Case report

False-negative synovial alpha-defensin

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ABSTRACT

We present a case of chronic periprosthetic hip infection diagnosed using the Musculoskeletal Infection Society criteria as the gold standard. The alpha-defensin test was falsely negative. The diagnostic workup of the patient is detailed, along with a discussion regarding the potential reasons behind the misleading alpha-defensin results. To our knowledge, this is the first reported case of a false-negative alpha-defensin test in the setting of an open sinus tract communicating with a culture-positive total hip implant. The alpha-defensin test should be interpreted cautiously, along with all relevant pertinent clinical data. In certain cases, similar to those described here, the Musculoskeletal Infection Society criteria may perform better than this particular biomarker.

Keywords: Alpha defensin  Biomarker  Periprosthetic joint infection  Total hip arthroplasty

Introduction

Despite attempts to establish a uniformly accepted gold standard definition of periprosthetic joint infection (PJI), the diagnosis of infection following total joint arthroplasty remains difficult. Outlier cases that do not fall into well-defined categories represent unique diagnostic and treatment challenges. We present a case of a symptomatic, initially culture-negative prosthetic hip, which was later determined to be infected based on the Musculoskeletal Infection Society (MSIS) criteria. The alpha-defensin test (Synovasure PJI; Zimmer Biomet, Warsaw, IN) was falsely negative. To our knowledge, this is the first reported case of a false-negative alpha-defensin test in the setting of an open sinus tract communicating with a culture-positive total hip implant.

Case history

A 57-year-old male underwent a primary right total hip replacement for osteoarthritis at another institution. Five months postoperatively, he noticed a firm area develop near the proximal aspect of his skin incision, as well as subjective fevers. A magnetic resonance imaging was obtained by his initial surgeon which was concerning for an abscess, and he was taken for irrigation and debridement with modular head and liner exchange 11 months following the index procedure. Multiple aspirations and cultures were obtained which were negative. Following this debridement, the patient underwent 6 weeks of treatment with intravenous (IV) vancomycin and daptomycin, followed by 3 weeks of oral ciprofloxacin. For several weeks prior to his presentation to our clinic, the patient noticed spontaneous cycles of drainage with intervals of skin healing (Fig. 1).

Eighteen months following the initial surgery, the patient presented to our institution for a second opinion. Plain radiographs were obtained, revealing a well-fixed cementless right total hip arthroplasty with a moderate amount of heterotopic ossification (Fig. 2). Serum erythrocyte sedimentation rate and C-reactive protein (CRP) were 17 mm/h (normal, <30 mm/h) and 65 mg/L (normal, <3 mg/L), respectively. After confirmation that the patient had been completely off of oral and IV antibiotics for several months prior to presentation, aspiration was performed. Synovial white blood count was 2833/mcL with a differential of 47%. The Synovasure test was negative (synovial alpha-defensin negative, synovial CRP 29.8 mg/L, synovial hemoglobin normal). Cultures remained negative after incubation periods of 14 days (aerobic and anaerobic), 28 days (fungal), and 8 weeks (mycobacterial).

Despite the negative cultures, negative alpha-defensin, and equivocal aspiration results, the patient met MSIS criteria for a culture-negative PJI based on the draining sinus tract communicating with the prosthesis. The patient was taken for a staged revision and placement of an antibiotic spacer (Fig. 3). Six
Intraoperative cultures were obtained prior to commencement of antibiotics. Three of the anaerobic cultures revealed growth of *Staphylococcus saccharolyticus*, and 3 grew *Propionibacterium acnes*. The other cultures remained negative after incubation periods of 14 days (aerobic), 28 days (fungal), and 8 weeks (mycobacterial). The patient was treated with 6 weeks of IV antibiotics, and ultimately underwent reimplantation of his right hip approximately 4 months after the first-stage debridement (Fig. 4). The patient was informed that his case would be submitted for publication, and he consented.

Discussion

Diagnosis of PJI is uncomplicated when patients meet the major MSIS criteria [1], either with 2 positive cultures from separate specimens or a draining sinus tract communicating with the joint. The decision-making process becomes more complex when minor criteria are relied upon, and potentially conflicting data exist. Although alpha-defensin has been validated as a reliable test to aid in diagnosing PJI [2-4], this case underscores the diagnostic complexity of PJI, and highlights the importance of interpreting this test cautiously with consideration of all pertinent clinical data.

We are unaware of any current literature that documents a case of a false-negative Synovasure test taken from a hip that
found to be falsely negative. This patient had 4 negative culture results, but 3 of 5 positive minor MSIS criteria classified this as an infected case. The follow-up expanded study described in the paper states that among 649 negative Synovasure samples, 1.4% demonstrated positive cultures. The paper concludes that this is due to “the expected false-positive rate of cultures in a population of synovial fluid samples” [5]. Of 156 patients included in their prospective study, Bonanzinga et al [6] reported only a single false-negative case that presented with a draining sinus. Unlike our case, however, this case demonstrated multiple negative intraoperative cultures, and the authors do not specify whether or not the sinus communicated with the implant, making it plausible that this did not represent true PJI. Finally, Frangiamore et al [7] reported a single case of a false-negative alpha-defensin in the setting of what the authors deemed to be a false-positive culture. Rather than these cases representing false-positive cultures, is it possible that the cut-offs for a positive alpha-defensin test should be adjusted for low-virulence organisms, or the presence of a draining sinus. Alpha-defensin is naturally produced by neutrophils, and in the presence of a draining sinus, it is possible that levels of this biomarker will not be replenished as the fluid is drained.

P acnes is known to be a low-virulence organism and S saccharolyticus is an anaerobic organism. These factors may perhaps play a role in the diminishing diagnostic accuracy of the alpha-defensin test in this scenario. Available literature on the topic is mostly suggestive of equivalent results in alpha-defensin test accuracy despite microbial profile. Deirmengian et al [8] demonstrated in a recent study that the alpha-defensin test provides consistent results regardless of the organism type, species, or virulence of the organism. However, a recent study by Frangiamore et al [7] investigating PJI of the shoulder, a joint commonly infected with low virulence organisms such as P acnes, showed that the alpha-defensin test demonstrated a lower sensitivity (63%), lower negative likelihood ratio (0.38), and only moderate correlation with positive cultures as compared to previous data published by multiple study groups in lower extremity PJI.

Just as there is a lack of information regarding the performance of this biomarker with low-virulence organisms, there is also a paucity of literature assessing the reliability of the alpha-defensin test in other outlier cases, for example, in the setting of acute inflammatory arthropathy. In a study by Ahn et al, alpha-defensin was described as playing a protagonist role in the pathophysiology of inflammatory arthropathy through its function in the synthesis of proinflammatory cytokines [6]. The Synovasure white paper, based on this study by Ahn et al, indicates that while alpha-defensin levels reach concentrations above 5.2 mg/L in patients with PJI, patients with rheumatoid arthritis demonstrate only a mean concentration of 0.039 mg/L [5]. The levels provided in this study were obtained in the outpatient setting from patients with pre-established rheumatoid arthritis, rather than patients with acute flares of inflammatory arthropathy, frequently encountered in the emergency room, or inpatient setting. As a result, while Synovasure may be useful in differentiating PJI from nonacute inflammatory arthropathy, it is plausible that the cut-offs established by the Synovasure test are not appropriate for differentiating PJI from acute gout, pseudogout, or other inflammatory conditions. Additional data on the diagnostic accuracy of alpha-defensin in specific arthropathies such as gout, pseudogout, and systemic inflammatory conditions in the acutely painful setting, rather than during routine surveillance outpatient appointments, would be useful.

Summary

We present a case of a false-negative alpha-defensin test in the setting of chronic periprosthetic hip infection. Fortunately, in this case, the diagnosis was easily made in the presence of a draining sinus. In cases without a draining sinus, however, a negative alpha-defensin test coupled with the aspiration results obtained, could have easily led to erroneous clinical decision making. This case highlights the importance of interpreting the Synovasure test cautiously, along with all relevant clinical data. Additionally, it underscores the need for an improved understanding of the pathophysiology of this biomarker in atypical cases.

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