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Pitfalls to a Definitive Diagnosis of Osteomyelitis in the Lower Extremity

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Abstract

Both minor and major lower extremity amputatio to the diabetic foot have reported 5-year mortality rates of 42.6% and 56.6% respectively, making it worse th n the rates for all cancers at 31.0%. Under-pinning this concerning mortality rate is the idea that timely diag sis of itis (OM), which is driving the need for the amputation, be consistent and reliable. More specifica , t atment t ams contemplating surgical amputation must understand whether function-critical portions of the lowe xtremity have OM and if amputation is warranted. In effort to universalize and streamline this d gn process, cli ians and researchers have relied on guidelines that help frame the clinical presentations, e-surgica esting protoc ls nd post-biopsy results. While these guidelines serve to form clinical standards glob it is impo ant to recogni e there are foundational issues associated with the OM diagnostic process that form the kbone me st ndards.

Keywords: Osteo yelitis; Bone b y; Trephine biopsy; Osteomyelitis histology; Pre-biopsy testing

Introduction

This review will focu on three proces ecific pitfalls associated with the characterizati n of OM and include: l of standardization of the histopathol gy definition of OM 2) p or pre-biopsy testing modalities use t rrelate w th OM presence and 3) inconsistencies associated with bo iop y methods s it relates to both pathologic and microbiologic res The intent of this work is meant to bring light t here there be i provement in global standards and per aps facili e adoption o sting standards more broadly in order t tter facili e treatment p ns.

Lack o teomyelitis histopathologic definition

One of th gest challenges with diagnosing OM is that there is not an industr wide accepted set of criteria used by pathologists to make a definitive diagnosis. This point was poignantly made in a study done by Meyr et al., [1-3]. In this work, 4 independent pathologists were asked to examine 39 bone biopsy specimens taken from diabetic patients with suspected OM. In the assessment of these specimens, these pathologists were asked to state one of three outcomes: 1) no evidence for OM, 2) no definitive OM but OM cannot be ruled out, or 3) there is evidence for OM. In 13/39 (33%) sample sets, all 4 pathologists were able to agree on the diagnosis of OM. In 41% of the cases there was one pathologist that reported there being no evidence of OM while another pathologist did report that there was evidence of OM. To further complicate the issue, it has been the experience of the authors that some pathologists will hesitate to report a definitive diagnosis for OM but then will go on to describe in the findings section histopathology criteria consistent with either acute or chronic OM.

Why is there such inconsistency in the reporting of OM?

The process of bone infection at the histologic level is complex. OM progression is multi-phasic and dynamic. When coupled with the lack of literature attempting to examine this continuum of OM behavior, the assessment gap for bone specimens becomes evident. Sybenga et al., specifically addresses this shortcoming by comprehensively detailing the OM process at the histopathologic level [4]. This work clusters these histologic features into a classification system consisting of 5 major categories of OM destruction (which include: Acute OM, acute and chronic OM, chronic OM, chronic active OM chronic inactive OM) [4]. Characteristic acute phase bone infection consists of an active bone destruction histologically seen as having hemorrhagic bone, with islands of micro-abscesses rich with neutrophils and other inflammatory cells, fibrinoid necrosis, interspersed with contaminates such as bacteria, yeast, or foreign bodies. As the OM process continues to a chronic stage, histologically what is seen is bone destruction consisting of a mix of irregular bone fragments in the marrow, lamellated bone or periosteal reaction, possible foci of avascular bone islands, plasma cell infiltrates and fibroplasia that increases with chronicity of the condition as the body attempts to wall-off the bone infection. These book-end descriptions of the OM histology make it clear that OM diagnosis is not a simple binary “present” or “not present” assessment but rather a spectrum of multiple features. Furthermore, this work also provides a framework of grading the same specimens in effort to appropriately classify the type of OM. Unfortunately, this definition and classification system for OM has yet to be broadly adopted by pathologists. Without an accepted definition of the very thing that is being sought in diagnosis, downstream team decisions and treatments are unfavorably impacted.

Inadequate pre-biopsy testing modalities

The use of pre-biopsy testing protocol for OM has been a long-sought for in OM diagnosis, especially considering the relative ease of obtaining tests (such as blood inflammatory markers and imaging) and the non-invasive nature of the test. Llewelly et al., recently published a systematic review of the various imaging methods that can be used in pre-biopsy OM determination [5]. This review included 81 studies that pooled results for the various imaging types-including the following (with associated sensitivity/specificity results) Magnetic Resonance Imaging (MRI) (95.6%/80.7%), Positron Emission Tomography (PET) (85.1%/92.8%), Single-Photon Emission Computed Tomography (SPECT) (95.1%/82.0%), Computed Tomography Scan (CT) (69.7%/95%), radiography (70.4%/95%), scintigraphy (83.6%/70.6%) and (87.3%/94.7%). While encouraging results are noted with MRI, PET and SPECT the authors note that there was high risk bias associated in a quarter of the included studies.

More recently, Hackenberg et al., in a pilot study investigated whether an OM indexing system could be used to predict the OM diagnosis [6]. Using a cohort of 55 patients, the patients' C-Reactive Protein (CRP), White Blood Cell counts (WBCs), MRI results and microbiologic and histopathologic samples were combined in forming an index score. Pooled results indicated a 93.3% success rate with correctly identifying OM using this predictive score. Unfortunately, one of the major limitations of the study was that it was limited to patients with post-traumatic injuries or surgical wounds (with no inclusion of patients with implants) and no patients with immunosuppressive diseases such as diabetes that would potentially obscure lab tests such as CRP and WBC.

Literature Review

Unfortunately, the majority of OM cases are overwhelmingly in the setting of diabetes. In effort to further explore a similar approach as that taken by Hackenberg et al., the authors have developed a numerical optimization program with pooled pre-biopsy testing data in patients with diabetes and suspected OM in effort to characterize if some pre-biopsy criteria in that population should have greater consideration. This work is anticipated to be published in the near future [5].

Inconsistency associated with biopsy methods

Bone biopsy analysis of suspected OM sites is considered the "gold standard" in OM diagnosis. Whereas pre-biopsy testing is viewed as a non-invasive approach to raise suspicion of OM, which unfortunately has low sensitivity (as discussed previously), the bone biopsy is considered to be a relatively low invasive approach to directly inspecting bone quality with anticipated higher sensitivity.

Unfortunately, this underlying assumption regarding the sensitivity of the bone biopsy has been recently placed into question. Sessions et al., reported in a study investigating 57 patients with suspected calcaneal OM that there is a significant difference in OM diagnosis results based on the technique used for sampling the bone [7]. This study compares two different bone biopsy techniques, trephine sampling *vs.* fine needle biopsy with fluoroscopy guidance, in terms of both histology and microbiology results. Not only was the trephine biopsy approach significantly more likely to result in an OM diagnosis than the fine needle technique (p-value: 0.13 for histology, p-value<0.001 for microbiology), but it also yielded significantly higher histologic and microbiologic concordance than the fine needle sampling group (p-value<0.001). Does this finding the notion that all biopsies should be done using a trephine approach? Or does it mean that perhaps the existence of OM is getting over-represented by trephine sample approaches since it obtains samples through a potentially contaminated wound site whereas the fine needle approach does not? The literature debate of this point continues [8,9]. However, what is clear from these biopsy sampling is that it can impact the potential diagnosis and should be considered a potential confounding variable in the ultimate OM diagnosis.

Discussion

In effort to refine the analysis of the obtained samples (regardless of being done with trephine or fine needles approaches), work done by Lavery et al., examines the differences in post-sampling analysis modalities namely traditional histology, culture and 16s ribosomal RNA genetic sequencing [10]. This study examined results obtained from traditional histology, culture and 16S ribosomal RNA genetic sequencing in isolation and in concert with each other following percutaneous bone biopsy. 16S ribosomal RNA testing yielded significantly more positive cases of OM than histology (83% *vs.* 67%) and non-significantly more cases than traditional culture (83% *vs.* 67%). If pooled results from histology and culture were compared with analogous pooling of histology and 16S ribosomal RNA testing the incidence of OM remained the same. This final point proves to be helpful in the broader context of the clinical environment, since the combination of histology/culture testing is more universal than the latter. Nevertheless, the larger point is well made, not only to treatment teams have to be aware of the potential impact of bone sampling methods on the OM diagnosis, they also must understand that reliance only on one post-sampling method can mis-represent the extent of the potential OM presence.

Conclusion

Framing the OM process inside of a well arranged algorithm is a difficult challenge. As discussed there are current barriers with standardizing the very definition of histologic criteria for OM reliable use of pre-biopsy testing modes and consistent methods for the actual bone biopsy as well as the post-biopsy analysis of the same. While these are significant pitfalls, it also represents an opportunity for further process improvement as well as research and development in a critical decision-point aspect of millions of patients' care.

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