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Elevated procalcitonin in a haematological disorder: case report

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Serum procalcitonin (PCT) is a biochemical marker of sepsis being routinely used in critical care setting for rapid diagnosis and early initiation of antimicrobial agents. Serial monitoring of procalcitonin also correlates well with the progression of sepsis. Though procalcitonin has a high specificity for bacterial sepsis, there are conditions associated with elevation of procalcitonin in the absence of sepsis which need to be considered when there are no signs of improvement with treatment in a patient suspected to have sepsis. We present a case of acute myeloid leukemia (AML) with elevated procalcitonin in a patient with no evidence of sepsis or autoimmune disorder. After initiation of chemotherapy, the patient's general condition improved and there was a dramatic fall in procalcitonin level.

Keywords: Serum procalcitonin, Biochemical marker, Sepsis, Acute myeloid leukemia (AML)

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Introduction

Procalcitonin is synthesized in C cells of the thyroid gland as a precursor molecule of calcitonin in normal healthy individuals. Normally, there is no significant production of procalcitonin in other tissues of the body. However, in the presence of sepsis the production of procalcitonin in other tissues of the body increases. The exact pathophysiology of procalcitonin in sepsis is Not known, but it is believed to play a modulatory role in the inflammatory reactions. It should be noted that the rise in procalcitonin is seen after bacterial, fungal and parasitic infections and not after viral infections. It is interesting to note that there is no significant rise in procalcitonin level with localized bacterial infections. Serum procalcitonin levels could also be raised in certain autoimmune conditions like Wegener's granulomatosis, microscopic polyangiitis and Goodpasture syndrome even without bacterial

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Sepsis. Procalcitonin is used in clinical practice for early detection of sepsis which aids in initiating antibiotics at the earliest. Also, unnecessary use of antibiotics could be avoided if there is no elevation in procalcitonin levels on serial testing in a suspected case of sepsis. The serum level of procalcitonin could indicate the severity of bacterial infection, with a rising value suggesting progressing sepsis [1-3].

Case report

A 40-year-old lady presented with intermittent, dull aching central abdominal pain for 1 day. Patient had fever of 100° F. She did not have any vomiting or jaundice. There was no history of cough or breathing difficulties. She did not notice any alteration in her bowel and bladder movements. Patient was a known diabetic on insulin therapy. She had undergone distal pancreatectomy with splenectomy for solid pseudopapillary neoplasm of tail of pancreas 5 years ago. There was no other significant history.

Investigations: Blood tests showed mild anemia, slightly elevated white cell count of 13040 cells/cumm with neutropenia (19%) and monocytosis (37%). Liver and renal function tests were within normal limits. Procalcitonin level was 10ng/ml. Blood and urine cultures were found to be negative. Autoimmune workup was negative. A contrast CT scan of the abdomen showed multiple enlarged mesenteric lymph nodes with no obvious source of infection. Peripheral smear of the blood showed blast cells. Bone marrow examination was done, which also showed increased blast cells. Flow cytometry of peripheral blood showed 100% positivity for CD45, 98.9% positivity for CD33, 94.2% positivity for CD13 and 98.4% positivity for CD38 confirming the diagnosis of AML.

Differencial diagnosis: As the procalcitonin level was high, a working diagnosis of sepsis was made. The blood and urine cultures were however negative and there was also no significant response to antibiotics and antifungal agents. As a high serum procalcitonin level could be observed in autoimmune conditions as well, investigations were done to exclude such a possibility. The autoimmune panel was also unremarkable. The possibility of a hematological condition was suggested by peripheral blood smear examination and was confirmed by flow cytometry and bone marrow analysis.

Treatment: Patient was initially started on cefoperazone sulbactam and ornidazole which was later upgraded to piperacillin tazobactam and fluconazole was added but with no apparent clinical and biochemical response. After the diagnosis of AML was made, induction chemotherapy was started with cytarabine arabinoside, daunorubicin and gemtuzumab.

Outcome and follow-up: After starting induction chemotherapy the clinical condition improved and a fall in serum procalcitonin level was noted. The patient needed growth factors and transfusion of blood products due to bone marrow suppression but otherwise had an uneventful recovery. The patient is symptom free on a regular follow-up.

Discussion

The exact pathophysiology of procalcitonin in sepsis is not known. It should be noted that the rise in procalcitonin is seen after bacterial, fungal and parasitic infections and not after viral infections. It is interesting to note that there is no significant rise in procalcitonin level with localized bacterial infections. Serum procalcitonin levels could also be raised in certain autoimmune conditions. Procalcitonin is used in clinical practice for early detection of sepsis which aids in initiating antibiotics at the earliest. Also, unnecessary use of antibiotics could be avoided if there is no elevation in procalcitonin levels on serial testing in a suspected case of sepsis.

Claeys R et al studied clinical and biological correlates of plasma PCT and C-reactive protein in acute septic shock. They observed elevated PCT levels as markers of sepsis, but their prognostic value and relation to other inflammatory parameters and calcium homeostasis remained controversial. Carrol ED et al studied PCT as a marker of sepsis. PCT, a precursor of calcitonin, is a 116 amino acid protein that has been proposed as a marker of disease severity in conditions such as septicemia, meningitis, pneumonia, urinary tract infection (UTI) and fungal and parasitic infection. In particular, serial measurements are useful in order to monitor response to therapy. They concluded that together with good clinical judgement and judicious use of antimicrobial agents, PCT should serve as a valuable adjunct in the diagnosis and management of sepsis [1,2].

Jekarl DW, Lee SY et al evaluated role of PCT as a diagnostic marker for sepsis. PCT showed the best

Diagnostic performance, with 74.4% and 93.7% sensitivity and 86.7% and 75.2% specificity among sepsis and severe sepsis/septic shock patients, respectively. PCT, IL-6, and CRP levels were significantly increased in non-survivors compared to survivors. Serial measurements at 0, 12, 24, 48, 72, and 96 h showed that IL-6 showed better kinetics in the survivor group and was decreased in more than 86% of survivors by the second day.PCT can support the diagnosis of bacterial infection, especially in septic shock and severe sepsis patients [3].

Dornbusch HJ studied non-infectious causes of elevated procalcitonin and C-reactive protein serum levels in pediatric patients with hematologic and oncologic disorders. In the majority of the non-infectious episodes PCT and CRP increased to serum levels statistically indistinguishable from Gram-negative sepsis. PCT and CRP are of limited value as diagnostic markers of sepsis during T-cell-directed immunomodulatory treatment, granulocyte support, or acute GvHD [4].

The aim of qualitative review by Sakr Y was to evaluate the role of PCT measurements in febrile neutropenic patients in differentiating between various causes of fever and to investigate the value of PCT levels in terms of diagnosing infection or predicting outcome in these patients. PCT seems to be able to discriminate fever due to systemic forms of infection from non-infectious etiologies. Patients with fungal infection may have a delayed increase in PCT levels. PCT has a minimal role, if any, in discriminating Gram-negative from Gram-positive infections. PCT may be useful in outcome prediction in patients with febrile neutropenia but is not superior to interleukin-6 or C-reactive protein concentrations for this purpose [5].

Assessment of procalcitonin as a diagnostic and prognostic marker in patients with solid tumors and febrile neutropenia was done by Jimeno A et al. It was concluded that baseline PCT levels were higher in patients who had febrile neutropenia with bacteremia compared with patients who had clinical infections or fever of unknown origin. PCT helped to identify patients who had microbiologic infections and patients who were at high risk of treatment failure, and PCT may constitute a complementary tool in the initial assessment of such patients [6].

In another study by Svaldi M et al on procalcitonin, there was a reduced sensitivity and specificity in heavily leucopenic and immunosuppressed patients, Procalcitonin (PCT) had proven to be a very sensitive marker of sepsis for non-leucopenic patients. Thus, it was concluded that procalcitonin is an excellent sepsis marker with a high positive and negative-predictive value in patients with WBC count >10x1.0^9/l, but it does not work satisfactorily below this leucocyte count [7].

Similar study by Al-Nawas B et al, the authors observed a high serum levels of PCT in patients with sepsis or severe infection. Patients with no alteration in their immune system showed high PCT values up to day 5, decreasing to normal levels by day 9. Patients with sepsis and immunodeficiency had high values on days 0 to 2, similar to the first group, but showed significantly lower levels on the following 3 days. PCT concentrations fell to base line levels on days 6 to 9 of the sepsis episode in both groups. The observed difference was not significantly related to the kind of causative microorganism or a culture negative sepsis. Leukopenia seemed to go together with lower PCT values after day 2 of the episode [8].

Procalcitonin concentrations in patients with neutropenic fever was also studied by Ruokonen E et al. The procalcitonin concentration increased rapidly in patients with infection; the response was detectable within 8 h of the onset of fever. Procalcitonin is a specific but not a sensitive marker of infection in patients with neutropenic fever. Its poor sensitivity was related to an absent or delayed response in patients with gram-positive infections. Considerable overlap between infected and noninfected patients was found in levels of endotoxin, tumor necrosis factor, and interleukin-6. Sarmati L et al inferred that procalcitonin is a reliable marker of severe systemic infection in neutropenic hematological patients with mucositis. Procalcitonin (PCT) has become increasingly popular as a novel marker of infection. The use of this marker in hematological patients has provided controversial results and no agreement exists about the capacity of PTC to differentiate fever by other inflammatory processes such as mucositis and Graft versus Host diseases (GVHD) [9,10].

Our patient also had a high procalcitonin level with a negative microbiological and autoimmune workup. Also there was no clinical and biochemical response to antibiotic and antifungal therapy. Once the diagnosis of AML was made, chemotherapy was initiated and the general condition of the patient improved and there was a dramatic fall in procalcitonin level.

To the best of our knowledge there has not been any report of AML presenting with high procalcitonin levels in the absence of bacterial infection.

Conclusion

It seems likely that hematological malignancies could be associated with an elevated procalcitonin level in the absence of systemic infections. An elevated procalcitonin level unresponsive to antibiotic therapy, with a negative microbiological and autoimmune workup, should prompt an evaluation for hematological conditions.

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