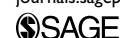


Knee Pain in a Boy With Hyper IgE Type I Syndrome (Job Variant)

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Case Report

A 15-year-old boy with autosomal dominant hyper IgE syndrome type 1 (HIES), Job variant presented to the emergency department (ED) with 2 days of mild knee pain and 1 day of fever.

The knee pain worsened with activity, but did not prevent him from walking. He had no associated redness or warmth of the joint. His eczema due to his syndrome was unchanged from baseline. He denied any other focal signs of infection including cough, shortness of breath, or change in bowel and bladder function.

He was evaluated in the ED and found to have swelling and limited extension, but no definite tenderness, erythema, or warmth. He also had normal hip range of motion and normal distal sensation and pulses. Laboratory evaluation revealed a white blood cell (WBC) count of $9.9 \times 10^3/\mu\text{L}$ (normal $4.5\text{--}12.0 \times 10^3/\mu\text{L}$), but an elevated C-reactive protein (CRP) of 43.5 mg/L (normal <8.2 mg/L). Knee joint aspiration was then performed, which revealed a WBC count of 1700/ μL , at which point he was discharged home.

There was improvement in his symptoms for approximately 48 hours. However, his pain gradually returned, and he returned to the ED 5 days later with increased knee pain, stiffness, and erythema. Laboratory evaluation at that time once again revealed a normal WBC count of $10.13 \times 10^3/\mu\text{L}$, but a CRP that increased to 92.9 mg/L. Repeat joint aspirate revealed a white count of 19900/ μL (normal 200 cells/ μL) with 90% segmented neutrophils. At this point, he was taken to the operating room for culture, irrigation, and debridement, followed by the initiation of intravenous cefazolin and vancomycin. Cultures grew methicillin-resistant *Staphylococcus aureus*.

Final Diagnosis

Septic arthritis associated with Job syndrome.

Discussion

This unusual presentation of septic arthritis is attributable to HIES, which made the diagnosis much more

challenging. Normally, septic arthritis presents with the acute onset of severe pain, swelling, redness, heat, and joint effusion.¹ Our patient did not have any redness until his second ED visit, and he did not ever display significant warmth or swelling. Looking at laboratory values, inflammatory markers can typically be good rule-out tests with high sensitivity, but low specificity for septic arthritis. Some specific cutoff points are: WBC count ($>10 \times 10^3/\mu\text{L}$: sensitivity 90%, specificity 36%), erythrocyte sedimentation rate (>30 mm/h: sensitivity 95%, specificity 29%), and CRP (>100 mg/L: sensitivity 77%, specificity 53%).² Our patient barely surpassed the WBC thresholds on his second ED visit, and did not surpass any of the other thresholds. However, clinical suspicion remained high due to his history of HIES and prior infections. Therefore, joint aspiration was warranted, as it remains the gold standard for confirming a diagnosis of septic arthritis and guiding therapy. The likelihood ratios (LRs) for various synovial WBC counts are as follows: $<25\,000$ cells/ μL (LR 0.32), $>25\,000$ cells/ μL (LR 2.9), $>50\,000$ cells/ μL (LR 7.7), and $>100\,000$ cells/ μL (LR 28.0).² With our patient's synovial WBC count below the first threshold ($25 \times 10^3/\mu\text{L}$), it would be hard to make the diagnosis based on laboratory values alone. In fact, his diagnosis relied on a combination of increasing clinical signs and symptoms of infection, and an upward trend in laboratory markers. Looking at the whole picture, rather than looking at numbers and probabilities helped yield the diagnosis. This is consistent with a 2007 literature review of 80 articles which concluded that “no investigation is more reliable in the diagnosis of septic arthritis than the opinion of an experienced doctor.”³

The particular challenge in diagnosing this patient can be attributed to the fact that HIES is a functionally

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immunocompromised state. Derangements in the inflammatory cascade make it less likely for patients to exhibit redness, warmth,⁴ or systemic signs of infection, such as fever, elevated WBC count, and other inflammatory markers.⁵ The mechanism for these derangements arises from a mutation of the signal transducer and activator of transcription 3 (STAT3), which mediates the signaling for about 40 cytokines and growth factors.⁶ It is unclear exactly which of these many signaling pathways are responsible for the immune defects. However, multiple reports have shown that those affected with HIES have lower production of Th17 cytokines, including IL-17A, IL-17F, and IL-22.⁶ In vitro studies have shown that neutralization of Th17 cytokines results in decreased production of chemokines and defensins. It has also been shown that patients with HIES have an approximately 50% reduction in chemoattractant receptors, including FPR, CXCR1, and CXCR2,⁷ which leads to a reduced level of PMN chemotaxis. With reduced PMN chemotaxis, these patients have an impaired ability to mount an acute inflammatory response. This helps explain why our patient was so slow to show erythema and have elevated synovial WBC counts.

Interestingly, the expression of some other pro-inflammatory markers, including interferon- γ (IFN- γ), interleukin-1 (IL-1), and tumor necrosis factor (TNF) is unaffected⁶ so these patients may still enter into a pro-inflammatory state when infected, and undergo permanent damage from infections. In fact, one of the most serious and devastating sequela of HIES is lung damage and remodeling from recurrent pulmonary infections. Within the first few years of life, patients are typically afflicted with *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* lung infections.⁵ Because of the lack of systemic signs and symptoms of infection, there are often delays in diagnosis and treatment, which can result in empyemas, bronchiectasis, and pneumatocele formation.⁵ Some of the signaling pathways in the disease also seem to be associated with impaired epithelial repair, which makes disordered remodeling of lungs a prominent feature in this disease, with approximately 70% of patients affected.⁵ This lung damage then makes patients more susceptible to opportunistic pathogens, including *Aspergillus fumigatus*, *Pseudomonas* sp., and nontuberculous mycobacteria.⁵ The focus of early treatment is on preventing recurrent infections and the subsequent lung remodeling. This treatment often utilizes prophylactic antibiotics such as cephalexin or trimethoprim/sulfamethoxazole once or twice daily for their activity against *S aureus*.⁵

In addition to lung infections, patients with HIES are very susceptible to skin infections, so patients should practice appropriate skin care to preventing infections.

This encompasses bleach baths, chlorhexidine washes, and prophylactic oral antistaphylococcal antibiotics to improve eczematoid dermatitis and to prevent abscesses. Prophylactic measures are not generally initiated against potential fungal infections.

Therapeutic bone marrow transplants have varied in efficacy and were initially reported to be unsuccessful, but a more recent report of 2 children with retrospectively identified STAT3 mutations were transplanted for high-grade non-Hodgkin lymphoma resulting in complete resolution of immunologic and nonimmunologic features seen in HIES.⁴

As one of the hallmark characteristics of HIES is a reduction in INF- γ , much investigation has been directed at its administration with reported success. INF- γ has been shown to reduce serum IgE levels and improve neutrophil chemotaxis. Intravenous immunoglobulin has also demonstrated benefit to patients in several cases.⁸

In 2008, Bard et al⁹ first described the successful use of recombinant monoclonal anti-IgE therapy (omalizumab) for severe recalcitrant eczematous dermatitis. In 2009, Chularojanamontri et al¹⁰ reported similar findings. Finally, the use of cyclosporine and isolated cases documenting the use of disodium cromoglycate, isotretinoin, double-filtration plasmapheresis, and recombinant human granulocyte colony-stimulating factor have demonstrated positive effects for patients with HIES. Despite the encouraging findings described, the low prevalence of HIES and the varying success in its treatment have rendered the task of determining the optimal treatment remains difficult.

Conclusion

HIES is a functionally immunocompromised state in which patients are less likely to exhibit typical signs, symptoms, and laboratory values of infection. The most common complications are lung and skin infections, but these patients are susceptible to a wide range of other infections, including septic arthritis. Prevention of infection through skin care and lung prophylaxis is warranted, although the optimal treatment plan is unclear at this time. When prevention fails, prompt diagnosis and treatment of infections are crucial to prevent long-term morbidity.

Author Contributions

TGK contributed to conception and design, analysis, drafted the manuscript, gave final approval and agrees to accountable for all aspects of work ensuring integrity and accuracy. GTM contributed to conception and design, analysis and drafted the manuscript. RWS contributed to conception, design, analysis, and critically revised the manuscript.

Declaration of Conflicting Interests

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