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Letters to the Editor

Letter to the Editor

First, we want to congratulate Dr Elmarsafi and his colleagues on their article ("Concordance Between Bone Pathology and Bone Culture for the Diagnosis of Osteomyelitis in the Presence of Charcot Neuro-Osteoarthropathy. J Foot Ankle Surg 2018;57:919–923). We all struggle with getting the diagnosis of osteomyelitis (OM) right in complex patients. Their report adds to that discussion.

We have several observations and questions about the authors' article. One of their pivotal factors is the presence of Charcot neuroarthropathy (CN), yet there is no definition provided for CN. We cannot find any pathologic definition of CN in the medical literature, and no pathology criteria or references were provided in the text, although it is also not clear that the CN diagnosis was histologic. The histology criteria to define OM also were not specified. We realize that pathology reports for OM and CN are often terse and provide very little description of specific criteria the pathologist used for the histologic assessment, so in a retrospective study, consistent criteria may simply not have been available.

The authors included only subjects with CN and OM. They confirmed the diagnosis of OM by using several criteria, including radiography, advanced imaging, erythrocyte sedimentation rate, C-reactive protein, positive probe to bone, exposed bone, and intraoperative assessment of bone. We realize that some studies use just 1 of these factors to define OM. However, it was unclear how all of these factors were incorporated together to "confirm the diagnosis of OM." The reference standard for the study to define OM seems to be histology.

When a diagnostic tool is being assessed, subjects with the disease and subjects without the disease are usually included in the analysis. Perhaps by including both, Dr Elmarsafi and his colleagues would have reached a different conclusion. CN may not be the factor that muddied the diagnostic waters. Those waters are already a bit murky, as the authors point out when they referenced publications by Weiner et al (1) and Meyr et al (2). Agreement by pathologists is often poor, and the criteria they use to define osteomyelitis are variable. To determine if CN is a factor, future research should include a broader spectrum of pathology that includes patients with CN with no bone infection, bone infection with no CN, and no CN and no bone infection, as well as more complete operational definitions of disease entities. The report by Weiner et al., (1) which the authors cite, has a very different protocol: histologic and microbiologic assessments were made on specimens suspected, rather than confirmed, of being OM. This changes the underlying prevalence of OM, suspected OM, and confirmed OM, and this in turn changes the sensitivity, specificity, etc.

Further muddying the waters is the fact that clean margins (before and after debridement) were taken from patients with confirmed OM. The supposition appears to be that the clean margins should be diagnosed as OM. The fact that neither the histologic nor microbiologic assessments declared OM in these cases is to be expected, rather than viewed as a failure. Perhaps these samples need to be more clearly classified and diagnosed. Finally, the fact that the 2 methods do not agree does not indicate, necessarily that one or the other is correct, or that one or the other is faulty. It may simply indicate that both, especially in the setting of CN, must be used to diagnose OM.

We would interpret the results of the study differently than did the authors. The disease process is in the bone. The gold standard still needs to be a direct measure from the bone biopsy. We need to develop systematic criteria to report histology and improve the information given to our pathologists and the reports that pathologists provide surgeons and infectious disease physicians. In the future, we might also be able to improve histology interpretation with computer-aided, pattern-recognition software. We may be able to improve our bone culture results with better intraoperative handling of specimens and by using DNA sequencing rather than traditional culture techniques to identify pathogens. We used 16s rRNA in a series of patients with DFO and identified many more pathogens, especially anaerobes and gram-positive bacilli, compared with traditional culture. Traditional culture techniques may simply not be suitable to identify all of the bacterial pathogens, so some cases would be misclassified as not having OM if culture was the sole criterion.

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References

1. Weiner RD, Viselli SJ, Fulkert KA, Aceetta P. Histologic versus microbiology for accuracy in identification of osteomyelitis in the diabetic foot. J Foot Ankle Surg 2011;50:197–200.
2. Meyr AF, Singh S, Zhang X, Khilko N, Mukherjee A, Sheridan MJ, Khurana JS. Statistical reliability of bone biopsy for the diagnosis of diabetic foot osteomyelitis. J Foot Ankle Surg 2011;50:663–667.

Reply to Letter to the Editor

We are equally frustrated with the lack of general consensus regarding the clinical, histologic, serologic, and genomic means to define

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Charcot neuroosteoarthropathy (CN). Sadly, all recent literature seems to reference old and antiquated, nonproven postulates relating to CN pathogenesis: the French and German theories. We presented our report with the expectation that the reader has a general gestalt and an overall understanding. Nonetheless, the question is an important one, and we acknowledge that a broad-spectrum definition is beneficial. We provide a definition as stated from the authors' perspective rather than with lackluster references. In short, CN is a progressive destructive bone and joint disorder that afflicts the insensate foot and ankle. The process begins with acute inflammation resulting in an osteolytic process that ultimately results in joint collapse and profound biomechanical sequela. The pathogenesis and etiology are both elusive, with multiple more recent theories suggested throughout the literature. Overall, the diagnosis requires an astute clinical suspicion in the high-risk patient, is driven mostly by the clinical presentation, and is supported by radiographic and advanced imaging. Histologic assessments are not helpful, as there are no accepted guidelines available to pathologists describing CN changes from bone biopsies, and thus bone biopsies are not required or recommended.

As for defining the histologic criterion related to osteomyelitis (OM) in our cohort, we were challenged by the confounding presentation imparted by the presence of CN. In fact, the very premise of our publication is built on the frequent encounter of concomitant CN and OM pathologies seen in real-world cases. In such instances, pathologists are placed in a clinical conundrum: to make 2 challenging diagnoses, which in some cases, based on the sample, may tend toward changes more "consistent" with CN or in other cases the specimen can reflect a predominance of changes "consistent" with OM. In such cases, that is, concomitant CN plus OM, histology results were less descriptive. Pathologists refrained from the use of words such as "acute inflammation," which are found in both pathologies, for example. Thus, pathologists used clearer, more deliberate terminology as to what was being ruled out: CN/OM. Our methods reflect how histopathology results were reported, which aligns with our statistical analysis.

All of the subjects were confirmed to have OM through a comprehensive approach. All patients were subjected to the same clinical algorithm, which includes imaging, erythrocyte sedimentation rate, C-reactive protein, probe vs exposed bone, and the intraoperative assessment of bone quality at the time of biopsy. The ultimate determination of OM, as reflected in the medical literature, remains the bone biopsy. However, the premise of this research brings into question the validity of this methodology in this subset of subjects —those with concomitant CN and bone infection. It is, thus, as per the guidelines of The Infectious Disease Society of America and International Working Group for the Diabetic Foot, to obtain a comprehensive panel of diagnostic information that cumulatively provides clinicians with a high degree of certainty of the diagnosis of OM. It is noteworthy, however, that it is still clinical suspicion that drives the diagnosis in these cases. With that said, more components that are positive increase overall diagnostic accuracy. The "confirmed" diagnosis of OM is based on high clinical suspicion and is not definitive.

In our Patients and Methods section, we define the reference standard for comparison as histopathology. Bone biopsy remains the gold standard in the literature, and, as we describe in the our discussion, there are many flaws attributed to the microbiology process, including contamination, sampling, etc., making the bone culture the lesser of the diagnostic modalities for the diagnosis of OM. Because our algorithm to diagnose OM reflects a series of tests that require the interpretation of the clinician to make a cumulative judgment, our cohort includes the possibility of subjects with and without OM. Certainly, it is our premise that the propensity toward false-negative results is high. And, indeed, we acknowledge this to be a flaw in our publication. It is also noteworthy to point out that the statistical analysis presented includes the test accuracy of each modality separately based on the concordance heat map, which is extremely telling. We argue that the findings from previous studies that do not include the CN population are certain to have drastically different results. In fact, our findings relating to diagnostic accuracy for microbiology matches those of the scientific literature for OM: about 50% in the diabetic foot. Regarding the results from Weiner et al (1), our results actually correlate rather similarly in numbers and conclusions; that is, biopsy specimens, even when paired with pathology and microbiology, are not good measures in a population at high risk for amputation, prolonged antibiotic exposure, etc.

We must make clear that we do not use the words "clean margins" in our report. Rather, we describe the surgical technique used to obtain surgical specimens. Bone biopsies from the initial surgical debridement are likely to carry the highest biologic yield for microbiology. Often the most contaminated bone is bone that is exposed and thus most likely to grow contaminants, and it is least helpful with respect to sensitivities when tailoring an antibiotic regimen. Thus, it is our practice to include a biopsy specimen from bone after the predominance of infected tissue and bone has been excised and the surgical site lavaged with normal saline. In the majority of cases, on subsequent debridement, additional bone is further resected. However, such samples were excluded from our analysis. Clean margins are obtained when the previous surgical pathology and microbiology results both show clearance of infection and often require multiple surgical interventions to reach the conclusion of "clean margin negativity." We argue that a comprehensive diagnostic approach is required to reach the ultimate conclusion for the diagnosis of OM. We use the terminology "confirmed OM" to establish a high degree of clinical suspicion toward the diagnosis. Thus, when both histopathology and microbiology fail to reach the diagnosis, we are left to reach 1 of 2 conclusions: both tests are inadequate or CN has a dramatic impact on the diagnosis. We argue both, as the κ coefficient is exceedingly low between both modalities.

Making a clinical diagnosis of OM in the presence of CN can be challenging. With the use of radiography and magnetic resonance imaging, combined with serologic markers of inflammation, probe-to-bone test, clinical judgment, and most certainly the addition of bone pathology/culture, the overall risk related to making the wrong diagnosis becomes rare. The purposes of our report were to isolate and challenge the methods most referenced in the literature and to present the largest cohort published to this effect. We leave the reader to interpret the information and opine with the preface that our research, as with all research, imparts inherent weaknesses. We argue that when more than 1 disease process occurs in the tissue, both of which change the morphology on which pathologists rely, and the gold standard becomes less reliable and even dangerous. Ponder on the notion of a positive pathology for OM with a negative culture, or the reverse. These occurrences lead to diagnostic confusion, delay in patient care, further testing, and further surgery, which may include major lower extremity amputation in this high-risk population. We argue that the multiplicity of research reflects our sentiment, that bone biopsies in the diabetic foot are of poor sensitivity, specificity, and positive predicative value, and we must question the status quo. Although it is outside the scope of our report, we agree that there are other modalities that are important to explore such as quantitative PCR. We would

argue, however, that, again, regardless of the modality, the diagnosis of OM in the presence of CN must include a comprehensive workup.

Certainly, there is much yet to be uncovered regarding CN and all related research. More research is needed and encouraged to further explore all such aspects.

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Reference

1. Weiner RD, Viselli SJ, Fulkert KA, Aceetta P. Histology versus microbiology for accuracy in identification of osteomyelitis in the diabetic foot. J Foot Ankle Surg 2011;50:197–200.