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Endocarditis sustained by *Streptococcus viridans* with normal levels of procalcitonin: an unexpected finding

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Abstract. – OBJECTIVE: Procalcytonin is a useful marker of bacterial infections. Several studies have reported elevated serum levels of PCT in patients with infective endocarditis (IE) and/or other infections sustained by *cocci*. We report a rare case of IE attributed to *Streptococcus viridans* in whom levels of PCT were normal.

CASE REPORT: A 67 years-old male was admitted to the Emergency Department for a 25-day history of recurring night fever. Upon admission, patient underwent blood test, including PCT, showing normal levels, except for a slight increased creatinine concentration (1.6 mg/dl). CBC showed WBC levels of 10.24 x 10^9/l with neutrophil concentration of 8.64 x 10^9/l. Three blood culture were performed, and all of them were positive for *Streptococcus viridans (S. oralis)*. Dosage of PCT was then repeated two times within the next 2 days after the admission, with negative results. An echocardiogram was performed, showing a lesion of the left anterior aortic leaflet. This finding was confirmed by a transoesophageal echocardiogram. The patient was then treated with G penicillin (6 million of Units quid) for 3 weeks; during the course of antibiotic therapy fever disappeared and blood cultures become negative.

CONCLUSIONS: In the literature there are just few data about the association between PCT levels and endocarditis and sepsis but there are not etiological differentiations particularly for those sustained by *Streptococcus viridans*. Only one study suggests that a *Streptococcus viridans*' infection could reduce PCT accuracy in diagnosis oh endocarditis. So, our observation although come from a single case, could merits, further investigation.

Key Words:
Endocarditis, Bacterial infection, *Streptococcus viridans*, Procalcitonin, Emergency Department.

Introduction

Serum Procalcitonin (PCT) is a 116-aminoacidic protein with a molecular weight of 14.5 kDa and a sequence identical to that of the prohormone of Calcitonin[1] that is encoded by the gene Calc-1, presents in chromosome 11. Its synthesis, during inflammation, is induced by transcription factors activated by the inflammatory process, which modulates its transcription[2]. The production of PCT is not related to C-cells of the thyroid gland, secreting calcitonin. In fact, in the course of serious bacterial infections, complicated by systemic inflammation (SIRS), high concentrations of PCT can be detected in the blood along with the absence of increased levels of Calcitonin. In infective mediated inflammation (SEPSI) the PCT is synthesized and released by leukocytes, macrophages and monocytes in various organs and neuroendocrine cells of lung and intestine. Bacterial endotoxins are the most effective stimulators of PCT synthesis and release. PCT synthesis can be induced by the "tumor necrosis factor-α", the interleukins 6, 1b and 2 and phytohemagglutinin. However, the incretion of PCT is not the only indication of bacterial infection, because its increase may also occur in different conditions such as: heat stroke, severe burns, multiple trauma and surgery. Therefore, it does not represent a direct manifestation of infection but reflects the body's systemic response to the presence of infection[2].

PCT is degraded by proteolysis and excreted by the kidneys[3], its half-life is 20 to 24 h. A peculiar characteristic is its plasma half-life, which is longer than that of the main cytokines, and for this reason has a wider diagnostic window.

PCT molecule is sufficiently stable in biological samples: in the 24 h after blood sampling the concentration decreases by about 12% when stored at room temperature and about 6% in the case of storage at 4°C. PCT concentration in the serum of healthy adults is < 0.5 g/L, while in the first days of life it is physiologically higher, requiring then a different range of reference

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and different interpretation criteria for premature and term infants. During the infectious processes, the concentration of PCT is correlated with the type and the spread of infection. The increase of PCT is not observed either in the course of inflammatory diseases in non-bacterial etiology, such as viral infections and autoimmune diseases, or in the course of bacterial infection confined to a single organ, with the exception of pneumonia. PCT can also be used for monitoring and prognostic evaluation as an increase and persistence of high values indicate the progression of the inflammatory process and so a poor prognosis, while its decrease is indicative of an attenuation of the inflammatory reaction, removal of the septic focus and then a kindly prognosis. Changes in the concentration of serum PCT may indicate the need for further investigation and the appropriateness of treatment strategy. Even in pediatric age PCT has proven useful for discriminating between viral and bacterial infections and as a marker for the detection of bacteremia and sepsis, showing a superior diagnostic specificity to that of C-reactive protein[4,5]. Also, PCT has been useful during the first diagnostic framework in cases of rising temperature in the absence of localizing signs, allowing early detection of bacterial infection cases with more severe evolution[6].

Several studies[7] have demonstrated that bacterial infection may induce higher concentrations of serum PCT and that following administration of antimicrobial agents, PCT measurement may predict the efficacy of the treatment as well as may help to protect against emerging antimicrobial-resistant strains by restricting unnecessary antibiotic use.

Previous studies[14] have reported higher levels of PCT in patients with infective endocarditis (IE), especially when is sustained by cocci[6-12]. Here we report the case of a patient with infective endocarditis (IE) sustained by *Streptococcus viridans* without evidence of elevated levels of PCT.

Case Report

A 67 years-old male with a previous history of acute myocardial infarction (AMI) occurred 14 months before and treated with PTCA and stenting was admitted to the Emergency Department of the *[name deleted to maintain the integrity of the review process]* because of a 25 day history of recurring fever, mostly during the evening and the night. He did not show urinary symptoms, vomiting or diarrhea. He had been smoking for forty years but he quick stopped after AMI occurred. The patient was not affected by diabetes mellitus and did not undergo any invasive treatment including dental care. He denied any contact with pets, or traveling in exotic countries.

Fever was associated with deep weakness and profuse swearing during the night and was responsive to Acetaminophen. The patient has also been treated with Ciprofloxacin 500 mg once day for 6 days without any improvement in his symptoms. The echocardiogram showed the presence of compensated aortic valve regurgitation with initial fibrosis without vegetation and a slight pericardial effusion. He reported the occurrence of a single episode of self-resolved high fever (around 39°C), 7 days before the onset of these symptoms. He denied the use of antibiotics for this episode.

Upon admission, patient-performed a blood test, including PCT, showing normal levels, except for a slight increased Creatinine concentration (1.6 mg/dl). CBC showed WBC levels of 10.24 × 10^9/l with neutrophil concentration of 8.64 × 10^9/l. Erithrosedimentation rate resulted to be 29 mm/h while CRP showed levels of 41 mg/l. Widal-Right, Weil-Felix, Waaler-Rose, immunological markers (ANA, ENA, ANCA, Rheumatoid factor), Mantoux test, Quantiferon, serology for Epstein-Bar virus, Cytomegalovirus, Herpes simplex virus, hepatitis B virus, hepatitis C virus, Echovirus, Coxackie A and B, HIV gave negative results. EKG and chest X-Ray did not show any significant result.

Three-blood culture was performed, and all of them were positive for *Streptococcus viridans (S. oralis).* The dosage of PCT was then repeated two times within the next 2 days after the admission, with negative results (0.27 ng/ml and 0.29 ng/ml [normality < 0.50 ng/ml]).

Moreover, an additional dosage of PCT was performed one day after the identification of *Streptococcus viridans* in the blood still yielding negative result [0.18 ng/ml].

Another echocardiogram was performed, confirming the absence of vegetation but showing a lesion of the left anterior aortic leaflet. This finding was confirmed by a trans-esophageal echocardiogram (Figure 1 a-c), possibly explaining aortic regurgitation.

The patient was then treated with G penicillin (6 million of Units quid) for 3 weeks; during antibiotic therapy fever disappeared and blood cultures become negative.

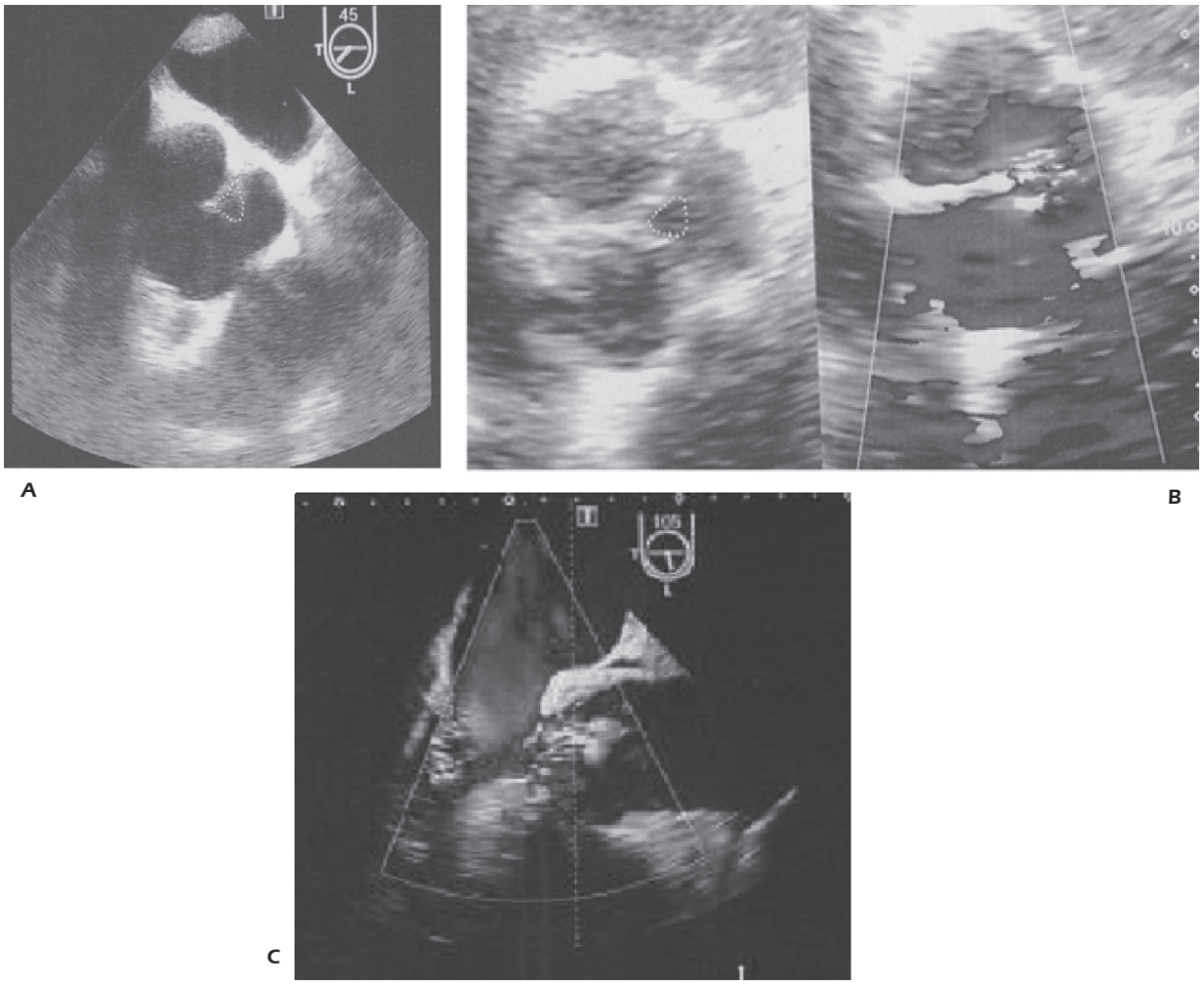

Figure 1. ***A,*** Trans-esophageal echocardiography: aortic valve, minus on left anterior leaflet. ***B,*** Trans-chest wall echocardiography: aortic valve Doppler minus on left anterior leaflet. ***C,*** Trans-esophageal echocardiography: aortic valve Doppler effect.

Discussion

Streptococcus viridans, a common cause of bacterial endocarditis[17] is not always associated with an elevated circulating level of PCT, although this biomarker has been shown to be a significant independent predictor of IE in multivariate analysis and its accuracy is comparable to the natriuretic peptide in the early diagnosis of heart failure[7]. While PCT has been shown to have a high specificity for the diagnosis of IE caused by *Staphylococcus aureus*, its role in immunological diseases is less defined[13]. On the other hand, there is evidence that not all-bacterial infection can affect PCT; therefore, even though increased levels of PCT are consistent with a bacterial infection, the opposite might not always be true[10].

The reason by which PCT was not increased in this patient is still unclear, but our case suggests that this biomarker is not necessarily useful in the diagnostic algorithm of IE[14]. PCT has an excellent specificity (the ability to rule-in bacterial infection) but still a not sufficient sensitivity (the ability to rule-out)[15]. We believe that it is important to highlight the limit of PCT especially in the emergency department, which is the first place where patients with endocarditis and/or sepsis are seen and treated. To confirm this data there is a recent meta-analysis[16] that evidences a PCT very low accuracy in diagnose IE to consider a rule in or rule-out role of PCT. On the other hand the meta-analysis presents potential limitations for a quite low number of patients and 3 different assay kits used in the 6 studies. At the end, it does

not difference from etiological kind of infection, so it does not give us more information about our "etiological hypothesis".

Conclusions

In the literature there are just few reports about the association between PCT levels, endocarditis and sepsis, but substantially there are not etiological differentiations, particularly for those sustained by *Streptococcus viridans*. Only one study suggests that a *Streptococcus viridans*' infection could reduce PCT accuracy in diagnosis of endocarditis[13]. So our observation, although come from a single case, could merit further investigation.

Conflict of Interest

The Authors declare that they have no conflict of interests

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