Elevated procalcitonin levels in anaphylaxis

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Abstract
Background: The most common role procalcitonin play in current-day medicine is in the diagnosis and management of sepsis. Aside from sepsis, there are other known causes of elevated procalcitonin, for example, trauma and severe pancreatitis. We herein present a case of markedly elevated procalcitonin levels with an unusual cause, that is, anaphylaxis.

Case report: A young lady presented to our hospital consecutively for anaphylaxis. Both presentations were associated with a markedly elevated procalcitonin level. She was discharged with an epinephrine autoinjector after the second visit. Recognition of anaphylaxis as a cause of elevated procalcitonin level can potentially change management as shown in this case report. This case report also highlights the importance of history taking and not to over rely on investigation results for patient management.

Keywords
Procalcitonin, anaphylaxis

Introduction
Procalcitonin is biomarker of great interest to many in recent times. Multiple studies on procalcitonin levels in a wide range of conditions from all specialties mostly relating to infection have been published. However, procalcitonin in noninfectious conditions is much less studied. Anaphylaxis is not recognized as a cause of elevated procalcitonin levels. We present a rare case report of a young lady who presented with anaphylaxis twice, both times associated with elevated procalcitonin levels.

Case report
A 26-year-old Chinese lady, with no known drug allergies and no past medical history of note, presented to the emergency department (ED) complaining of fever of 5-day duration. There was abdominal pain, vomiting and diarrhoea which only started on the day of visit. She was started on oral amoxicillin-clavulanate by the general practitioner (GP) 2 days prior to the ED visit. She noted rashes 90 min after taking the medications but continued with them after a repeated consultation with the GP. She had a positive contact history, namely, her husband having symptoms of a respiratory tract infection, although patient herself denied having any respiratory tract symptoms. She had also been taking a multi-vitamin tablet Lipesco-E daily for approximately 10 days prior to presentation, but this information was not volunteered by the patient nor elicited by the medical staff. Her amoxicillin-clavulanate was consumed together with Lipesco-E.

At presentation, her vitals were as follows: temperature 37.8°C (100°F), blood pressure 96/52 mm Hg, pulse rate 104/min and oxygen saturation of 100% on room air. Physical examination revealed a general flushed appearance with upper abdominal tenderness. Rest of the examination was unremarkable. She was alert. Her lungs were clear and there was no stridor.

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Her full blood count showed a mildly low total white cell count of 3.0 × 10⁹/L and mildly low platelet count of 138 × 10⁹/L. Her renal panel, liver function test and amylase levels were generally unremarkable with the exception of a low potassium level of 3.2 mmol/L. Her dengue screen was also negative. Her electrocardiogram showed sinus tachycardia and her chest x-ray was reported as ‘patchy air space opacification is seen in the right lower zone and may represent a new focus of infection’ (see Figure 1).

The initial impression of the treating physicians then was an allergic reaction. She was given intravenous (IV) hydrocortisone, IV diphenhydramine and IV cimetidine. She was also started on IV levofloxacin in view of the chest x-ray report. Nasoendoscopy by otorhinolaryngology cleared the upper airway of obstruction. Her blood pressure dropped to a lowest of 78/36 mm Hg and her pulse rate reached a maximum of 128/min. She was started on a noradrenaline infusion via a central venous catheter as her systolic blood pressure was persistently in the 80s despite 2 L of 0.9% sodium chloride. The treating ED physicians felt there could be a component of sepsis in view of the persistent hypotension. She was admitted to the medical high dependency (MHD) ward on a noradrenaline infusion dose of 0.15 µg/kg/min. Procalcitonin levels were noted to be raised in the MHD at 6.42 µg/L. The normal reference range in our laboratory is 0.00–0.05 µg/L. Her C-reactive protein (CRP) was minimally raised at 6.3 mg/L. Her procalcitonin was markedly elevated at 13.22 µg/L. Her electrocardiogram showed sinus tachycardia and her chest x-ray was reported as ‘no focal consolidation’.

The impression of her presentation was that of anaphylaxis. She was again given IV hydrocortisone, IV diphenhydramine and IV cimetidine. Intramuscular epinephrine 0.3 mg was given this time. She was again covered empirically with IV levofloxacin after noting the result of procalcitonin. Her blood pressure stabilized after treatment with the above medications and 4 L of 0.9% sodium chloride. Her blood pressure ranged from 97/49 to 105/53 mm Hg. She was admitted to the medical general ward.

She was reviewed by the allergist again. The history of taking Lipesco-E since 10 days prior to the first visit was revealed. An alert for allergy to Lipesco-E was raised in her EMR. Levofloxacin was not continued on beyond the first dose in the general ward. Two sets of blood cultures taken were negative for bacterial growth. She was treated as for anaphylaxis (secondary to excipients in Lipesco-E) and discharged well after 2 days with an epinephrine autoinjector.

Discussion
In this case, the patient meets the criteria for anaphylaxis (see Table 1) during both the first and second visits. For the first visit, the first clinical criterion of anaphylaxis was met. There was involvement of the skin as evidenced by rashes.
Table 1. Diagnostic criteria for anaphylaxis.

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue or both (e.g. generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   A. Involvement of the skin mucosal tissue (e.g. generalized hives, itch-flush, swollen lips-tongue-uvula)
   B. Respiratory compromise (e.g. dyspnoea, wheeze-bronchospasm, reduced peak expiratory flow, stridor, hypoxaemia)
   C. Reduced blood pressure or associated symptoms (e.g. hypotonia, collapse, syncope, incontinence)
3. Reduced BP (blood pressure) after exposure to a known allergen for that patient (minutes to several hours)
   A. Infants and children: low systolic BP (age-specific) or greater than 30% decrease in systolic BP
   B. Adults: Systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline

As well as hypotension. For the second visit, both the first and second criteria of anaphylaxis were met. There were skin involvement (rashes), respiratory compromise (dyspnoea), reduced blood pressure and gastrointestinal symptoms (vomiting and diarrhoea), as well as exposure to a likely allergen, that is, the multi-vitamin Lipesco-E.

During the patient’s first visit, the ED differentials were mainly that of septic shock and anaphylactic shock. The history of fever with a chest x-ray being reported as possibly abnormal points more towards sepsis but the rapid onset of a flushed appearance was more suggestive of anaphylaxis. Despite having a high procalcitonin level during the first presentation, the total white cell count was almost normal and blood and urine cultures were negative for bacterial growth. The lactate level, which is elevated in septic shock,\(^1\) was normal as well.

During the second visit, the working differential in the ED was that of anaphylaxis rather than sepsis given the rapidity of onset of symptoms after exposure to the multi-vitamin, also with hindsight of the first visit. She was nevertheless covered with antibiotics given the fever, raised total white cell count and markedly elevated procalcitonin level. However, blood cultures were again negative for bacterial growth and CRP level was near normal as well. Patient’s condition improved swiftly despite discontinuation of antibiotics after the first dose. This suggests that there is unlikely any sepsis on board.

Procalcitonin is increasingly used in clinical practice. The turn-around time for procalcitonin is within an hour for this case. The main utility of procalcitonin levels is in diagnosing sepsis and septic shock and to guide antibiotic therapy. As compared to other biomarkers, for example, CRP and erythrocyte sedimentation rate (ESR), procalcitonin has the highest specificity for infection.\(^2\) However, in the critically ill population, procalcitonin levels are also elevated in systemic inflammatory response syndrome (SIRS) of noninfectious origin.\(^3,4\) Procalcitonin has been described to be elevated in trauma, haemorrhage, burns, post-operative states, post-myocardial infarction and cardiogenic shock, severe pancreatitis, autoimmune disorders, severe organ dysfunction, post-cardiac arrest, malignancy and neonates,\(^5\) but not in anaphylaxis. Anaphylaxis is also not traditionally listed as a cause of SIRS.

To date, a literature search revealed only three case reports of elevated procalcitonin levels in association with anaphylaxis.\(^6–8\) Anaphylaxis resulting in elevated procalcitonin may be significantly under-recognized. Release of procalcitonin from thyroid C cells, neuro-endocrine cells in the lungs and intestines as well as various other parenchymal cells in the body is mediated by cytokines including interleukin-6 (IL-6), tumour necrosis factor-α and interleukin-1β. IL-6 is shown to be elevated in anaphylaxis\(^8,10\) and it could be responsible for procalcitonin release during anaphylaxis.

In this case, intramuscular adrenaline (gold standard treatment in anaphylaxis) was administered during the second visit in the ED in view of the high suspicion of anaphylactic shock. Patient’s condition improved after adrenaline and she avoided a potential admission to the high dependency ward, minimizing cost for the patient and freeing up resources for the hospital. She also avoided the risks of invasive lines.

With the recognition that procalcitonin may be elevated in anaphylaxis, and multiple studies showing the non-exclusivity of elevated procalcitonin, clinical correlation is important when interpreting procalcitonin result. The author suggests that in situations where procalcitonin is elevated in cases of anaphylaxis with no other evidence of sepsis, the patient should be treated with adrenaline first and monitored for improvement. Antibiotics should be withheld unless there is no clinical improvement with adrenaline, for example, refractory hypotension.

In addition, the importance of good history taking should not be forgotten. In drug-related illnesses, patients often neglect to report innocuous medications or supplements which they themselves feel do not contribute to the illness. And when clinicians anchor on certain available information, for example, elevated procalcitonin, they may fail to
take further history. In this case, the history of patient consuming the multi-vitamin prior to the first visit was only elicited during the second visit.

Summary

This case report illustrates elevated procalcitonin levels in anaphylaxis. With increasing number of cases being reported, anaphylaxis should be considered as a cause of elevated procalcitonin. This information can change patient management, benefitting the patient and minimizing cost and resources used as shown in the case. More studies can be done in this area.

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