Histological Findings of Osteomyelitis in Patients with Diabetic Foot and Their Correlation with Radiologic Findings

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Objective: Osteomyelitis in patients with diabetic foot has been diagnosed clinically, radiologically, and histologically. However, the accuracy of these diagnostic modalities is not well established. In this study, we histologically reviewed patients who underwent surgical procedures for diabetic foot osteomyelitis and correlated these histological features with radiological findings.

Methods: Eighty patients who were clinically diagnosed with diabetic foot osteomyelitis, who underwent surgical treatment between November 2017 and February 2022, were enrolled. Hematoxylin and eosin-stained slides and radiological findings were reviewed.

Results: Eighty patients were radiologically examined by magnetic resonance imaging (MRI) (49 cases) and/or 99mTc-hexamethylpropylene amine oxime-labeled white blood cells single-photon emission computed tomography (SPECT)/computed tomography (CT) (65 cases). MRI findings were suggestive of osteomyelitis in 35 cases (71.4%) and soft tissue inflammation in 46 cases (93.8%). In SPECE/CT, 60 cases (92.3%) and 64 cases (98.4%) showed signs of osteomyelitis and soft tissue inflammation, respectively. Histologically, both bone and soft tissue lesions were found in 32 cases (40%), only bone tissue lesions in seven cases (8.8%), and only soft tissue lesions in 40 cases (50%). The sensitivity and specificity of MRI for osteomyelitis were 83.3% (10/12) and 28.6% (4/14), and that of SPECT/CT was 100.0% (12/12) and 12.5% (2/16), respectively. Moreover, those of by MRI findings for soft tissue inflammation were 90.6% (29/32) and 0% (0/12), while that of SPECT/CT was 97.4% (38/39) and 0% (0/18), respectively.

Conclusion: For accurate histological diagnosis of diabetic foot osteomyelitis, sufficient specimens should be obtained. White blood cell SPECT/CT seems to be a more sensitive modality than MRI for the detection of osteomyelitis.

Keywords: Diabetes mellitus; Leukocytes; Magnetic resonance imaging; Osteomyelitis; Single-photon emission computed tomography; Computed tomography

INTRODUCTION

Diabetes mellitus (DM) is associated with several vascular diseases. A significant proportion of individuals with long-standing diabetes develop peripheral neuropathy and peripheral vascular disease. Approximately 25% of people with diabetes experience foot complications at least once in their lifetime [1,2]. Most of these involve infections of the soft tissue. If not appropriately treated, the infection spreads contiguously to the underlying bone and soft tissue, resulting in osteomyelitis of the DM foot. Osteomyelitis of the DM foot is the most common cause of non-traumatic lower-extremity amputations [3]. Therefore, prompt diagnosis and appropriate medical intervention for this condition are crucial to prevent an unfavorable prognosis [4].

Definitive diagnosis of osteomyelitis of the DM foot relies on the detection of distinctive histopathological features and the presence of positive cultures from a sterile bone sample [5]. However, performing a bone biopsy and microbial examination is an invasive procedure that requires time and effort. Thus, imaging studies are being used as an alternative, complementary diagnostic tool for osteomyelitis of the DM foot, because of its low invasiveness and risk. Various panels of modalities, including magnetic resonance imaging (MRI), scintigraphy with 99mTc-hexamethylpropylene amine oxime (HMPAO)-labeled white blood cells (99mTc-HMPAO WBCs) with single-photon emission computed tomography (SPECT), and 18F-fluorodeoxyglucose positron
emission tomography–computed tomography, are available [6-8]. These diagnostic tools have shown high sensitivity and specificity in several individual studies and meta-analyses [9-13].

Currently, both histological and radiological findings are used as diagnostic criteria for osteomyelitis [5]. In addition to positive histology, with positive bone culture, and purulence in the bone found during surgery, detached bone fragments removed from the ulcer and intraosseous abscess found on MRI are definitive findings for the diagnosis of osteomyelitis of the DM foot.

However, the accuracy of these diagnostic radiologic modalities, as well as the correlation of these radiological findings with pathological examination, has not been well established. In the present study, we histologically and radiologically reviewed patients who underwent surgical procedures for DM foot osteomyelitis.

**MATERIALS AND METHODS**

Eighty patients who were clinically diagnosed with DM foot osteomyelitis in the single medical center, who underwent surgical treatment, such as bone excision and biopsy, amputation, or soft tissue excision between March 2017 and February 2022, were enrolled. Hematoxylin and eosin slides and radiological findings from MRI and $^{99m}$Tc-HMPAO WBC SPECT/computed tomography (CT) were reviewed.

Osteomyelitis was histologically confirmed when the specimen included bone necrosis, acute inflammation or abscess formation, chronic inflammation (fibrosis), or indications of reparative processes in the marrow space or bone tissue. Soft tissue inflammation (STI) was histologically confirmed when the specimen showed acute or chronic inflammation, fibrosis, or abscess formation. Representative images of pathologic findings are shown in Fig. 1. On MRI, osteomyelitis was suggested if there was increased signal intensity and enhancement in the bone marrow. On WBC SPECT/CT, osteomyelitis was suggested if there was abnormal radioactive leukocyte accumulation in the soft tissue extending to the bone.

Sensitivity was defined as the probability of positive cases on

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**Fig. 1.** Representative images of pathology specimen. (A, B) A case showing both osteomyelitis and soft tissue inflammation. Acute inflammatory cell infiltration is noted in left side (soft tissue, blue arrow) and marrow space (right side, red arrow) (hematoxylin and eosin [H&E], ×40 and ×100). (C) A case showing bone necrosis. Acellular bone trabeculae and marrow space is noted (H&E, ×100). (D) A case showing no definite evidence of osteomyelitis and soft tissue inflammation. Mildly degenerated bony trabeculae is noted (H&E, ×100).
imaging tests among cases diagnosed with osteomyelitis on biopsy. Specificity was defined as the probability of negative results among cases that were negative for osteomyelitis on biopsy.

This retrospective study was approved by the Institutional Review Board of Soonchunhyang University Seoul Hospital (approval no., 2023-02-009), and informed consent from individual participants was waived because of the retrospective design of this study.

RESULTS

The patients were radiologically examined by MRI (49/80, 61.3%) and/or WBC SPECT/CT (65/80, 81.3%). Forty patients underwent both MRI and SPECT/CT. The MRI findings were suggestive of osteomyelitis in 35 patients (35/49, 71.4%) and of STI in 46 patients (46/49, 93.8%). The SPECT/CT findings indicated osteomyelitis in 60 patients (60/65, 92.3%) and STI in 64 patients (64/65, 98.4%). A summary of the results is presented in Table 1.

Histologically, both bone and soft tissue involvement was found in 32/80 patients (40%), bone tissue involvement only in 7/80 patients (8.8%), and soft tissue involvement only in 40/80 patients (50%). A summary of the results is presented in Table 2. Among the 32 cases in which both bone and soft tissue were involved, 11 cases had both osteomyelitis and STI (34.4%), three had osteomyelitis only (9.4%), and six had STI only (18.8%).

Of the abovementioned 32 patients, 22 and 21 underwent MRI and SPECT/CT, respectively. Among these patients who underwent MRI, 17 (17/22, 77.2%) and 21 (21/22, 95.5) showed findings suggestive of osteomyelitis and STI, respectively. In contrast, in patients who underwent SPECT/CT, 19 (19/21, 90.5%) and 21 (21/21, 100%) showed findings suggestive of osteomyelitis and STI, respectively. A summary of the results is presented in Table 3.

The sensitivity and specificity of MRI findings for diagnosing osteomyelitis were 83.3% (10/12) and 28.6% (4/14), respectively. For WBC SPECT/CT, the corresponding values were 100% (12/12) and 12.5% (2/16), respectively. The sensitivity and specificity of MRI for STI were 90.6% (29/32) and 0% (0/12), respectively. In WBC SPECT/CT, the corresponding values were 97.4% (38/39) and 0% (0/18).

The positive-predictive value (PPV) of MRI for osteomyelitis was 50.0% (10/20), and that of SPECT/CT was 46.2% (12/26). In contrast, the PPV of MRI for STI was 70.7% (29/41), and that of SPECT/CT was 67.9% (38/56). Representative MRI and WBC SPECT/CT images are shown in Fig. 2. A summary of the results is presented in Table 4.

DISCUSSION

This pilot study reviewed the concurrent histological and radiological findings of patients with osteomyelitis and/or soft tissue inflammation of the DM foot and sought to identify the validity of MRI and WBC SPECT/CT diagnosis based on correlations with histological findings. We found that the PPV of MRI for osteomyelitis was 50.0%, while that of WBC SPECT/CT was 46.2%. The
PPV of MRI for STI was 70.7%, while that of WBC SPECT/CT was 67.9%. Consequently, histological examination, based on sufficient specimens, remains important for the diagnosis of DM foot osteomyelitis, although imaging modalities may be useful adjunctive tools. In particular, the sensitivity of WBC SPECT/CT exceeded that of MRI.

Although various imaging tools with high accuracy have been developed, histological examination has been considered the gold standard for the diagnosis of DM foot osteomyelitis [14]. In addition, to determine the causative pathogen for appropriate antibiotic treatment, it is necessary to obtain evidence of bacterial growth in bone cultures. Therefore, accurate histological evaluation is important.

Imaging modalities are convenient and noninvasive. In particular, MRI has been the imaging mainstay for diagnosing osteomyelitis and has the advantage of not involving radiation exposure. However, people with claustrophobia may find it difficult to tolerate the long test times involved in MRI. In addition, patients with implanted electrical devices or metallic materials cannot undergo MRI. On the other hand, WBC SPECT/CT exposes the patient to radiation. Another disadvantage of imaging studies is the lack of complete differentiation from Charcot neuropathic arthropathy [15].

In this study, the positive diagnosis rate of osteomyelitis on histological examination was 43.8% (14/32). In other studies, the positive diagnosis rate by histological examination ranged from 23.4% to 88.5%, with an average of 55.5% [10-12,16-27]. The sensitivity, specificity, and PPV of osteomyelitis diagnosis by MRI, matched by histological examination results, were 83.3%, 28.6%, and 50.0%, respectively. With WBC SPECT/CT, the corresponding values were 100%, 12.5%, and 46.2%, respectively. Compared with other studies, the sensitivity of MRI ranged from 29% to 100%, with an average of 81%. In terms of specificity, the corresponding values were 37% to 100% (68.5%), and the PPV values were 50% to 81.8% (72.4%) [10,16-22]. For WBC SPECT/CT, the previously reported sensitivity ranged from 88% to 100%, with an average of 90.7%. For specificity, the corresponding values were 35% to 100% (84.5%), and the PPV was 73.8% to 100% (91.2%).

The low positive diagnosis rate of histological examination in this study increased the false-positive rate of imaging modalities,
which affects the specificity and PPV. The cause of this result may be the application of strict diagnostic criteria, using histological examination only, or the acquisition of inappropriate tissue sections due to insufficient decalcification.

This study had some limitations. Because of the retrospective nature of the study, the methods of specimen acquisition, slide creation, and image data could not be controlled. In future, a prospective study using matched imaging studies and tissue sampling should be performed. However, the present study was meaningful in that it proved the diagnostic usefulness of MRI and $^{99m}$Tc-HMPAO WBC SPECT/CT by analyzing a number of samples and confirming that these are mutually complementary diagnostic tools. Less than half of the pathological samples from the clinical DM foot patients in this study contained both bone and soft tissue. Only half of the patients underwent MRI or WBC SPECT/CT. Finally, the proportion of cases in which it was possible to evaluate the concordance between imaging study and histologic evaluation was smaller than that in the cohort.

In conclusion, accurate histological diagnosis of DM foot osteomyelitis is important, and sufficient specimens should be secured. According to the guidelines on the diagnosis and treatment of foot infections in persons with diabetes, when osteomyelitis of a DM foot is suspected, a combination of the probe-to-bone test, erythrocyte sedimentation rate, and plain radiography is used for initial studies. If a diagnosis of osteomyelitis of a DM foot is doubtful based on these evaluations, advanced imaging studies, such as MRI and WBC SPECT/CT can be considered [27]. In a study by Meyr et al. [28] on the level of agreement using a multi-test approach for the diagnosis of DM foot osteomyelitis, the interobserver or inter-test agreement was low for tests commonly used for the diagnosis of osteomyelitis of the DM foot (range, 42%–62%). These results show that objective standard criteria for accurate diagnosis of DM foot osteomyelitis have not yet been established. Further research is required to achieve a consensus. We expect that this study will contribute to the establishment of better standards for the diagnosis of DM foot osteomyelitis. Our results indicate that WBC SPECT/CT may be a more sensitive modality than MRI for the detection of osteomyelitis of the DM foot.

**CONFLICT OF INTEREST**

No potential conflict of interest relevant to this article was reported.

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**FUNDING**

This study was supported by the Soonchunhyang University Research Fund.

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