The changing face of malignant (necrotising) external otitis: clinical, radiological, and anatomic correlations

Jennifer Rubin Grandis, Barton F Branstetter IV, and Victor L Yu

Malignant (necrotising) external otitis is an invasive infection of the external auditory canal. Although elderly patients with diabetes remain the population most commonly affected, immunosuppressed individuals (eg, from HIV infection, chemotherapy, etc) are also susceptible to malignant external otitis. *Pseudomonas aeruginosa* is isolated from the aural drainage in more than 90% of cases. The pathophysiology is incompletely understood although aural water exposure (eg, irrigation for cerumen impaction) has been reported as a potential iatrogenic factor. The typical patient presents with exquisitely painful otorrhoea. If untreated, cranial neuropathies (most commonly of the facial nerve) can develop due to subtemporal extension of the infection. The diagnosis of malignant external otitis is based on a combination of clinical findings, an increased erythrocyte sedimentation rate, and radiographic evidence of soft tissue with or without bone erosion in the external canal and infratemporal fossa. Treatment consists of prolonged administration (6–8 weeks) of an antipseudomonal agent (typically an orally administered quinolone). With the introduction and widespread use of both oral and topical quinolones, there are reports of less severe presentation of malignant external otitis and even the emergence of ciprofloxacin resistance. Reservation of systemic quinolones for the treatment of invasive ear infections is recommended.

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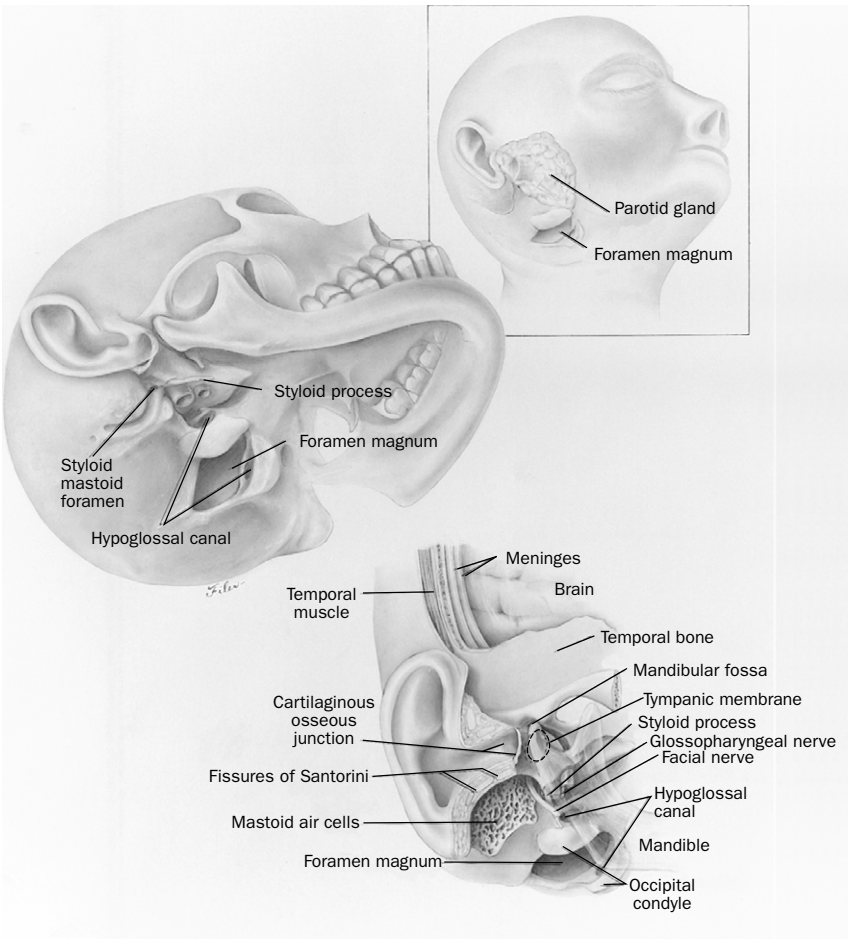

Figure 1. Anatomical sites of infection in malignant external otitis. The infection starts in the external ear canal, crosses the osseous-cartilaginous junction, and invades the temporal bone and temporomandibular joint. Contiguous spread to the meninges, brain, sinuses, and parotid can rarely occur (reprinted with permission from reference 4).

Malignant (necrotising) external otitis was first recognised as a distinct clinical entity by Meltzer in 1959[1] and Chandler presented the first comprehensive description in a case series from 1968 to 1974.[2,3] At that time the disease was uncommon, but by the 1990s several notable developments had occurred. Discrete syndromes were recognised as variants of malignant external otitis including pseudomonas mastoiditis and pseudomonas skull-based osteomyelitis. The pathogenesis was more clearly delineated.[4] A link was established between aural irrigation and malignant external otitis thus implicating a iatrogenic cause in some patients. An increased erythrocyte

JRG and BFB are at the Department of Otolaryngology, VLY is at the Department of Medicine, and BFB is also at the Department of Radiology, of the University of Pittsburgh School of Medicine, Pittsburgh, PA, USA.

Correspondence: Dr Victor L Yu, Infectious Disease Section, VA Medical Center, University Drive C, Pittsburgh, PA 15240, USA. Tel +1 412 688 6643; fax +1 412 688 6950; email vly+@pitt.edu

sedimentation rate (ESR) was identified as a helpful tool in screening for this syndrome and monitoring response to therapy.[4,5] Computed tomography (CT) and magnetic-resonance imaging (MRI) scans were shown to be useful for diagnosis and for assessment of treatment.

Ciprofloxacin, an antipseudomonal antibiotic that could be administered orally, became available in the 1990s and ultimately supplanted intravenous therapy with antipseudomonal β-lactam agents and aminoglycosides. Unfortunately, treatment with oral quinolones has been threatened since their use has become widespread and, in our opinion, indiscriminate. In this review we summarise the major changes in aetiology and epidemiology of this evolving disease and comment on newer approaches to its management.

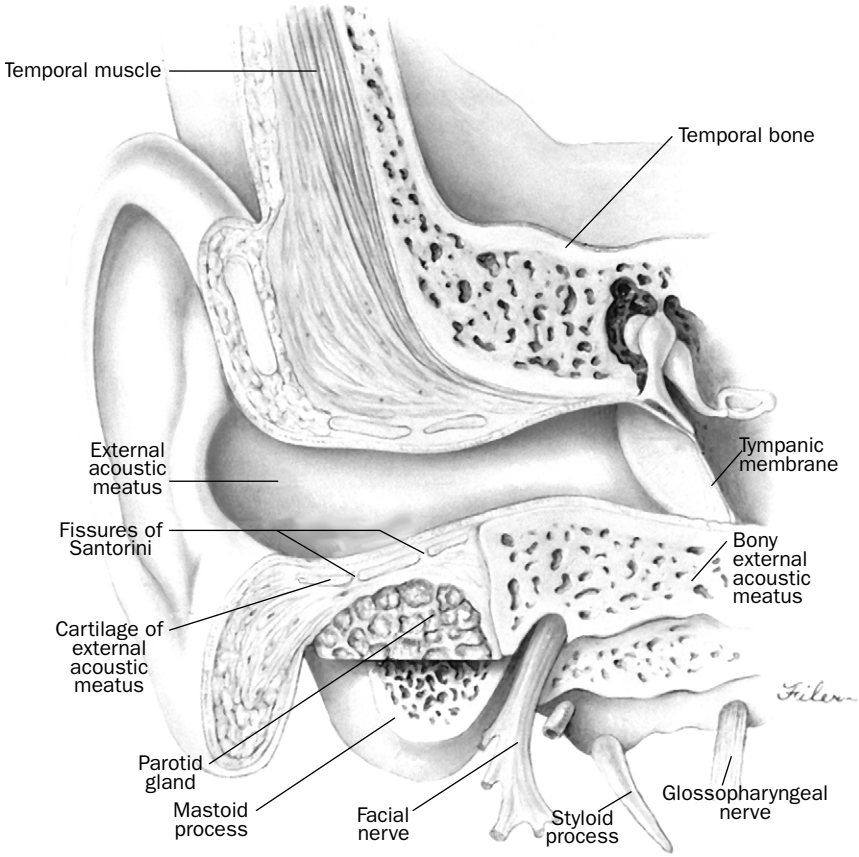

Figure 2. Infection enters the mastoid and skull base through the fissures of Santorini. The most frequent sites of cranial nerve involvement are the facial nerve as it exits through the stylomastoid foramen, the glossopharyngeal, the vagus, and the accessory nerves as they exit through the jugular foramen, and the hypoglossal nerve as it passes along the hypoglossal canal (reprinted with permission from reference 34).

Pathophysiology

Malignant external otitis is an invasive infection of the external auditory canal and skull base (figure 1) that typically arises in the elderly patient with diabetes mellitus. Most cases (86–90%) have been reported in diabetic patients. *Pseudomonas aeruginosa* is nearly always the causative organism (>98% of cases),[4] although the administration of topical antibiotics before culture often precludes isolation of the pathogen. Since both ageing and diabetes mellitus are associated with abnormalities of small blood vessels, it has been postulated that microangiopathy in the ear canal predisposes elderly diabetic patients to malignant external otitis.[2,4] Although no direct relation has been delineated between the degree of glucose intolerance and disease susceptibility,[4] an increased pH in diabetic cerumen has been reported, which may contribute to the development of malignant external otitis.[6] Increasing life expectancy and obesity may lead to a growing incidence of diabetes mellitus and hence, malignant external otitis.

Epidemiology

The epidemiology of malignant external otitis has changed in the past 10 years. Although it is difficult to document precisely, it seems that this syndrome has been more frequently diagnosed as the index of suspicion for malignant external otitis has increased for generalist physicians. Although rare, paediatric cases are also being seen. By contrast with adults, children are more likely to be immunocompromised on the basis of malignancy and malnutrition. Although no deaths have been reported to our knowledge, children tend to be more toxic with their illness, as illustrated by the development of fever, leucocytosis, and *P aeruginosa* bacteraemia.[4,7]

Malignant external otitis is now being reported in patients with AIDS.[8–14] AIDS patients who develop malignant external otitis tend to be younger than the typical elderly patient with this invasive ear infection, and most are not diabetic. In addition, *Aspergillus fumigatus* has been isolated in AIDS patients as well as *P aeruginosa*. Most patients have been cured with systemic antipseudomonal or antifungal regimens. Although malignant external otitis seems to be uncommon in AIDS patients, the diagnosis should be considered in any patient who presents with painful otorrhoea that is unresponsive to treatment regimens for simple external otitis (ie, topical antibiotics and local debridement).

Malignant external otitis is caused by *P aeruginosa* in nearly all cases. When more than one organism is recovered on culture, the other isolates tend to represent normal skin flora. It is important to isolate the organism from the ear drainage before instituting therapy. If *P aeruginosa* has never been isolated from the otorrhoea, then a biopsy of the bone for culture is indicated to eliminate the possibility of malignancy and establish the necessity for long-term antibiotic therapy. *P aeruginosa* is a Gram-negative bacterium that is ubiquitous in water.[15,16] The recovery of *Pseudomonas* spp on culture is indicative of infection since pseudomonas are not a component of normal ear canal flora. Exposure to water colonised with pseudomonas has been shown to cause simple external

otitis.[17,18] Moreover, aural water exposure has been linked to the development of malignant external otitis. We did a case-control study in elderly diabetics to assess the hypothesis that malignant external otitis may also be a iatrogenic disease precipitated by ear irrigation with tap water. In this study, more than two-thirds of our patients with malignant external otitis had a history of ear irrigation (generally for the purpose of disimpacting cerumen) compared with 15% in matched controls.[19] Subsequent reports have confirmed this causative association.[20,21]

Other bacteria that have been reported to cause malignant external otitis include *Staphylococcus aureus*,[22] *Proteus mirabilis*,[23] *Klebsiella oxytoca*,[24] *Pseudomonas cepacia*,[25] and *Staphylococcus epidermidis*,[6] although it is uncertain whether all of these bacteria were true pathogens. The rare cases of fungal malignant external otitis were most often due to *A fumigatus;* although *Aspergillus niger, Scedosporium apiosperumum*, *Pseudallescheria boydii*, *Candida ciferri*, and *Malassezia sympodialis* have been implicated in a few case reports.[11,26–33]

Clinical presentation

Malignant external otitis is an infection whose clinical presentation is sufficiently variable that patients may present to physicians in several specialties. Since most patients are diabetics, the internist is frequently the first physician to see the patient presenting with intractable headache. The otolaryngologist may see the patient with persistent earache and drainage. Finally, the emergency room physician or neurologist may see the patient with focal signs and cranial nerve palsies as an acute neurological emergency.

Patients with malignant external otitis typically present with severe otalgia accompanied by otorrhoea that has been unresponsive to topical agents. The pain tends to be more severe than in simple external otitis (swimmer's ear) or chronic otitis media with tympanic membrane perforation. The pain often extends to the temporomandibular joint and is aggravated by chewing, a clinical clue that raises the possibility of malignant external otitis in a patient with otalgia (figure 1). On physical examination, the typical finding is granulation tissue in the floor of the ear canal at the bony–cartilaginous junction (at the site of the fissures of Santorini). The tympanic membrane is almost always intact. Disease progression is associated with osteomyelitis of the skull base and temporomandibular joint. Cranial nerve palsies generally indicate advancing infection (figure 1, figure 2, figure 3). Paralysis of the facial nerve is most common, followed (in order) by the glossopharyngeal, vagal, and spinal accessory nerves at the jugular foramen, and the hypoglossal nerve as it exits the hypoglossal canal (figure 2, figure 3). The trigeminal and abducens nerves can be affected at the petrous apex and there is one report of optic nerve involvement.[34] The remaining cranial nerves (olfactory, oculomotor, and trochlear) are not affected. Children with this disease have a higher incidence of facial palsy due to the underdeveloped mastoid process and the more medial location of the fissures of Santorini, which places the facial nerve in closer proximity to the ear canal (figure 2).[35] Other central nervous system complications, including meningitis, brain abscess, and dural sinus thrombophlebitis, are rare, but are fatal when they occur (figure 1).[36]

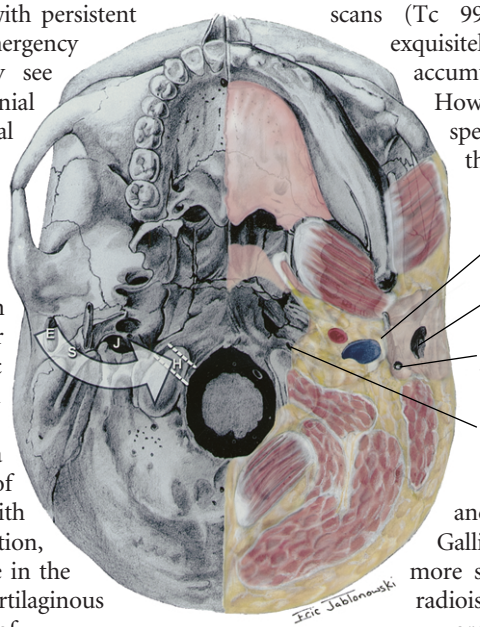

Figure 3. Illustration of the skull as seen from below. The left side depicts the bony structures; the right side is overlaid with soft tissue. The large arrow indicates the path of spread for malignant external otitis: the external auditory canal (E), the facial nerve at the stylomastoid foramen (S), the glossopharyngeal, vagus, and spinal accessory nerves at the jugular foramen (J), and the hypoglossal nerve at the hypoglossal canal (H). The hypoglossal canal is oriented horizontally through the skull base, and is therefore denoted with dotted lines.

Diagnosis

There is no single pathognomonic criterion that defines malignant external otitis. The diagnosis is generally made from a range of clinical, laboratory, and radiographical findings (figure 4). Typical signs of infection are notably absent: patients are afebrile and white blood cell count and differential are generally normal. Although non-specific, we have seen that the ESR is usually markedly increased and can be used to monitor disease activity.[4] In a study of 13 consecutive patients, the ESR (Westergren method) dropped from a mean pretreatment value of 81 mm/h (range, 41–138 mm/h) to a mean value of 18 mm/h (range 3–45 mm/h).[5]

Certain imaging modalities have proven valuable in the diagnosis and follow-up of malignant external otitis. Bone scans (Tc 99m methylene diphosphonate) are exquisitely sensitive because the radiotracer accumulates at sites of osteoblastic activity. However, bone scans are relatively non-specific because they can be abnormal in the setting of simple external otitis.[37] In addition, bone scans remain positive indefinitely and cannot be used to follow disease progression or resolution. There is some evidence that a quantitative bone scan can distinguish malignant external otitis from its more benign counterparts and can correlate with disease activity.[38,39] Gallium scans (gallium citrate Ga67) are more specific than bone scans because the radioisotope is incorporated directly into granulocytes and bacteria. While some authors have reported that gallium scans can be used to follow disease activity, others have noted normal scans in the setting of recurrent disease (figure 5).[40–42] It has been suggested that gallium scans with single photon emission computed tomography (SPECT) may help in the diagnosis and follow-up of malignant external otitis.[43–45] In general, however, anatomic imaging modalities such as CT

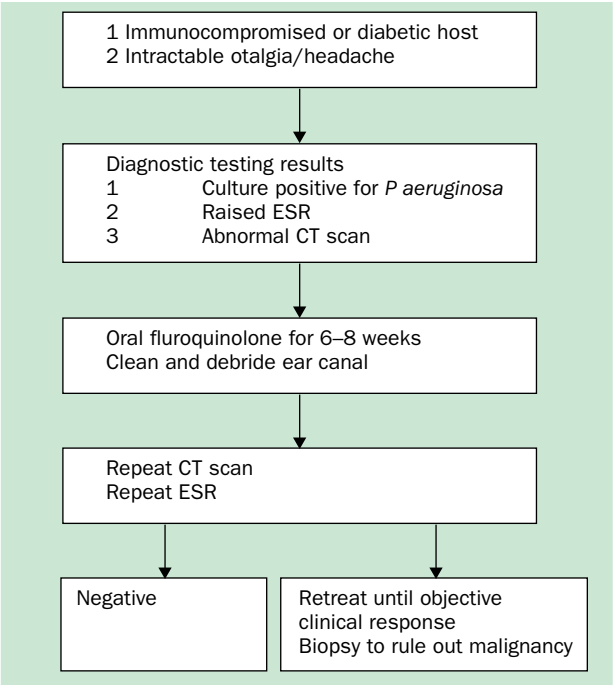

Figure 4. Diagnostic and treatment algorithm for malignant external otitis. The approach is based on obtaining a history to identify a high-risk patient, and on focused laboratory testing including ESR, culture, and radiography.

or MRI are more useful than nuclear medicine studies in the assessment of malignant external otitis.

Anatomic imaging allows for both disease localisation and an assessment of disease progression or resolution (figure 6). CT scans are ideal to assess for bone erosion. In a prospective study, presence of bone erosion and soft tissue abnormalities in the infratemporal fossa were most helpful in making the diagnosis of malignant external otitis.[46] Although eroded bone does not remineralise, resolution of the soft tissue component does correlate with disease activity. In a 1-year prospective comparison of CT and MRI, we found that MRI was slightly better than CT at showing medial skull base disease because MRI was capable of delineating changes in the fat content of the marrow.[46]

Squamous cell carcinoma can occasionally present as a painful, draining ear. Anatomic imaging studies cannot distinguish tumour from malignant external otitis. A positive culture for *P aeruginosa* and an increased ESR are more commonly associated with infection. However, simultaneous occurrence of temporal bone cancer and malignant external otitis has been reported.[47,48] Therefore, a biopsy is the only definitive method to distinguish this invasive infection from cancer.

Treatment

Systemic antipseudomonal antibiotics are the primary therapy for malignant external otitis. The introduction of parenteral semisynthetic penicillins reduced mortality from over 50% to 20% in the 1960s.[2] However, prolonged combination parenteral therapy with aminoglycosides and antipseudomonal β-lactam antibiotics was associated with long-term hospitalisation and renal and vestibular toxicity, in addition to the morbidity of the disease itself. In the past 15 years, oral

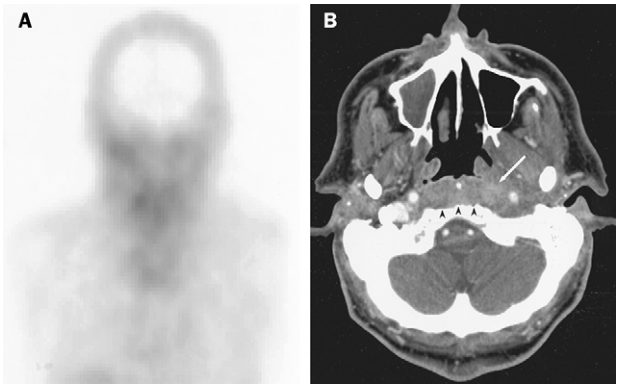

Figure 5. False-negative gallium scan. (A) Galluim citrate Ga67 was administered to assess the progression of known malignant external otitis. Coronal SPECT image shows no increased uptake. (B) CT 2 days later shows extensive inflammation of the soft tissues around the skull base (arrow), as well as erosion of the inferior surface of the clivus (arrowheads). Follow-up CT after further treatment (not shown) documented resolution of the soft tissue abnormalities.

quinolones, especially ciprofloxacin, have revolutionised the treatment of malignant external otitis and replaced combination intravenous therapy.[48,49] The availability of oral agents has eliminated the need for hospitalisation in all but the most recalcitrant cases. The advantages of quinolones include its low toxicity profile, and excellent penetration into bone.[50] The dosing of ciprofloxacin does not require adjustment in the elderly patient with renal dysfunction.[49,51] Although quinolones have not generally been given to children due to problems with joint development in animal models, one child with malignant external otitis has been effectively treated with ciprofloxacin after failure of prolonged intravenous therapy with antipseudomonal penicillin and aminoglycoside.[7] Ciprofloxacin has also been safely administered to children with cystic fibrosis and is therefore indicated for treatment of malignant external otitis in the rare paediatric patient. With the introduction of quinolones, the cure rate has increased to 90%, with few adverse effects reported. Ciprofloxacin (750 mg orally twice per day) seems to be the antibiotic of choice, based on clinical experience and comparative in-vitro susceptibility studies; however, comparative trials have not been done.[5,52–56] Despite the rapid relief of symptoms (pain and otorrhoea), prolonged treatment for 6–8 weeks is still recommended, as indicated for an osteomyelitis. In earlier years, surgical debridement had a role in the treatment of malignant external otitis, but with the advent of quinolone therapy, we have seen no indication for surgical management other than diagnostic

Search strategy and selection criteria

We did computer-assisted searches of the Pubmed database, primarily for English language published material. Articles with the terms "malignant external otitis", "necrotising external otitis", "invasive external otitis", or malignant/necrotising/invasive "otitis externa" formed the basis of the reference material. Articles chosen described individual cases or case series of patients with this disease. Preference was given to the most recently published information. Early sources were also identified from references in the more recent papers.

biopsies. Hyperbaric oxygen has been used on occasion with mixed results and may be considered as an adjuvant treatment for refractory cases although its efficacy remains unproven.[57–60]

If a fungus (eg, aspergillus) is the causative organism, prolonged treatment (>12 weeks) with amphotericin B is indicated. A liposomal amphotericin preparation is recommended to keep to a minimum the incidence of nephrotoxicity in diabetic patients.

There is no role for topical antibiotics, even quinolones, in the treatment of malignant external otitis. Instillation of antipseudomonal topical agents only increases the difficulty of isolating the pathogenic organism from the ear canal.

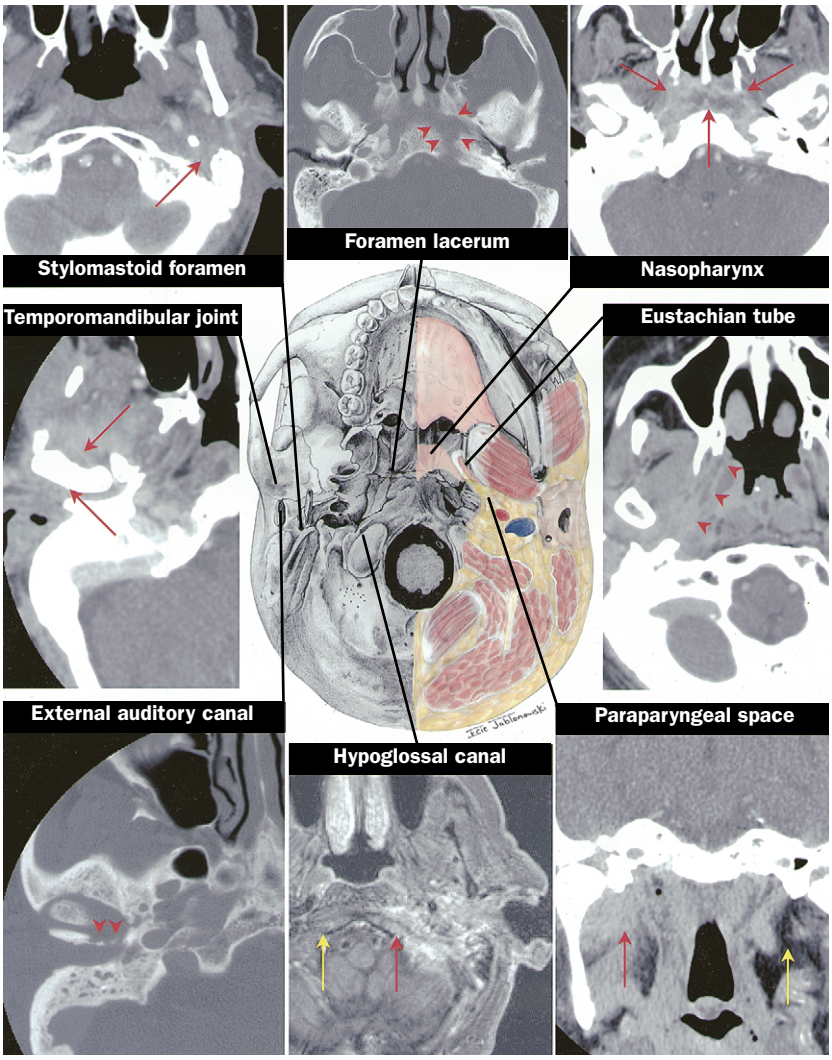

Figure 6. The radiographic appearance of malignant external otitis. Select images from various patients with malignant otitis externa are shown, with a central drawing for anatomic correlation. The left half of the drawing shows bony features of the skull base; the right half of the drawing shows overlying soft tissues. Images are listed clockwise from the upper left. Stylomastoid foramen: axial CT shows abnormal enhancement and obliteration of the fat planes around the stylomastoid foramen (arrow), which transmits the facial nerve (cranial nerve VII). Foramen lacerum: axial CT on bone window shows bone erosion surrounding the foramen lacerum (arrowheads), which transmits only small nerves and vessels, but is a route of intracranial spread of infection. Nasopharynx: axial CT shows expansion and heterogeneous enhancement of the adenoids (arrows), with obstruction of the nasal airway. Eustachian tube: axial CT shows abnormal enhancement and obliteration of fat planes along the course of the Eustachian tube (arrowheads), which communicates between the middle ear and the nasopharynx. Parapharyngeal space: coronal CT through the parapharyngeal space, which normally contains fat (yellow arrow). On the affected side, the fat is inflamed, with soft tissue infiltration (red arrow). Hypoglossal canal: axial T1-weighted MR shows abnormal enhancement throughout the left skullbase, including the hypoglossal canal (red arrow). The yellow arrow marks the location of the normal contralateral hypoglossal canal, which transmits the hypoglossal nerve (cranial nerve XII) to the tongue. External auditory canal: axial CT on bone window shows erosions (arrowheads) in the anterior wall of the external auditory canal. These erosions are the radiographic hallmark of malignant external otitis. Note that the anterior wall of the external auditory canal is also the posterior wall of the temporomandibular joint. Temporomandibular joint: axial CT shows abnormal enhancement (arrows) around the head of the mandibular condyle, indicating septic arthritis of the temporomandibular joint.

Emergence of resistance

With the widespread use of quinolones for all ear infections, patients with malignant external otitis are being diagnosed and treated earlier in the course of their disease, thus confounding the typical clinical spectrum of this infection. Individuals with "limited-malignant external otitis" may present with a lower or even normal ESR and no evidence of bone destruction on anatomic imaging studies. A primary-care provider may prescribe a short course of an oral quinolone, and an otolaryngologist is consulted only when symptoms persist or worsen. In the past few years ciprofloxacin-resistant *P aeruginosa* have been isolated from patients with malignant external otitis.[61] We have encountered a case of malignant external otitis with protracted symptoms over 18 months. The patient received 12 courses of oral antibiotics, usually with quinolones, but the longest duration was only 2 weeks with most courses averaging 7 days.

Patients with resistant *P aeruginosa* generally require hospitalisation for biopsy, debridement, and parenteral antibiotics. Most cases have been effectively treated with a prolonged (>12 weeks) course of an antipseudomonal β-lactam agent (ceftazidime, piperacillin, imipenem) with or without an aminoglycoside. At one institution, 33% of *P aeruginosa* isolates from patients with malignant external otitis were resistant to ciprofloxacin in the past 2 years.[61] The increasing incidence of ciprofloxacin resistance may result from a low threshold for prescribing topical and systemic quinolones for all otitities and upper respiratory tract infections, in addition to the recalcitrant nature of pseudomonal infections.

Conclusion

Malignant external otitis remains a serious invasive infection despite the recent success of quinolones antibiotics. It is important to maintain a high index of suspicion when the typical host (an elderly diabetic or immunocompromised patient) presents with otalgia or intractable headache that is disproportionate to findings on physical examination. A history of ear irrigation should be sought because of the noted association between malignant external otitis and water exposure.[19,20] The diagnosis of malignant external otitis is based on physical examination findings, raised ESR, and CT evidence of bone erosion and infiltrated infratemporal soft tissues. CT remains the most appropriate initial imaging method because it addresses many differential considerations in the external auditory canal. MRI is preferred when documenting progression or resolution of soft tissue infection and osteomyelitis. Quinolone antibiotics, especially ciprofloxacin, have emerged as the treatment of choice for malignant external otitis. However, the emergence of ciprofloxacin resistance in *P aeruginosa* is becoming a major problem. Given the plethora of oral antibacterial agents available for the more common otitides, especially otitis media, we recommend that quinolones should be reserved only for the treatment of invasive ear infections.

Conflicts of interest

We have no conflicts of interest.

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