate cancers showed high MMP-3 levels, >400 ng/ml. The remaining two, who had lung cancers, showed lower levels of MMP-3 (107.9 and 130 ng/ml, respectively. Significantly higher serum MMP-3 in patients with paraneoplastic RS3PE syndrome may reflect the production of MMP-3 in situ of carcinoma tissues as well as in synovial tissues, and relatively high CRP and ESR levels might be associated with MMP-3. As this was a retrospective study, we could not obtain and compare differences in serum vascular endothelial growth factor (VEGF) concentrations between patients with and without paraneoplastic RS3PE syndrome. We plan to solve this problem by a prospective study.

Previous studies have reported an increased risk of cancer in several rheumatic syndromes, particularly Sjögren's syndrome, dermatomyositis, and temporal arthritis [19]. Rheumatic manifestations of cancer are usually indistinguishable from idiopathic rheumatic disease; however, certain features of rheumatic syndrome are more likely to be associated with a hidden malignancy. Although the search for malignancy in patients presenting the typical PMR is not justified, in atypical PMR, there is a significant risk for cancer, which should be assessed. Although RS3PE syndrome, like PMR, develops in the elderly population, there was no significant difference in clinical features except age and MMP-3 levels between the paraneoplastic and nonneoplastic RS3PE groups. This fact has been overlooked by most general physicians. Importantly, seven of the eight patients in our study with paraneoplastic RS3PE syndrome were not diagnosed within 1 week. We conclude that early diagnosis of RS3PE is important and that an especially high MMP-3 level is a meaningful biomarker of RS3PE syndrome complicated with malignancy.

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Conflict of interest None.

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