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Is there any influence of immune deficit on procalcitonin results?

Tomasz Mikuła [a,*], Janusz Cianciara [a], Alicja Wiercińska-Drapało [a]

[a] Department of Hepatology and Acquired Immunodeficiences, Medical University of Warsaw, Warsaw, Poland

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ABSTRACT

The role of procalcitonin (PCT) in immunocompromised patients is still under investigation. This study evaluated the influence of immune deficiency on the value of PCT concentrations in the diagnosis of early stages of bacterial infections in human immunodeficiency virus (HIV)–infected patients compared with other inflammatory markers, such as C-reactive protein and white blood cell count. We analyzed major immunologic markers including CD4, CD8, and HIV-1 viral load. PCT concentrations in the early stages of bacterial infections correlated negatively with CD4 count in HIV-infected patients. However, a similar relation was not seen in patients with acquired immune deficiency syndrome. We support the recommendation to change the cutoff value ranges of PCT in patients with immune deficiency. PCT concentrations can be influenced by various factors and hence should be carefully analyzed, especially in immunocompromised patients.

1. Introduction

C-reactive protein (CRP) serum concentration; white blood cell (WBC) count; and body temperature remain the most common "classic" inflammatory markers in clinical diagnosis. However; these markers are not characteristic; making it difficult to confirm the early stages of bacterial infection in some patients [1]. CRP serum concentration may be above the normal reference range even in healthy individuals and is influenced by various factors. WBC counts must also be analyzed carefully; particularly in leukopenic patients. The signs and symptoms of bacterial infections are often noncharacteristic; and confirming the diagnosis is often problematic.

In immunocompromised human immunodeficiency virus (HIV)–infected patients; the early diagnosis of bacterial infections is often difficult because the inflammatory response is less adequate than in noninfected individuals. Even a minor elevation of inflammatory markers can be a sign of advanced infection in HIV-infected patients. Early detection of bacterial infection can assist effective therapy and is necessary to prevent disease progression.

Antigens (bacteria; fungi; viruses) initiate inflammatory responses and stimulate cells of the immune system (e.g.; macrophages; dendritic cells; Kupffer cells; histiocytes; mastocytes; and leukocytes; mainly neutrophils). The complement system is activated in response to inflammation caused by bacteria. This system contains many protein precursors that are synthesized in the liver. It has 3 pathways—classic; alternative; and mannose-binding. The classic pathway is stimulated by antigen–antibody complexes. In all 3 pathways; a C3-convertase activates component C3; creating C3a and C3b; which bind to the surface of pathogens. For instance; macrophages and Kupffer cells clear complement-coated pathogens from the blood. The complement system controls inflammatory reactions; activation; clearance of immune complexes; and autoimmunity.

The role of the complement system in HIV-associated pathogenesis is complex. The virus employs elements of the complement system to facilitate its entry into CD4 T lymphocytes to activate replication in lymph follicles and other latently infected cells. In the course of HIV infection; especially when the WBC count is depleted; these mechanisms are not clear. However; some associations between increased procalcitonin (PCT) concentrations and leukocyte-derived cytokines during sepsis have been confirmed. Lipopolysaccharides and various proinflammatory cytokines (e.g.; interleukin [IL]-1β, IL-6, tumor necrosis factor-α, and IL-2) have pronounced stimulatory effects on the expression of PCT mRNA. For example, lipopolysaccharides impact the expression of PCT in human peripheral blood mononuclear cells, and these cells may be one of many sources of PCT in patients with sepsis. However, under the same experimental conditions, the anti-inflammatory cytokine IL-10 has no effect on PCT mRNA expression [2].

1.1. Procalcitonin

PCT, a 116-amino-acid pro-hormone of calcitonin, is a newly emerging inflammatory marker. In healthy individuals, PCT is released from the C cells of the thyroid gland; its plasma concentration is 0.0 to 0.5 ng/mL as measured by immunoluminometric methods. In severe bacterial infections and sepsis, PCT is synthesized by other cells, including leukocytes, macrophages, monocytes in the liver, and neuroendocrine cells in lungs and intestines, with a serum concentration increasing up to 1,000.0 ng/mL [3]. Reports in the literature suggest that PCT is an important inflammatory marker, even in fungal infections. However, in fungal infections its

* Corresponding author.
E-mail address: tomasz.mikula6@wp.pl (T. Mikula).

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serum concentration is significantly lower than in bacterial infections. Hence, PCT can be used to distinguish bacterial from fungal infections [4]. Serum CRP increases in patients with acquired immune deficiency syndrome (AIDS) during bacterial and nonbacterial opportunistic infections [5]. When urine tests positive for pneumococcal C-polysaccharide antigen, CRP can be an additional inflammatory marker for confirming *Streptococcus pneumoniae* infection [6]. By contrast, because of the significantly lower initial count in immunocompromised patients, WBC counts are not very useful for interpreting all stages of bacterial infection. High plasma PCT concentrations have been particularly reported in patients with severe bacterial infections, sepsis, or septic shock as scored according to the American College of Chest Physicians/Society of Critical Care Medicine criteria [7]. Among HIV-infected patients without other bacterial infections, the serum PCT concentration is normal or slightly elevated and is similar to that seen in patients with other viral infections, such as hepatitis B virus or hepatitis C virus. Hence, the PCT serum concentration is above the normal reference range in HIV-infected patients with generalized bacterial infection [8].

This study was designed to assess the influence of immune deficiency on the serum concentration of PCT in the early stages of bacterial infection in HIV-infected and AIDS patients in comparison with other conventional inflammatory markers (*e.g.*, CRP and WBC).

2. Subjects and methods

A total of 135 HIV-infected and AIDS patients suspected to have bacterial infections, who were subsequently admitted to the Department of Hepatology and Acquired Immunodeficiency at the Warsaw Medical University, Poland, were considered for the study. Fever >38°C, flu-like symptoms, and the presence or suspicion of bacterial infection of less than 3 days were the main inclusion criteria. Of these 135 patients, 65 were enrolled in 2 groups. Group 1 comprised 28 HIV-infected patients and group 2 comprised 37 patients with full-blown AIDS. All patients in the 2 groups had bacterial infections confirmed by microbiological procedures (cultures and smears). Thirty-seven healthy health care workers comprised the control group. Blood samples were taken for analysis from all HIV and AIDS patients during the first hour of their admission.

2.1. Pathway analyses

Serum PCT concentrations were evaluated by an immunoluminometric method (Lumitest PCT kit, BRAHMS AG, Berlin, Germany). The normal reference range for PCT was taken as 0.0 to 0.5 ng/mL. Serum CRP concentrations were measured by an immunoturbidometric method and the normal reference range was taken as being below 10.0 mg/L. WBC counts were measured by the classic method with the normal reference range taken to be 4.0 to 10.0 cells/μL. Blood and urine were cultured for the presence of bacteria.

2.2. Data analyses

All statistical analyses (mean, median, standard deviation, Kolmogorov–Smirnov test [K–S test], Pearson's *r*-correlation coefficient [*r*], Spearman's rank correlation coefficient [ρ], χ-square test, Student's *t* test, and Mann–Whitney *U* test) were performed using Statistica 9.0 Statsoft (StatSoft Inc., Tulsa, OK). A *p* value below 0.05 was considered statistically significant. This study was conducted in compliance with the principles of good clinical practice. All patients provided written informed consent before their enrollment in the study. All authors made substantial contributions in writing and revising the manuscript and approved the final version.

3. Results

Of the 102 individuals included in the analyses, 42 (41%) were female. Table 1 presents the baseline characteristics of all patients.

Patients from groups 1 (HIV) and 2 (AIDS) (total $n = 65$) were compared with the controls ($n = 37$) using Student's *t* test for WBC and the Mann–Whitney *U* test for PCT and CRP (Table 2).

The results from the comparison of CD4, CD8, and viral load (VL) between groups 1 and 2 using the K–S test are given in Table 3. These data were checked with Student's *t* test and the Mann–Whitney *U* test.

Table 4 shows the Pearson and Spearman correlations for PCT, CRP, WBC, CD4, CD8, and HIV-1 VL. There was a negative correlation between CD4 count and PCT concentration among HIV-positive patients. A similar correlation did not exist among AIDS patients.

3.1. Microbacterial results in HIV-infected patients (group 1)

Microbiological analysis was positive for all 28 patients in group 1. Blood cultures indicated the presence of *Acinetobacter baumannii, Corynebacterium diphtheriae, Enterobacter asburiae, Enterococcus faecium, Escherichia coli, Staphylococcus aureus, Staphylococcus hominis, Staphylococcus sciuri,* and *Streptococcus* species. Urine cultures showed the presence of *S aureus*. Cultures or smears from other sites showed the presence of *A baumannii, Citrobacter freundii, Enterobacter cloacae, E coli, Haemophilus influenzae, Proteus mirabilis, S aureus, Staphyloccocus pneumoniae,* and *Streptococcus pyogenes.*

3.2. Microbacterial results in AIDS patients (Group 2)

Microbiological analysis was positive for all 37 patients in group 2. Positive blood cultures indicated *Enterobacter agglomerans, E cloacae, Enterococcus faecalis, Rhodococcus equi, S hominis, S aureus, Staphylococcus epidermidis, Streptococcus* species, and *Staphylococcus haemolyticus*. Urine cultures showed the presence of *A baumannii, E faecium, Pseudomonas aeruginosa, and Streptococcus faecalis*.

4. Discussion

Our study assessed the value of inflammatory markers such as PCT, CRP, and WBC in patients with bacterial infection and immune

Table 1
Baseline characteristics

Parameters	Group 1 HIV-infected patients ($n = 28$)	Group 2 AIDS patients ($n = 37$)	Control group ($n = 37$)
Female (*n*/%)	8/28.5	6/16.2	28/75.6
Age (years) (mean ± SD/median)	36.5 ± 8.7/37.0	37.0 ± 10.4/35.0	39.7 ± 8.9/40.0
PCT (ng/mL)[a] (mean ± SD/median)	3.1 ± 6.0/0.5	4.8 ± 14.7/0.5	0.13 ± 0.05/0.11
CRP (mg/L)[b] (mean ± SD/median)	83.1 ± 131.8/27.5	75.7 ± 84.1/39.0	2.3 ± 5.4/0.0
WBC (cells/mL)[c] (mean ± SD/median)	8.4 ± 6.3/6.0	5.3 ± 2.4/5.1	6.2 ± 1.5/5.9
CD 4 (cells/μL) (mean ± SD/median)	492.3 ± 231.4/395.0	181.9 ± 147.3/135.0	Not analyzed
CD 8 (cells/μL) (mean ± SD/median)	1176.0 ± 459.5/1,110.5	811.2 ± 588.3/598.0	Not analyzed
HIV-1 VL (copies/mL) (mean ± SD/median)	29,876.6 ± 41,898.5/7,355.0	259,847.0 ± 980,929.0/100,001.0	Not analyzed

[a]PCT, $\chi^2(2) = 27.3$; $p < 0.001$.
[b]CRP, $\chi^2(2) = 51.4$; $p < 0.001$.
[c]WBC, $F(2,99) = 5.7$; $p = 0.004$.