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Brief Report

Procalcitonin as marker of infection in patients with Goodpasture's syndrome is misleading

Christian Morath[1], Jeanne Sis[1], Gertrud M. Haensch[2], Martin Zeier[1], Konrad Andrassy[1] and Vedat Schwenger[1]

[1]Department of Nephrology and [2]Department of Immunology, University of Heidelberg, Heidelberg, Germany

Abstract

Background. Procalcitonin (PCT) is routinely measured to differentiate autoimmune disorders from infection. There are reports, however, where PCT is high in the absence of infection, i.e. in vasculitis. To investigate the value of PCT in Goodpasture's syndrome, we reviewed the charts of patients with Goodpasture's syndrome who were treated from 1996 to 2006.

Methods. PCT (normal range <0.5 ng/ml) was measured with an immunoluminometric assay, C-reactive protein (CRP; normal range <5 mg/l) with nephelometry. Anti-glomerular basement membrane antibodies (normal range <1:10) were measured with ELISA.

Results. During the last 10 years we diagnosed seven patients with Goodpasture's syndrome. Six out of seven patients had biopsy proven crescentic and necrotizing glomerulonephritis. Five patients had a severe manifestation with pulmonary involvement ($n = 3$) and/or severe renal insufficiency ($n = 4$). Mean CRP levels were 145.7 mg/l, mean PCT levels were 34.1 ng/ml. Therapy consisted of plasmapheresis ($n = 3$), pulse cyclophosphamide therapy ($n = 4$) and glucocorticoids ($n = 6$). Remarkably, all patients with elevated PCT levels had life-threatening disease ($n = 4$) and remained dialysis-dependent (as compared to with only one out of three patients with normal PCT). In two out of five patients with severe Goodpasture's syndrome, PCT levels remained high. After thorough exclusion of infection, resumption of high dose glucocorticoids normalized PCT and CRP levels.

Conclusions. The measurement of PCT as a marker of infection in patients with Goodpasture's syndrome is misleading. High PCT values might rather point to a severe form of Goodpasture's syndrome with a more unfavourable prognosis. However, further studies with larger patient numbers are needed to prove this hypothesis.

Keywords: Goodpasture's syndrome; infection; inflammation; procalcitonin

Introduction

Goodpasture's syndrome is a rare disease with pulmonary and/or renal involvement. Diagnosis of Goodpasture's syndrome is challenging, because clinical presentation of infection, i.e. atypical pneumonia, can be similar, necessitating different therapeutic strategies. Inflammatory disorders such as vasculitis might also mimic Goodpasture's syndrome and must always be considered in the differential diagnosis of the disease [1]. Among several markers of inflammation and sepsis, C-reactive protein (CRP) and procalcitonin (PCT) are the most useful indicators. Although CRP is a sensitive marker of inflammation, it does not discriminate between infection and autoimmune diseases. PCT levels were found to be more specific for differentiating bacterial from non-infective causes of inflammation as compared with CRP [2,3]. There are several reports in the literature, however, where high PCT levels were found in the absence of any infection, i.e. in Behcet's disease, Kawasaki disease and active Wegener's granulomatosis [4–7]. In patients with Goodpasture's syndrome, the diagnostic value of PCT has not been investigated so far. In this regard, we report on seven consecutive patients with Goodpasture's syndrome (five patients with life-threatening disease) where PCT levels were high in four of seven patients in the absence of any infection.

Subjects and methods

The charts of seven patients with Goodpasture's syndrome who were treated at our department from 1996 to 2006 were reviewed.

Correspondence and offprint requests to: Dr Christian Morath, Department of Nephrology, University of Heidelberg, Im Neuenheimer Feld 162, 69120 Heidelberg.
Email: christian_morath@med.uni-heidelberg.de

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Table 1. Clinical characteristics of seven patients with Goodpasture's syndrome

Patient	Age	Gender	Clinical features	Therapy	Outcome
1	41	M	Renal failure, pulmonary infiltrates	Pulse steroids, fresh frozen plasma	Alive, dialysis
2	19	F	Renal failure, pulmonary bleeding	Pulse steroids, cyclophosphamide, plasmapheresis (4×)	Alive, dialysis
3	29	F	Renal failure	Pulse steroids, cyclophosphamide, plasmapheresis (4×)	Alive, renal insufficiency
4	70	F	Renal failure	Pulse steroids, cyclophosphamide	Alive, renal insufficiency
5	72	M	Renal failure	Steroids	Alive, dialysis
6	18	M	Renal failure, pulmonary bleeding	Pulse steroids, cyclophosphamide, plasmapheresis (2×)	Alive, dialysis
7	61	M	Renal failure	No specific therapy	Alive, dialysis

M, male; F, female.

Table 2. Laboratory values and serology in seven patients with Goodpasture's syndrome

Patient	Anti-GBM antibodies [normal <1:10]	Maximal PCT [normal <0.5 ng/ml]	Maximal CRP [normal <5 mg/l]	Creatinine on admission [normal <1.3 mg/dl]
1	1:20480	186	226	8.7
2	1:1280	0.2	219	1.9
3	1:20480	0.19	54	3.6
4	1:80	0.2	114	1.8
5	1:320	47.5	178	7.4
6	1:81920	0.84	29	9.8
7	1:2560	3.43	200	32.0

anti-GBM antibodies, anti-glomerular basement membrane antibodies; PCT, procalcitonin; CRP, C-reactive protein.

PCT (normal range <0.5 ng/ml) was measured with an immunoluminometric assay (B.R.A.H.M.S., Henningsdorf, Germany) using an EG&G Berthold Lumat LB 9507 Luminometer (Berthold, Bad Wildbach, Germany). CRP (normal range <5 mg/l) was measured with nephelometry. Anti-glomerular basement membrane antibodies (anti-GBM antibodies) (normal range <1:10) were measured with ELISA. Calcitonin (normal range <4.5 pg/ml females, <11.5 pg/ml males) was measured with a chemiluminescence assay. Removal of anti-GBM antibodies was performed with a commercially available protein-A column (Amersham-Pharmacia Biotech, Piscataway, NJ, USA).

Results and case report

A total of seven patients (mean age 44.3 years; range 18–72 years, four ♂ and three ♀) with Goodpasture's syndrome were treated in our department from 1996 to 2006. Patient characteristics for all patients are given in Table 1. Initial presentation included renal insufficiency in all patients with a mean serum-creatinine of 9.3 mg/dl (1.8–32.0 mg/dl; Table 2) and anaemia (mean haemoglobin 7.9 mg/dl; range 3.6–11.7 mg/dl). Six out of seven patients had biopsy proven crescentic and necrotizing glomerulonephritis with linear glomerular basement membrane deposits (IgG and C3). In one patient no biopsy was performed (patient 7). Severe manifestation of Goodpasture's syndrome was seen in five patients (patients 1, 2, 5, 6 and 7), i.e. pulmonary involvement (patients 1, 2 and 6) and/or severe renal insufficiency, i.e. serum-creatinine > 5 mg/dl (patients 1, 5, 6 and 7) upon admission. During the clinical course three out of seven patients underwent plasmapheresis and four out of seven patients received repeated pulse cyclophosphamide therapy (750 mg). Six out of seven patients had initially high dose glucocorticoids (methylprednisolone 500 mg/d, then tapered). End-stage renal disease occurred in five out of seven patients during the clinical course (patients one, two, five, six and seven). Median anti-GBM antibody levels were 1:2560 (1:80–1:81920; Table 2). Mean CRP levels were 145.7 mg/l (29–226 mg/l; Table 2), mean PCT levels were 34.1 ng/ml (0.19–186 ng/ml, Table 2). Six out of seven patients did not receive immunosuppression prior to admission; one patient with severe Goodpasture's syndrome (patient 6) received high doses of glucocorticoids and two plasmapheresis sessions prior to admission. PCT in this patient was 0.84 ng/ml after this therapy. In two out of five patients (patients 1 and 5) with severe Goodpasture's syndrome, PCT levels were high on admission and remained high (Figures 1A and B). An underlying infection could not be identified despite intensive search; prolonged treatment with various anti-infective drugs had no influence. Finally, resumption of high dose glucocorticoids normalized PCT and CRP levels in all patients. In one patient, CRP normalized prior to PCT.

In the following, one case is reported in more detail (patient 1). A 41-year-old male person was referred to a

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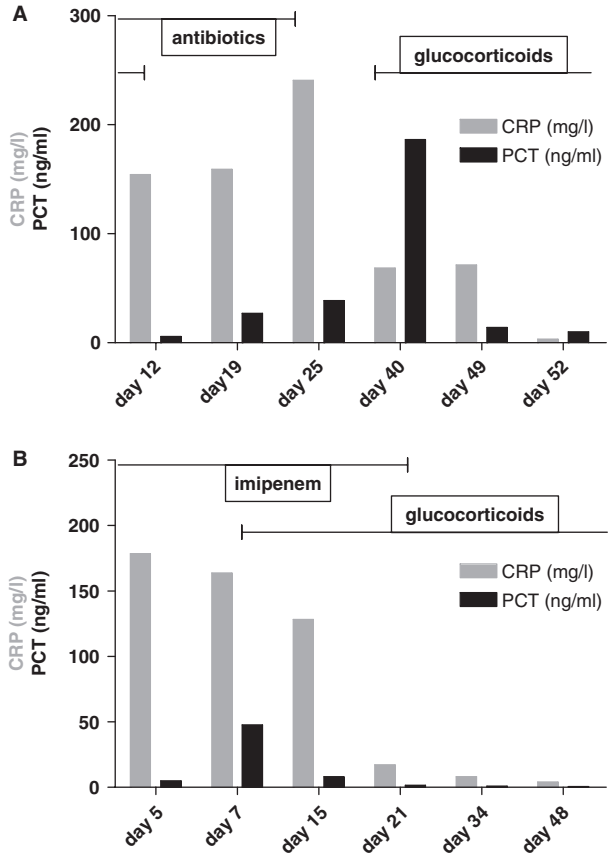

Fig. 1. Time course for procalcitonin (PCT) and C-reactive protein (CRP) in patient 1 (**A**) and patient 5 (**B**) with Goodpasture's syndrome and no evidence of infection. Note that in patient 1 antibiotics were stopped on day 24. Patient 5 had imipenem for more than 1 week with no significant drop of CRP and a significant rise of PCT from initially 4.88 ng/ml to 47.5 ng/ml on day 7. A decrease of PCT and CRP in both patients was noted only after steroids were introduced at day 31 (patient 1) and day 7 (patient 5), respectively.

district hospital for fever (> 39°C), chills, fatigue, dry cough, nausea and vomiting for 14 days. Chest X-ray 10 days before admission showed infiltrates in both lungs. Abnormal laboratory parameters upon admission included serum-creatinine 8.7 mg/dl, serum-urea 206 mg/dl, haemoglobin 9.7 g/dl, white blood cell count 10 700 µl and LDH 395 U/l. Urinary analysis revealed a nephritic sediment with dysmorphic erythrocytes and casts; urinary protein excretion was 1.1 g/day. Serology for hantavirus (Hantaan and Puumula), hepatitis A, B and C, HIV, anti-nuclear antibody (ANA), ENA, anti-ds DNA and anti-neutrophil cytoplasmic antibodies (ANCA) (MPO-ANCA and PR3-ANCA) were negative. Anti-GBM antibodies were high (1:20480). Renal histology revealed crescentic glomerulonephritis and interstitial inflammation. Immunofluorescence showed linear glomerular basement membrane deposits (IgG and C3) and the diagnosis of Goodpasture's syndrome was established. Dialysis in the intensive care unit and therapy with high dose steroids (methylprednisolone 500 mg/day) was initiated the same day. After referral to our hospital, 2 days after the initial hospitalization, the patient had oligo-anuric renal failure and was dialysis-dependent but had only mild pulmonary symptoms. Steroids were continued at the same dose for another 3 days and subsequently tapered to 80 mg/day. Steroid pulse-therapy was interrupted at day 7 after initial presentation because of high temperatures (> 39°C) and a suspected diagnosis of catheter-related sepsis. CRP at this time was between 154–240 mg/l (normal value <5 mg/l) and PCT was increased up to 186 ng/ml (normal value <0.5 ng/ml; Figure 1A). Calcitonin was only slightly elevated at 15.4 pg/ml (normal range <11.5 pg/ml). Intensive search for a septic focus remained negative, including culture of the catheter tip, serial blood cultures, leucocyte scintigraphy, CT scan of the abdomen and chest, repeated abdominal and renal ultrasound, repeated transthoracal and transesophageal echocardiography, repeated X-ray of chest and sinuses as well as ENT, dentist, urologist and ophthalmologist evaluation. In addition, the patient was tested for Clostridium, Aspergillus, Candida, Brucella, Legionella, Listeria, Leishmania, Parvo virus B19, CMV, EBV and Mycoplasma which were all negative. Empirical antibiotic therapy for a total of 24 days with different agents had no effect, i.e. levofloxacin, cefotaxime, imipenem, vancomycin, tazobactam and piperacillin, fluconazole and doxycycline. Cross-reactivity of anti-GBM antibodies and PCT were excluded by the measurement of PCT, which was unaltered after removal of anti-GBM antibodies by a protein-A column (PCT before protein-A adsorption: 14.1 ng/ml; PCT after protein–A adsorption 13.4 ng/ml). After thorough exclusion of potential foci, antibiotic therapy was stopped on day 24 and steroid therapy was again introduced (methylprednisolone 80 mg/day) on day 31. High temperatures and the septic-like clinical syndrome vanished and PCT levels decreased significantly to 2.53 ng/ml (maximum 186 ng/ml) within 18 days but remained elevated. The patient was discharged with end-stage renal failure 49 days after the initial hospitalization, in good health with no demonstrable pulmonary infiltrates. PCT levels normalized within 8 weeks.

Discussion

We report on seven consecutive patients with Goodpasture's syndrome who were treated from 1996 to 2006 in our department. Five out of seven patients had life-threatening manifestation of disease (pulmonary and/or severe renal involvement on admission). These five patients remained dialysis dependent upon follow-up. Three out of five patients with severe disease had highly elevated PCT and one patient had a slightly elevated PCT (after initiation of immunosuppressive therapy and two plasmapheresis sessions; patient 6) in the absence of any demonstrable infection (there was a thorough exclusion of infection in all patients as exemplarily shown for patient 1 in the results section). Neoplastic thyroidal disease as a cause

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of high PCT in those patients was excluded by the measurement of calcitonin, which was only slightly elevated as usually seen in patients with renal insufficiency [8]. Accumulation of PCT in those patients (all patients had impaired renal function) is not likely since PCT had been shown to be a reliable marker in patients with acute and chronic renal insufficiency as well as in haemodialysis [9]. We conclude that PCT as a marker of infection is misleading in Goodpasture's syndrome. This observation is of special clinical relevance. A delay of immunosuppressive therapy in patients with Goodpasture's syndrome solely based on elevated PCT levels (in the absence of infection) might have deleterious effects on the patient in terms of renal recovery and overall survival. From our case series, one might speculate that elevated PCT values in Goodpasture's syndrome are a marker of more severe disease with an unfavourable prognosis; however, larger patient numbers are needed to confirm this hypothesis. All four patients with elevated PCT had severe renal insufficiency on admission and remained dialysis dependent on follow-up and two out of three patients with elevated PCT had pulmonary involvement. Therefore, the demonstration of high PCT levels in patients with Goodpasture's syndrome is not helpful in the differential diagnosis of Goodpasture's syndrome and infection. Elevated PCT values in the absence of infection had also been demonstrated in other diseases. Moosig *et al*. [7] found elevated PCT levels in the absence of infection in severe active Wegener's granulomatosis but not in stable inactive disease. Goodpasture's syndrome and Wegener's granulomatosis share several distinct features, i.e. pulmonary and renal involvement with severe septic-like disease. This might point to a general mechanism of PCT release in the absence of infection. However, like in our study, a close dose-response relationship between PCT levels and the severity of Wegener's granulomatosis could not be established. PCT is the precursor hormone of calcitonin, which is normally secreted by the C-cells of the thyroid gland in response to hypercalcaemia. The mechanisms of PCT production after inflammation are not yet fully understood. The site of PCT release, however, is different from the thyroid gland since patients after thyroidectomy also show increased PCT release in inflammation [10]. One explanation is the release of PCT from other organs with the highest PCT concentrations i.e. in lungs and kidneys of baboons in response to LPS as shown by Morgenthaler *et al*. [11]. In addition, they found that CT-mRNA expression is increased in these tissues, indicating that kidneys and lungs are the site of PCT production. In patients with inhalation injury, secretion of PCT from pulmonary neuroendocrine cells was observed by Nylen *et al*. [12] thus providing further evidence that injured tissue, either lungs or kidneys, might be the site of PCT production and release even in the absence of infection.

In conclusion, PCT is not a reliable marker for infection in patients with Goodpasture's syndrome. High PCT values in pulmo-renal syndromes like Goodpasture's syndrome might rather reflect severe organ damage of lungs and/or kidneys than infection as seen with four out of five patients with severe Goodpasture's syndrome in our series. However, larger patient numbers are needed to definitely prove this hypothesis.

Conflict of interest statement. None declared.

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