99mTechnetium-Ubiquicidin Scan with Single-Photon Emission Computed Tomography/Computed Tomography in Skull Base Osteomyelitis

Abstract

Malignant otitis externa (MOE) with skull base osteomyelitis (SBO) is an aggressive infection that predominantly affects elderly, diabetic, or immunocompromised patients, and is associated with high disease-specific mortality. *Pseudomonas aeruginosa* is the most isolated microorganism. External otitis associated with granulation tissue and pain is the most common presenting feature; a biopsy is obtained to rule out malignancy. A proper consensus is lacking regarding the best imaging modality for early initial diagnosis and follow-up. 99mTechnetium (99mTc)-labeled ubiquicidin (UBI) 29–41 is a bacterial attaching peptide that does not bind to activated leukocytes. We report a case of SBO initially misdiagnosed as a chronic otitis media, but later proved to be a case of MOE. 99mTc methylene diphosphonate bone scan and 99mTc-UBI 29–41 scan with single-photon emission computed tomography/computed tomography scans were performed to corroborate the clinical diagnosis. SBO remains a great challenge due to its increasing prevalence and high morbidity are difficult to diagnose and are often confused with cholesteatoma and neoplastic process. The UBI scan could be an auxiliary noninvasive diagnostic alternative in early diagnosis.

Keywords: *99mTechnetium, 99mTechnetium-ubiquicidin 29–41, malignant otitis externa, methylene diphosphonate, single-photon emission computed tomography/computed tomography, skull base osteomyelitis*

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Introduction

Malignant otitis externa (MOE) is an aggressive, highly morbid, and rarely life-threatening infection of the soft tissues of the external ear and surrounding structures, which spreads to involve the periosteum and bone of the skull base leading to skull base osteomyelitis (SBO). This infection is mostly seen in old-age patients, especially those who are immunocompromised with associated conditions such as diabetes, hematological disorders (e.g., leukemia or granulocytopenia), or arteriosclerosis. In most cases, the causative agent of MOE is *Pseudomonas aeruginosa*, which is a Gram-negative obligate aerobe not normally found in the external auditory canal (EAC). Infection due to other bacteria has also been reported to cause MOE, including *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Proteus mirabilis*, *Klebsiella oxytoca*, and *Pseudomonas cepacia*, however, these organisms may have been colonizers and not true pathogens.[1] The search for a modality to aid early diagnosis is still on. Common modalities like computed tomography (CT) scan have been proven as a useful tool for diagnosis and prognosis in cases of SBO, but its role in diagnosing MOE early and in routine follow-up is debatable. The suggestive features in CT scans like bone erosion, may take months to develop and are irreversible.[1]

99m Tc-methylene diphosphonate (MDP) bone scan is highly sensitive for diagnosing MOE but is less specific[2] because uptake can also be seen in other etiologies such as trauma and metastases and can show a persistent uptake in healed lesions. As the scan remains positive until the cessation of osteoblastic activity, its role in follow-up is very limited.[1-4]

The 67Ga-citrate scan was the imaging modality of choice for follow-up because the uptake resolves once inflammation subsides. However, it is known to have a poor anatomical resolution.[5] Magnetic resonance imaging (MRI) is useful for soft-tissue involvement, but it is less adequate for bone involvement and is

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expensive. MRI scans also mandate the patient to lay still for a prolonged period. Positron emission tomography with 2-deoxy-2-(fluorine-18 fluoro-D-glucose integrated with CT was found to have a high sensitivity and specificity for SBO but is not a good modality to differentiate MOE from temporal bone malignancies.[6] Several pharmaceuticals labeled with various radioisotopes are available commercially; some of them are liposomes labeled with 99mTechnetium (99mTc), immunoglobulins, antigranulocyte antibodies and antibody fragments, chemotactic peptides, cytokines, interleukins, platelet factor-4, and ciprofloxacin labeled with 99mTc. An optimal radiotracer has not been established yet, and they are often unable to differentiate between sterile inflammation and infection.

111In- or 99mTc-hexamethylpropyleneamineoxime-labeled autologous leukocytes are still considered the gold standard despite their limitations.[7]

99mTc-labeled ubiquicidin (UBI) 29–41 is a bacterial attaching peptide, which originated from human UBI (amino acid sequence TGRAKRRMQYNRR), which does not bind to activated leukocytes.[8] UBI 29–41 shows greater effectiveness against bacterial diseases. The UBI scans have depicted the most promising results for discriminating between infection and inflammation in animal models. Thus, it has great potential in diagnosing soft-tissue bacterial infections like MOE. It has been shown that the UBI scan can be a useful diagnostic study for pyogenic vertebral osteomyelitis.[9]

Case Report

Here, we report a case of a 55-year-old man, who had a history of chronic myeloid leukemia since 2005 (in remission now), diabetic for the past 5 years (on oral hypoglycemic agents), and developed right ear pain 1 year ago. It was insidious in onset and intermittent in nature with exacerbation on exposure to cold or water. It was not associated with impaired hearing, ear discharge, ear trauma, tinnitus, vertigo, vomiting, facial deviation, seizure, or headache. It was not associated with recurrent episodes of fever or any other ear, nose, and throat complaints. He was found to have EAC retraction pocket with keratin debris and was diagnosed as squamous active chronic otitis media (COM). He underwent a right modified radical mastoidectomy with intraoperative findings suggestive of a retraction pocket with keratin debris over EAC and middle ear with granulation tissue over the aditus. Postoperative histopathology was suggestive of squamous active COM. Postsurgery, he continued to have severe pain in the temporal region, for which he underwent a UBI scan [Figure 1], which showed an increased radiotracer uptake in soft-tissue thickening at the posterior and inferior margins of the postoperative cavity in the right mastoid region. The findings of the UBI scan were interpreted with the 99mTc-MDP bone [Figure 2] scan, which was done later that showed an increased tracer uptake in the right squamous temporal bone, right mastoid air cells, and right petrous temporal bone with sclerotic and erosive changes on CT, findings which were consistent with osteomyelitis with adjacent soft-tissue infection. The patient then underwent a biopsy of the soft tissue, which on histopathology showed inflammatory tissue, acute on chronic inflammatory cell infiltrate, and foreign-body giant cell reaction to keratin compatible with squamous active COM. No malignancies were seen in the section examined. Pus around the granulation tissues on Gram staining showed Gram-negative bacteria (*P. aeruginosa*). The patient was then managed with injectable antipseudomonal antibiotics such as aztreonam, ceftazidime, and amikacin for 4 weeks, and his condition improved and he was

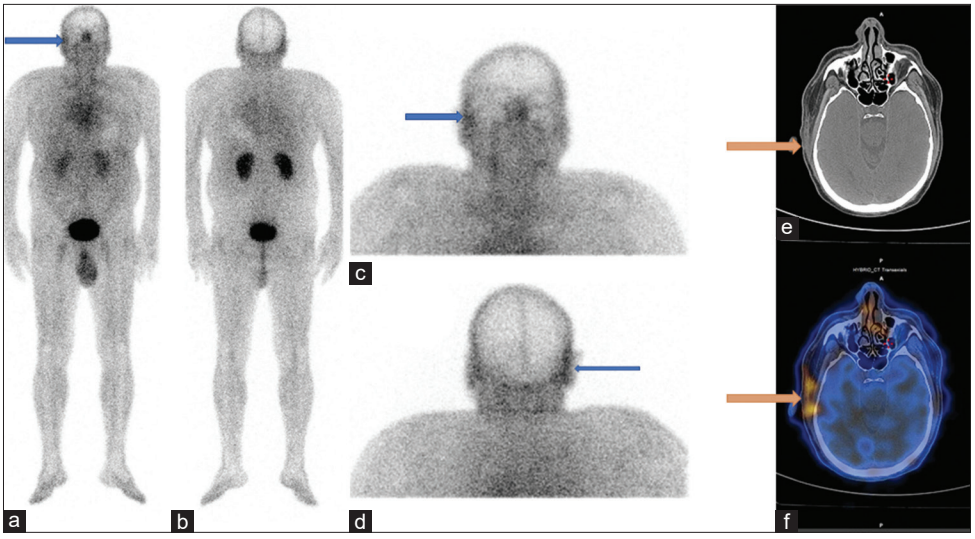

Figure 1: 99m Tc-UBI scan whole body (a-b), spot (c-d) and CT (e), SPECT/CT (f) images show an increased radiotracer uptake in soft tissue thickening at the posterior and inferior margins of the postoperative cavity in the right mastoid region

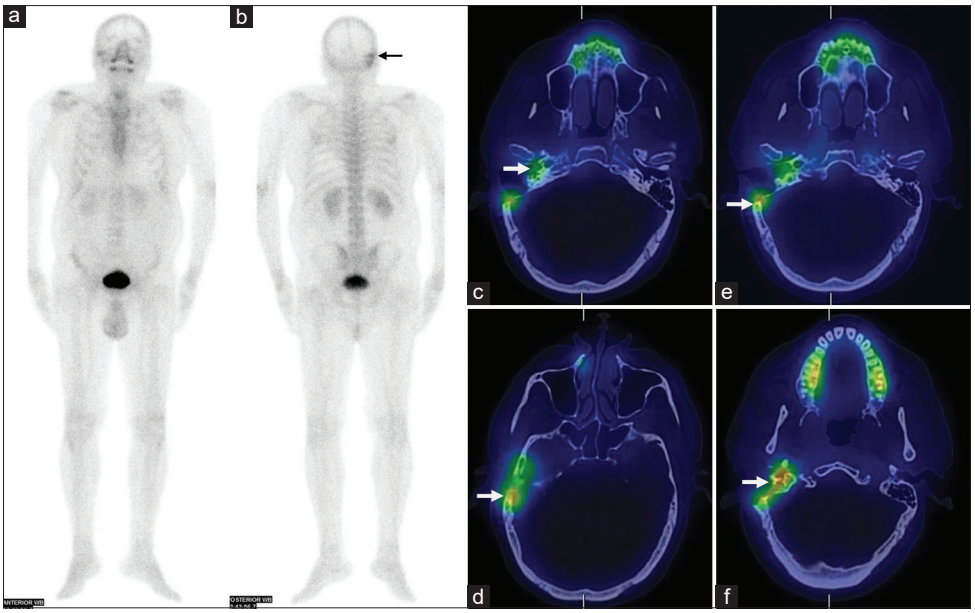

Figure 2: 99m Tc- MDP bone scan anterior and posterior image showing increase uptake in the right temporal bone (a-b). SPECT/CT images showed increased tracer uptake in the right squamous temporal bone, right mastoid air cells, and right petrous temporal bone (c-f)

discharged on oral antibiotic ciprofloxacin, and currently, he is symptom-free.

Discussion

Cohen and Friedman were among the pioneers who studied MOE in detail in 1987; they described the diagnostic criteria, which include pain, exudates, edema, and granulation tissue of EAC, and positive bone scan with 99m Tc MDP as a major criterion and positive radiography as minor.[10] Different staging systems for MOE have been suggested; they combine clinical and radiological features. Each has its own advantages, but none is comprehensive. A more comprehensive clinicopathological classification system can be achieved by combining the existing staging methods.[11] In stage 1, there is a clinical evidence of MOE with infection of soft tissues beyond the external auditory canal, but negative bone scan. In stage 2, soft-tissue infection is present beyond the EAC with a positive bone scan. Stage 3 includes substages 3A and 3B; 3A is stage 2 features with the addition of single cranial nerve involvement, and stage 3B includes stage 2 features with multiple cranial nerve involvement. Finally, stage 4 involves the complications like meningitis, empyema, sinus thrombosis, brain abscess, cranial nerve palsy, especially the facial nerve and meningitis. The effective treatment of MOE requires an early diagnosis which demands a high index of suspicion, especially in the early stages of the disease, which is identical to the classic otitis externa. Given that MOE is an infection mostly due to *Pseudomonas* bacteria, radiotracers that detect bacteria colonization early in the disease can prevent it from progressing to SBO. This highlights the importance of the UBI scan, where 99mTc-labeled UBI 29–41, which is a bacterial attaching peptide, originating from human UBI picks the exact region of soft-tissue bacterial infected areas. Diagnosis of MOE can be established by getting a definite culture report from a biopsy taken from the UBI scan-highlighted soft-tissue areas. As it does not bind to activated leukocytes, it won't highlight any area of inflammation; this makes the UBI scan different and superior to many other available radiotracers. Although the literature is limited, studies show that the UBI scan is a useful radiotracer in the diagnosis of pyogenic vertebral osteomyelitis with a high sensitivity and specificity (96.3% and 94.1%, respectively). The diagnostic accuracy for osteomyelitis is 100% in studies with UBI scan versus 90% reported in 99mTc three-phase bone scan with single-photon emission computed tomography/CT (SPECT/CT).[12] We performed 99mTc three-phase bone SPECT/CT and 99mTc-UBI 29-41 bone SPECT/CT scans in this patient, to screen for the signs of active infection. The diagnosis of MOE relies on the specific elements of the history and physical examination and laboratory and imaging studies with a positive bacterial culture confirming the diagnosis. Finally, the diagnosis and treatment of MOE in the absence of an identifiable pathogen (culture-negative specimen) have been described. These studies diagnosed MOE based on clinical history, signs and symptoms, biopsy to rule out malignancy, markedly elevated erythrocyte sedimentation rate, and imaging studies.[1] We consider that 99mTc-UBI 29–41 scan with SPECT/CT could be a promising auxiliary diagnostic and follow-up method in patients for early detection of MOE and tackling it before progression to SBO osteomyelitis, thus reducing morbidity and mortality.

Conclusion

MOE remains a great challenge due to its increasing

prevalence, and when it gets complicated to SBO, it is associated with high morbidity and mortality. It is difficult to diagnose and is often confused with COM and neoplastic processes. The 99mTc-UBI 29–41 scan with SPECT/CT bone SPECT/CT scan showed a promising diagnostic role in MOE, especially in confirming the presence of active infection. The validation of 99mTc-UBI 29–41 scan in cases of MOE requires further studies.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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