Diagnostic value of procalcitonin measurement in febrile patients with systemic autoimmune diseases

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Abstract

Objective

To determine the usefulness of plasma procalcitonin (PCT) measurement to suspect infectious etiology in febrile patients with systemic autoimmune disease.

Methods

PCT, C-Reactive protein (CRP), erythrocyte sedimentation rate (ESR) and white blood cell count (WBC) were measured in 44 consecutive inpatients with a diagnosis of systemic autoimmune disease and fever >38° C. After careful microbiologic screening no obvious infection was demonstrated in 24 patients (Group A) while an infectious bacterial complication was diagnosed in 20 cases (Group B).

Results

Median PCT levels were significantly higher in the group B (1.11 vs 0.24 ng/ml; p = 0.0007), whereas the differences for CRP, WBC and ESR did not reach statistical significance. PCT also exhibited a good sensitivity and specificity (75%) in differentiating patients with infection from those with disease flare. With respect to positive and negative predictive values (71.4% and 78.2%), PCT markedly exceeded the other variables. By analyzing PCT values by disease we identified a false positive subgroup of patients suffering from adult onset Still's disease (AOSD), showing markedly elevated PCT levels in absence of infection. By excluding these patients, PCT showed a very good sensitivity and specificity (73.6% and 89.4%) and the area under receiver operating characteristics (ROC) curve rose from 0.801 to 0.904.

Conclusion

Our data indicate that elevated PCT concentrations offer good sensitivity and specificity for the diagnosis of systemic bacterial infection in febrile patients with systemic autoimmune diseases. However, in fever associated with AOSD PCT may be elevated even in the absence of infectious complication.

Key words

Procalcitonin, fever, autoimmune diseases, adult onset Still's disease.

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Introduction

Fever is a troublesome clinical feature in patients with systemic autoimmune disease and it is often a clinical challenge since the differential diagnosis between infection and disease flare may be difficult. Acute-phase reactants routinely tested do not generally allow discriminating between infectious and non-infectious etiology of febrile episodes. An exception could be C-reactive protein (CRP) levels in systemic lupus erythematosus (SLE) since serum CRP levels are generally poorly increased with active SLE, while a bacterial infection can elicit a marked CRP production, following a different response of monocytes to the activation by LPS or immune complexes (1-3). However, there are currently no evidence-based data to justify the use of CRP as for management decisions regarding the institution, continuation or withholding of antibiotic therapy, or for differentiating between bacterial and viral etiology (4).

Procalcitonin (PCT), a precursor peptide of calcitonin, has been reported as a useful and reliable marker in systemic bacterial and fungal infections (5). It has proven to be more specific than CRP and white blood cell count for inflammatory processes due to bacterial or fungal infection and it may be helpful in distinguishing between infectious and noninfectious causes in acutely ill patients (6). Some reports also underline a possible role for differential diagnosis between infection and disease flare in patients with autoimmune systemic diseases, such as SLE and ANCA-associated vasculitis (AAV) (7, 8). However, several cases of non-infectious PCT increase have been reported, so limiting the specificity of this test (9-11).

Therefore, how PCT can be regarded as a marker of disseminated bacterial infection and a reliable tool for differential diagnosis of fever in systemic autoimmune diseases is still an open question.

Patients and methods

Patients

Over a 6 months period, all consecutive inpatients admitted to the Rheumatology Unit of Pavia University Hospital with diagnosis of systemic autoimmune disease who presented or developed fever > 38°C entered the study. A total of 52 patients were enrolled and carefully screened for infection by classical methods including chest radiograph and cultures of blood, midstream urine, stool, sputum, bronchoalveolar lavage (when indicated) and pharyngeal tampon, taken before antibiotic treatment. Twenty-four cases resulted infection-free (group A) whereas an infectious complication was diagnosed in 20 cases (group B).

Group A included patients with negative microbiologic screening and fever responsive to increased doses of steroids and/or immunosuppressants. No case was treated with antibiotics or antifungal and antiviral drugs at the time of the study. The main clinical and laboratory characteristics of these patients are reported in Table I.

Group B included febrile patients with microbiologic demonstration of infection, including nosocomial infection, and those presenting clinical features highly suggestive for infection (i.e.: pulmonary infiltrate on chest x-ray responsive to empiric antibiotic therapy), responsive to antibiotic therapy alone. We considered all kinds of infection, both localized and generalized. Infections were microbiologically proven in 17 out of 20 patients. The main clinical and laboratory characteristics of these patients are reported in Table II.

The length of the fever (median, 25th and 75th percentile) at the start of the study was 6 days (4.5-8) for the group A and 4 days (1.5-5.5) for the group B (p value. < 0.001).

Eight patients were not included because of self-limiting fever or indefinite fever treated with both antibiotics and steroids.

Laboratory analysis

All patients were tested for the white blood cell count (WBC), erythrocyte sedimentation rate (ESR), CRP and PCT levels at admission or at the onset of fever. In those patients with elevated PCT levels who were treated with antibiotics, additional tests were per formed during treatment until fever

Table I. Main characteristics of non-infectious patients (Group A).

Case	Disease	PCT (ng/ml)	CRP (mg/dl)	ESR (mm/h)	WBC (x1000/μl)
1	AAV	0.21	0.27	109	2.86
2	AAV	0.38	9.00	105	10.80
3	AAV	0.19	27.90	60	14.00
4	AAV	0.96	0.88	140	11.50
5	AAV	0.13	0.32	48	7.99
6	AOSD	11.9	27.80	63	21.20
7	AOSD	71	14.90	83	26.40
8	AOSD	0.65	15.40	32	23.70
9	AOSD	14.46	19.30	78	12.40
10	AOSD	0.09	11.40	100	25.60
11	LVV	0.31	15.80	108	6.99
12	LVV	0.08	1.67	84	5.73
13	PM	0.35	3.00	60	10.00
14	PM	0.08	8.40	75	11.70
15	PMR	0.16	5.19	39	2.59
16	RA	0.1	4.70	48	16.20
17	RA	0.75	15.40	88	13.00
18	RA (Felty)	0.25	10.20	71	4.47
19	SLE	0.35	1.20	45	4.20
20	SLE/RA overlap	0.25	9.36	38	0.95
21	SLE	0.1	0.60	70	4.00
22	SSc	0.24	1.00	50	6.00
23	SWEET	0.11	8.64	38	13.06
24	UCTD	0.22	4.19	9	10.00

AAV: ANCA-associated vasculitis; AOSD: adult onset Still's disease; LVV: large vessel vasculitis; PM: polymyositis; PMR: polymyalgia rheumatica; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; SSc: systemic sclerosis; UCTD: undifferentiated connective tissue disease; PCT: procalcitonin; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; WBC: white blood cell count.

disappeared.

ESR was evaluated according to the Westergren method (cut-off 20mm/h). Serum CRP was measured by nephelometric assay; normal values ranged from 0.1 to 0.6 mg/dl.

Plasma PCT was measured by immunoluminometric assay (BRAHMS PCT LIA; Brahams Diagnostica, Berlin, Germany). According to the manufacturer's recommendations, normal ranges were from 0.08 to 0.5 ng/ml for PCT (5). The detection limit calculated using the imprecision profile has been assessed as being 0.08 ng/ml. The intra-assay CV and the inter-assay CV are 6-10% in the clinically relevant PCT concentration range.

Statistical analysis

Continuous variables were described as median and interquartile range (IQR), and categorical variables as absolute and relative (%) frequencies. Results were analyzed using the Mann-Whitney U-test for unpaired samples and by computing the area under the receiver operating characteristics (ROC) curve. Sensitivity, specificity, positive and negative predictive values of the differ-

Table II . Main characteristics of infectious patients (Group B).

Patient	Disease	Infection	Etiology	PCT (ng/ml)	CRP (mg/dl)	ESR (mm/h)	WBC (x1000/μl)
1	AAV	peritonitis	-	5.06	28.50	63	10.20
2	AAV	pneumonia	*Streptococcus pneumoniae*	0.93	10.00	70	9.00
3	AAV	pneumonia	*Pneumocistis carinii*	0.45	8.28	93	1.94
4	AOSD	soft tissue infection	*Staphylococcus aureus*	2.2	6.00	50	15.00
5	CV	soft tissue infection	*Staphylococcus aureus*	0.48	0.33	62	9.90
6	PM	pneumonia	*Legionella pneumophila*	0.77	21.00	63	21.70
7	PM	pneumonia	*Pseudomonas aeruginosa*	1.82	15.00	80	12.00
8	PMR	pneumonia	(community acquired)	0.5	14.20	78	3.27
9	RA	acute pyelonephritis	*Enterobacter intermedius*	0.29	16.60	78	9.50
10	RA	bacteriemia	*Staphylococcus aureus*	0.68	6.64	107	9.56
11	RA	bacteriemia	*Staphylococcus epidermidis*	0.74	16.00	110	17.90
12	RA	septic arthritis	*Staphylococcus aureus*	1.3	19.30	83	9.80
13	SLE	acute pyelonephritis	*Escherichia coli*	0.73	1.74	50	4.20
14	SLE	bacteriemia	*Stenotrophomonas maltophilia*	0.11	2.74	68	2.28
15	SLE	gastroenteritis	*Salmonella tiphi*	8.92	12.00	85	3.80
16	SLE	pneumonia	(community acquired)	5.73	23.90	120	15.71
17	SLE	pneumonia	*Pseudomonas aeruginosa*	1.5	8.00	70	8.00
18	SLE	pneumonia	*Stenotrophomonas maltophilia*	44.07	17.30	69	22.20
19	SLE	sepsis	*Salmonella tiphi*	2.46	8.80	79	5.00
20	SSc	pneumonia	*Stenotrophomonas maltophilia*	59.58	15.00	60	6.00

AAV: ANCA-associated vasculitis; AOSD: adult onset Still's disease; CV: cryoglobulinaemic vasculitis; PM: polymyositis; PMR: polymyalgia rheumatica; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; SSc: systemic sclerosis; PCT: procalcitonin; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; WBC: white blood cell count.

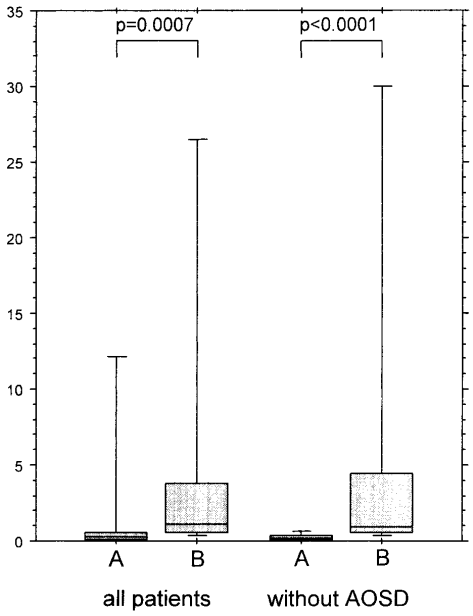

Fig. 1. Plasma levels of PCT in all study patients split by infection (group A = non-infectious, Group B = infectious) and in the patient selection without AOSD cases. Data are presented as box plots with median lines, 25- and 75- percentile boxes and 10- and 90- percentile error bars.

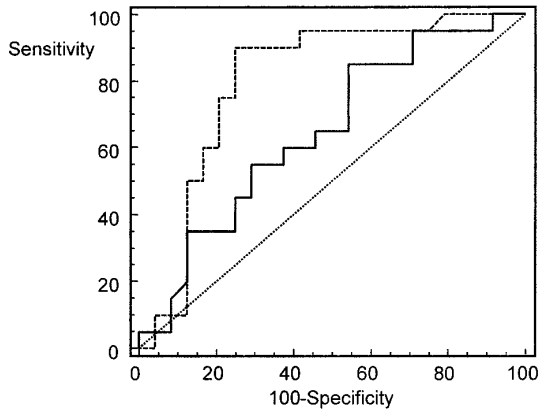

Fig. 2. Receiver operative characteristics curves (ROC) of PCT and CRP in all patients.

ent variables were also calculated. Stata 8 (StataCorp, College Station, TX) was used for computation. A 2-sided p-value < 0.05 was considered statistically significant.

Results

Median PCT levels were 0.24 ng/ml (0.12-0.51) for the group A and 1.11 ng/ml (0.59-3.76) for the group B (p = 0.0007) (Fig. 1, left side), while median CRP levels were 8.52 mg/dl (1.44-15.15) and 13.10 mg/dl (7.32-16.95) respectively (p=0.0966). Median WBC levels were similar in both groups (10.40 x 10^3/µl (5.1-13.53) in group A and 9.53 x10^3/µl (4.6-16.8) in group B (p = 0.5245)) as were ESR levels (66.5mm/h (46.5-86) in group A and 74 mm/h (63-84) in group B (p = 0.2073)). The median serum PCT value of the 8 patients excluded from the study because non definite diagnosis was 0.5 ng/ml (0.32 -1.31).

As for infections, serum PCT concentration (cut-off value = 0.5 ng/ml) gave a sensitivity of 75% (95% CI 62.21-87.79), a specificity of 75% (95% CI 62.21-87.79), a positive predictive value of 71.43% (95% CI 58.08-84.78) and a negative predictive value of 78.26%. The same figures for CRP (cut-off = 0.6 mg/dl), were 95% (95% CI 88.56-100), 8.33% (95% CI 0.17-16.5), 46.34% (95% CI 31.61-61.08) and 66.67% (95% CI 52.74-80.60) respectively. No significant sensitivity/specificity values resulted from ESR and WBC (Table III).

A follow-up of PCT values during the course of antibiotic treatment for infection was performed in 15 patients with elevated PCT values. In all cases a reduction to normal range was observed along with the recovery from the febrile status (Fig. 3). In 5 cases with the higher pre-treatment values a further control carried out 15 days later showed persistently normal values.

The area under the ROC curve for prediction of infection was higher for PCT as compared with the other variables (Table III) even if the difference did not reach statistical significance (p = 0.073).

As for serum PCT levels, 6 positive patients were found in group A: one with AAV (PCT 0.96 ng/ml), one with rheumatoid arthritis (RA) (PCT 0.75 ng/ml) and four with adult onset Still's disease (AOSD) (median and IQR 13.18 ng/ml; 9.09-28.6).

We also found 5 negative cases in group B, one SLE with *Stenotrophomonas maltophilia* bacteriaemia, one RA with *Enterobacter intermedius* acute pyelonephritis, one polymyalgia rheumatica (PMR) with community-acquired pneumonia, one cryoglobulinemic vasculitis (CV) and localized *Staphylococcus aureus* soft tissue infection.

Data analysis excluding adult onset Still's disease

Grouping all febrile patients by underlying disease, we found that 4 out of 5 patients with AOSD showed highly elevated PCT levels even in the absence of detectable systemic infection. Median PCT levels resulted 0.23 ng/ml (0.13-0.35) for the group A and 0.93 ng/ml (0.54-4.41) for the group B (p = 0.0000) (Fig. 1, right side). After AOSD patients exclusion, PCT sensitivity in identifying infectious patients turned into 73.68% (95% CI 59.68-87.68) and specificity rose to 89.47% (95% CI 79.72-99.23). On the other side, CRP was nearly unaffected by AOSD exclusion (Table III).

The area under ROC curve rose to 0.904 for PCT and to 0.742 for CRP (p = 0.053). No significant changes resulted from ESR and WBC values.

Discussion

Our data confirm a role for PCT in discrimination between infectious or non-infectious etiology in febrile patients

Table III. Diagnostic performance of different acute phase reactants. Sensitivity, specificity, predictive values and area under the ROC were calculated for the literature cut-off.

	All patients				Without AOSD			
	PCT	CRP	ESR	WBC	PCT	CRP	ESR	WBC
Sensitivity (%)	75	95	100	35	73.68	94.74	100	31.58
Specificity (%)	75	8.33	4.17	50	89.47	10.53	5.26	63.16
Positive predictive value (%)	71.43	46.34	46.51	36.84	87.50	51.43	51.35	46.15
Negative predictive value (%)	78.26	66.67	100	48	77.27	66.67	100	48
Area under ROC curve	0.801	0.646	0.611	0.556	0.904	0.742	0.646	0.520

PCT: procalcitonin (cut-off: 0.5 ng/ml); CRP: C-reactive protein (cut-off: 0.6 ng/m)l; ESR: erythrocyte sedimentation rate (cut-off: 20mm); WBC: white blood cell count (cut-off: 10x1000/μl).

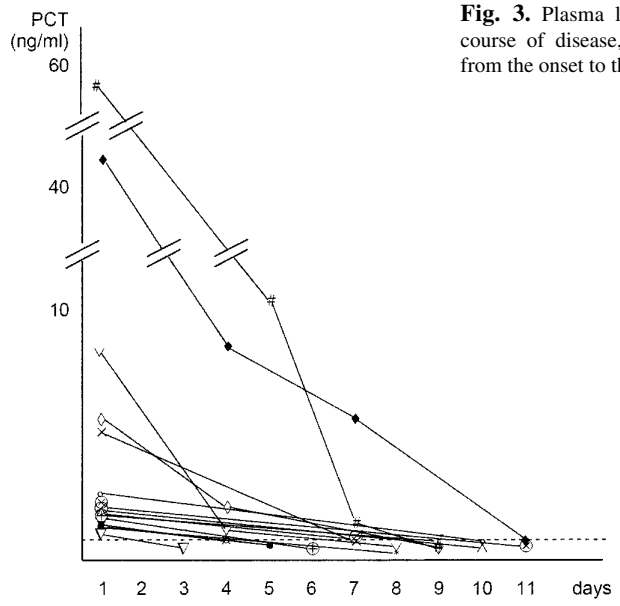

Fig. 3. Plasma levels of PCT following the course of disease, during antibiotic treatment, from the onset to the recovery of febrile status.

suffering from systemic autoimmune diseases. However we found that fever in AOSD can be associated with a very high increase of PCT values even in the absence of infection.

PCT has been reported as a useful and reliable marker in diagnosis and monitoring systemic bacterial and fungal infections, even if its role in viral infections is limited (5).

Eberhard and colleagues first observed that systemic infections occurring in patients affected by AAV were associated with a marked elevation of PCT plasma levels (7). Further studies performed in patients affected by various systemic autoimmune diseases showed that PCT levels in patients with an underlying infection are generally higher than those detected in course of disease flare (8, 12-14). In our study we confirm the elevation of PCT values in infectious complications in patients with diagnosis of autoimmune systemic disease, extending this results in a selected population of febrile patients.

Despite mounting evidence of an increase in PCT levels, this marker can not always be regarded as a reliable indicator of infection in patients suffering from autoimmune systemic diseases. Schwenger and colleagues demonstrated, in patient with Wegener's granulomatosis (WG), that PCT levels can rise to 1ng/ml in absence of infectious complications, but also demonstrated that PCT measurement may be useful in the presence of systemic bacterial infection (8). Our data confirm the usefulness of PCT in AAV even if, according to previous findings (8, 10), we found a false positive patient affected by WG, showing a PCT level again lower than 1 ng/ml. A further false positive was affected by elderly onset RA, with a slight (< 1 ng/ml) PCT level increase.

In our study, a first analysis of PCT test performance showed a specificity lower than that reported by other authors. However, by splitting our data by disease, we found that the majority of false positive cases referred to a single group of patients suffering from AOSD. These patients showed high PCT levels despite the lack of evidence of disseminated bacterial infection, and their clinical course was characterized by rapid favorable evolution after proper steroidal and/or immunosuppressive therapy. As a result, our general specificity was clearly decreased by the presence of this well defined subgroup of false-positive cases. By excluding AOSD patients, a specificity of 89.49% was reached, in keeping with previous reports in which specificity ranged from 84 to 96%.

PCT values were very high in three of the AOSD patients. This picture is similar to that recently reported by Okada and colleagues in Kawasaki disease (11). Due to the significant high plasmatic levels often reached in this illness, PCT has been regarded by the same authors as a reliable marker of disease's activity in children suffering from this vasculitis (11). Previous studies reported either normal PCT values in AOSD (14) or an elevation in about 20% patients. However, in these studies it was not specified whether PCT measurement had been performed during febrile states (15). Therefore, the

observed differences may be due to a different timing of sampling.

The striking increase of PCT levels we found in AOSD-related fever extends the previous findings and highlights that a consistent elevation of this parameter may occur in the absence of septic complication in these patients.

From a pathophysiologic point of view, the non-specific PCT increase in AOSD patients can be interpreted as a response to stimuli other than infections. Some authors have suggested a role for inflammatory cytokines in inducing PCT release rather than a direct action of lipopolysaccharide or any bacterial products (16, 17). Accordingly, the highest PCT levels are seen during infections associated with marked tumor necrosis factor α (TNF-α) release, such as Gram-negative infections and malaria.

High serum levels of TNF-α were detected in patients affected by AOSD in association with disease activity, and anti-TNF-α biologic therapies have been demonstrated to be useful in disease flares of this particular form of systemic arthritis (18, 19). Therefore, TNF-α might play a role in non-infectious induction of PCT in AOSD febrile patients.

In conclusion, in our study we evaluated for the first time only patients with fever and previous diagnosis of systemic autoimmune disease. In this setting, PCT determination could be regarded as the better available test in identifying a possible infectious etiology and a useful laboratory tool in therapeutic decision. However we should be aware that the serum concentration of PCT can dramatically increase during febrile spikes in AOSD patients even in the absence of detectable infection.

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