RESEARCH ARTICLE

Skull base osteomyelitis (SBO): a dreaded clinical entity

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Abstract

Objective: To identify the risk factors and clinical manifestations associated with skull base osteomyelitis.

Method: The retrospective study was conducted at the Aga Khan University Hospital, Karachi, and comprised data from July 2013 to October 2020 related to adult patients who presented with skull base osteomyelitis. All relevant data was retrieved from hospital records. Data was analysed using SPSS 16.

Results: Of the 56 patients with a mean age of 58.12±17.79 years, 39 (69.6%) were males. Diabetes was the most common comorbidity (n 39, 69.6%). The majority of patients had chronic sinusitis (n 34,60.7%) otitis media (n 20, 35.7%) or head and neck surgery (n 18, 32.1%) within the preceding 2 years. The mean duration between onset of symptoms and presentation to healthcare facility was 12±13.96 weeks. The most common presenting symptom was headache (n 38, 68%). The majority of patients (n 34 ,59.6 %) had fungal organisms isolated from tissue culture. Cranial nerve palsies were present in 44 (77%) patients. Out of 56 patients, 22(39.2%) were lost to follow and overall mortality was high (n 11, 19.6%). Sepsis was found to be associated with increased mortality (p=0.008).

Conclusion: Skull base osteomyelitis was associated with significant morbidity and mortality, and posed significant diagnostic and therapeutic challenges.

Key Words: Magnetic resonance imaging, Skull base, Infections, Osteomyelitis, Mortality.

(JPMA 74: 1767; 2024) **DOI: https://doi.org/10.47391/JPMA.9604**

Introduction

Skull base osteomyelitis (SBO) is a relatively rare disease which is clinically associated with an increased risk of neurological and systemic complications. It is challenging for clinicians due to diagnostic difficulties, prolonged duration of treatment, serious morbidities and a high mortality rate. SBO is reported to affect both genders equally but is generally seen in the older age groups.[1,2] Predominantly, SBO involves sphenoidal and temporal bones. This is likely due to contiguous spread from local infection in the sinuses, the external/middle ear, the nasal cavity or the pharynx.[2,3] The main sources of infection are malignant otitis externa, sinusitis and chronic mastoid infection.[4] The other possible causes of infection are haematogenous spread from another infection in the body, like lung infection, meningitis or direct inoculation after trauma or surgery. Certain systemic diseases also predispose patients to SBO due to reduced bone vascularity, altered host defence, and changes in the course of illness. These include diabetes mellitus (DM), chronic kidney disease (CKD), hepatic failure, tobacco use, malignancies, small vessel diseases (SCDs), vasculitis and immunosuppression.[5]

The most common pathogen for bacterial SBO is *Pseudomonas aeruginosa*((P. *aeruginosa*), but other bacteria, like *Staphylococcus aureus (S. aureus*), *klebsiella* and *proteus species*, and *Mycobacterium chelonae*, a non-tuberculous mycobacterium, have been reported in the literature.[6] Fungi are responsible for a substantial percentage of SBO and include *Aspergillus species, Rhizopus, Zygomycetes* and *Scedosporium*.[2,7,8] SBO typically presents with severe otalgia, headaches, ear discharges and cranial neuropathies. Fever, frontal headache, photophobia, retro-orbital pain and focal neurological signs are the presentations associated with SBO involving the frontal bone.[9]

There are no specific diagnostic criteria available for SBO, and the diagnosis is usually made on a combination of clinical, radiological and laboratory findings. The treatment of SBO requires an extended duration of anti-microbial therapy, while surgical intervention is done in a few cases.[1]

The current study was planned to identify risk factors as well as clinical manifestations associated with SBO.

Materials and Methods

The retrospective study was conducted at the Aga Khan University Hospital (AKUH), Karachi, and comprised data from July 2013 to October 2020 related to adult patients who presented with SBO. After approval from the institutional ethics review board, data including

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Submission complete: 03-05-2023 **Review began:** 19-06-2023

Acceptance: 24-07-2024 **Review end:** 08-06-2024

demographic details, clinical characteristics, comorbidities, laboratory and radiological investigations, treatment, complications and outcomes was retrieved from hospital records using a structured proforma. Data of patients aged <18 years was excluded, and so was the case with those having incomplete data.

Magnetic resonance imaging (MRI) was performed in line with standard protocol, which included routine sagittal T2W, axial T2W and axial T1W without and with intravenous (IV) contrast. DWI and SWI sequences had also been performed. For the DWI sequences, (with TR / TE = 3700 / 109 ms, b = 1000 s/mm^2, slice thickness = 5 mm, slice number = 28, and matrix = 128 x 128) and generated ADC maps. For the transverse 3-dimensional (3D) SWI sequences, TR / TE = 49 / 40 ms, flip angle = 15°, slice thickness = 2 mm with 60 sections per slab, matrix = 224×256, 64 slices, and (integrated parallel acquisition technique (iPAT) acceleration factor = 2. The phase, magnitude (mag), minIP, and SWI images were uploaded and made available on a picture archiving and communication (PACS) system (Rogan). In addition, high-resolution thin cuts were performed from the skull base. MR imaging was performed on 1.5 Siemens Avanto and 3T Toshiba Vintage. Some patients also underwent CT imaging on 164 and 640 Toshiba slicer scans.

Data was analysed using SPSS 16. Data was expressed as frequencies and percentages, mean and standard deviation, as appropriate. Univariable and multivariable logistic regression models were used to identify the risk factors associated with mortality in SBO patients. The difference between survivors and non-survivors was assessed using chi-square test or Fisher exact test, as appropriate. Two-sided $p<0.05$ was considered significant.

Results

Of the 56 patients with a mean age of 58.12±17.79 years, 39 (69.6%) were males. Diabetes was the most common comorbidity (n 39, 69.6%). The majority of patients had chronic sinusitis (n 34,60.7%) otitis media (n 20, 35.7%) or head and neck surgery (n 18, 32.1%) within the preceding 2 years. The mean duration between onset of symptoms and presentation to healthcare facility was 12±13.96 weeks. The most common presenting symptom was headache (n 38, 68%). The majority of patients (n 34 ,59.6%) had fungal organisms isolated from tissue culture. Cranial nerve palsies were present in 44 (77%) patients. Out of 56 patients, 22(39.2%) were lost to follow and overall mortality was high (n 11, 19.6%). Sepsis was found to be associated with increased mortality (p=0.008).

Out of the 56 patients with mean age 58.12±17.79 years, 39 (69.6%) were males. DM was the most common comorbidity (n 39, 69.6%). The mean duration between the onset of symptoms and presentation to the healthcare facility was 12±13.96 weeks. The most common presenting symptom was headache (n 38,68%) (Table 1). Chronic sinusitis (n 22,39.3%) and chronic otitis media (n 20,35.7%) were present in the majority of the patients, and 12 (21%) patients had head and neck surgeries in the preceding 2 years. (Table 1)

Table-1: Baseline characteristics of patients with skull base osteomyelitis (SBO).

	n (%), mean (+/-SD)
Age	59.12 (+/- 16.12)
Comorbidities	
DM	39(39.6)
HTN	35(62.5)
IHD	17(30.4)
Asthma	2(3.6)
CLD	4(7)
CKD	10(17.9)
TB	2(3.6)
Malignancies	2(3.5)
CVA	3(5.3)
Duration of illness	12 (+/- 13.9) weeks
Clinical Features	
Fever	22(39.3)
Earache	17(30.4)
Ear discharge	10(17.9)
Facial pain	14(25)
Hearing loss	17(30.4)
Vomiting	8(14.3)
Peri-orbital swelling	10(17.9)
Loss of smell	1(1.8)
Loss of taste	1(1.8)
Dysphagia	9(16)
Dysphonia	8(14)
Headache	38(68)
Altered metal status	18(32)
Facial Asymmetry	23(41.1)
Seizure	4(7)

DM: Diabetes mellitus, HTN: Hypertension, IHD: Ischaemic heart disease, CLD: Chronic liver disease, CKD: Chronic kidney disease, TB: Tuberculosis, CVA: Cerebral vascular accident.

Mean C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and procalcitonin (PCT) levels at presentation were 13.4±16.69, 74.68±38.3 and 3.17±5.8, respectively. Among 42(75%) patients in whom serum fungal markers were available, mean beta D glucan (BDG) was 170±184.96 and mean serum galactomannan (GALA) was 0.96±1.69. The mean glycosylated haemoglobin (HbA1c) level was 7.89±1.60.

Pus specimens for microbiological evaluation were

Table-2: Radiological investigations, treatment, complications and outcomes.

	n (%), mean (+/-SD)
CT brain	56 (100)
Temporal bone involvement	30(52.6)
Orbit	20(35.1)
Ethmoid sinus	27(47.4)
Maxillary sinus	25(43.9)
Sphenoid	29(50.9)
MRI brain	
Diffuse involvement	56(98.2)
Focal involvement	1(1.8)
Meningeal involvement	28(49.1)
Venous sinus involved.	17 (29.8)
Ischaemic stroke	19 (33.3)
Treatment	
Steroids	3(5.3)
Antibiotics	36(64)
Antifungal	33(60)
Anti-tuberculous therapy	7(12.5)
Therapeutic Surgical Intervention	22(39.2)
Complications	
Stroke	26(46.4)
Sepsis	18(32.1)
Cerebral venous sinuses thrombosis	14(25)
Meningitis	31 (55.4)
SAH	1(1.8)
Cranial nerve involvement	44 (77)
Lost to follow up	22 (39.2)

DM: Diabetes mellitus, HTN: Hypertension, IHD: Ischaemic heart disease, CLD: Chronic liver disease, CKD: Chronic kidney disease, TB: Tuberculosis, CVA: Cerebral vascular accident.

obtained in 22(39.3%) patients from nasal sinuses, middle and external ear cavities and/ or infected foci at the time

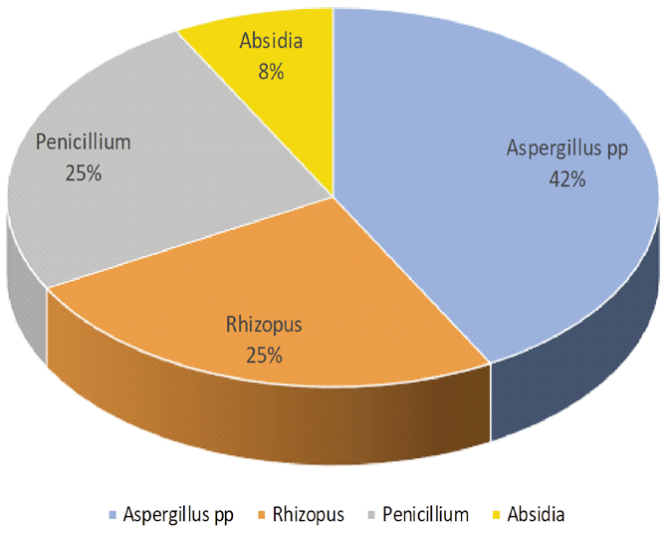

Figure-1: Fungal pathogens identified in skull base osteomyelitis (SBO) patients.

Table-3: Comparison between survivor and non-survivor data.

n 34	Survivor (23)	Non-survivors (11)	p Value
Age	56.7 ± 20.7	54.9 ± 14.9	0.76
Gender			
Male	15(65.2)	8(72.7)	1.00*
Female	8 (34.8)	3(27.3	
Asthma	0 (0.0)	2 (18.2)	0.09*
DM	14(60.9)	9 (81.8)	0.27*
HTN	14 (60.9)	7(63.6)	1.00*
IHD	7(30.4)	1(9.1)	0.23*
CLD	1(4.3)	2(18.2)	0.24*
CKD	3 (13)	4 (36.4)	0.18*
Malignancy	0 (0.0)	1 (9.1)	0.32*
Chronic otitis externa	20 (87.0)	11 (100.0)	0.53*
Chronic otitis media	14 (60.9)	9 (81.8)	0.27*
Chronic sinusitis	15 (65.2)	3 (27.3)	0.06*
Surgical intervention	16 (69.6)	8 (72.3)	1.00*
Complication			
stroke	15 (65.2)	1 (9.1)	0.0023*
sepsis	20 (87.0)	2 (18.2)	<0.001*
CVST	18 (78.3)	9 (81.8)	1.00*
Meningitis	15 (65.2)	1 (9.1)	0.003*
SAH	0 (0.0)	1(9.1)	0.32*
Cranial Nerve	8 (34.8)	1 (9.1)	0.21*
Duration, illness- admission Symptoms			
Fever	9(39.1)	7 (63.6)	0.27*
Earache	9(39.1)	2(18.2)	0.27*
Ear discharge	3(13)	0 (0.0)	0.53*
Facial pain	6(26.1)	1(9.1)	0.38*
Hearing loss	8(34.8)	2(18.2)	0.44*
Peri-orbital swelling	4(17.4)	2(18.2)	1.00*
Vomiting	5(21.7)	1(9.1)	0.64*
Dysphonia	2(8.7)	2(18.2)	0.58*
Dysphagia	3(13.0)	2(18.2)	1.00*
Headache	19(82.6)	6(54.5)	0.11*
Alt conscious level	19 (82.6)	2 (18.2)	0.001*
Facial Asymmetry	5(21.7)	4(36.4)	0.42*
Seizure	1(4.3)	2(18.2)	0.24*

*Fischer exact's p-value

DM: Diabetes mellitus, HTN: Hypertension, IHD: Ischaemic heart disease, CLD: Chronic liver disease, CKD: Chronic kidney disease, CVST: Cerebral venous sinuses thrombosis, SAH: Subarachnoid haemorrhage.

of surgical intervention. The microorganisms isolated were *P. aeruginosa* in 5(22.7%) patients, *methicillin-resistant S. aureus* (MRSA) in 4(18.2%), *methicillin-sensitive S. aureus* (MSSA) 1(4.5%), A*spergillus species* and *mucoraceous mould* in 5(22.7%) patients. Tissue culture and histopathology data was available for 24(43%) patients, and microorganisms were isolated in 16(66.7%) of them. Majority of patients (n 34,59.6 %) had fungal organisms isolated from tissue culture (Figure 1). Histopathology results showed chronic nonspecific inflammation in 21(37.5%) patients. CT head and brain were available in all 56(100%) patients, and showed predominant involvement of temporal bone (n 30,52.6%).

Table-4: Factors related to risk of mortality.

Complication	Survivor (n=23)	Non survival (n=11)	Univariate		Multivariable	
			OR(95% CI)	p-value	OR(95% CI)	p-value
Stroke	15 (65.2)	1 (9.1)	18.7 (2.0 – 173.9)	0.01	-	-
Sepsis	20 (87.0)	2 (18.2)	30.0 (4.2 – 211.8)	0.001	26.8 (2.3 – 307.6)	0.008
Meningitis	15 (65.2)	1 (9.1)	18.7 (2.0 – 173.9)	0.01	-	-
Chronic sinusitis	15 (65.2)	3 (27.3)	5.0 (1.0 – 24.3)	0.05	-	-
Altered conscious level	19 (82.6)	2 (18.2)	21.4 (3.3 – 139.2)	0.001	18.9 (1.6 – 219.6)	0.019

OR: Odds ratio, CI: Confidence interval.

A total of 36(64.3%) patients received either antibiotics or antifungal agents alone, and15(26.8%) patients received combination therapy. Empirical anti-TB therapy (ATT) was given to 7(12.5 %) patients. The mean duration of antibiotics was 6.68±5.52 weeks and antifungals were given for 23±26.1 weeks.

Surgical intervention was done in 22(39.3%) cases, and 12 out of 22 (54.5%) underwent functional endoscopic sinus surgery (FESS). The other procedures done included debridement and biopsy of the skull base, exploration of mastoid, mastoidectomy, or drainage of intracranial/nasopharyngeal abscesses.

The majority of the patients (n 44,77%) had cranial nerve (CN) paresis at the time of admission, and the most commonly affected was the 7th CN (n 30,68.2%). Other complications were meningitis, ischemic stroke, sepsis and cerebral venous sinuses thrombosis (CVST) (Table 2).

The course of illness and disease outcomes up to 2 years were not available for 22(39.2%) as they had been lost to follow-up. The overall mortality was 19.6% and 16(47%) patients had 6-month survival.

Subgroup analysis between survivors and non-survivors univariable logistic regression showed that frequent complications in the non-survivor group were sepsis, stroke, altered consciousness level and meningitis (Table 3), but multivariable logistic regression showed that sepsis and altered consciousness level were the only elements significantly associated with higher mortality (Table 4).

Discussion

SBO is common in the elderly population, particularly among the male gender, and is frequently observed in patients with immunocompromised conditions, like DM.[7,10-12] The current study corroborated these observations. Since both ageing and DM are associated with abnormalities of small blood vessels, it has been postulated that microangiopathy in the ear canal predisposes elderly diabetics to SBO.[13] Predisposing conditions for SBO could be haematogenous dissemination, the contiguous spread of infections, like chronic sinusitis, otitis externa, mastoiditis, trauma or post-surgical intervention in the head and neck region.[14] Prior to surgical intervention, chronic sinusitis and chronic otitis media were found as risk factors for SBO among the current study population as well.

SBO poses a diagnostic challenge due to its non-specific clinical manifestation, as the majority of patients present with headache, fever, earache and CN neuropathies.[15] Multiple CN palsies occur with invasion of the stylomastoid foramen, jugular foramen, and hypoglossal canal, and are among the frequently observed complications in SBO patients. It is associated with bad outcomes with residual neurological deficits, and is an indication of disease progression.[1] The facial nerve is the most commonly affected CN in published studies,[2,16] and the current findings endorsed the assertion. Facial nerve paralysis is traditionally claimed to be a poor prognostic indicator with higher mortality rates.[17]

Computed tomography (CT), MRI and nuclear imaging are the modalities utilised for the diagnosis of SBO, and play a critical role in evaluating bone involvement, extension of the disease process and presence of complications. Radiological features can help distinguish between bacterial and fungal infections. For example, fungal infection-related skull base osteomyelitis (SBO) is more likely when the paranasal sinuses are the initial site of infection, and there is orbital, vascular, and intracranial extension along with permeative bone destruction. Moreover, on T2-weighted MRI sequences and unenhanced CT scans, regions affected by fungal infections in SBO exhibit hypointense and hyperdense signals respectively. However, the requirement for microbiological evidence to reach a definitive diagnosis cannot be overlooked.[18-20]

The causative organism often remains unidentified in SBO patients, and is primarily attributable to factors such as non-specific clinical features leading to diagnostic delay, prolonged empirical antimicrobial therapy, and challenges in sample acquisition. Das et al. reported positive cultures in 61% patients, and Sokolowski et al. reported up to 30% positive cultures.[1, 21] *P. aeruginosa* is the most common pathogen associated with SBO, especially secondary to ear infections, while other causative

organisms include *S. aureus, klebsiella species*, coagulase-negative staphylococci and fungi. The current findings were consistent with literature.[21-23] A similar microbiological profile was reported by another study done in Pakistan.[12] Fungal SBO is often associated with either contiguous ear infection or preceding sinusitis, mostly common among patients with immunosuppressed status, but has also been reported in immunocompetent persons.[24] The type of fungus isolated may be related to the local epidemiology and environment, with *Aspergillus species* being the most common isolated fungus, followed by zygomycetes. The current findings were consistent with prior studies.[7,21]

Substantial morbidities associated with SBO have been reported in the literature due to the involvement of the critical area of the skull base. CN neuropathies, meningitis, ischaemic stroke and CVST were common complications of SBO in the current study, which was a finding similar to those reported earlier.[21,25-27]

Cerebral arteries involvement in SBO is a rare complication and could be due to arterial stenosis secondary to inflammatory or infectious arteritis, external compression and/or septic emboli.[28] While ischaemic stroke may manifest as a silent radiological finding, it can be a major clinical feature of SBO at the time of presentation to healthcare facilities[29,30]. Although rare, the majority of patients developed ischaemic stroke, which has been reported earlier as well.[21]

CVST and meningitis are also important complications of SBO.[2,21] There is a spread of infection to meninges and central venous sinuses from the surrounding infective foci, leading to septic thrombophlebitis of cerebral venous sinuses. Prolonged antibiotics and source control (surgical debridement) are the mainstay of treatment. The role of anticoagulation and its effect on outcome in the case of CVST associated with SBO is not documented in the literature.[31,32] In general, anticoagulation can be safely given in septic CVST cases if there is no contraindication to anticoagulation.[33,34]

Management of SBO is complex, and involves administering culture-directed antimicrobials over an extended period, typically 3-6 months, or until complete radiological and clinical recovery is achieved. Surgical debridement aids in treatment by decreasing microbiological load and enhancing antimicrobial effectiveness, but concrete guidelines for surgical management are still unavailable.[14,35] The mortality associated with SBO has decreased due to advances in diagnostic modalities and early commencement of appropriate therapy, but is still high in patients with severe complications, suboptimal duration of therapy, and poor source control, intracranial extension and extensive disease.[1,2,3,7,36] The high mortality noted in the current study could have been due to delayed presentation to healthcare facilities, diagnostic delays and the presence of severe complications, like sepsis, stroke and meningitis. It is, therefore, vital to diagnose and start therapy early in the course of illness to prevent the progression of the disease, and thereby prevent fatal complications.

The current study has limitations as it had a retrospective design, and a small sample size. A significant number of patients did not complete the follow-up which affected the interpretation of outcomes. Besides, the data related to a single centre, and, as such, the findings cannot be generalised. Larger prospective multicentre studies are needed to validate the current findings.

Conclusion

Cranial neuropathies, sepsis, CVST, ischaemic stroke and meningitis were common complications seen in SBO patients. Early recognition and appropriate management of this challenging condition is crucial to improve clinical outcomes.

Disclaimer: None.

Conflict of Interest: None.

Source of Funding: None.

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IK: Study design, data collection, analysis, writing and editing.
DK: Data collection, analysis and writing.
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FM: Data collection, entry and writing.