CLINICOPATHOLOGICAL CONFERENCE

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An elderly man with cranial nerve palsies, otalgia and otorrhoea

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THE STORY

In 2001, a retired seaman in his seventies presented with a progressive history of ear pain, deafness, double vision and facial weakness. Several months prior to this he had started to notice discomfort in his right ear and parotid area, with an aural discharge. Soon afterwards he noticed a similar pain in his left ear. He consulted an ear, nose and throat (ENT) surgeon who syringed both ears and drained a right middle ear effusion by inserting a grommet and performing a myringoplasty. A nasal polyp was removed at the same time. He received a two-week course of coamoxiclav. Despite these interventions, the pain worsened and he began to have difficulty hearing in both ears. Four months later he began to experience intermittent double vision and his hearing became worse. After a short course of oral steroids he developed left facial weakness. His ENT surgeon arranged a consultation with a general physician where a number of imaging investigations were performed. He was referred back to his surgeon who performed a biopsy of his post-nasal space, which showed no diagnostic abnormalities. He was treated with oral ciprofloxacin and steroids without improvement.

Over the next two months he lost two stones in weight, had a poor appetite, and was tired for much of the time. His bilateral ear pain was by this stage severe enough to be treated with significant doses of opiates. His hearing was too poor to follow conversations and he was having some difficulty swallowing.

As the patient continued to worsen, his ENT surgeon arranged for him to see a rheumatologist who quickly arranged for his admission to the local neurological centre six months after his symptoms had started. On admission he was taking a number of medications for pain, including morphine, carbamazepine and gabapentin. He was also taking 5 mg of prednisolone a day and ciprofloxacin. He drank alcohol in moderation, did not smoke and lived at home with his wife. There was no history of recent foreign travel.

He had been diagnosed with diabetes mellitus in 1990 and his blood sugars had been well controlled with diet. He had had a basal cell carcinoma removed from his left inner canthus in 1995 followed by a course of local radiotherapy. In 1996 he had had a lentigo maligna removed from the right side of his neck without signs of recurrence on follow up.

EXAMINATION

He was alert with a normal mini mental state examination. There were left 6th and 7th cranial nerve palsies with profound hearing loss in both ears. He was areflexic. The rest of the neurological examination was normal. He was cachectic and afebrile. There were no abnormalities on examination of his skin and he had neither organomegaly nor lymphadenopathy.

INVESTIGATIONS

Blood tests

Sodium 126 mmol/L, potassium 5.5 mmol/L, urea 10.8 mmol/L, glucose 15 mmol/L. Haemoglobin 114 g/L, mean cell volume 90.4 fl, white cell count normal, platelet count normal, clotting studies normal. ALT 12 U/L, alkaline phosphatase 100 U/L, gamma GT 82 U/L (normal < 49), albumin 22 g/L (normal 35–50). Erythrocyte sedimentation rate 92 mm/h, C-reactive protein 9.5 mg/dL (normal < 1.0)

The following tests were normal or negative: antinuclear antibodies, ANCA (PR3 and MPO), rheumatoid factor, thyroid peroxidase, thyroid function, treponema pallidum haemagglutination antibody, chorioembryonic antigen, prostate specific antigen, alpha-fetoprotein, calcium, creatinine kinase, protein electrophoresis, C3, C4, serum angiotensin converting enzyme.

Urine tests

Dipstick blood +, protein + +, Mycobacterium tuberculosis culture negative after six weeks incubation.

Cerebrospinal fluid tests

Protein 2.2 g/L, glucose 6.1 mmol/L (plasma glucose 15 mmol/L), 10 lymphocytes/mm³ (although normal lymphocyte count on second and third occasions). Cytology (on three occasions) revealed a mixed inflammatory infiltrate without atypical cells. No oligoclonal bands. No bacterial growth, and Mycobacterium tuberculosis culture negative after six weeks incubation.

Imaging

CT brain (two months prior to presentation at neurological unit): right inferotemporal fossa mass obliterating normal fat planes with thickening of the ethmoidal air cells (Fig. 1)

Radioisotope bone scan (two months prior to presentation at neurological unit): increased uptake in the base of the skull

Figure 1 Non-enhanced CT of base of skull showing external ear full of tissue (long arrow) with bony destruction of the right petrous apex (thick arrow). The mastoid air cells are full of fluid (thin arrow)

Figure 2 (a) T1 MR brain scan showing an ill-defined bilateral nasopharyngeal mass (thin arrow), infiltrating and traversing fat planes and involving the marrow of the clivus (arrow). (b) both middle ear clefts (arrow) are filled with soft tissue (arrow)

Figure 3 MRI brain showing dural enhancement with contrast (arrow).

CT neck (on admission to neurological unit): extensive mass in nasopharynx, with direct invasion of the clivus and encasement of the carotid sheath vessels and lymphadenopathy in the posterior triangle.

CT chest, abdomen and pelvis: normal

MRI face/sinuses/brain (Fig. 2) (on admission to neurological unit): ill-defined bilateral nasopharyngeal mass, infiltrating and traversing fat planes and involving the marrow of the clivus, with dural thickening which enhances with contrast (Fig. 3). Both middle ear clefts were filled with soft tissue.

Needle biopsy (on admission to neurological unit)

Taken from the skull base next to the foramen ovale: normal muscle, adipose and fibroconnective tissue.

CLINICAL COURSE

His pain was managed palliatively and he was discharged home taking an increased dose of prednisolone. He seemed to improve initially, but a few days later he had a generalized epileptic seizure and became comatose. He died soon afterwards at home. A post-mortem examination was performed.

CASE DISCUSSION

Dr Peter Rudge

I will first review the history. Here is an elderly man with a seven-month-long fatal illness. His symptoms progressed rapidly from a right to a left aural pain. His initial evaluation was by an ENT surgeon, who concluded his right aural pain and discharge with a middle ear effusion were infective. However, the rapid progression from right- to left-sided symptoms would be very unusual for a bacterial middle ear infection. With severe bilateral aural pain, one is immediately suspicious of a systemic inflammatory process.

As his hearing worsened, he developed diplopia on looking to the right, suggesting a right 6th nerve palsy, with difficulty swallowing, although with no suggestion of a cranial neuropathy. Without a clear diagnosis, he was treated with steroids, a left facial nerve palsy developed, and his pain and hearing worsened. Although there is no audiogram available, we know he was unable to hear speech. This suggests a cochlear or neural component of his deafness, as pure conductive deafness does not usually go below

60dB, and this can be treated with amplification. He then began to show signs of a systemic illness, losing weight and his appetite. By the time he was admitted to the neurology ward his pain was intractable. He died suddenly after a seizure

On examination he had left 6th and 7th cranial nerve palsies, with profound hearing loss. He was cachectic and had lost his reflexes. This collection of signs localizes the lesion to the left petrous temporal bone, and is reminiscent of Gradenigo's syndrome (5th and 6th nerve palsies due to a lesion at the petrous apex). His swallowing difficulties are unexplained by palsies of the lower cranial nerves, and may have been due to pain.

His blood tests revealed only raised inflammatory markers and the anaemia of chronic disease. His CSF showed raised protein, and a glucose concentration 30% that of plasma. However he had diabetes, and was poorly controlled. Although one normally considers a CSF glucose concentration below 40% that of plasma as low, I am not sure this is helpful in the differential diagnosis here.

I will now review the imaging studies. His first scan was ordered by the ENT surgeons (Fig. 1), where the mastoids and middle ear are crammed full of material. It is difficult to see whether there is any erosion of the small bones of the inner ear. One can see the involvement of the stylomastoid foramen, where the 7th nerve was involved in this process. On the later MRI of the base of the skull (Fig. 2), one can see a loss of definition of the tissue planes and pterygoids. There is also infiltration of the clivus, and I note the nasal cavities are empty. There is marked dural enhancement in the posterior fossa with gadolinium (Fig. 3), and an infiltrating mass in the nasopharynx. There is an area of reduced flow in the transverse sinus, which I think may represent sinus thrombosis. An isotope scan shows uptake from ear to ear across the base of the skull.

Differential diagnosis

With this history, one would consider granulomatous, malignant and infective processes.

Wegener's granulomatosis is a multisystem disease, which often affects the kidneys. His renal function was impaired, and there was blood on a dipstick, although dipsticks are very sensitive for the smallest amount of blood. However, his renal impairment could equally have been caused by his poor diabetic control by the time of admission. He did have systemic symptoms, and rapid involvement of both ears, which can

occur in Wegener's. However his chest X-ray, neutrophil count and ANCA, particularly PR3, were all normal (85% of cases of Wegener's granulomatosis have a positive PR3). He had infiltration of bone, and normal nasal cavities, both very unusual in this condition.

Cancer is of course very common in people of this age group. He had had two prior malignancies – a basal cell carcinoma that is probably not relevant, and a lentigo maligna with no sign of recurrence locally after several years. Lentigo maligna has the same outlook as melanoma – if it has not infiltrated more than 0.5 mm, it is very unlikely to metastasize, while if it spreads more than 3 mm, metastasis is very common. However, the history is unusual for a melanoma (it does not usually spread through fascial planes), and severe pain is not a common feature of malignant infiltration of the skull base. Lymphoma can spread this way, although I have never seen it cause an aural discharge, nor fill the mastoid and middle ear. Moreover, lymphoma is unlikely as he had no organomegaly, lymphadenopathy or fever.

Infection may have been precipitated by a mass blocking the Eustachian tube, leading to problems with pressure equilibration, but we have no evidence on imaging for such a process.

Malignant, or necrotic, otitis externa is an infection of the middle ear that is found mainly in older people with diabetes. It is an extraordinarily painful condition, and having seen a case recently, I realize it is one of the most severe pains that I have ever seen. It often starts unilaterally, spreading to the other side with infiltration of the bone and vascular structures. His seizure suggests vascular involvement, and malignant otitis externa often does cause intracranial venous thrombosis, a potent cause of seizures.

Diagnosis

The most likely diagnosis here is malignant otitis externa, a condition described by Chandler in 1968 (Chandler 1968). This is found most often in immunosuppressed patients, particularly people with diabetes. Infection spreads through the epithelium into the cartilage of the external ear and then into the mastoid along the fissures of Santorini. The epithelium of the external ear has a tremendous rate of turnover: it grows out from the tympanic membrane, and over the hair in the external ear where it is peeled off like cheese from a grater. Perhaps a disturbance of this process leads to a breach in the epithelium through which organisms can invade deeper structures.

The most common cause of this condition is *Pseudomonas*, although there was no evidence of a bacterial infection in this man. A small proportion are fungal, of which most are due to *Aspergillus* that spreads through bone and blood vessels, which it often thromboses. *Mucormycosis*, another fungal inner ear infection, is a much more rapid infection with sloughing of the inner ear.

Dr Peter Rudge's Diagnosis

Malignant otitis externa due to *Aspergillus* infection.

Discussion of the clinical features

Dr Dorward, patient's general practitioner: I was impressed by his fluctuating cranial neuropathies over the months I looked after him.

Dr Jeremy Farrar, Director, Wellcome Research Group, Ho Chi Min City, Vietnam: I agree with the diagnosis of *Aspergillus* causing malignant otitis externa. He may have had a mild response to ciprofloxacin, which does have a minor effect on fungal metabolism. I would also comment that with a potentially undiagnosed infection, steroids can have numerous adverse consequences.

Audience member: You have argued for *Aspergillus* very persuasively. I have two concerns. Firstly this seems to be a long time course for an infection such as this, and secondly this is a man who has had several biopsies of the area of abnormality – how often are you unable to find *Aspergillus* in biopsy specimens?

Dr Peter Rudge: I think the time course of this illness is variable. *Aspergillus* infection can often be missed on biopsy, as it can be quite a patchy process.

Dr Debashish Chowdry, Associate Professor of Neurology, G.B. Pant Hospital, New Delhi: In view of the normal chest X-ray and normal sinus imaging, do you think that *Aspergillus* is the most likely possibility, or could it be *Pseudomonas*, the most common cause of this condition (more than 90% of cases)?

Dr Peter Rudge: You are quite right that *Pseudomonas* is by far the commonest organism in this condition. However, I have given weight to *Aspergillus* because I think that he had venous sinus thrombosis.

Dr Peter Harvey, Consultant Neurologist, London: I wonder whether adenoid cystic carcinoma, a rare ENT cancer which characteristically spreads along planes of tissue, would be a possible differential diagnosis in this case?

Dr Peter Rudge: I think this is unlikely without bone loss in the mastoid and middle ear.

PATHOLOGY

Dr Colin Smith

On examination of the whole brain there was extensive subarachnoid haemorrhage due to a ruptured right internal carotid artery aneurysm (Fig. 4). There was effacement of the tissues at the skull base, and anatomical spaces were filled with necrotic material. The occipital, temporal and petrous temporal bones showed some signs of erosion.

Samples for histology were taken from throughout the skull base and retropharynx. Most specimens showed a sparse inflammatory infiltrate, not typical of lymphoma or adenoid cystic carcinoma and without evidence of granulomatous inflammation. After decalcification, some of the fragments of bony tissue showed a prominent infiltrate, with plasma cells and smaller lymphocytes, appearances typical of a reactive lymphocytic infiltrate.

One section showed evidence of active bony destruction associated with a dense inflammatory infiltrate. On PAS staining, branching fungal hyphae were evident. This branching, septate morphology is typical of an *Aspergillus* species. As the fungal hyphae were sparse they were only seen on one or two sections (Fig. 5).

This presentation of *Aspergillus* in the nervous system is very unusual. We have more commonly seen multiple cerebral aneurysms from haematogenous spread to the brain from a primary lung focus. But here, the microscopic appearance of the right internal carotid artery aneurysm was typical of a berry aneurysm, where the internal elastica had been replaced by collagenous tissue. There was no evidence of fungal invasion of the vessel wall.

Dr Colin Smith's Neuropathological Diagnosis

- 1 Malignant otitis externa due to *Aspergillus* species infection.
- 2 Ruptured right internal carotid artery berry aneurysm.

Discussion

Professor Charles Warlow: Do you think that you missed the disease during life despite repeated biopsies because it was so patchy?

Dr Colin Smith: This does appear to have been a very patchy process – the inflammation

Figure 4 Whole brain at post mortem showing subarachnoid haemorrhage.

Figure 5 Section from skull base stained with PAS showing branching, septate hyphae typical of an *Aspergillus* species.

was only pronounced in areas of fungal growth. We stained for organisms on all the biopsy specimens, and they were all negative

Dr Richard Davenport, Consultant Neurologist, Western General Hospital, Edinburgh: How treatable do you think this would have been had we made the diagnosis in life?

Dr Peter Rudge: In its earliest manifestations, the diagnosis is very hard to make – otalgia is so common. By the time it presented to you, the disease was bilateral, hence there was no hope of removing the fungus at surgery.

Dr Jeremy Farrar: By the time the infection presented to you it would have been almost impossible to treat. Antifungal drugs have poor tissue penetration and can have toxic side-effects, and surgery would not have been possible at that stage.

Dr Mark Lewis, Specialist Registrar in Neurology, Hull Royal Infirmary: We wrote up a case of invasive intracranial Aspergillosis, and the patient is still alive. She had similar disease to this, starting in the sinuses and spreading intracranially. She started to have seizures and was treated with itraconazole with quite a dramatic reduction in the extent of her disease. She remains on itraconazole and is still alive several years later. The fungus is still present (Lewis & Henderson 1999).

COMMENT

Malignant otitis externa is not a common condition, though it is important because it may be treatable in its early stages, and with disease progression may be fatal. The presenting symptoms may be ear pain, cranial neuropathies or fever, so neurologists, ENT surgeons and general physicians should all be aware of it (Grandis & Branstetter 2004). Patients generally complain of a very severe ear pain, sometimes accompanied by an aural discharge. The infection, initially based in the external ear canal, may spread through the bones of the skull, giving rise to other symptoms. It may involve the temporo-mandibular joint, leading to pain on chewing, or the petrous temporal bone where the infection may lead to Gradenigo's syndrome (Grandis *et al.* 2004). Most patients are immunosuppressed in some way – usually as a result of diabetes or old age, though cases are described in people with HIV infection, or neutropenia as a result of chemotherapy or haematological disease.

The precipitant for infection is generally unclear. Ear irrigation has been proposed, after temporal association between irrigation and

malignant otitis externa in case reports, and a case-control study where more patients described a history of ear irrigation than controls. It has been proposed that an aural microangiopathy in some way makes diabetics more likely to develop infection. The infecting organism penetrates the skin of the external ear and enters the osseous ear canal, from where it may pass through the fissures of Santorini into the soft tissue around the stylomastoid foramen. From here it may spread into the mastoid bone and temporomandibular joint. Inferior extension results in facial nerve involvement, and postero-medial spread into the jugular foramen leads to palsies of the 9th, 10th and 12th cranial nerves, and later the hypoglossal nerve at the hypoglossal canal.

The infection does not commonly reach the middle ear, although where it does so the tympanic membrane is usually intact, implying invasion from the mastoid bone. Usually there is no intracranial spread, though case reports have described meningitis, intracranial abscess formation and venous sinus thrombosis. Advanced infection leads to a diffuse skull base osteomyelitis.

Diagnosis requires a combination of clinical, microbiological and imaging findings. Growth of an organism from the aural discharge or biopsy specimen will usually make the diagnosis, although this can be supported by CT findings of fluid in the mastoid or middle ear, abnormal soft tissue around the Eustachian tube and involvement of the carotid, parapharyngeal and masticator spaces. MRI may demonstrate bone marrow oedema, dural enhancement and involvement of blood vessels. Technecium-99m methylene diphosphonate bone scanning may show areas of increased bone activity, though the technique has a low specificity, and may be confusing in the setting of surgery (Swartz & Harnsberger 1997).

The most common infecting organism is *Pseudomonas aeruginosa*, a Gram negative bacillus. This infection is usually responsive to ciprofloxacin, which penetrates bone well and has good antipseudomonal activity. A long course, of between six and eight weeks, is recommended. Failure of treatment may be due to pseudomonal quinolone resistance, an infecting organism other than *Pseudomonas*, as in this case, or coexistent squamous cell carcinoma (Grandis *et al.* 2004).

Aspergillus infection is far less common, and appears to result in a more protracted illness.

Malignant otitis externa spreads from the external ear through the fissures (canals) of Santorini into the soft tissues around the base of the skull. The infection may involve the facial nerve as it exits the skull through the stylomastoid foramen, the glossopharyngeal, vagus and accessory nerves as they pass through the jugular foramen, or the hypoglossal nerve, which runs through the hypoglossal canals on either side of the foramen magnum. The temporomandibular joint, mastoid and temporal bones may all be involved by infection. Reprinted from Rubin & Yu (1988) from Excerpta Medica, Inc.

Aspergillus fumigatus (Gordon & Giddings 1994; Rushton *et al.* 2004) and *niger* (Bellini *et al.* 2003) infections have both been described. Isolation of the organism is difficult, and usually requires culture of a biopsy specimen. The only data we have for the treatment of malignant otitis externa due to *Aspergillus* are from case series, case reports or extrapolation from trials on pulmonary aspergillosis. Expert opinion (Stevens *et al.* 2000) suggests the use of amphotericin B, although this penetrates bone poorly, in addition to antifungal agents which penetrate bone well, such as itraconazole, rifampicin or flucytosine.

Surgical debridement probably does not have a role outside providing material for histology and culture. Hyperbaric oxygen therapy has been used for some refractory cases, though reports of success are only anecdotal.

ACKNOWLEDGEMENTS

Thanks to Dr Steven McDonald for a helpful discussion of the otolaryngological aspects of the case.

It is notable that a post-mortem was achieved, even though the patient died at home – this provided the diagnosis for the family, and education for all of us. The post-mortem remains a crucial

investigation and its decline must be reversed (see Bell 2004).

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