Original Article

Skull Base Osteitis: Our Experience and Systematic Review of Literature

Khalid Munir Cheema, Mohammad Amjad, Tahir Ayub, Malik Masood Ahmad, Kashif Ilyas and Damish Arsalan

Objective: This article discusses etiopathogenesis, diagnostic problems and various management modalities available to manage skull base ostietis (SBO) which is a rare but life threatening disorder and in addition national and international references will be reviewed.

Material and Methods: Cross sectional, retrospective study carried out at ENT unit-I SIMS/SHL which included 17 patients with SBO which were sorted out for etiological diagnosis based on detailed history, physical examination and labs.

Results: Mean age was 52 years. Diabetes is the most significant risk factor and was seen in 82% of patients, pseudomonas was isolated in 8 patients. The main complication facial paralysis was present in 64% of patients.

Conclusion: SBO remains a severe debilitating and life-threatening condition. It may develop in patients with benign otitis media and externa, and must be considered in all patients with temporal bone inflammation; especially those with risk factors and those who fail to improve with more conservative measures. Small-vessel vasculopathy and immune dysfunction associated with diabetes are primarily responsible for this predisposition. Cranial nerves most commonly the facial, can be affected by inflammation along the skull base or by a neurotoxin produced by Pseudomonas species. We, in this article, intend to share our experience in managing seventeen patients with SBO over a period of three years and review the relevant and recent global literature suggesting updates.

Keywords: Skull Base, Otitis, Necrotizing.

Introduction

Skull base osteitis (SBO) or necrotizing (malignant) external otitis, an infection involving the temporal and adjacent bones, occurs primarily in immunocompromised persons, especially elderly with diabetes mellitus, and is often initiated by self-inflicted or iatrogenic trauma to the external auditory canal. The most frequent pathogen is Pseudomonas Aeruginosa. Toulmousch (1838) reported the first case of otitis externa but was discussed in details by Meltzer(1959).[1] however Chandler (1963).[2] coined the term "Malignant otitis externa because of its propensity to cause complications however it must not be construed in a histological sense.[1,2.]

The typical patient with SBO is an elderly diabetic, with males outnumbering females by twice the number. This could be due to the possibility of males being more prone to secrete wax which are more acidic in nature. Studies reveal that it is more common among insulin dependent diabetics and current literature also reports a few such cases involving young insulin dependent diabetics.[3] Patients with SBO complain of severe otalgia that worsens at night, and otorrhea. Clinical findings include granulation tissue in the external auditory canal. Cranial nerve palsies, typically facial nerve, and intracranial complications indicate poor prognosis. Diagnosis requires culture of ear secretions and pathologic examination of granulation tissue. Imaging studies may include computed tomographic scanning, technetium (Tc) 99m medronate bone scanning and gallium citrate (Ga 67) scintigraphy. Treatment includes improvement of immunosuppression status, local treatment of the auditory canal, narcotic analgesics, longterm systemic antibiotic therapy and in selected patients, surgery. Currently fluoro- quinolones hold lots of promise in managing these patients.

Material and Methods

It is a retrospective study conducted in the department of ENT Unit-1 of SIMS/Services Hospital, Lahore over a period of about three years from April, 2010 to March, 2013. Seventeen patients were included in the study that fulfilled the criteria of SBO. All of these patients were admitted in the department and were assessed in details. Data was assembled with the help of a self administered structured questionnaire. This Performa sought information on demographic characteristics and specific sign symptoms and progress of disease. All patients were followed up at least for six months. Data

was analyzed using statistical package for social sciences 16 and for categorical variables measure of association was chi square test.

Results

The study spanned over a period of 3 years included 17 patients fulfilling the inclusion criteria. The results of this study were analyzed after feeding the data in statistical package for social sciences and calculated by using chi square test. Out of 17 patients there were 12 males (70.5%) and 5 (29.5%) females. The mean age of presentation was 52 years. The highest proportion of patient who presented amongst the whole range of the study were mostly in their 60s followed by the ones in 50s.14 out of 17 (82%) were diabetics and all with suboptimal control of their disease. Other three were having gross anemia, renal transplantation and hepatitis C. Facial paralysis was seen in 11 patients (64%). Others presented with severe unremitting otalgia refractory to routine analgesics otorrhorea, aural fullness. headache and facial paralysis of variable degree. Pseudomonas was isolated in 8, fungus in 2 and negative culture in 7 Granulations sent for Histopathology came as inflammatory. Skull base lesion with necrosis was evident on CT scan.

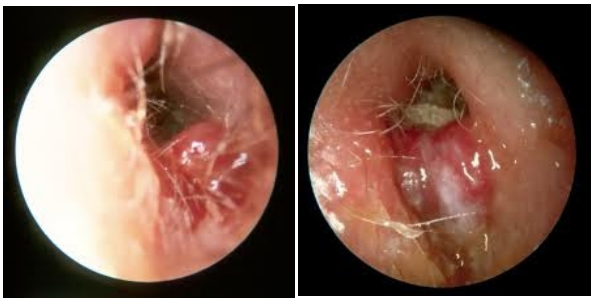

Fig-1: External canal granulation.

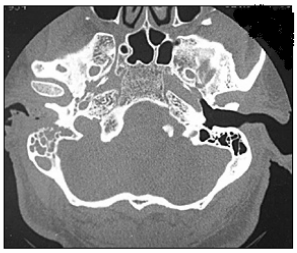

Fig [illegible] temporal bone and posterior wall of the external auditory canal is missing. Mastoid air cells are secondarily involved and are pacified compared with the well-aerated left side.

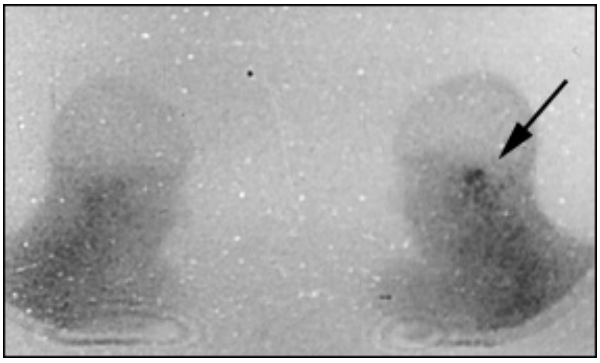

Fig-3: Gallium citrate Ga 67 scintigraphy in a patient left-sided temporal bone osteitis.the left temporal bone shows enhanced uptake of 67Ga *(arrow)*.

Discussion

Diabetic microangiopathy plays a vital role in the reduction of tissue perfusion causing opportunistic infections involving the area.[4] Rubin identified triggering factor for SBO in more than 60% of cases and was able to elicit history of frequent attempts at removing wax with ear buds.[5] Diabetic patients secrete wax which has less lysozyme content than normal thereby reducing the effectiveness of wax as an antimicrobial agent. It should also be remembered that diabetic patients have impaired phagocytosis, poor leukocytic response, and impaired intracellular digestion of bacteria. Pseudomonas Aeruginosa is a gram negative aerobe which invariably behaves like an opportunistic pathogen. The pathogenicity of this organism is due to ability to secrete exotoxin and various enzymes like lecithinase, lipase, esterase, protease etc. Since this organism is clothed by a mucoid layer it is resistant to digestion by macrophages. Radionucleotide scan using Technitium 99 helps in the diagnosis. Fixation of Technitium correlates with high degree of osteolytic activity which is commonly seen in these patients. This test is highly accurate (100%) but its specificity is rather low. [6] Gallium-67 scintigraphy is very useful for prognostic evaluation because of its high specificity .[7] Levenson has designed a diagnostic criteria which includes refractory otitis externa, severe nocturnal otalgia, purulent , discharge, grand tissue in the external auditory canal, growth of pseudomonas aeruginosa from external canal and presence of diabetes/Immunocompromised state.[8] Patients with SBO of the skull sometimes have extra-auricular manifestations, such as cervical lymphadenopathy, trismus (because of temporomandibular joint involvement)or irritation of the masseter muscle.[9] As the infection spreads in the temporal bone, it may

extend into the cranium and result in cranial nerve palsies. These palsies generally are caused by the secretion of neurotoxins or the compressive effect of the destructive process through the relevant foramina. Because of its anatomic location in the temporal bone, the facial nerve is usually the first nerve to become involved.

Cranial nerve involvement indicates a poor prognosis. Death is usually due to intracranial complications such as sigmoid sinus thrombosis, but it also may occur because of treatment complications, including bone marrow suppression induced by long-term antibiotic therapy. Prognosis is adversely affected by comorbid conditions, which are common in patients who develop SBO. CT scanning is used to determine the location and extent of diseased tissue **(Fig 2**)

The temporal bone is the first bone to be affected, with imminent involvement of the petrous apex and mastoid.In evaluating the CT scan, it is important to remember that at least one third of bone mineral must be lost before radiologic changes become apparent; conversely, bone remineralization continues long after the infection is cured. Thus, as related to the infectious process, pathology is late to appear on the CT scan and late to disappear. These factors limit the usefulness of CT scanning as a follow-up tool. Both osteoclasts and osteoblasts absorb 99mTc. Hence, bone scanning can locate a Pathologic process in bone but is not informative

Table-1: Radiological staging of skull base osteitis.

Grade	Diagnostic Criteria
I	Disease limited to soft tissue not involving bone refractory to standard antibiotic therapy for more than 4 weeks.
II	Earliest form of SBO with involvement of Mastoid bone.
III	SBO extending medially to involve petrous portion of temporal bone.
IV	SBO extending medially to involve the petrous apex or withcranial nerve involvement or pread Anteriorly to involve thefacial bones, posteriorly to involve the occipital bone, orspread to the contralateral base of skull

Table-2: Other staging and classification system.

Stage	Ga67	Tc99	Extent of Disease
I	+	-	Soft tissue (Necrotising Otitis)
I	+	+	Ear and mastoid (mastoid (Skull base osteomyelitis)
II	+	+	Extensive skull base osteomvelitis

Table-3: Systemic antibiotic therapy for necrotizing external otitis.

Drug	Dosage	Comments
Ciprofloxacin	750 mg orally every 12 hours	Fluoroquinolone for oral therapy
	400 mg IV every 12 hours	
Ticarcillinclavulanate potassium	3 g IV every 4 hours	Antipseudomonal penicillin
Piperacillin-tazobactam	4 to 6 g IV every 4 to 6 hours	Antipseudomonal penicillin; at this dosage, combine Piperacillintazobactam with an aminoplycoside.
Ceftazidime	2 g IV every 8 hours	Third-generation cephalosporin
Cefepime	2 g IV every 12 hours	Fourth-generation cephalosporin
Tobramycin	According to patient weight: 1 to 1.66 mg per kg IV or IM every 8	Aminoglycoside; combine tobramycin with a pencillin.

According to uri et al the99m Tc scan remains positive as long as bone repair continues, this imaging modality is not helpful in follow-up.[10]

Since 67 Ga is absorbed by macrophages and cells of the reticuloendothelial system, scanning with this radioisotope is a sensitive measure of ongoing infectious process **(Fig-3)** If 67 Ga scintigraphy is available, it should be used for initial diagnosis and as a follow-up. By using imaging modalities in combination, it is possible to prove that the temporal bone is afflicted with an infectious process .[12] In many patients with SBO, the initiating event may be self-inflicted or iatrogenic trauma to the ear canal. Therefore, susceptible patients should be instructed to avoid manipulation of the external auditory canal (i.e., they should not use cotton swabs to remove cerumen). Cleaning of the external auditory canal, including aural irrigation by medical staff, should be carried out with extreme caution to avoid injuring delicate skin in the canal.[5]

Treatment of SBO otitis includes correction of immunosuppression (when possible), local treatment of the auditory canal, long-term systemic antibiotic therapy and, in selected patients, surgery. Strict control of diabetes mellitus is mandatory, although it can be difficult to achieve during the acute illness. Other immunosuppressive states and comorbid conditions also must be aggressively managed.

Local treatment of the auditory canal includes meticulous cleaning and debridement plus topical application of antimicrobial agents. Sequestra and other necrotic tissue should be removed. Initially, treatment may include the application of antimicrobial-impregnated dressings to the canal. As in other infections involving bone, long-term administration of systemic antibiotics is the mainstay of treatment. Antibiotics that are effective **(table-3)** against *P. aeruginosa* include aminoglycosides, penicillins (especially piperacillintazobactam), ceftazidime cefepime and occasionally, imipenem . Depending on bacterial sensitivity, a combination of agents may be needed. The introduction of orally administered antipseudomonal agents in the 1980s simplified the ambulatory treatment of osteitis of the base of the skull.[12] Fluoroquinolones, primarily ciprofloxacin and ofloxacin, are DNA-gyrase inhibitors that are effective against *P. aeruginosa* and well tolerated by patients. Poor vascularization of the target area is one of the reasons that high-dose antibiotic therapy is needed to treat SBO. For example, the appropriate dosage of ciprofloxacin is 750 mg twice daily.[13] Because of the reported emergence of ciprofloxacin resistant pseudomonal strains,[14] culture should be performed before topical or systemic antimicrobial therapy is initiated.

Verifying the response to treatment can be difficult. Thus, determining the proper timing for its cessation can be problematic. Treatment should be continued for at least four weeks, but the duration of therapy must be individualized on the basis of the clinical presentation, ESR, and imaging studies. Hyperbaric oxygen, an adjunct to antibiotic therapy, is believed to increase the ability of polymorphonuclear cells to fend off pathogen bacteri.[15] A Cochrane Review found no clear evidence exists to demonstrate the efficacy of hyperbaric oxygen therapy when compared to treatment with antibiotics and/or surgery.[24]

Surgery has a definite but limited role in the treatment of SBO. Although bone sequestra and abscess are treated surgically, further extension of the operation may be counterproductive because it may expose healthy bone to the infection.[16] A combination of technetium scanning to detect osteoblastic activity gallium 67 imaging to detect granulocytic activity and is recommended a mean of monitoring response to treatment. Boustard can also be used to monitor therapeutic response.[18] Resistant strains of pseudomonas have been described following treatment with ciprofloxacin Staphylococcus aureus (MRSA) has been identified and can be methicillin-resistant staphylococcus aureus and rarely staphylococcus epidermidis is isolated. Fungal SBO is mostly due to aspergillus and candida but some unusual organisms have been identified as a cause such as scediosporum apiospermum and malassezia sympodialis.[19] The pathogenesis of this condition is unclear, however a number of factors are thought to contribute; microangiopathy, hypoperfusion and diminished host resistance (impaired phagocytosis, poor leukocytic response, impaired intracellular digestion of bacteria)ndue to diabetes. Their susceptibility to pseudomonas infection is increased by their ear wax being less acidic and having a lower lysozyme content, more favourable to pseudomonas infection. Isolated cases have been reported in a small number of non-diabetic patients, particularly in children who are immunocompromised due to malignancy, malnutrition and severe anaemia as well as in patients with HIV SBO. In a case series of 37 patients with, 51% had diabetes, 40% had facial nerve palsies and 24% had multiple cranial nerve palsies.[21] A Study on the various radiological and radionuclide investigations for SBO concluded that CT and/or

MRI should be supported by routine SPECT bone imaging for initial diagnosis of SBO.[22] Dual handershot et al suggested that WBC/Tc-99m MDP bone SPECT scintigraphy provides an accurate imaging modality for diagnosis and follow-up of temporal and facial osteomyelitis when existing clinical or postoperative bone changes make it Difficult to detect active osteomyelitis by computed tomographic scan.[22] Immunomodulators, such as topical tacrolimus to the affected ear have also been reported in the literature as being effective when used in combination with other treatments.[25] However, due to the increased use of ciprofloxacin for both simple ear infections and upper respiratory tract infections there is concern pseudomonas malignant otitis externa infections are increasingly resistant to ciprofloxacin.[23]

Conclusion

Despite advances in the treatment of malignant otitis externa, multiple complications can ensue including parotiditis, mastoiditis, meningitis, cerebral abscess and jugular vein thrombosis. There is the emergence of resistant strains of causative organisms to the fluoroquinolones that have improved treatment of these cases. Morbidity and mortality from this condition is still high especially with skull base osteomyelitis and cranial nerve involvement. Several investigative modalities are currently available and include MRI CT Scans, and gallium 67 SPET29, Therapies being used with varying success include immunomodulators and hyperbaric oxygen. The central management principles remain meticulous aural toileting, long-term antibiotics and ensuring adequate glycaemic control. This disorder could be caused by a combination of poor immune response and peculiar characteristics of the offending micro argmisam. All health care professionals providing medical care for immunocompromised patients should sort out the possibility of this condition in patients complaining of otalgia, particularly if they have diabetes mellitus and otitis externa that has been refractory to standard medical therapy. Susceptible patients should be educated to avoid manipulation/cleaning of the ear canal and to minimize exposure of the ear canal to water with a high chloride concentration. The aim of otolaryngologist is also to differentiate this condition from that of real malignancy.

Department of ENT
SIMS/Services Hospital, Lahore
www.esculapio.pk

References

1. Meltzer PE, Keleman G. Pyocyaneous osteomielitis of the temporal bone, mandible, and zygoma. Laryngoscope. 1959; 69:1300-16)
2. Chandler JR. Malignant external otitis. Laryn goscope. 1968;78: 1257-94.
3. Ceruse P, Colleaux B, Truy E, Disant F, Morgon AH, Lahneche B. Malignant external otitis. Apropos of 7 recent cases. Ann Otolaryngol Chir Cervicofac. 1993;110:332-6.
4. Cohen D, Friedman P. The diagnostic criteria of malignant external otitis. J Laryngol Otol. 1987;101:216-21.
5. Rubin J, Yu VL, Kamerer DB, Wagener M. Aural irrigation with water: a potential pathogenic mechanism for inducing malignant external otitis? Ann Otol Rhinol Laryngol. 1990;99:117-9.
6. Ress BD, Luntz M, Telischi FF, Balkany TJ, Whiteman ML. Necrotizing external otitis in patients with AIDS. Laryngoscope. 1997;107:45660.
7. Pacini DL, Trevorrow T, Rao MK, Birck HG, Barson WJ. Malignant external otitis as the presentation of childhood acute lymphocytic leukemia. Pediatr Infect Dis J. 1996;15:11324.
8. Levenson MJ, Parisier SC, Dolitsky J, Bindra G. Ciprofloxacin: drug of choice in the treatment of malignant external otitis (MEO). Laryngoscope. 1991;101:8214.
9. Drew SJ, Himmelfarb R, Sciubba JJ. Invasive (malignant) external otitis progressing to osteomyelitis of the temporomandibular joint: a case report. J Oral Maxillofac Surg. 1993;51:42931.
10. Uri N, Gips S, Front A, Meyer SW, Hardoff R. Quantitative bone and67Ga scintigraphy in the differentiation of necrotizing external otitis from severe external otitis. Arch Otolaryngol Head Neck Surg. 1991;117:6236.
11. Stokkel MP, Boot CN, van Eck-Smit BL. SPECT gallium scintigraphy in malignant external otitis: initial staging and follow-up. Case reports. Laryngoscope. 1996;106 (3 pt 1):33840.
12. Amorosa L, Modugno GC, Pirodda A. Malignant external otitis: review and personal experience. Acta Otolaryngol Suppl. 1996;521:316.
13. Gehanno P. Ciprofloxacin in the Treatment of malignant external otitis. Chemotherapy. 1994;40 (suppl 1):3540.

14. Cahana Z, Gilboa A, Raz R. Changes in susceptibility to ciprofloxacin in a community in northern Israel. Drugs. 1995;49(suppl 2):1734.
15. Davis JC, Gates GA, Lerner C, Davis MG Jr, Mader JT, Dinesman A. Adjuvant hyperbaric oxygen in malignant external otitis. Arch Otolaryngol Head Neck Surg. 1992;118:8993.
16. Kraus DH, Rehm SJ, Kinney SE. The evolving treatment of necrotizing external otitis. Laryngoscope. 1988;98
17. Boustred N. Practical guide to otitis externa. Aust Fam Physician. 1999;28:21721.
18. Bath AP, Rowe JR, Innes AJ. Malignant otitis externa with optic neuritis. J Laryngol Otol. 1998;112:2747.
19. Illing E, Olaleye O. Malignant Otitis Externa: A Review of Aetiology, Presentation, Investigations and Current Management Strategies . Webmed Central OTORHINO-LARYNGOLOGY2011;2(3):WMC001725
20. Hern J.D.,Almeyda J.,Thomas D.M.,Main J.,PatelK.S. Malignant otitis externa in HIV and AIDS. Journalof Laryngology and Otology, Aug 1996, vol./is.110/8(770-775), 0022-2151.
21. Ali T., Meade K.,Anari S.,ElbadaweyM.R., Zammit-MaempelI. Malignant otitis externa: Case Series. Journal of Laryngology and Otology, August2010, vol./is. 124/8(846-851), 0022-2151;1748-5460. Okpala N.C.E.,Siraj Q.H., Nilssen E.,Pringle M. Radiological and radionuclide investigation of malignant otitis externa. Journal of Laryngology and Otology, Jan 2005, vol./is. 119/1(71-75), 0022-2151.
22. Hendershot EF. Fluoroquinolones. Infectious Disease Clinics of North America, September 1995, vol./is. 9/3(715-30), 0891-5520.
23. Phillips J.S., Jones S.E. Hyperbaric oxygen as anad juvant treatment for malignant otitis externa. Cochrane database of systematic reviews (Online), 2005, vol./is./2(CD004617), 1469-493X.
24. Topical immunomodulation. A milestone for thetreatment of therapy-resistant noninfectious chronic external otitis? Caffier PP, Harth W, Mayelzadeh B,Haupt H, Scherer H, Sedlmaier HNO 2008, 56(5):530-4, 536-7.