CASE REPORT

Differentiating osteoradionecrosis from nasopharyngeal carcinoma tumour recurrence using $^{99}\text{Tc}^{\text{m}}$ -sestamibi SPECT/CT

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ABSTRACT. Osteoradionecrosis (ORN) of the base of skull is a known complication of external beam radiotherapy in the treatment of nasopharyngeal carcinoma, and is widely believed to be sequelae of radiation-induced endarteritis, leading to cellular death and fibrosis. Differentiating ORN from tumour recurrence is challenging and has direct clinical implications. We present a case where $^{99}\text{Tc}^{\text{m}}$ -sestamibi SPECT/CT was used to differentiate ORN from tumour recurrence and in which prior imaging using bone scintigraphy and fluorodeoxyglucose PET/CT were equivocal.

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Nasopharyngeal carcinomas are tumours that arise from or near the fossa of Rossemüller, and occur in endemic numbers among people of southern Chinese descent, with reported incidence rates of 11.8 per 100 000 among males and 5.2 per 100 000 in females [1]. The mainstay of therapy is external beam radiation therapy to the nasopharyngeal bed and primary draining lymph node echelons and cisplatin-based chemotherapy [2].

Accurate assessment of treatment response and early detection of tumour recurrence is essential to initiate early salvage therapies, but radiation-induced necrosis of the bone or osteoradionecrosis (ORN) can confound post-treatment evaluations.

We present a case in which $^{99}\text{Tc}^{\text{m}}$ -sestamibi single photon emission (SPECT)/CT was used to differentiate ORN from nasopharyngeal carcinoma tumour recurrence.

Case report

The patient was a 70-year-old Chinese male who was diagnosed with locally advanced nasopharyngeal carcinoma in 2009 and was treated with combination chemoradiation therapy.

Follow-up imaging using $^{99}\text{Tc}^{\text{m}}$ -methylene diphosphonate (MDP) planar scintigraphy, SPECT/CT (Philips Precedence integrated SPECT/CT, Amsterdam, the Netherlands) and 18-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT (Siemens Biograph integrated PET/CT Siemens, Erlangen, Germany) demonstrated increased tracer uptake at the base of skull in both scans, corresponding to bony erosive changes at the base of

skull. There was mild but otherwise symmetrical thickening of the nasopharyngeal soft tissues (Figure 1 and 2).

Remnant tumour or tumour recurrence were of clinical concern and $^{99}\text{Tc}^{\text{m}}$ -sestamibi SPECT/CT of the base of skull was performed. 20 mCi of $^{99}\text{Tc}^{\text{m}}$ -sestamibi was injected intravenously into a peripheral vein and SPECT/CT was performed as a single examination at 120 min post-tracer administration using the Philips Precedence 16-slice integrated SPECT/CT system.

SPECT acquisition was based on a dual head camera system rotating 180 degrees, in 3 degree, 30 s angular steps. A low-energy high-resolution collimator was used, with imaging captured on a 128 × 128 matrix. Unenhanced spiral CT acquisition was performed at the same sitting (10.6 mm rotation⁻¹, 0.6 s rotation time, 130–140 kV, 100 mA) with 2 mm reconstructed axial slices at 2 mm intervals. SPECT images were iteratively reconstructed with ordered subset expectation maximisation algorithm implemented on a clinical workstation, with a final pixel size of 3.2 mm. CT data were used for attenuation correction, anatomical correlation and morphological assessment.

The fused images were reviewed using the Philips Jetstream workstation after processing, which allowed for coronal and sagittal reconstruction and fusion.

$^{99}\text{Tc}^{\text{m}}$ -sestamibi images demonstrated no significant tracer uptake at the base of skull region of interest, in converse to noted increased $^{99}\text{Tc}^{\text{m}}$ -MDP and FDG tracer uptake (Figure 3 and 4).

A biopsy of the posterior nasopharynx was subsequently performed, and histopathology demonstrated only scattered acute and chronic inflammatory infiltrates admixed with giant cell reaction. No granulomas or malignancy was detected.

Additionally, the bony changes demonstrate long term interval stability (15 months), further collaborating with our imaging findings and histopathology results (Figure 5). The final diagnosis for the patient was radiation-induced necrosis of the base of skull.

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Discussion

ORN is essentially an area of non-viable bone in a site of radiation therapy, and is believed to result from sequelae of radiation, hypoxic-hypocellular-hypovascular tissue, tissue breakdown and chronic non-healing wound [3]. The irradiated bone becomes inflamed and endarteritis occurs, leading to cellular death, progressive hypovascularity and fibrosis.

CT imaging and MRI may allow for the diagnosis of ORN, but there are known limitations of CT and MRI in differentiating viable tumour from post-radiotherapy changes [4].

FDG PET/CT has been used in recent years in the post-treatment response assessment of head and neck tumours [5], but as shown in our own case, and in several other published reports, areas of ORN have been known to demonstrate avid FDG uptake, leading to false-positive evaluations of tumour recurrence [6, 7].

Methoxy-isobutyl-isonitrile is a cation originally synthesised for use as a myocardial perfusion agent [8], and accumulates in cells rich in mitochondrial content and is affected by the electric potentials generated across mitochondrial plasma membrane [9]. Malignant tumours tend to maintain a more negative transmembrane potential, as a result $^{99}\text{Tc}^{\text{m}}$ -sestamibi has been found to concentrate in a number of neoplasms. Particularly in nasopharyngeal carcinomas, it has been demonstrated to

be a sensitive, specific and accurate tracer in pre- and post-therapy assessment [10, 11].

Our case demonstrates the possible use of $^{99}\text{Tc}^{\text{m}}$ -sestamibi in differentiating osteoradionecrosis from viable tumour, in which negligible uptake of $^{99}\text{Tc}^{\text{m}}$ -sestamibi is expected in areas of radiation necrosis, and our findings collaborate with a case series evaluating bisphosphonate-induced mandibular osteonecrosis, in which no sestamibi uptake was evident in the patients with jaw osteonecrosis, while FDG-PET/CT showed focal uptake in all of them [12].

The suspected pathophysiology underlying these imaging findings is possibly related to the cellular constituents pertaining to necrotic bone.

FDG is known to accumulate in areas of inflammation and infection, and this appears to be related to glucose uptake and metabolism in granulocytes, macrophages, fibroblasts and T-cell lymphocytes [13]. Basic science investigations have demonstrated that fibroblasts show the highest FDG uptake, followed by neutrophils, with a small amount accumulated in resting macrophages and the lowest amount seen in T-cell lymphocytes. In the presence of hypoxia and inflammatory cytokines, there is a dramatic increase in FDG uptake seen in macrophages and fibroblasts [14]. Another study evaluating FDG uptake and cellular localisation in infections found that FDG predominantly accumulated in neutrophils in the acute phase and macrophages in the chronic phase [15].

Figure 1. Post-therapy fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT. Axial CT and fused FDG PET/CT of the base of skull (a and b) shows bony erosive changes (clivus) with corresponding increased FDG uptake (white arrowhead).

Figure 2. Post-therapy $^{99}\text{Tc}^{\text{m}}$ -MDP scan. (a) $^{99}\text{Tc}^{\text{m}}$ -MDP bone scan lateral spot view of the head and neck shows increased tracer uptake projected over the base of skull (black arrow). (b) Axial CT and fused $^{99}\text{Tc}^{\text{m}}$ -MDP single photon emission CT (SPECT)/CT of the base of skull demonstrates bony erosive change at the clivus with corresponding avid bony tracer uptake (white arrowhead).

Figure 3. $^{99}\text{Tc}^{\text{m}}$ -sestamibi scan. $^{99}\text{Tc}^{\text{m}}$ -sestamibi scintigraphy. (a,b,c) Axial, coronal and sagittal views of the base of skull region of interest (black arrow) show bony erosion of the clivus with no significant tracer avidity. Tracer uptake in the salivary glands is physiological in nature.

Figure 4. Direct comparison between fluorodeoxyglucose (FDG), $^{99}\text{Tc}^{\text{m}}$ -sestamibi and $^{99}\text{Tc}^{\text{m}}$ -MDP radiotracers. (a) Axial fused FDG positron emission tomography (PET)/CT; (b) axial fused $^{99}\text{Tc}^{\text{m}}$ -sestamibi single photon emission CT (SPECT)/CT; and (c) axial fused $^{99}\text{Tc}^{\text{m}}$ -MDP SPECT/CT images through the same section of the base of skull. The region of interest (black arrowhead) shows increased FDG and $^{99}\text{Tc}^{\text{m}}$ -MDP uptake, but there is no significant uptake of $^{99}\text{Tc}^{\text{m}}$ -sestamibi.

Figure 5. Interval stability of bony changes. Axial CT views of the base of skull taken in (a) June 2009 and (b) October 2010 show overall interval stability of bony erosive change. No interim treatment was given, and long-term interval stability correlates with histopathology results.

$^{99}\text{Tc}^{\text{m}}$ -sestamibi has also been shown to accumulate in inflammatory areas, although the avidity of uptake does not appear to directly correlate to the degree of inflammation present [16]. Of specific interest is the direct comparison of intratumoral distribution of $^{99}\text{Tc}^{\text{m}}$ -sestamibi and FDG performed in mouse breast cancer models, which showed low $^{99}\text{Tc}^{\text{m}}$ -sestamibi uptake in areas damaged by radiation and that $^{99}\text{Tc}^{\text{m}}$ -sestamibi accumulated in viable cancer cells, but not in areas containing fibroblasts and infiltrating macrophages, which are typically found in conjunction with the elimination of dead cells from post-radiotherapy necrosis [17].

This is consistent with our imaging findings of markedly increased FDG uptake in osteonecrotic bone, probably secondary to tracer uptake in chronic inflammatory infiltrates, while there was little or no $^{99}\text{Tc}^{\text{m}}$ -sestamibi uptake seen.

Conclusion

We have presented a case of a patient in which $^{99}\text{Tc}^{\text{m}}$ -sestamibi SPECT/CT was used to support the diagnosis of ORN in a patient with treated nasopharyngeal carcinoma, demonstrating the potential clinical use of such a technique in differentiating ORN from viable tumour.

References

1. Yang TL, Tsao SY, Chua EJ. Nasopharyngeal cancer treated in Singapore. *Singapore Med J* 1994;35:583–6.
2. Wei WI. Nasopharyngeal cancer: current status of management. *Arch Otolaryngol Head Neck Surg* 2001;127:766–9.
3. Marx RE. Osteoradionecrosis: a new concept of its pathophysiology. *J Oral Maxillofac Surg* 1983;41:283–8.
4. Bisdas S, Chambron Pinho N, Smolarz A, Sader R, Vogl T, Mack MG. Bisphosphonate-induced osteonecrosis of the Jaws: CT and MRI spectrum of findings in 32 patients. *Clin Radiol* 2008;63:71–7.
5. Andrade RS, Heron DE, Degirmenci B, Filho PAA, Branstetter BF, Seethala RR, et al. Post-treatment assessment of response using FDG-PET/CT for patients treated with definitive radiation therapy for head and neck cancers. *Int J Radiat Oncol Biol Phys* 2006;65:1315–22.
6. Hung GU, Tsai SH, Lin WY. Extraordinarily high F-18 FDG uptake caused by radiation necrosis in a patient with nasopharyngeal carcinoma. *Clin Nucl Med* 2005;30:558–9.
7. Liu SH, Chang JT, Ng SH, Chan CC, Yen TC. False positive fluorine-18 fluodeoxy-D-glucose positron emission tomography finding caused by osteoradionecrosis in a nasopharyngeal carcinoma patient. *Br J Radiol* 2004;77:257–60.
8. Jones AG, Abrams MJ, Davison A. Biological studies of a new class of technetium complexes: The hexakis (alkylisonitrile) technetium (I) cations. *Int J Nucl Med Biol* 1984;11:225–34.
9. Ciu ML, Kronauge JF, Piwnica-Worms D. Effects of mitochondrial and plasma membrane potentials on accumulation of hexakis(2-methoxyisobutyl isonitrile) technetium in cultured mouse fibroblast. *J Nucl Med* 1990;31:1646–53.
10. Kostakoglu L, Uysal U, Ozyar E, Elahi N, Hayran M, Uzal D, et al. Pre and post therapy thallium-201 and technetium-99m-sestamibi SPECT in nasopharyngeal carcinoma. *J Nucl Med* 1996;37:1956–62.
11. Kostakoglu L, Uysal U, Ozyar E, Hayran M, Uzal D, Demirkazik FB, et al. Monitoring response to therapy with thallium-201 and technetium-99m-sestamibi SPECT in nasopharyngeal carcinoma. *J Nucl Med* 1997;38:1009–14.
12. Catalano L, Vecchio SD, Petruzzello F, Fonti R, Salvatore B, Martorelli C, et al. Sestamibi and FDG-PET scans to support diagnosis of jaw osteonecrosis. *Ann Hematol* 2007;86:415–23.
13. Zhuang HM, Yu JQ, Alavi A. Applications of fluorodeoxyglucose-PET imaging in the detection of infection and inflammation and other benign disorders. *Radiol Clin North Am* 2005;43:121–34.
14. Matsui T, Nakata N, Nagai S, Nakatani A, Takahashi M, Momose T, et al. Inflammatory cytokines and hypoxia contribute to 18F-FDG uptake by cells involved in pannus formation in rheumatoid arthritis. *J Nucl Med* 2009;50:920–6.
15. Achim HK, Weber B, Buck A. Autoradiographic quantification of 18F-FDG uptake in experimental soft-tissue abscesses in rats. *Radiology* 2002;223:446–51.
16. Tiling R, Stephan K, Sommer H, Shabani N, Linke R, Hahn K. Tissue-specific effects on uptake of ^{99}Tc -sestamibi by breast lesions: a targeted analysis of false scintigraphic diagnoses. *J Nucl Med* 2004;45:1822–8.
17. Ohira H, Kubota K, Ohuchi N, Harada Y, Fukuda H, Satomi S. Comparison of intratumoral distribution of ^{99}Tc -Mibi and deoxyglucose in mouse breast cancer models. *J Nucl Med* 2000;41:1561–8.