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Use of tobramycin-impregnated antibiotic beads in frontal sinus osteomyelitis

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Abstract

Objective. Osteomyelitis of the frontal bone is a rare but devastating complication of frontal sinusitis. Treatment involves aggressive surgery to remove all sequestra in combination with long-term antibiotic therapy. However, systemic antibiotics may struggle to penetrate any remaining infection in devascularised areas, and the morbidity associated with surgical resection of some areas of the skull base is too high. In contrast, locally implanted antibiotics provide a reliable, high concentration of treatment to these areas while also minimising potential systemic side effects. The clinical application of tobramycin beads has primarily been used in orthopaedics as an adjunct to the treatment of tibial osteomyelitis or prosthetic joint infection.
Case report. To the best of the authors' knowledge, the two cases discussed here represent the first use of tobramycin antibiotic beads in frontal sinus osteomyelitis secondary to chronic rhinosinusitis.
Conclusion. These cases show promising use of tobramycin beads in recalcitrant frontal osteomyelitis.

Clinical Record

Dr E Richards takes responsibility for the integrity of the content of the paper

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Introduction

Osteomyelitis is a complex condition associated with the progressive inflammatory destruction of bone.[1] It often occurs following trauma or surgery but also arises secondary to chronic infection. Osteomyelitis can be broadly classified into acute and chronic, depending on the onset and duration of symptoms following infection. Chronic osteomyelitis is associated with avascular necrosis and the formation of sequestrum. These fragments of necrotic bone necessitate surgical debridement.[1] The increasing prevalence of predisposing conditions such as diabetes mellitus, as well as greater recognition of the disease through improved imaging, is thought to explain the rise in cases of osteomyelitis.[2]

Staphylococcus aureus is the most common cause of both acute and chronic osteomyelitis in patients of all ages. *Methicillin-resistant S aureus* has been increasingly isolated, particularly in adult patients. Other common pathogens in chronic osteomyelitis include *Staphylococcus epidermidis, Pseudomonas aeruginosa, Serratia marcescens* and *Escherichia coli*.[2] The management of osteomyelitis involves surgical excision of infected and necrotic tissue, including bone, as well as long-term systemic antibiotic therapy.[2] However, despite this dual approach, recurrence rates remain high at about 30 per cent by 12 months for adults.[3]

Antibiotic-impregnated beads have been used for some time by orthopaedic surgeons to deliver a high concentration of antibiotics locally to the infected bone and wound bed in the treatment of osteomyelitis of the long bones.[4] However this principle is not used widely elsewhere. Frontal osteomyelitis is a rare but potentially life-threatening complication of frontal sinusitis.[5] We present the first reported use of tobramycin antibiotic beads in the treatment of frontal sinus osteomyelitis.

Case report

Case 1

A 59-year-old man presented to our centre with a discharging left supraorbital fistula on a background of chronic frontal sinusitis. Computed tomography (CT) scan showed chronic frontal sinusitis with a markedly sclerotic margin and focal defect in the anterior orbital roof (Figure 1).

The patient underwent a combined Draf III endonasal operation with an osteoplastic flap. Following radical surgical debridement, the frontal sinus was obliterated with a vascularised pericranial flap, and the fistulous tract was closed. Two weeks later he re-presented with headache and pus discharging from the fistula associated with necrosed skin over his forehead (Figure 2). This was thought to be secondary to a combination of devascularisation of the skin when the pericranial flap was raised and local infection.

Imaging showed a collection in the surgical bed, and he was taken back to operating theatre where the bicoronal approach was re-explored and the necrosed skin excised.

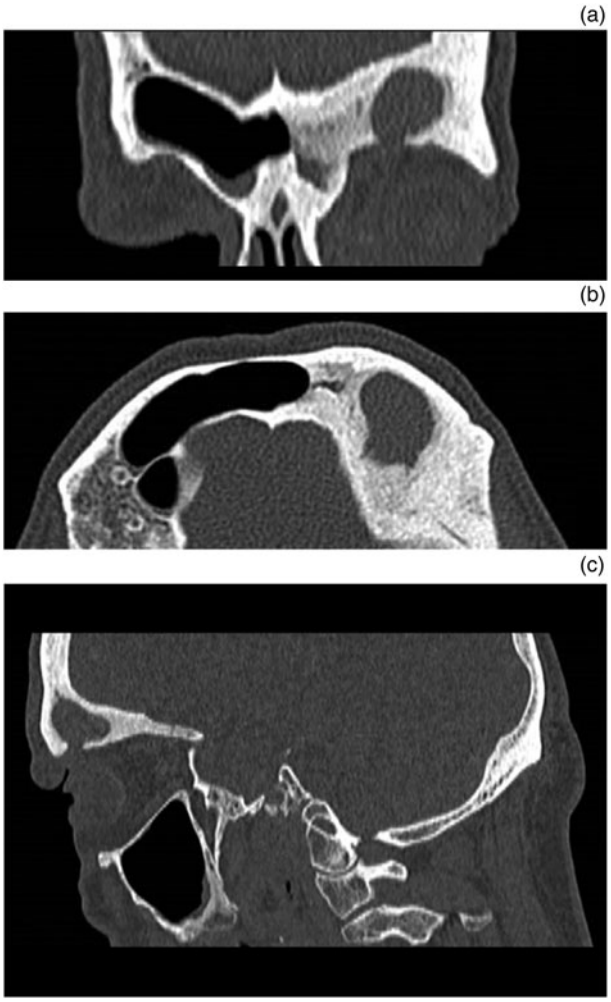

Figure 1. (a) Coronal, (b) axial and (c) sagittal plane computed tomography of the sinuses showing erosion of the floor of the left frontal sinus.

The frontal sinus was then obliterated again with vascularised pedicled pericranial tissue and following consultation with our microbiology department tobramycin antibiotic beads (Figure 3) were placed in the frontal sinus and around the border of the pericranial flap underneath the bone flap.

All samples grew *E coli*. The patient completed a six-week course of rifampicin and ciprofloxacin to maximise chances of disease control, and this time remained well post-operatively, with successful management of the osteomyelitis. His forehead skin healed completely within six months by secondary intention (Figure 4). The patient sadly died 21 months following this surgery from an unrelated spontaneous posterior fossa haemorrhage.

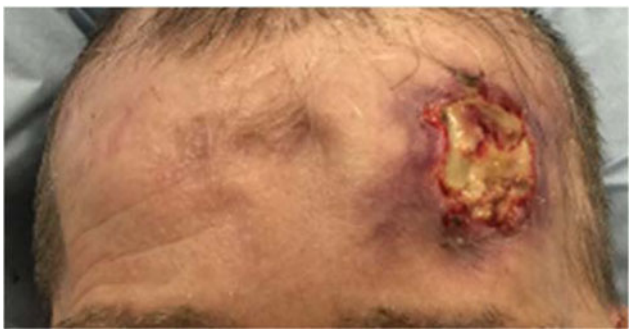

Figure 2. Image of the patient who re-presented with necrosed tissue and a discharging fistula.

Figure 3. Image of tobramycin beads ready for implantation.

Case 2

A 58-year-old man presented to his local hospital with sepsis and bilateral discharging sinocutaneous fistulae and erosive pansinusitis affecting the lamina papyracea and skull base. He was taking immunosuppression in the form of infliximab infusions for ulcerative colitis and also had pyoderma gangrenosum and bronchiectasis. He had undergone functional endoscopic sinus surgery to debride necrotic material from the para-nasal sinuses, which showed invasive aspergillosis, and was initially treated with further surgical debridement, intravenous voriconazole and tazocin. This was then changed to oral posaconazole, ciprofloxacin and co-amoxiclav. Repeat CT imaging prior to this admission showed chronic invasive fungal sinusitis with multiple bony erosions, especially involving the orbital floor.

He was put back on intravenous tazocin alongside posaconazole and underwent a further endoscopic sinus operation that showed extensive crusting and a cerebrospinal fluid leak

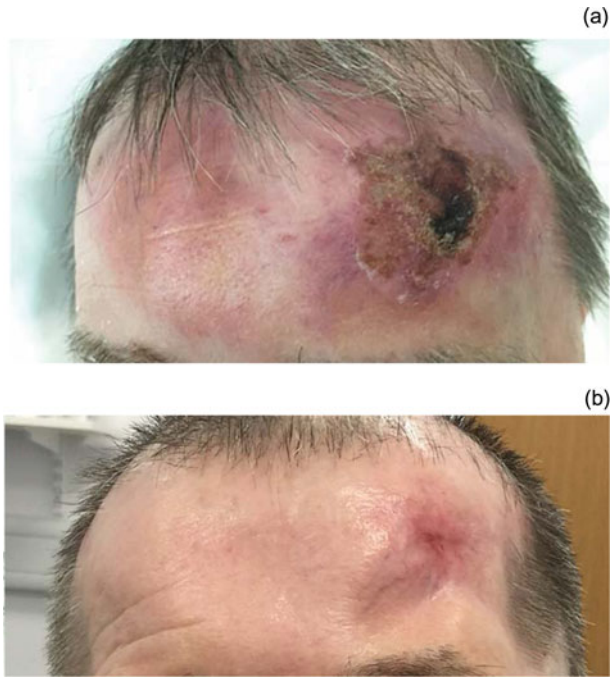

Figure 4. (a) Image of early post-operative healing and (b) image at six-month follow up: the wound had healed by secondary intention.

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through a pre-existing skull-base dehiscence. Following this surgery, his symptoms improved and his simultaneous fistulae healed. Unfortunately, they both reopened a few months later at which point he was referred to our regional skull base department. He had lost a significant amount of weight by this time and had an erythematous rash with skin lesions in the mid-face and bilateral conjunctivitis.

At the Queen Elizabeth Hospital, he was managed in conjunction with our microbiology department and underwent radical frontosphenoethmoidectomy and debridement of necrotic tissue. Following a number of septic episodes, he had revision surgery, which included closure of the sinocutaneous fistulae at the medial canthus bilaterally and placement of tobramycin-impregnated beads into the frontal cavity. Tissue samples sent intra-operatively grew *S aureus,* pseudomonas, candida and vancomycin-resistant enterococcus. His osteomyelitis improved following this intervention, and he was transferred back to his local hospital. Unfortunately, he developed pericardial and lung disease, which was felt by the local multidisciplinary team to represent a separate underlying disease process. He declined further investigations for these and died four months later. His sinocutaneous fistulae at his medial canthus remained healed.

Discussion

Osteomyelitis of the frontal bone is a rare but devastating complication of chronic rhinosinusitis. The frontal bone is the second most common site of head and neck osteomyelitis, with the mandible most frequently affected.[5] Because of the complex craniofacial skeleton and critical neural structures that cannot be easily debrided, osteomyelitis of the fronto-ethmoid region presents particular management challenges.[6]

The presentation of chronic frontal osteomyelitis, as in our cases, is often with a sinocutaneous fistula as well as pain, swelling and a low-grade fever. It can lead to complications such as meningitis, brain abscess, including Pott's puffy tumour,[7] and cavernous sinus thrombosis.[5] This is a potentially life-threatening inflammatory condition, and therefore it requires early diagnosis and management to reduce morbidity and mortality.[8]

Classical treatment of chronic frontal osteomyelitis involves surgical debridement and long-term antibiotic therapy. Other interventions include frontal sinus trephining, particularly for the initial drainage of infected material, catheter irrigation and antibiotic delivery systems. As the inflammatory process causes compression and obliteration of the vasculature, ischaemia occurs, which contributes to necrosis of the bone. Sequestra arise as a result of separation of the segments of bone devoid of blood supply. These avascular areas need to be debrided. If complete excision is not possible, these areas can continue to harbour bacteria despite antibiotic treatment, contributing to the difficulty in achieving complete resolution.[1,9]

The recurrence rates of chronic frontal osteomyelitis are high, resulting in significant morbidity. Additionally, given the high economic burden of current treatment, novel approaches are required.[8] The local delivery of antibiotics in the treatment of osteomyelitis has been used safely and effectively by orthopaedic surgeons for decades.[4] The most commonly used antibiotics are aminoglycosides, such as gentamicin and tobramycin, which are effective in the management of aerobic gram-negative bacilli and staphylococci as well as streptococci, enterococci and anaerobes.[10]

In 1979, Klaus Klemm created gentamicin-impregnated beads. These were used to occupy dead space after debridement of infected bone. Klemm reported that in a sample of over 100 patients, a cure rate of 91.4 per cent was achieved following this treatment.[11] Hoff *et al.*[12] demonstrated that the antibiotic delivery from local antibiotic beads provides significantly higher concentration levels in desired tissues than achieved by systemic therapy.[12] Given that both *S aureus* and *S epidermidis* are known to form biofilms that act as a barrier to antibiotics, this higher concentration is of particular value.[1] It has been shown that concentrations 10 to 100 times that usually needed to be bactericidal are required to kill bacteria enclosed by biofilm.[11] Wahlig *et al.*[13] showed that when polymethylmethacrylate beads with gentamicin incorporated are implanted into bone and the wound closed, the local concentrations of antibiotic achieved are 200 times those achieved with the administration of systemic antibiotic.[10,13]

Several different bead compositions have been described including polymethylmethacrylate and calcium sulphate.[10] The variations in these, including bead size and the number of beads used, all influence the local dose achieved, and further research is required to ascertain exact dosing in each scenario.

The beads, when made of polymethylmethacrylate, have classically been removed in a second stage procedure, approximately three weeks after implantation.[10] This was based on a concern that they could act as a substratum for bacteria, particularly once drug elution has ended, and add to the development of bacterial resistance. A case report demonstrated measurable but sub-inhibitory levels of gentamicin five years after the placement of the beads with subsequent isolation of gentamicin-resistant bacteria.[14] Fernando *et al.* tested whether polymethylmethacrylate beads required removal. They found that where the wound had healed well and where there was sufficient subcutaneous tissue to cover the beads to prevent pain, the beads could be left with no complications detected in their follow-up period of 6 months to 5 years.[14] The intention in both of our cases was to leave the polymethylmethacrylate beads in-situ indefinitely. Additionally, they reported that no patients developed antibiotic resistance.[14] Beads made from calcium sulphate or phosphate also exist; these biodegrade and do not require removal.[10]

There have been reports of the use of antibiotic-impregnated beads made from polymethylmethacrylate powder and gentamicin for the treatment of infected nasal implants. Villanueva *et al.*[15] used this approach in conjunction with a continuous catheter-based antibiotic irrigation system and systemic antibiotics. This enabled a two-stage procedure in removal of the beads, and reconstruction was performed after resolution of the infection.[15]

To the best of our knowledge, there are no reported cases of antibiotic-impregnated bead use in the management of frontal osteomyelitis secondary to chronic rhinosinusitis. Given the already existing space within the frontal sinus, which is then enlarged following surgical debridement, there is an excellent cavity for the placement of the impregnated beads to facilitate local delivery of antibiotics. Antibiotic beads have the advantage of also helping through eliminating dead space.[15] Dagum *et al.*[16] reported the use of combined vancomycin and tobramycin-impregnated beads or cement spacers in the management of post-traumatic frontal sinus infections. The cases all occurred 1 week to 8 months after primary

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surgery. The patients underwent debridement, obliteration of the nasofrontal ducts and placement of impregnated beads or cement spacer followed by 4–6 weeks of parenteral antibiotics. These patients had second stage procedures for reconstruction, with removal of the beads or cement at this stage. All three patients were free of infection at 14–76 month follow up. [16]

Topical therapy also comes without the side-effects of systemic antibiotic therapy, which can include end-organ failure and gastrointestinal side effects.[17] Eckman *et al.* found that locally therapeutic levels of tobramycin were associated with serum levels well below therapeutic range, with no local or systemic complications.[18] Given the severity of the disease in our cases, with multiple previous surgical procedures and antibiotic treatment, a belt and braces approach was adopted. The novel use of tobramycin beads formed part of triple therapy management alongside systemic treatment to maximise the chances of disease control. Evidence from orthopaedic departments suggests that antibiotic beads alone are likely to be sufficient, but further work is required to replicate this in the management of frontal osteomyelitis. Finally, there is a lower economic burden with topical therapy, especially if it helps to reduce recurrence.[17]

- Chronic osteomyelitis may occur secondary to chronic infection and is associated with avascular necrosis and formation of sequestrum
- *Staphylococcus aureus* is the most common cause of osteomyelitis in patients of all ages
- Frontal osteomyelitis is a rare but potentially life-threatening complication of frontal sinusitis
- Surgical debridement and administration of long-term systemic antibiotics is the mainstay of treatment; however, recurrence rates remain high
- Topical antibiotic-impregnated beads are used in other specialties such as orthopaedics
- This study proposed the use of antibiotic-impregnated beads in the management of frontal osteomyelitis to deliver high levels of antibiotics topically

Frontal osteomyelitis is a rare but potentially life-threatening condition. Despite surgical debridement and systemic antibiotic therapy, recurrence rates remain high. Antibiotic-impregnated beads offer the ability to deliver high concentrations of antibiotic locally and have been used safely in orthopaedic surgery for decades. Our cases show promising use of tobramycin beads in recalcitrant frontal osteomyelitis. We propose that antibiotic-impregnated beads should be considered as a useful adjunct in the contemporary management of frontal osteomyelitis.

Competing interests. None declared

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