Diagnostic Utility of Galium 67 SPECT/CT and Role of Pentoxifylline-Tocopherol in Chronic Multifocal Osteomyelitis

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Abstract

Advances in radiology have helped in early diagnosis, surveillance and proper management of disease processes. SPECT scintigraphy is an imaging modality that helps in the detection & diagnosis of facial & skull osteomyelitis and is also useful for detecting silent lesions. Pentoxifylline –tocopherol together helps in faster healing of diseased bone. Pentoxifylline reduces blood viscosity and thus improves microcirculation. Tocopherol has a synergistic action with pentoxifylline and increases the oxygenation of tissues. Here, a case of chronic multifocal osteomyelitis, involving the mandible and occipital bone is presented which was diagnosed with conventional radiographs and gallium 67 bones SPECT. Simultaneous treatment with pentoxifylline-tocopherol and antibiotics relieved the patient's symptoms.

Key Words: Galium 67, Osteomyelitis, Pentoxifylline, SPECT, Tocopherol

Introduction

Osteomyelitis is an infection of the bone and bone marrow characterised by progressive destruction & apposition of new bone. Early diagnosis helps in preventing sepsis, chronic infection and deforming bone damage. The clinical course of the disease often depends on host resistance and early introduction of treatment.

Conventional radiography remains the first imaging modality that one must start with in the diagnosis of diseases. However, recent advances in technology have introduced a variety of morphologic and functional imaging modalities, which can help in the detection of often asymptomatic disease processes much earlier than the advent of clinical signs & symptoms. Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Ultrasound, Nuclear medicine imaging are useful methods in locating exact extent of osseous lesions, fluid collections, periosteal changes, bony erosions etc.

Nuclear medicine imaging is particularly useful in identifying multifocal osseous involvement and can detect osteomyelitis 10 to 14 days before changes are visible on plain radiographs.

Conventional management of osteomyelitis is with antibiotic therapy, non steroidal anti-inflammatory drugs and surgical debridement. However, evidence based therapeutic measures have been found to significantly alter disease processes [1].

Pentoxifylline, is a known drug in the treatment of osteoradionecrosis and is also an effective treatment drug for venous ulcers [2,3]. A number of studies support the effectiveness of pentoxifylline as adjunctive therapy and as monotherapy. Vitamin E (Vit E) or alpha-tocopherol in combination with pentoxifylline has been well documented to give better results in the treatment of radiation induced fibrosis. However its use in Osteomyelitis is not been documented, although useful conclusions can be made from evidence based decisions.

Here we present a patient diagnosed with multifocal osteomyelitis with the help of SPECT/CT and gallium scintigraphy and treated with Pentoxifylline-tocopherol and antibiotics.

Case Presentation

A 30 year old male patient was presented to the Oral Medicine Department of the dental school with a complaint of repeated bouts of pain and swelling in the lower chin region over a period of one and half years. Patient had observed that that the swelling and pain regressed on intake of 'painkiller' medication, only to reappear after a month. There was mild paresthesia and pruritis associated with the swelling. Medical, social and past dental histories were unremarkable.

Clinical examination revealed that lower anterior teeth crowding, mild tenderness over the gingiva in the region of the lower left lateral and canine and over the submental region. Presence of dental carious lesions involving the upper premolar and periodontal pockets involving the maxillary molars were also noted.

Orthopantomograph (OPG) revealed generalised bone loss with furcation involvement in the posterior teeth and PDL space widening of most of the lower anterior and left posterior teeth. The alveolar bone along the entire left lower quadrant showed a hazy, irregular trabecular bone pattern almost resembling a 'ground glass appearance' seen in Fibrous Dysplasia (*Figure 1*). Intra Oral Peri Apical radiographs (IOPA) of the teeth in the left maxilla and mandible revealed Periodontal Ligament space (PDL) widening of the maxillary second premolar and mandibular canine. Pulp vitality tests gave a delayed response.

Oral prophylaxis and curettage was carried out along with endodontic management of pulpally involved teeth. Patient was totally relieved from pain.

However, patient reported to the clinic a year later with the same complaint of pain & swelling in the lower jaw but on the right side. Further evaluation with IOPA's and OPG on the right side revealed diffuse irregular trabecular bone pattern suggestive of osteomyelitis. There was PDL space widening

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involving the canine and bone loss and PDL space widening associated with mandibular first molar (*Figure 2*).

Complete haemogram did not reveal any abnormality.

The radiographic appearance of the bone in relation to the right & left mandible was suggestive of osteomyelitis. Patient underwent a bone scan, initially with 15mCi of 99m Tc-MDP (Methylene diphosphate) and immediate vascular, soft tissue phase & delayed skeletal phase images of skull & facial bones were acquired using Dual Head variable angle gamma camera. SPECT CT of skull was also performed. Subsequently, Galium scan with 2mCi of Galium citrate injected IV was done. Delayed high resolution images were obtained with gamma camera followed by SPECT CT of the skull.

These investigations revealed a significantly increased galium uptake in the body of the mandible when compared to MDP tracer uptake, which was highly suggestive of an active inflammatory or infective pathology (*Figures 3 and 4*). However, the Galium uptake in the occipital bone was not as significantly increased when compared to the mandible. A bone biopsy in the region of right mandibular molar was inconclusive except for few inflammatory cells and patient was not willing for a repeat biopsy. Diagnosis of active and silent chronic low grade osteomyelitis was arrived at and patient was put on NSAIDS, Ciprofloxacillin 500 mg BD,

***Figure 1**. OPG taken at first visit.*

***Figure 2**. OPG taken at second visit.*

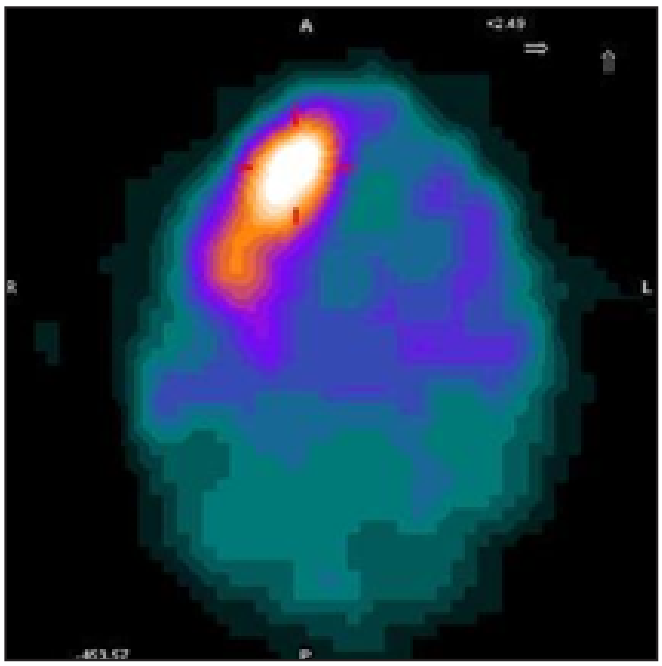

***Figure 3**. SPECT /CT images confirm significantly increased galium tracer uptake in the body of mandible when compared to MDP tracer.*

Pentoxifylline 400 mg BD and Tocopherol 400 mg BD for three months and kept under observation on a regular basis. Ciprofloxacillin is a drug prescribed in bacterial infections with excellent results. The combination PTX-Vit E was expected to enhance the action of the antibiotic, thereby leading to faster resolution and healing.

The patient was found to be totally asymptomatic on clinical and radiographic evaluation at twelve months and fifteen months.

Discussion

The causes of osteomyelitis of the craniofacial skeleton are multifactorial and its presentation varies. Most cases of osteomyelitis of the mandible and the occipital bone arise from infections of the maxillary sinuses or from odontogenic causes. Osteomyelitis at the base of the skull results from the inadequate treatment of localized, chronic otitis external [4-6].

Chronic osteomyelitis may follow an unresolving acute osteomyelitis or may arise in *de novo* following infections with organisms of low virulence. It occurs in both children and adults but is more common in adults. Patients usually complain of pain, swelling or tenderness [7].

Atypical (idiopathic) osteomyelitis of the skull base, however, occurs much less frequently and is not associated with otitis external or sinusitis [8].

In adults as with neonates & infants, the onset of osteomyelitis is insidious. The clinical picture & laboratory findings in early stage of osteomyelitis are confusing and nonspecific for bone infection. An inadequate or late diagnosis significantly diminishes the cure rate and increases the degree of complications and morbidity. Hence, imaging modalities are necessary to confirm a diagnosis, and to know the exact site and extent of the disease process. It can also be helpful to the clinician in planning medical or surgical treatment and for follow up [9,10].

Osteomyelitis frequently requires more than one

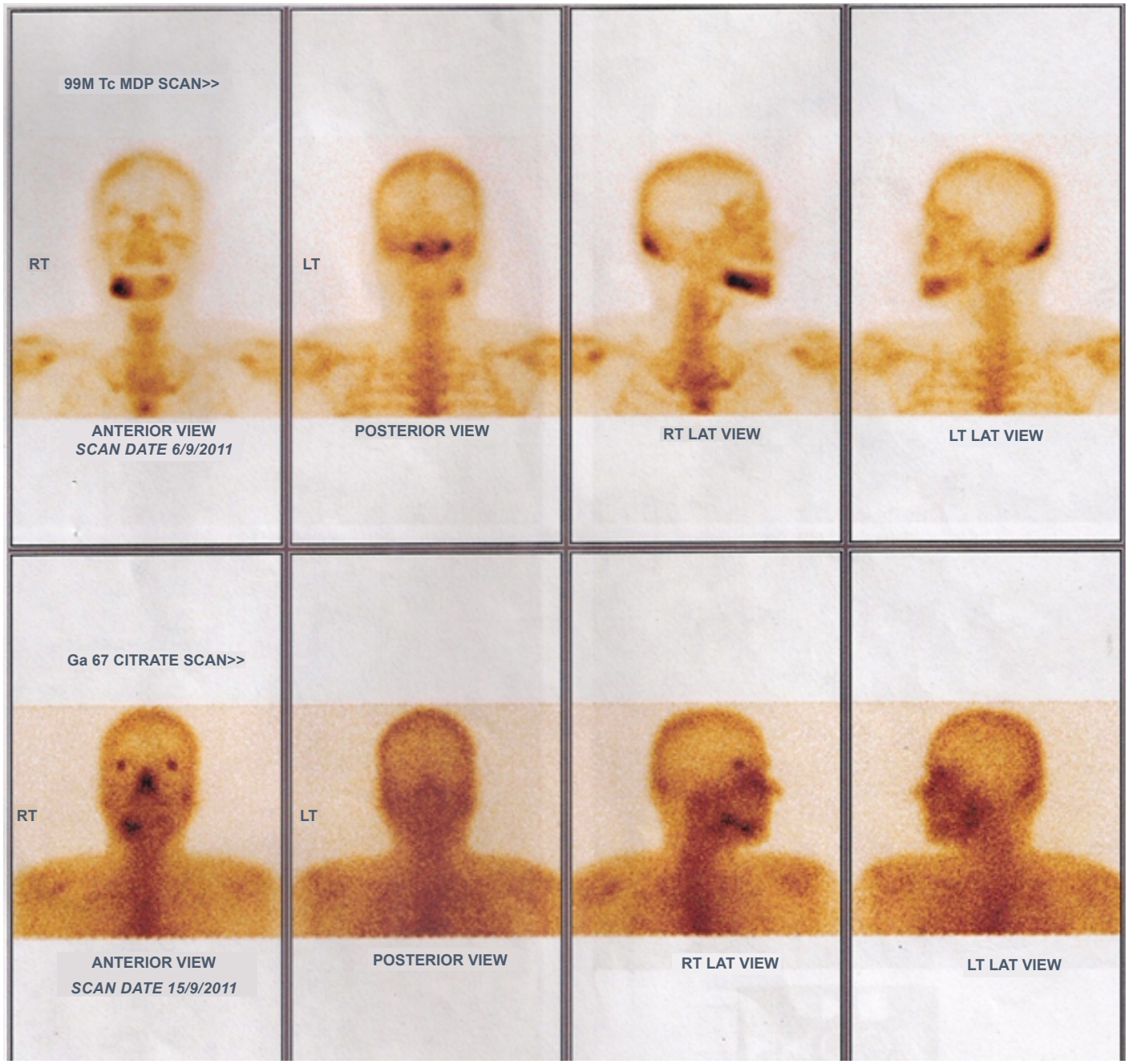

Figure 4. *Bone scan with MDP & Galium tracer uptake.*

imaging technique for an accurate diagnosis. Although, conventional radiography remains the first line of imaging modality, MRI and nuclear medicine are the most sensitive and specific methods for the detection of osteomyelitis. Nuclear medicine imaging utilises radiopharmaceuticals like the 99m Tc-MDP, 67Ga-citrate and radiolabeled leukocytes in the evaluation of bone for the assessment of osteomyelitis. The functional images of Single Photon Emission Tomography (SPECT) when fused with the structural images of high resolution CT allows for precise anatomic delineation of bone activity [11].

In a bone, scintigraphic study on osteomyelitis of the mandible conducted by Rohlin [12]. He found that scintigraphy revealed a larger extent of the lesion than radiography, while Boronat-Ferrater et al. [13,14]. Study revealed that bone scintigraphy has a sensitivity of 100%, a specificity of 6.7%, a positive predictive value of 62%, and a negative predictive value of 100%.

In a literature review of 44 original articles SPECT studies contributed significantly to diagnosis of bone & joint infections and gallium scanning was useful in monitoring the effectiveness of treatment because the uptake significantly reduced with the control of infection [14,15].

In our patient, SPECT/CT with Galium 67 was beneficial in determining the precise anatomic location of active and silent infection sites.

The mainstay of management in osteomyelitis has been antibiotic treatment, nonsteroidal anti-inflammatory drugs, and steroid drugs. Surgical intervention, including resection may be required in severe cases to achieve adequate margins and removal of devitalized teeth [16]. However, in the present case, the patient was managed with combination of pentoxifylline and tocopherol (PTX-Vit E) along with conventional treatment of antibiotics and NSAIDS.

The rationale of this management protocol was that the tissue uptake of antibiotics in bone is a function of vascularity and the combination of pentoxifylline and tocopherol would help in faster healing of the diseased bone [6]. Traditionally, PTX-Vit E has been successfully used in the treatment of oste Oradio Necrosis (ORN). ORN is osteomyelitis with radiotherapy as its predisposing cause [17]. Radiotherapy induces endarteritis of vessels, compromising the already tenous blood supply. With the development of infection, the features are no different from conventional osteomyelitis [18]. The pathophysiology of ORN and osteomyelitis primarily involves hypovascular- hypoxic bone and histopathologically, osteoclastic and osteoblastic cells can be seen.

Pentoxifylline, a methylxanthine derivative, is an inhibitor of platelet aggregation, which reduces blood viscosity and inturn, improves microcirculation. It has been known to improve peripheral and cerebral microcirculation by increasing the flexibility of erythrocytes and improving the oxygen delivery to tissues. It is widely used in the treatment of peripheral vascular disease, various cerebrovascular disorders and in other conditions where impaired or inadequate blood flow situations have to be corrected [19-24]. Haddad et al. treated 34 radiation-induced superficial fibrotic lesions of the skin with Pentoxifylline and vitamin E for 3 months and reported a significant effect of the Pentoxifylline-vitamin E combination in improving radiation-induced fibrosis.

Vit E provides antioxidant activity and has a synergistic role with PTX [25,26]. Numerous non randomised trials have reported better treatment results with combination PTX- Vit E than monotherapy with PTX.

Hence the strategy to improve bone healing was to reduce infection by broad spectrum antibiotics and to further the treatment penetration with the synergistic action of PTX- Vit E. Moreover, the drugs used were inexpensive, well tolerated and safe.

The patient was monitored on a regular basis and was found to be symptom free clinically, after twelve and fifteen months.

Conclusion

SPECT/CT with Galium 67 bone scintigraphy is undoubtedly an important tool in the detection and diagnosis of active and silent infections of the bone. Pentoxifylline plays an active role in a wide spectrum of diseases. Tocopherol when given in combination with pentoxifylline enhances the beneficial effects of pentoxifylline. The effect of PTX-Vit E in the management of osteomyelitis is by improvement of perfusion, which would require continuous and prolonged medication. However, even a temporary improvement in the quality of life is preferable and welcome to the patient. Although evidence based decisions and its outcome cannot be ignored, it is important to evaluate these pharmacological approaches in larger clinical trials.

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