

Peer Review File

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Reviewer A

Comment 1: What is meant by the initial radiograph being “interpreted as a stress injury?” Was this imaging available to the authors? Was there any evidence of lucency or sclerosis? Was there any active drainage at this time?

Reply 1: The radiographs are available to the authors and did demonstrate an increased density in the mid-tibial shaft associated with lateral periosteal thickening. There was also a band of sclerosis in the proximal tibia that was stable compared to a radiograph taken roughly three years prior. The radiologist interpreted the imaging as a possible stress injury. In the absence of fever and systemic symptoms, the initial radiograph was mis-interpreted and the diagnosis of osteomyelitis was delayed. Ten days later, the patient was seen by plastic surgery to evaluate his skin flap, by which time he had developed redness over the mid-tibia with increased pain and swelling.

Changes in the text: We have added additional information detailing the patient’s physical exam and interpretation of the radiographs from his initial presentation for added clarity (Figure 1A&B) (Lines 88-91)

Comment 2: Lines 100-101. Was there any evidence of a retained foreign body? I assume not (or the authors would have stated it), however, given the nature of the original injury, this should probably be made explicit. Admittedly, this is not picking.

Reply 2: We agree that this is an important point to state explicitly. There was no foreign body identified during his operation.

Changes in the text: We have made explicit that there was no foreign body identified during his surgical procedure (Line 104)

Comment 3: Lines 106-110. Just a comment- there has previously been reported a poor correlation between histology findings in osteomyelitis and duration of symptoms (PMID: 33902075).

Reply 3: Thank you for this helpful comment. This is an important point as the approach to treatment duration may be impacted by the classification of infection as acute or chronic, but histology alone should not be the sole arbitrator of this distinction. The text has been modified.

Changes in the text: We have modified the text to be descriptive of the histology findings without making a distinction between his indolent presentation. (Lines 109-110)

Comment 4: While it is most likely that the *Serratia* from the prior infection is causing the patient's osteomyelitis, were the susceptibility patterns for the two organisms similar? I agree that the previous infection almost certainly contributed to the more recent osteo, however, in the absence of the ability to perform paired molecular characterization (such as by PFGE, MLST, or whole genome sequencing), susceptibility patterns should be compared at a minimum (it seems that the authors have the susceptibility profile for the initial *Serratia* isolate).

Reply 4: The isolate from his initial infection had an identical susceptibility profile to the isolate from his recurrent infection. There is a brief reference to both isolates having similar susceptibility profiles (line 222), but this can be stated more clearly.

Changes in the text: We have modified the last paragraph in the discussion to highlight the similarity between susceptibility patterns (Lines 218-219)

Comment 5: It is at least probable that the area of lucency observed at the fixation pin site after trauma (Figure 2) represented smoldering osteomyelitis. Were there any radiographs or musculoskeletal symptoms between the patient's initial infection and the presentation with frank osteomyelitis described?

Reply 5: This is an important point. He had chronic intermittent pain over the ensuing eight years after his injury. The pain did not limit activity and was not associated with grossly observable changes in his exam. It is suspected that these symptoms were subtle clues to a smoldering osteomyelitis that were not detected until the infection progressed to overt clinical manifestations. We agree that it is important to include these details to raise awareness of subtle manifestations of chronic osteomyelitis in the right clinical context. He also had serial imaging to monitor bone healing and leg-length discrepancy during this period, but outside of the pin site infection, none of them raised suspicion for infection to the providers caring for the patient at the time.

Changes in the text: We have clarified his course during this time (Lines 138-142), adding the details of his intermittent pain and radiographs that occurred between his initial injury and subsequent presentation for osteomyelitis.

Comment 6: Minor trauma has anecdotally been reported to precipitate “reactivation” of chronic osteomyelitis. Did this patient experience any such trauma prior to the described event?

Reply 6: The patient had recently started lifting weights, including leg-specific workouts, around the time of his symptom onset. It is possible that the new stress from weight-lifting precipitated reactivation.

Changes in the text: We have added the specific detail of this increased physical activity into his initial presentation (Lines 87-88).

Comment 7: Figure 3 and the Table are very helpful at conveying the authors’ message

Reply 7: Thank you. Additional information has been added to the table describing the treatment approach. See response to Review B, comment 5, below.

Changes in the text: See below

Reviewer B

Comment 1: Line 86: I would recommend to mention explicitly in the case report section that there were no other medical disorders, no immunodeficiency and no nicotine or drug abuse in the patient's medical history.

Reply 1: We agree that it is important to clearly state his lack of underlying immunodeficiency or other medical condition that might have predisposed him to the *S. marcescens* infection.

Changes in the text: We have modified the reporting of his past medical history to include the explicit statement that he had no history of immunodeficiency, drug use/abuse, or other medical disorders that would have increased his risk for this infection. (Lines 142-146)

Comment 2: Moreover, I would recommend a further description of the initial trauma and its management 8 years before: fracture displacement/imaging/classification? what kind of ORIF (provide postoperative x-ray check if possible)? When was osteosynthesis material removed? How about functional outcome?

Reply 2: Following his injury and initial debridement, he had a Delta frame type construct for fixation which was subsequently changed to a Taylor spatial frame. All hardware was removed approximately five months after his injury.

Changes in the text: Additional details on his orthopedic surgeries, including images spanning from his initial injury to removal of all hardware have been added (Figure 2A-C, Figure 3B) (Lines 118-119, 133-138)

Comment 3: L116: I suppose it was a local reconstruction of a small tissue defect or was there a need for microvascular surgery? Please clarify briefly how soft tissue reconstruction was carried out.

Reply 3: The dorsalis pedis and posterior tibialis vessels remained patent after his injury, and he underwent an autologous muscle flap with end-to-end anastomosis of the posterior tibial and thoracodorsal arteries.

Changes in the text: Additional information on the soft tissue constructions, including debridement for the infected skin flap, have been added (Lines 119-122, 124-125)

Comment 4: Please mention briefly how you could exclude other types of juvenile osteomyelitis.

Reply 4: This is an important topic to address, as the mechanism by which the osteomyelitis is suspected to have occurred is important in both guiding the approach to treatment as well as the workup for underlying conditions that may have predisposed to the given infection. It is also important to note that current clinical practice guidelines for pediatric osteoarticular infection focus on hematogenous osteomyelitis, not other routes of infection.

Changes in the text: We have expanded the discussion on different forms of juvenile osteomyelitis (Lines 161-168), including why other mechanisms of infection were considered unlikely in our patient.

Comment 5: Please provide a therapeutic strategy concerning antibiotic and surgical treatment in case of a *Serratia marcescens* induced osteomyelitis in the discussion section.

Reply 5: We agree this is an important topic to address. There is insufficient data to guide the optimal approach to treatment of chronic *Serratia marcescens* osteomyelitis in children, including agent, route, or duration. While fluoroquinolones have more literature to support their use in the treatment of bone infections, use is generally discouraged in children and carries a risk of potentially severe side effects, especially with long-term use. Other oral options, including TMP/SMX, may be better tolerated, though still with important side effects. Unfortunately, there is less data to support TMP/SMX use in osteoarticular infections.

Changes in the text: We have added additional details in the table to describe the treatment approach taken for each of the cases of chronic, recurrent osteomyelitis. We have also added a paragraph to the discussion describing the challenges of determining the optimal treatment approach based on the current, limited data. (Lines 187-210)