The Journal of Foot & Ankle Surgery 50 (2011) 663–667

Contents lists available at ScienceDirect

The Journal of Foot & Ankle Surgery

journal homepage: www.jfas.org

Statistical Reliability of Bone Biopsy for the Diagnosis of Diabetic Foot Osteomyelitis

Andrew J. Meyr, DPM, FACFAS [1], Salil Singh, DPM [2], Xinmin Zhang, MD [3], Natalya Khilko, MD [4], Abir Mukherjee, MD [4], Michael J. Sheridan, ScD [5], Jasvir S. Khurana, MD [3]

[1] *Assistant Professor, Department of Podiatric Surgery, Temple University School of Podiatric Medicine, Philadelphia, PA*
[2] *Resident, Temple University Hospital Podiatric Surgical Residency Program, Temple University Hospital, Philadelphia, PA*
[3] *Associate Professor, Department of Pathology, Temple University Hospital, Philadelphia, PA*
[4] *Assistant Professor, Department of Pathology, Temple University Hospital, Philadelphia, PA*
[5] *Epidemiologist and Biostatistician, Department of Medicine, Inova Fairfax Hospital, Falls Church, VA*

ARTICLE INFO

Level of Clinical Evidence: 3
Keywords:
bone marrow
correlation
diabetes mellitus
histology
infection
surgery

ABSTRACT

Bone biopsy is often referred to as the reference standard for the diagnosis of diabetic foot osteomyelitis (OM), and it also serves as an important interventional tool with respect to diabetic foot infections and limb salvage. However, the phrase *bone biopsy* lacks a standardized definition, and the statistical reliability of the pathologic diagnosis has not been previously examined. The objective of the present study was to quantify the reliability of the histopathologic analysis of bone with respect to the diagnosis of diabetic foot OM. Four pathologists, kept unaware of the previous pathology reports and specific patient clinical characteristics, retrospectively reviewed 39 consecutive tissue specimens and were informed only that it was "a specimen of bone taken from a diabetic foot to evaluate for OM." As a primary outcome measure, the pathologists were asked to make 1 of 3 possible diagnoses: (1) no evidence of OM, (2) no definitive findings of OM, but cannot rule it out, or (3) findings consistent with OM. There was complete agreement among all 4 pathologists with respect to the primary diagnosis in 13 (33.33%) of the 39 specimens, with a corresponding kappa coefficient of 0.31. A situation of clinically significant disagreement, or in which at least 1 pathologist diagnosed "no evidence of OM," but at least 1 other pathologist diagnosed "findings consistent with OM," occurred in 16 (41.03%) of the specimens. These results indicate agreement below the level of a "reference standard" and emphasize the need for a more comprehensive diagnostic protocol for diabetic foot OM.

Bone biopsy is often referred to as the "reference standard" for the diagnosis of diabetic foot osteomyelitis (OM) (1–12), and it has repeatedly served as the standard reference marker in the investigation of other diagnostic techniques for OM, including the clinical findings (e.g., probing to the bone), laboratory data, and advanced imaging analyses (13–32). In addition to these diagnostic considerations, bone biopsy also plays an important interventional role with respect to the treatment of diabetic foot infection and limb salvage. The therapeutic decisions that can be based on the bone biopsy results include the course and duration of antibiotic therapy, need for subsequent wound debridement, indication for hyperbaric oxygen therapy, timing of wound closure, and level of lower extremity amputation (1,2,6,7,28,30,33–36).

However, there is no standard definition for the phrase *bone biopsy*. It might refer either to microbiologic bone culture (1,2,4,14,28–31,34,37) or to the histologic analysis of a bone specimen by a pathologist (1,2,4,13,25,32,34). These are 2 separate and independent methods of specimen analysis, providing the treating physician with 2 different pieces of information.

From the microbiologic standpoint, bone cultures can generate inaccurate results secondary to contamination by contiguous tissue, misrepresenting the number of infecting pathogens, and the variable periods in which patients are cleared from antibiotic therapy before specimen collection (2,4,28,30,31,34,37,38). Surgeons must also decide which specific microbiologic testing is indicated (i.e., aerobic, anaerobic, fungal, acid-fast, chocolate), and risk a false-negative result if the correct test is not ordered. These limitations have led some to consider genetic testing of the microbiologic specimens for results with greater accuracy (39,40).

The histopathologic analysis of bone for infection also has potential difficulties. There is no standardized definition or classification for OM with this analysis (5,37,41,42), and only a few clinical studies have attempted to define characteristics of bone samples affected by OM

Financial Disclosure: None.
Conflicts of Interest: None.
Address correspondence to: Andrew J. Meyr, DPM, FACFAS, Assistant Professor, Department of Podiatric Surgery, Temple University School of Podiatric Medicine, 8th at Race Street, Philadelphia, PA 19107.
E-mail address: ajmeyr@gmail.com (A.J. Meyr).
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doi:10.1053/j.jfas.2011.08.005

(25,26). In addition, we are unaware of any study that has specifically examined the statistical reliability of this assessment. The objective of the present study was to quantify the reliability of the histopathologic analysis of bone with respect to the diagnosis of diabetic foot OM.

Patients and Methods

Tissue specimens from 39 consecutive patients retrospectively identified from the primary author's (A.J.M.) foot and ankle surgery service at a large teaching hospital during a 3-month data collection period (December 2009 to February 2010) were included in the analysis. To be included, a pathology specimen only had to be procured from a diabetic patient for whom the diagnosis of OM was in question. The specimens included primarily amputated bone, apparently clean osseous margins after partial foot amputation, and bone biopsy through full-thickness chronic wounds in the setting of Charcot neuroarthropathy. The original pathology report, intra-operative microbiologic culture data, and eventual diagnosis with the patient course were not considered for specimen inclusion, only a preoperative situation in which the diagnosis of OM was in question.

After these tissue specimens had been identified, 4 members of the pathology department at the hospital, all board-certified surgical pathologists who routinely diagnose OM, independently evaluated the specimens and were informed only that it was a specimen of bone obtained from a diabetic foot as a bone biopsy to "evaluate for OM." These pathologists were unaware of the original pathology reports, microbiologic culture data, and specific patient clinical characteristics. A standardized form (Fig. 1) was used for data collection.

The primary outcome measure of the present investigation was agreement among the pathologists' diagnosis as assessed using the kappa coefficient. The pathologists were asked to make 1 of 3 primary diagnoses: (1) no evidence of OM, (2) no definitive findings of OM, but cannot rule it out, or (3) findings consistent with OM. If the pathologist arrived at a primary diagnosis of "findings consistent with OM," they were also asked to determine the presence of a secondary diagnosis of any of the following forms of OM: (1) acute, (2) chronic, (3) both acute and chronic, or (4) cannot differentiate between acute and/or chronic.

As a secondary outcome measure, the pathologists were asked to identify either the presence or absence of certain histologic findings on the slide, specifically the presence of sequestrum, involucrum, necrotic bone, necrotic-inflammatory exudate, bone erosion, marrow edema/fat necrosis, marrow fibrosis, acute inflammatory changes, and chronic inflammatory changes. From our understanding of the published data (5,25,26,37,41,42), and the experience of the pathologists as determined by a pre-investigation interview, these pathologic findings were selected as suggestive of OM.

The data were procured from the data collection sheets by a nonpathologist author (A.J.M.) and stored on a microcomputer for subsequent analysis. All statistical analyses

Slide #: _____

Pathologist identifier: _____

Institution: _____

This slide contains a specimen taken from a diabetic foot as a bone biopsy to "evaluate for osteomyelitis"

Are there any findings in this slide consistent with (please answer "yes" or "no" for each question):

-**Sequestrum**?:	YES	NO
-**Involucrum**?:	YES	NO
-**Necrotic Bone**?:	YES	NO
-**Necrotic-inflammatory exudates?:**	YES	NO
-**Bone erosion?:**	YES	NO
-**Marrow edema/fat necrosis?:**	YES	NO
-Marrow fibrosis?:	YES	NO
-**Acute inflammatory changes**?:	YES	NO
-**Chronic inflammatory changes**?:	YES	NO

Which of the following best fits your histological diagnosis based on this slide? (please choose only one option):

1. No evidence of osteomyelitis
2. No definitive findings of osteomyelitis, but cannot rule it out
3. Findings consistent with osteomyelitis

If #3 is selected, then (circle one): Acute? Chronic? Acute and Chronic? Cannot differentiate?

Fig. 1. Standardized form used for data collection.