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SHORT COMMUNICATION

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Procalcitonin—a marker of invasive fungal infection?

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Abstract Procalcitonin (PCT) has been described as a marker of bacterial sepsis. However, little is known of its diagnostic value in fungal infections. We calculated the sensitivity of PCT for detection of invasive fungal infections (IFI) by analyzing 55 episodes of proven or probable IFI (three in our series, 52 reported in the recent literature). In the early phase of IFI, PCT was elevated in fewer than half of invasive candidiasis episodes and in only one patient (5.3%) with invasive aspergillosis. Due to low sensitivity and specificity, PCT adds little to the diagnosis of IFI.

Keywords Procalcitonin · Marker · Invasive fungal infection · Aspergillosis · Candidiasis

Introduction

In several articles [5, 7, 13–16] procalcitonin (PCT) is mentioned as a marker of systemic bacterial as well as fungal infection. A serum concentration of 2 ng/ml is considered the cutoff level for sepsis. Many authors have investigated PCT in bacterial infection with different results. In some studies fungal and bacterial infections were examined, but not analyzed separately. Only a few reports specifically describing PCT in patients with invasive fungal infection (IFI) are to be found in the literature [2–4, 6–11, 18]. The authors drew different, and even contradictory, conclusions regarding the value of PCT as a diagnostic marker in IFI.

Patients and methods

We report on the characterization of PCT levels (determined by means of an immunoluminometric assay—BRAHMS Diagnostika, Berlin, Germany) in two patients with probable invasive aspergillosis and one patient with proven systemic candidiasis according to EORTC/NIAID criteria [1].

Case reports

Case 1 An 11-year-old girl after a second relapse of c-ALL was scheduled for allogeneic stem cell transplantation. She developed fever and cough during neutropenia induced by reinduction chemotherapy. Chest radiography as well as CT scan showed a mass in the right upper lung adjacent to the large vessels highly suggestive of mould infection. Aspergillus antigen and DNA were detected in multiple samples of blood, BAL and sputum. Resection was not performed due to the high surgical risk in this clinical situation. Treatment with liposomal amphotericin B and caspofungin as well as granulocyte support led to negativity of fungal markers, and CT scan showed shrink-

ing of the lesion, eventually with complete resolution of aspergillus pneumonia. During the whole period of 8 weeks with multiple blood samples positive for *Aspergillus* antigen and DNA, PCT serum levels (normal range <0.5 ng/ml) showed only a marginal increase to 0.53 ng/ml on day 2 after diagnosis, and another slight elevation to 0.83 ng/ml on day 16.

Case 2 A 16-year-old male had been neutropenic for 14 days after induction chemotherapy for AML. He developed fever, cough and dyspnea not responding to broad-spectrum antibiotics. Despite a normal chest radiograph, liposomal amphotericin B (3 mg/kg per day) was started empirically. Blood cultures remained sterile. Cultures, antigen tests, and PCR of sputum did not reveal bacterial, viral or fungal infection. However, CT scan of the lung showed multiple lesions typical of fungal etiology, and the dose of liposomal amphotericin B was increased to 6 mg/kg per day. BAL and histology from an open lung biopsy were inconclusive, but *Aspergillus* DNA was repeatedly detected in blood by PCR from 3 days before the start of antifungal treatment until 1 week after neutrophil recovery. Thereafter, the patient improved clinically and radiologically.

As found in case 1, over a period of 4 weeks with clinical and molecular evidence of invasive *Aspergillus* infection, PCT increased only slightly with a delay of approximately 2 weeks on three consecutive days to a maximum level of 0.7 ng/ml.

Case 3 A 7-year-old boy diagnosed with c-ALL and poor response to prednisolone treated with intensified conventional chemotherapy repeatedly showed colonization with *Candida albicans* in stool cultures. After a viral gastroenteritis under myelosuppression the patient developed clinical sepsis with blood cultures positive for *C. albicans*. The patient showed a rash, pulmonary congestion and septic shock leading to multiple organ failure. He required mechanical ventilation and hemofiltration for 2 weeks. Under these procedures and treatment with liposomal amphotericin B and caspofungin, the candidemia rapidly resolved prior to removal of the CVC, but clinically the patient did not improve until 4 weeks after the first signs of sepsis. During the whole period blood cultures remained negative for bacteria. PCT elevation (1.4 ng/ml) occurred concomitantly with fever onset and the first positive blood culture and was followed by a rapid increase to 29.3 ng/ml over 2 days. Thereafter, PCT showed a slow decrease paralleling the clinical improvement, and reached normal values 4 weeks after the onset of candida sepsis.

Review of the literature

Scanning international medical databases (Medline, PubMed), we found ten articles [2–4, 6–11, 18] containing evaluable PCT data of 57 patients with deep-seated fungal infections (Table 1). Six articles [2–4, 7, 9, 11] provided data on PCT in 23 cases of invasive aspergillosis (proven *n*=9, probable *n*=9, possible *n*=5). PCT peak values remained below 2 ng/ml (*n*=14) or showed a delayed increase up to 30.7 ng/ml 2 to 4 weeks after diagnosis. Only in one patient with invasive pulmonary aspergillosis did PCT levels exceed 2.0 ng/ml during the first 3 days following diagnosis [7].

Table 1 Review of reported patients with invasive fungalinfection and concurrently documented procalcitonin values

Reference	Aspergillosis			Culture proven candidiasis	
	Possible	Probable	Proven	Blood	Other normally sterile sites
8	–	–	–	1	–
11	–	–	1	1	–
2	1	1	–	–	–
18	–	–	–	3	–
7	4	1	4	–	–
3	–	1	–	–	–
6	–	–	–	5	14[a]
9	–	–	1	–	2[b]
4	–	6	3	2	2[c]
10	–	–	–	4	–

[a]Various sites
[b]Both hepatosplenic candidiasis
[c]Hepatosplenic candidiasis, necrotic otitis

Seven articles [4, 6, 8–11, 18] provided data on PCT levels in 34 cases of culture-proven candidiasis (candidemia *n*=16, hepatosplenic candidiasis *n*=3, necrotic otitis *n*=1, culture from various normally sterile sites *n*=14). A wide range of PCT peak levels (0.38–238 ng/ml) were reported. In most patients with markedly elevated PCT concentrations, peak levels were reached at the time of diagnosis or shortly thereafter. However, in 6 of 34 patients, PCT levels even remained within the normal range.

The only article in which a considerable cohort of patients (*n*=19) with microbiologically documented invasive *Candida* infection (including five with candidemia) was described attests to the diagnostic value of PCT (sensitivity 94.7%, specificity 89.5%) using an upper normal value of 0.75 ng/ml. However, more than 50% of the investigated patients including at least one patient with fungemia had PCT levels below the usual cutoff for sepsis (2.0 ng/ml) accounting for a low sensitivity of 47.3% [6].

Analysis of data

In order to assess the sensitivity of PCT as a diagnostic marker for invasive fungal infection, serum levels from previously reported patients with IFI and our own patients (two with probable invasive aspergillosis, one with candidemia) were analyzed. Clinical, radiological and micro-

Table 2 Sensitivities of procalcitonin as indicator ofproven/probable invasive fungal infection related to different cutoff levels ortime after diagnosis

	PCT cutoff (ng/ml)	PCT-positive patients (evaluable patients)	Sensitivity (%)
Proven/probable invasive aspergillosis			
Peak	>0.5	18 (20)	90
	>2.0	8 (20)	40
Day 1–3	>0.5	10 (19)	53
	>2.0	1 (19)	5.3
Proven/probable invasive candidiasis			
Peak	>0.5	29 (35)	82.9
	>2.0	19 (35)	54.3
Day 1–3	>0.5	6 (11)	54.5
	>2.0	5 (11)	45.5

biological findings reported in the respective articles [2–4, 6–11, 18] were correlated with the EORTC/NIAID diagnostic criteria for invasive fungal infections [1]. If a report did not contain sufficient data to allow a clear diagnosis of possible, probable or proven IFI, the missing information was added by means of direct correspondence with the authors [3, 7, 9, 11]. This procedure resulted in the inclusion in the analysis of 55 patients who fulfilled the EORTC/NIAID definition criteria for proven or probable IFI [1].

Results

In Table 2 the sensitivity of PCT for detection of proven/probable IFI is shown in relation to different cutoff levels and to different periods (early/late) during the course of fungal infection. The overall sensitivity of PCT considering serum levels above the upper normal value of 0.5 ng/ml any time during the course of IFI was 83% for candidiasis and 90% for aspergillosis. These scores came down to 45.5% and even 5.3%, respectively, when the standard cutoff for bacterial sepsis of 2 ng/ml was applied in the clinically important early phase (days 1 to 3) of symptomatic IFI.

Discussion

Reasons for the different PCT patterns in response to yeast and mould invasion may be found in the different pathophysiological pathways of these fungal infections. While aggravation of *Candida* infection usually leads to fungemia resembling bacterial sepsis, aspergillosis tends toward local (although progressive) invasion causing only intermittent fungemia with a low number of circulating fungal cells. This is reflected by the almost negligible yield of blood cultures even in the most severe cases of invasive aspergillosis. Furthermore, a potential difference in cytokine response to the respective fungal species has to be considered as already described for bacterial (e. g. Gram-positive versus Gram-negative) organisms [7].

Christofilopoulou et al. attributed no diagnostic value, but did attribute a prognostic value, to PCT in severe fungal infections [4]. However, the clinical relevance of this observation seems questionable in light of missing therapeutic consequences. Once diagnosed with suspected or proven systemic fungal infection, patients are usually treated with high doses of antifungal agents, irrespective of any prognostic laboratory finding.

In a small study evaluating PCT as a marker of invasive candidiasis, lowering the cutoff value to 0.75 ng/ml resulted in a considerable increase in sensitivity to almost 95%. However, only fewer than half of these *Candida* infections were detected by PCT using the standard cutoff for sepsis (2.0 ng/ml) [6]. This corresponds well with the result of our analysis. In contrast, independent of cutoff values, PCT was generally an unreliable indicator of the early (and therapeutically important) phase of invasive *Aspergillus* infection with a potential role as a prognostic marker thereafter. The particularly low sensitivity of PCT in indicating invasive aspergillosis may partly be explained by the usually concomitant profound leukopenia, which has been reported to be correlated with lower PCT levels [17]. However, for both candidiasis and aspergillosis single case reports suggest a correlation between PCT levels and the severity of invasive infection [7, 10].

The roles of other inflammatory parameters in the diagnosis of IFI have been poorly defined in the literature. C-reactive protein (CRP) was measured concomitantly with PCT in six of ten studies analyzed in the present study [2, 3, 6–8, 10]. The available data from 8 *Aspergillus* and 24 *Candida* infections were too incomplete and small in number for a serious statistical evaluation comparing CRP with PCT. However, the authors mostly attributed a low diagnostic value, mainly due to varying sensitivity and low specificity, as also seen in another study of 22 patients with invasive aspergillosis (CRP peak levels ranging from 5 to 384 mg/l, median 58 mg/l) [12].

We are aware that only a prospective multicenter study could provide a definitive answer to the question as to whether or not PCT is useful in the diagnosis of IFI. However, analysis of published data on PCT as a marker of IFI as well as our own observations lead to the following preliminary conclusions:

- PCT response appears to be different in mould and yeast infections.
- There was only a delayed increase in PCT, or none in invasive aspergillosis.
- Candidemia may lead to a PCT response similar to that seen in bacterial sepsis, but this was not observed in all cases.

– According to available data—and particularly in light of more promising, specific diagnostic methods for IFI such as antigen detection and PCR—PCT cannot be recommended as a reliable marker of invasive fungal infection.

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