

Serum Levels of Interleukin-6 in Patients with Cutaneous Polyarteritis Nodosa

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Cutaneous polyarteritis nodosa (CPN) is a necrotizing vasculitis of small-to-medium-sized arteries within the skin without the involvement of internal organs (1). We previously reported the presence of anti-phosphatidylserine-prothrombin complex (anti-PS/PT) antibodies and/or lupus anticoagulant (LAC) in patients with CPN, while they were not detected in any of the normal subjects tested (2). Interleukin-6 (IL-6) is a strong inducer of the acute-phase response, which can result in elevations in acute-phase proteins, such as C-reactive protein (CRP). We have now retrospectively evaluated the correlation between these biological parameters and the clinical manifestations.

PATIENTS AND METHODS

We reviewed the sequential records of 45 patients with CPN (14 men, 31 women; age range 18–80 years, mean age 46.5 years) who presented at the Department of Dermatology, St. Marianna University School of Medicine, between 2003 and 2009. These patients were diagnosed according to Japanese criteria (1) and the KAWAKAMI algorithm (3). The patients did not satisfy the criteria for the classification of antiphospholipid syndrome (4) because of the presence of histopathological necrotizing vasculitis and involvement of the skin but not internal organs. None of the patients had been treated with corticosteroids, immunosuppressants or vasodilators at the time of serum sampling. Furthermore, none of them demonstrated any evidence of a co-existing malignancy, other autoimmune disease or viral hepatitis, nor were any of the patients positive for mixed cryoglobulinaemia or anti-neutrophil cytoplasmic autoantibody. Thirty healthy persons with comparable sex and age distributions were recruited as normal controls.

The first immunological assessments were performed on sera collected at the same time as the skin biopsies. LAC, anti-PS/PT antibodies and anticardiolipin (aCL) antibodies were measured according to our previously published methods (2, 5, 6). Serum CRP, IL-6, IL-8 and tumour necrosis factor- α (TNF- α) were measured according to the manufacturer's protocol.

Statistics

The Mann-Whitney *U* test was used to determine the relationships between blood parameters and the various clinical symptoms. χ^2 tests were used to compare the prevalence between the elevated IL-6 group and the normal group for gender, direct immunofluorescence (DIF) findings and treatments.

The study protocol was approved by St Marianna University, and informed consent was obtained from all patients and healthy controls (No. 1117).

RESULTS

Thirty-two (71.1%) of the 45 patients with CPN had arthralgia, 23 (51.1%) had myalgia, and 31 (68.9%) had mononeuritis multiplexes on their lower extremities. Twenty-six (57.8%) of the patients with CPN had skin

ulcerations. Cutaneous nodules (100.0%) were the most common skin manifestations and were observed in all of our patients with CPN. Forty (88.9%) of the patients with CPN had livedo racemosa, and 33 (73.3%) had purpuric lesions on their lower extremities. Twenty-seven (60.0%) of the patients with CPN were positive for serum CRP, and LAC activity was observed in 27 of them (60.0%). Nineteen (42.2%) of the patients with CPN had elevated serum IL-6 levels and 29 (66.4%) had elevated serum IL-8 levels, while only 4 (8.9%) had elevated serum TNF- α levels. Seven (15.6%) were positive for serum IgG anti-PS/PT antibody, 33 (73.3%) for IgM anti-PS/PT antibody, and 6 (13.3%) for IgG aCL antibody. DIF studies were performed on skin biopsy samples from 29 of the patients with CPN, and revealed complement 3 expression within affected vessels of the lesions in 21 (72.4%) of them. In addition, 18 (62.1%) of those 29 patients with CPN showed IgM deposition within affected vessels. Thirty-four (75.6%) of the patients with CPN were treated with warfarin, and prednisolone therapy was administered to 27 (60.0%) of them.

We divided the 45 patients with CPN into two groups; the elevated IL-6 group and the normal IL-6 group (Table I). The number of men in the elevated IL-6 group was significantly higher than in the normal IL-6 group. Patients with elevated IL-6 had a significantly higher frequency of arthralgia compared with patients without elevated IL-6. Skin ulcerations were also significantly more prevalent among patients with elevated IL-6 compared with patients without elevated IL-6. Elevated IL-6 patients had significantly higher CRP serum levels than normal IL-6 patients. LAC in the elevated IL-6 group was significantly more prevalent than in the normal IL-6 group. Serum IgG anti-PS/PT antibody levels differed significantly between the elevated IL-6 group and the normal IL-6 group. Similarly, serum IgG aCL antibody levels were significantly higher in the elevated IL-6 group compared with the normal IL-6 group. In contrast, IgM anti-PS/PT antibody levels in patients with CPN with elevated IL-6 were significantly lower than in normal IL-6 level patients with CPN. The selected prevalence of prednisolone in the elevated IL-6 group was significantly higher than in the normal IL-6 level group.

DISCUSSION

This study is the first to characterize levels of IL-6 in patients with CPN to our knowledge. The elevated IL-6 group had a significantly greater incidence of arthralgia

Table I. Comparison of clinical, serological and direct immunofluorescence (DIF) findings and treatments of patients with cutaneous polyarteritis nodosa with or without elevated serum levels of interleukin (IL)-6

Characteristic	Elevated IL-6 (n=19)	Normal IL-6 (n=26)	p
Age, years, median	54	43	0.0695
Gender, n (%)			0.00027** $\chi^2=15.76$
Female	7 (36.8)	24 (92.3)	
Male	12 (63.1)	2 (7.7)	
Arthralgia, n (%)	18 (94.7)	14 (53.8)	0.0031**
Myalgia, n (%)	12 (63.1)	11 (42.3)	0.172
Mononeuritis, n (%)	15 (78.9)	16 (61.5)	0.218
Skin ulcer, n (%)	15 (78.9)	11 (42.3)	0.0151*
Livedo, n (%)	17 (89.5)	23 (88.5)	0.916
Purpura, n (%)	15 (78.9)	18 (69.2)	0.472
CRP, mg/dl, n (%) [median]	18 (94.7) [2.2]	9 (34.6) [0.105]	0.0011**
LAC, n (%)	15 (78.9)	12 (46.2)	0.0283*
IL8, pg/ml, n (%) [median]	10 (52.6) [2.1]	19 (73.1) [3.25]	0.8
TNF- α , pg/ml, n (%) [median]	1 (5.3) [1.3]	3 (11.5) [1.1]	0.744
PS/PT IgG, U/ml, n (%) [median]	5 (26.3) [6]	2 (7.7) [5]	0.0473*
PS/PT IgM, U/ml, n (%) [median]	11 (57.9) [12]	22 (84.6) [17]	0.0350*
aCL IgG, U/ml, n (%) [median]	5 (26.3) [3]	1 (3.9) [3]	0.043*
aCL IgM, U/ml, n (%) [median]	1 (5.3) [3]	2 (7.7) [3]	0.422
Treatment, n (%)			
Warfarin	17 (89.5)	17 (65.4)	0.063 $\chi^2=3.449$
Prednisolone	16 (84.2)	11 (42.3)	0.00460** $\chi^2=8.0314$

* $p < 0.05$, ** $p < 0.01$.

CRP: C-reactive protein; DIF: direct immunofluorescence; LAC: lupus anticoagulant; PS/PT: anti-phosphatidylserine-prothrombin complex antibody; TNF α : tumour necrosis factor- α ; PS/PT: phosphatidylserine-prothrombin; aCL: anticardiolipin.

and skin ulcerations compared with the normal IL-6 group. There was a significantly greater level of LAC in the elevated IL-6 group compared with the normal IL-6 group. We found a significantly higher titre of serum IgG anti-PS/PT antibody and IgG aCL antibody in the elevated IL-6 group. IL-6 elevation in the serum probably contributed to the aggressive clinical condition. The high prevalence of aggressive clinical events in the elevated IL-6 group could be related to the IgG anti-phospholipid antibodies. Based on these data, we suggest that serum IL-6 leads to the severe condition of CPN and could play an important role in the pathogenesis of the elevated IL-6 group.

We previously reported the successful treatment of CPN with warfarin (7). However, warfarin therapy alone cannot effectively treat active inflammatory disease. Systemic glucocorticosteroids represent anti-inflammatory agents and are the mainstay of therapeutic strategies for autoimmune diseases. We used prednisolone with a significantly higher rate of usage in the elevated IL-6 group compared with the normal IL-6 group for the treatment of severe conditions. TNF- α -targeted therapies are increasingly used for a rapidly expanding number of rheumatic and autoimmune diseases. However, the use of anti-TNF- α agents has been associated with various side-effects, principally cutaneous vasculitis (8). Only 4 (8.9%) of our 45 patients with CPN had elevated serum levels of TNF- α , and TNF- α is probably not prominently involved in the pathogenesis of CPN.

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