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Non-pseudomonal malignant otitis externa and jugular foramen syndrome secondary to cyclosporin-induced hypertrichosis in a diabetic renal transplant patient

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Abstract
We present the case of a 58-year-old diabetic renal transplant patient who developed a left jugular foramen syndrome, secondary to an ipsilateral staphylococcal malignant (necrotizing) otitis externa. This followed a protracted episode of uncomplicated otitis externa with no evidence of bone involvement on computed tomography (CT) scanning. Cyclosporin-induced hypertrichosis (excess hair growth) in his external auditory canal contributed greatly to the initial difficulty in managing his otitis externa. Following an initial successful treatment with prolonged intravenous antibiotics the patient relapsed with a secondary infection in the same anatomical site due to *Candida parapsilosis*. Despite further intensive treatment including antimicrobials, a subtotal petrosectomy and hyperbaric oxygen therapy he eventually succumbed to his disease.

Key words: Otitis externa; Cyclosporin; Hypertrichosis

Introduction

Malignant otitis externa (MOE) although named by Chandler[1] in 1968, was in fact described nine years earlier by Meltzer and Keleman.[2] This aggressive infection almost exclusively effects elderly diabetics and can result in cranial polyneuropathies following infectious spread beyond the bone of the external auditory canal via vascular and fascial planes. The infective organism is typically *Pseudomonas aeruginosa*.[3] We report a case of recurrent MOE which is unusual for two reasons. Firstly, failure to resolve the initial otitis externa resulted from cyclosporin-induced hypertrichosis of the external auditory canal. Secondly, on both occasions, the pathogenic organisms were non-pseudomonal. Gallium-67 single photon emission computerized tomography (SPECT) scans are presented illustrating a radiological advance which has recently been publicised for its usefulness in monitoring both the disease activity and the response to antibiotic therapy in the treatment of MOE. As our case acts to demonstrate however, caution is needed in their interpretation as false negative results are possible.

Case report

A 58-year-old patient presented to the Otolaryngology department at the Royal Liverpool University Hospital with a history of left-sided otalgia. He reported no other otological symptoms. He was a known insulin-dependent diabetic, and had been so for 20 years. His poor diabetic control had previously resulted in renal failure for which he had undergone a renal transplant some four years earlier. As a consequence his medications included azathioprine, prednisolone and cyclosporin.

On examination he was apyrexial. Hypertrichosis of the external auditory canals (Figure 1) with a marked left-sided otitis externa was observed. The remaining ENT examination was unremarkable. Serum analysis revealed that his renal function, although slightly impaired, was consistent with previous tests, whilst his glucose was significantly raised at 24 mmol/l (3.5–5.5 mmol/litre). He was admitted for daily suction clearance, *Tri-adcortyl* cream dressings, intravenous co-amoxiclav and oral ciprofloxacin. The diabetic team was involved early in an attempt to improve his difficult diabetic control. He settled on these measures and on discharge the external auditory canal oedema had settled sufficiently to allow visualization of a normal left tympanic membrane.

His subsequent management involved regular suction clearances and aural dressings on an out-patient basis. In the ensuing two months he developed two further acute exacerbations of his left otitis externa requiring admission. During the second of these admissions a new otoscopic finding was made of an erythematous polyp on the left anterior external auditory canal wall, at the bony-cartilaginous junction. Biopsy of this revealed it to be an inflammatory polyp with no evidence of malignancy. A CT scan of the left temporal petrous bone failed to show any abnormality other than soft tissue swelling within the external auditory canal.

As the ear was not improving with conservative management a decision was made to proceed to examination under anaethetic of the left ear and surgical debridement as necessary; however a further episode of

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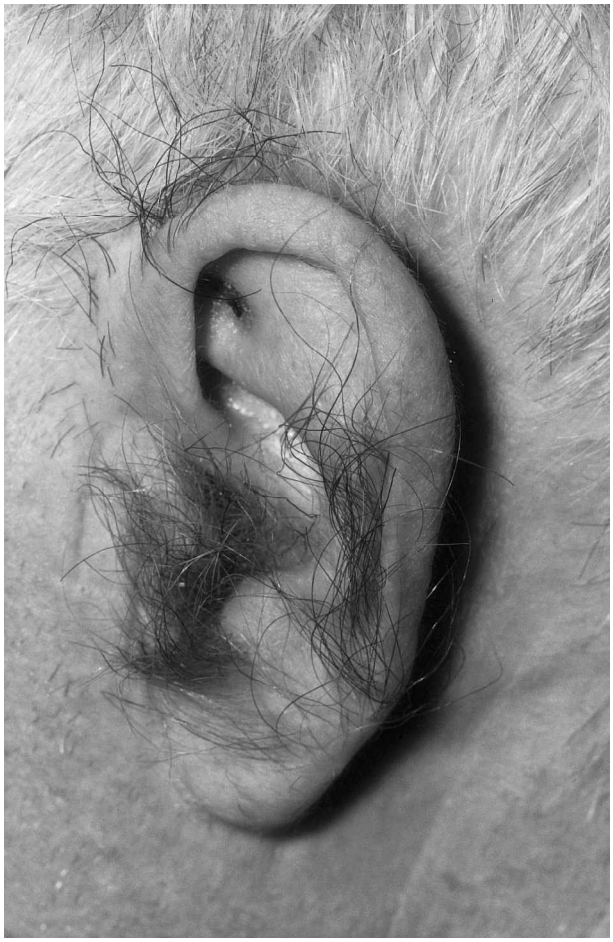

FIG. 1
Gross hypertrichosis of the left external ear.

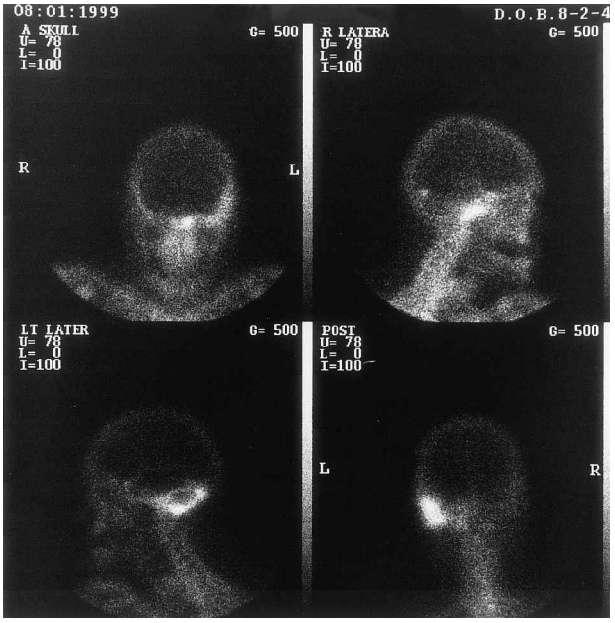

FIG. 2
Gallium-67 citrate SPECT (single photon emission computerized tomography) scan demonstrating increased activity in the left temporal petrous bone.

acute otalgia precipitated his admission before this could be arranged. On this occasion concerns were heightened by the additional complaint of generalized headache. On initial assessment there was no evidence of either meningism or cranial nere palsy, however 48 hours later he had developed a left hypoglossal nerve palsy and hoarse voice secondary to a left vocal fold palsy. At this stage there was no clinical evidence of aspiration and his gag reflex was intact. These findings led to a provisional diagnosis of MOE with left jugular foramen syndrome. An urgent repeat CT scan of the left temporal petrous bone showed some decreased aeration of the left mastoid air cell system, but again no evidence of bony destruction. A magnetic resonance imaging (MRI) scan, however, revealed an area of abnormal signal, suggestive of either infection or malignancy, involving the left external auditory canal and extending into the subcutaneous tissues over the left mastoid, the skull base, side of the clivus, carotid space and longus colli muscle. At operation the left external auditory canal was debrided and a polyp from the junction of bony and cartilaginous parts of the anterior wall sent for histology (later to be reported as a benign inflammatory polyp). The tympanic membrane, middle-ear mucosa, attic, antrum and mastoid air cells all appeared normal with no evidence of bony necrosis of the cortical mastoid bone. Samples were sent for both histology and microbiology. Cultures from both the external auditory canal and mastoid bone were heavily colonized with *Staphylcoccus aureus*, sensitive to both flucloxacillin and fusidic acid, both of which were then given to the patient intravenously. Although no *Pseudomonas* species were isolated, he was given oral ciprofloxacin and topical *Gentisone HC*^{TM} on the recommendations of the Medical Microbiology department. In the subsequent week it became clinically apparent that he was aspirating, confirmation of which was made following speech therapy assessment and video-fluoroscopy. The patient was initially fed nasogastrically and later via percutaneous enteral gastrostomy feeds.

Intravenous antibiotics were administered over an eight-week period. Progress was monitored both clinically and by serial Gallium-67 citrate SPECT scans every four weeks (Figure 2). On discharge compensation of his swallowing mechanism had resulted in a cessation of aspiration and his percutaneous enteral gastrostromy tube was removed. Although his hypoglossal and vocal fold palsies persisted, his voice quality had significantly improved, again due to compensatory mechanisms. Oral antibiotics were continued for a further four weeks following discharge.

One month after discharge the patient was re-admitted from the out-patient clinic with symptoms of worsening left otorrhoea and otalgia. New examination findings included a posterior marginal pars tensa perforation. The patient was hypotensive and despite a normal temperature and white cell count the patient was thought to be septic and was accordingly treated aggressively with rehydration and intravenous antibiotics. A re-occurrence of infection involving the left temporal petrous bone, extending up to the clivus and involving the soft tissues on the ipsilateral base of skull was confirmed by a marked increase in activity with a repeat ^{111}Indium-labelled white cell scan. On this occasion blood cultures became positive for *Candida parapsilosis*. Antimicrobial therapy was altered accordingly to liposomal amphotericin, teicoplanin, flucytosine and rifampicin. Advice was taken from the regional neuro-otology unit and the patient was transferred for a left subtotal petrosectomy. The patient made a good recovery from this and returned to our unit for continued antimicrobial therapy. His condition remained stable for three weeks before he again developed severe headaches and persistent nausea and vomiting. The difficulty in managing the patient was compounded by wildly alternating serum potassium and glucose levels. Following the

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development of a right hemiplegia a decision to send him for a course of hyperbaric oxygen treatment was made on a literature-found evidence base.[4,5] Despite 14 consecutive treatments the patient deteriorated quickly and eventually died.

Discussion

Malignant otitis externa is a condition typically presenting with severe otalgia, otorrhoea and hearing loss in the early stages of the disease. Classical otoscopic findings are granulation tissue at the bony - cartilaginous junction in the floor of the external auditory canal. Infection spreads from the external auditory canal through the naturally-occurring fissures in the meatal cartilage to the adjacent soft tissues either by the tympanomastoid suture or via the clefts of Santorini, spreading to the parotid gland, temporomandibular joint and the soft tissues at the base of the skull.[6] Hence involvement of the facial nerve usually results from infection affecting the extra-temporal segment of the nerve at the stylomastoid foramen.[7] Pathological studies suggest that the initial invasion of the external auditory canal bone is dependent on localized bone death, as with osteomyelitis in other areas of the body.[8] Unlike pneumococcal petrositis, in which an abscess forms by breaking down pneumatic spaces, in MOE the more susceptible route for spread is via the compact bone and submucosal blood vessels of the pneumatic spaces.[8] In earlier reported series of MOE mortality as high as 80 per cent was reported if the lower cranial nerves or the jugular vein was involved.[9] Today, with good control of the underlying disease and adequate antimicrobial therapy, the survival rates have much improved.[10]

Most previously documented cases of MOE have been secondary to infection with *Pseudomonas aeruginosa*. Our case is therefore unusual because both the primary and recurrent infections were due to non-pseudomonal organisms. Our literature search has isolated only three similar cases of Staphylococcus aureus MOE.[11-13]

In the case presented, cyclosporin played a central role in the infection's aetiology. The drug belongs to a family of cyclic polypeptides of fungal origin, and is used because of its very selective inhibitory effect on T lymphocytes which relates to its usefulness in the management of prevention of organ transplant rejection and several other common conditions such as type I diabetes mellitus and rheumatoid conditions. One of its recognized complications is hypertrichosis, defined as an increase in non-androgenic modulated hair, typically around the eyebrows, forehead and cheeks. In one study of 56 insulin-dependent diabetics on long-term cyclosporin, unequivocal hypertrichosis was observed in 94.6 per cent.[14] Hypertrichosis was noted in the head and neck region predominantly on the upper lip, scalp, parotid area, eyebrows, ear lobes and nose. The hairs not only appeared to increase in number, but fine blonde vellous hairs tended to become thicker, pigmented terminal - type hairs. These changes were found to be reversible upon discontinuation of the cyclosporin therapy. In the case presented, the initial management of the patient's otitis externa was difficult due to the hypertrichosis of the external auditory canal. This not only prevented visualization of the canal but also prevented adequate aural toilet and dressings. Only one such similar case was found following review of the literature in which a patient with minoxidil-induced hypertrichosis developed otitis externa and mastoiditis.[15] Once the infection had started, the cyclosporin was also causative in the failure to mount an immune reaction to the microorganism.

The role of the various imaging techniques for both diagnostic purposes and the monitoring of disease progression remains a point of debate. Facilitation of early diagnosis and treatment before progression of the infection to involve lower cranial nerves will reduce both the morbidity and mortality associated with this infection. Of equal importance in the management of MOE is ascertaining that infection has been completely eradicated before stopping treatment. Under-treatment may lead to recurrence, (approximately 20 per cent in one large clinical series),[16] which is usually more resistant to treatment than the initial infection.[17]

In our case, CT scans of the temporal petrous bones were essentially normal in both the early and late stages of the disease. The use of diagnostic CT in the early stages of MOE has previously been discredited by some, claiming a sensitivity as low as 30 per cent.[18] In such studies, their assessment was confined to the documentation of osteomyelitic changes which only occur after a significant loss of bone mineral content.[19] Advocates of CT however believe it to be a far more sensitive diagnostic tool when one looks for particular changes in the soft tissues beneath the affected temporal bone.[20] The role of CT in monitoring the resolution of the infection is generally considered limited because if demineralization has occurred, the scan rarely, if ever returns to normal.[17] MR plays a similarly complimentary role to CT in as much as it is helpful only in determining the initial severity of the disease,[7] in particular the soft tissue involvement where it has proved superior to all other imaging modalities.[17]

A technetium phosphate radionucleotide bone scan does not depend upon bone demineralization in order to be positive and can permit early detection of osteomyelitis of the temporal bone and skull base before radiological evidence of demineralization has appeared.[21] It will show up any site of osteoclastic or osteoblastic activity and may be positive in a variety of conditions including metastatic and primary neoplasms, trauma, arthritic conditions, post-surgical procedures and infection. Such scans will become positive with as little as a 10 per cent increase in the osteogenic activity[18] impairing its usefulness by its low specificity.[16] Scans may also become positive in cases of severe simple otitis externa due to inflammation of the underlying periostium.[19] Therefore, apart from early confirmation of bony involvement, their use in monitoring response to treatment is limited by the fact that they may be positive for months after the initial infection has resolved.[7]

Treatment response is now frequently monitored by way of a gallium-67 citrate SPECT scan. This is a tomogram which gives cross-sectional pictures of the affected area (Figure 2). Gallium-67 citrate is absorbed by macrophages and reticular endothelial cells and thus highlights areas of both bone and soft tissue infection with uptake quickly returning to normal after the infection has subsided.[7] One of its few draw-backs is its imprecision in the anatomical localization of disease. Those who advocate its use suggest a scan is performed at the commencement of the treatment and antimicrobial therapy should continue until the scan reverts to normal.[22]

As demonstrated in the above case caution must be taken in interpreting the Gallium-67 SPECT scans since false negatives may occur with devastating results for the patient.

Conclusions

Beware of persisting otitis externa in the diabetic patient, especially if the patient complains of persistent pain. Hypertrichosis in patients on cyclosporin may impede the

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diagnosis and treatment of malignant otitis externa. A normal CT scan of the temporal petrous bone does not exclude the diagnosis of MOE and isotope scans may be a more sensitive diagnostic investigation. MOE may rarely be caused by other organisms other than *Pseudomonas aeruginosa* and therefore the treatment should always be based upon microbiological sensitivity results. Treatment should continue until Gallium-67 SPECT scans show resolution of infection however caution is advised since false positives can occur.

References

1 Chandler JR. Malignant external otitis. *Laryngoscope* 1968;**78**:1257–94
2 Meltzer P, Kelemen G. Pyocyaneus osteomyelitis of the temporal bone, mandible and zygoma. *Laryngoscope* 1959;**69**:1300–16
3 Barrow HN, Levenson MJ. Necrotizing 'malignant' external otitis caused by *Staphlococcus epidermidis. Arch Otolaryngol Head Neck Surg* 1992;**118**:94–6
4 Davis JC, Gates GA, Lerner C, Davis MG, Mader JT, Dinesman A. Adjuvant hyperbaric oxygen in malignant external otitis. *Arch Otolaryngol Head Neck Surg* 1992;**118**:89–93
5 Shupak A, Greenberg E, Hardoff R, Gordon C, Melamed Y, Meyer WS. Hyperbaric oxygenation for necrotizing malignant otitis externa. *Arch Otolaryngol Head Neck Surg* 1989;**115**:1470–5
6 Wright D. Diseases of the external ear. In: Booth JB, ed. *Scott-Brown's Otolaryngology*: *Otology*, 6th edn. Oxford: Butterworth-Heinneman, 1997
7 Slattery WH, Brackmann DE. Skull base osteomyelitis. Malignant otitis externa. *Otolaryngol Clin North Am* 1996;**29**:795–806
8 Kohut RI, Lindsay JR. Necrotizing ('malignant') external otitis histopathological processes. *Ann Otol* 1979;**88**:714–20
9 Gates GA, Montalbo PJ, Meyerhoff WL. Pseudomonas mastoiditis. *Laryngoscope* 1977;**87**:483–92
10 Bernheim J, Sade J. Histopathology of the soft tissue parts in 50 patients with malignant external otitis. *J Laryngol Otol* 1989;**103**:366–8
11 Bayardelle P, Jolivet-Granger M, Larochelle D. Staphylococcal malignant external otitis. *Can Med Assoc J* 1982;**126**:155–6
12 Babiatzki A, Sade J. Malignant external otitis. *J Laryngol Otol* 1987;**101**:205–10
13 Keay DG, Murray JAM. Malignant otitis externa due to *Staphylococcus* infection. *J Laryngol Otol* 1988;**102**:926–7
14 Wysocki GP, Daley TD. Hypertrichosis in patients receiving cyclosporin therapy. *Clin Exp Dermatol* 1987;**12**:191–6
15 Toriumi DM, Konior RJ, Berktold RE. Severe hypertrichosis of the external ear canal during Minoxidil therapy. *Arch Otolaryngol Head Neck Surg* 1988;**114**: 918–9
16 Rubin J, Yu VL. Malignant external otitis: insights into pathogenesis, clinical manifestations, diagnosis and therapy. *Am J Med* 1988;**85**:391–8
17 Paramsothy M, Khanijow V, Ong TO. Use of Gallium-67 in the assessment of response to antibiotic therapy in malignant otitis externa - A case report. *Singapore Med J* 1997;**38**:347–9
18 Strashun A, Nejatheim M, Goldsmith SJ. Malignant external otitis: early scintigraphic detection. *Radiology* 1984;**150**:541–5
19 Parisier SC, Lucente FE, Som PM, Hirschman SZ, Arnold LM, Roffman JD. Nuclear scanning in necrotizing progressive 'malignant' external otitis. *Laryngoscope* 1982;**92**:1016
20 Rubin J, Curtin HD, Yu VL, Kamerer DB. Malignant external otitis: Utilty of CT in diagnosis and follow-up. *Radiology* 1990;**174**:391–4
21 Gold S, Som P, Lawson W, Lucente F. Radiographic finding in progressive necrotizing malignant external otitis. *Laryngoscope* 1984;**93**:279–81
22 El-Silimy O, Sharnuby M. Malignant external otitis: management policy. *J Laryngol Otol* 1992;**106**:5–6

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