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Original Research

Concordance Between Bone Pathology and Bone Culture for the Diagnosis of Osteomyelitis in the Presence of Charcot Neuro-Osteoarthropathy

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ABSTRACT

The diagnosis of osteomyelitis (OM) is a challenging but critical pathology to uncover in patients with concomitant Charcot neuro-osteoarthropathy (CN). The reference standard to diagnose OM is bone biopsy for histopathologic and microbiologic examination. The presence of CN, however, can have a negative effect on the accuracy of either method to identify OM. The aim of the present study was to examine the concordance between bone pathology and bone cultures in the presence of CN in the diagnosis of OM. A total of 286 patients with diabetes mellitus (DM) and CN were identified retrospectively, with 48 patients identified with OM. OM was confirmed by radiographs, magnetic resonance imaging, erythrocyte sedimentation rate, and C-reactive protein, positive probe-to-bone test results, and intraoperative inspection. Seventy matched pairs of bone pathology and cultures with complete data were compared and analyzed. Statistical analysis included concordance, positive predictive value, negative predictive value, sensitivity, specificity, and kappa coefficient. Concordance between bone pathology and bone culture was 41.4%, with agreement in 29 of 70 paired specimens. The diagnostic test accuracy of histopathologic examination to diagnose OM in CN bone in our study was 51.4%. The diagnostic test accuracy of microbiologic examination to diagnose OM in CN bone was 50%. The positive predictive value was 72.2%. The negative predictive value was 44.1%. The sensitivity was 57.8%. The specificity was 60.0%. The kappa coefficient was 0.165. The reference standard method of histopathologic and microbiologic examination of bone specimens has little concordance and can lead to inaccurate or inconclusive information. The low sensitivity and specificity demonstrated in the present study does not support the use of the current reference standard method of bone biopsy for histologic and microbiologic diagnosis of OM when CN is present. Thus, a diagnosis of OM in patients with CN should only be considered in the presence of strong clinical, laboratory, and imaging correlates.

Charcot neuro-osteoarthropathy (CN) is a devastating consequence of peripheral polyneuropathy most often seen in patients with longstanding diabetes mellitus (DM). The diagnosis of CN is predominantly determined by clinical and imaging findings. The unfortunate long-term sequelae results in osseous and articular destruction, leading to profound biomechanical compromise of the foot and ankle. These patients often develop ulcerations, which frequently lead to concomitant osteomyelitis (OM). The diagnosis of OM in the presence of CN can be difficult. It is, however, paramount to establish the presence of bone infection to direct both medical and surgical management.

The reported data are clear in expressing the importance of bone biopsy as the reference standard for diagnosing OM (1,2). Clinical guidelines encourage bone biopsy for evaluation using histopathologic and microbiologic examination to make a definitive diagnosis of OM in the diabetic foot (3). We hypothesized that the concordance rates between these 2 modalities could be low and might further lead to confounding information to extrapolate a definitive diagnosis of OM when CN

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is present. The osseous morphologic changes that occur secondary to CN can obscure the histologic evidence of infection and lead to inaccurate clinical interpretation when bone suspicious for infection is sent for pathologic examination. Furthermore, biopsies obtained surgically from bone that was exposed to an ulcer can yield microbiologic evidence of infection that can be attributed to contamination from the surrounding infected and/or contaminated soft tissue. Although bone specimens sent for both histopathologic and microbiologic examination are intended to provide a tissue-based diagnosis for OM, in the presence of CN, the low test reliability can lead to erroneous and/or conflicting results. The consequences of misdiagnosing OM have dire implications.

No consensus has been reached in the scientific data discussing the clinical relevance of bone histopathology and bone microbiology to diagnosis OM when CN is coexistent. The purpose of the present study was to retrospectively examine the results from paired bone specimens sent for both histopathologic and microbiologic examination to evaluate the concordance of these 2 modalities.

Patients and Methods

Institutional review board approval was obtained for a retrospective, cohort study from a single institution dedicated to diabetic limb salvage. The patients were identified within a 7-year period from January 1, 2004 to December 26, 2011. Office notes, hospital records, operative dictations, and radiographic and laboratory results were analyzed. A total of 286 patients with concomitant DM and CN were identified. Of the 286 patients, 71 had a confirmed diagnosis of OM determined by radiographic and advanced imaging findings, surrogate markers (e.g., erythrocyte sedimentation rate, C-reactive protein), positive probe-to-bone test findings, exposed bone, and intraoperative evaluation of the bone involved. In many cases, the evidence of OM after interpretation of these modalities precluded the necessity of obtaining bone specimens. All cases without both histologic and bone microbiology results obtained simultaneously were excluded from analysis. The intraoperative bone specimens sent for histopathology and microbiology were included for analysis, resulting in a total 70 paired samples obtained from 48 patients.

All patients in the present study required osseous reconstruction to re-establish a plantigrade, biomechanically more functional foot. All patients were hospitalized and treated by internal medicine, vascular surgery, orthopedic surgery, plastic surgery, and infectious disease, as well as other specialists as needed. A staged approach was performed, with operative debridement of nonviable bone and soft tissue when infection was present. In all cases, bone samples were intraoperatively collected and sent for histopathologic and microbiologic examination. A specimen taken before debridement and another after debridement were sent on the date of initial resection. A clean rongeur was used to obtain the sample from the most clinically suspicious segment of bone. These samplings were sent for microbiologic examination in sterile aerobic and anaerobic specimen kits. The remainder of bone was sent in a sterile specimen collection container and sent for histopathologic examination. Both the microbiology and the pathology laboratories are located in the same hospital, and the specimens were sent within 30 minutes after the end of each case for processing.

The histopathologic results were reported as "no evidence of Charcot nor osteomyelitis," "Charcot without evidence of osteomyelitis," and "acute or chronic osteomyelitis," represented as 0, 1, and 2, respectively. The microbiology bone cultures identified species when cultures were positive or "no growth" when negative. This scaling allowed for ease of statistical interpretation. The histopathologic results were compared against the bone culture results to establish concordance; that is, how often the histopathologic and microbiologic results matched.

In addition to concordance between the histopathologic and microbiologic results, statistical analysis included calculating the specificity, sensitivity, positive predictive value, and negative predictive value for histopathology to detect OM in the presence of CN. To calculate the sensitivity, specificity, positive predictive value, and negative predictive value, the false-negative, false-positive, true-negative, and true-positive results were first calculated. False-negative results were those findings identified by histopathology as "no evidence of Charcot nor osteomyelitis" or "Charcot without evidence of osteomyelitis" but with positive speciation by microbiology. False-positive results were those findings identified as "acute or chronic osteomyelitis" by histopathology but with "no growth" reported by microbiology. True-positive results were those identified by histopathology as "acute or chronic osteomyelitis" with positive speciation by microbiology. True-negative results were those identified by histopathology as "no evidence of Charcot nor osteomyelitis" or "Charcot without evidence of osteomyelitis" and with "no growth" reported by microbiology. A generated contingency table and related equations (Table 1) reflect these findings. Cohen's kappa coefficient (κ) was derived as a measure of the interrater reliability between histopathology and microbiology.

Table 1
Contingency table (N = 70)

Result	Result	
	Positive	Negative
Positive	TP (Path 2; Cx+): 26	FP (Path 2; Cx–): 10
Negative	FN (Path 0, 1; Cx+): 19	TN (Path 0,1, Cx–): 15

Positive predictive value = TP/(TP + FP); negative predictive value = TN/(FN + TN); sensitivity = TP/(TP + FN); specificity = TN/(TN + FP); Cohen's kappa statistic: Kappa coefficient = (po – pe)/(1 – pe), with po = 0.586, indicating observed agreement between tests; pe = 0.504, indicating agreement due to chance; marginal1 = 23.143; marginal2 = 12.143.
Abbreviations: Cx, microbiology culture; FN, false-negative; FP, false-positive; Path, histopathology; Path 0, no osteomyelitis and no Charcot; Path 1, Charcot only; Path 2, acute or chronic osteomyelitis; TN, true-negative.

When microbiology identified growth, the organism and frequency of occurrence was tabulated to identify the most common pathogen causing OM in the diabetic CN foot in our cohort.

Results

In our cohort, all 48 patients had a definitive diagnosis of DM, CN, and confirmed OM. Of the 48 patients, 33 (68.8%) were male and 15 (32.2%) were female. Also, 33 (68.8%) patients had hypertension, 14 (29.2%) had chronic kidney disease, 9 (18.8%) had end-stage renal disease, 9 (18.8%) had peripheral arterial disease, and 4 (8.3%) patients were active smokers. The mean glycated hemoglobin was 8.8% ± 1.48% (range 5.3% to 15%), the mean body mass index was 32.5 ± 8.37 (range 21.3 to 47.3) kg/m^2, and the mean age was 54 ± 14.85 (range 34 to 86) years (Table 2).

The overall concordance between histopathology and microbiology was 41.4%. The 2 modalities were in agreement in 29 of 70 paired specimens. A heat-map schematic shows the differences between the histopathologic and microbiologic results (Fig.). These results, however, did not consider whether the reports were, in fact, accurate. Further analysis was undertaken to more specifically identify other methods to understand the relationship between these 2 modalities for diagnosing OM in the presence of CN.

In the evaluation of test accuracy, histopathology was evaluated independently of the microbiologic assessment. Because all patients had undergone a comprehensive OM evaluation composed of clini-

Table 2
Demographic data and comorbidities

Variable	n (%)
Sex	
Male	33 (68.8)
Female	15 (31.2)
Age* (y)	
Mean	54
Range	34 to 86
HbA1c (%)	
Mean	8.75
Range	5.3 to 15
DM	48 (100)
OM	48 (100)
HTN	33 (68.8)
CKD	14 (29.2)
ESRD	9 (18.8)
PAD	9 (18.8)
Smoker†	4 (8.3)

Abbreviations: CKD, chronic kidney disease; DM, diabetes mellitus; ESRD, end-stage renal disease; HbA1c, glycated hemoglobin; HTN, hypertension; OM, osteomyelitis; PAD, peripheral arterial disease.
* Age at time of reconstruction.
† Active smoking at reconstruction.