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ORIGINAL RESEARCH

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Skull base osteomyelitis in patients with head and neck cancer: Diagnosis, management, and outcomes in a case series of 23 patients

Mary M. Czech MD, MS[1] | Peter H. Hwang MD[2] | Alexander Dimitrios Colevas MD[2,3] | Nancy Fischbein MD[2,4,5,6] | Dora Y. Ho MD, PhD[1]

[1]Division of Infectious Diseases and Geographic Medicine, Department of Medicine, Stanford University School of Medicine, Stanford, California, USA

[2]Department of Otolaryngology—Head and Neck Surgery, Stanford University School of Medicine, Stanford, California, USA

[3]Division of Medical Oncology, Department of Medicine, Stanford University School of Medicine, Stanford, California, USA

[4]Department of Radiology, Stanford University School of Medicine, Stanford, California, USA

[5]Department of Neurology and Neurological Sciences, Stanford University School of Medicine, Stanford, California, USA

[6]Department of Neurosurgery, Stanford University School of Medicine, Stanford, California, USA

Correspondence
Mary M. Czech, Division of Infectious Diseases and Geographic Medicine, Department of Medicine, Stanford University School of Medicine, 300 Pasteur Drive, Lane Building, L134 MC:5107, Stanford, CA 94305-5107, USA.
Email: mmc16@stanford.edu

Abstract

Background: Skull base osteomyelitis (SBO) is an infection of the central cranial bones, most commonly resulting from contiguous spread of infection from adjacent head and neck structures. SBO is a well-recognized complication of treatment of head and neck cancer (HNC) that results in significant morbidity.

Methods: We conducted a retrospective chart review of HNC patients diagnosed with SBO.

Results: SBO was commonly diagnosed with nasal endoscopy showing mucosal breakdown between the naso/oropharynx and skull base and with characteristic changes on CT/MRI. Culture data were often polymicrobial, inclusive of naso/oropharyngeal flora, but half of the patients additionally had antibiotic-resistant or atypical pathogens. The mean duration of antimicrobial therapy was 117 +/− 94 days. Recurrent SBO was found in half of the patients, associated with *Pseudomonas aeruginosa* and with persistent defects in the mucosa abutting the skull base.

Conclusions: Diagnosis and management of SBO in HNC patients are challenging. Recommendations to aid in clinical care are proposed.

Level of evidence: 4, case series.

KEYWORDS
head and neck cancer, nasopharyngeal carcinoma, osteoradionecrosis, skull base osteomyelitis

1 | INTRODUCTION

Skull base osteomyelitis (SBO) is an infection of the central cranial bones, involving parts of the sphenoid, occipital, and/or temporal bones. These infections most commonly result from contiguous extension of infection from the ear, paranasal sinuses, and/or naso-oropharyngeal cavity.[1,2] SBO is classically and most commonly described in patients with uncontrolled diabetes who have otitis externa complicated by temporal bone osteomyelitis with extension into the central skull base.[3,4] However, SBO is increasingly being described in other patient populations.

Our clinical experience demonstrates a significant number of SBO cases occurring in patients with head and neck cancer (HNC), though there are only limited case reports describing SBO in HNC patients.[5,6] Patients with HNC have underlying anatomic abnormalities resulting from tumor destruction, surgical intervention(s), and/or

chemo-radiation. These abnormalities predispose patients to mucosal barrier breakdown and infections of the head and neck (i.e., otitis, paranasal sinusitis, and infections of the oropharyngeal cavity[7–10]), which can lead to SBO. These unique host characteristics of patients with HNC warrant further investigation regarding SBO diagnosis and management in this population.

There are currently no accepted guidelines for the diagnosis or management of SBO in any patient population. Specific to HNC patients, diagnosis of SBO is often challenging given the overlap of clinical symptoms and radiographic findings with residual or recurrent malignancy and/or treatment-related osteoradionecrosis.[5,6,11,12] Diagnosis is further hindered by procedural difficulties with accessing the skull base to obtain specimens for pathology and microbiology.[5,6] Treatment of SBO remains an even more challenging clinical dilemma given limited opportunities for surgical source control, an often-unknown pathogen, and an unknown optimal duration of antimicrobial therapy.

To our knowledge, this is the largest case series to describe SBO in patients with HNC. The purpose of our study is to investigate the diagnosis, treatment, and clinical outcomes of SBO in patients with HNC.

2 | METHODS

We conducted a retrospective chart review of HNC patients diagnosed with SBO and managed at our tertiary university-affiliated medical center in Northern California from 2001 to 2020. This study was approved by the Stanford University Institutional Board Review. We used a database of de-identified patient data to search for cases managed at our medical center in adults ≥18 years of age with clinical documents and/or radiology reports containing ("skull base osteomyelitis" or/and "osteoradionecrosis") AND ("head and neck cancer" or "head and neck malignancy"). These search terms identified a total of 316 patients, and 23 cases were further included for analysis based on the following criteria:

1. Medical history inclusive of head and neck cancer; AND
2. Radiographic imaging showing an inflammatory process at the skull base involving the central parts of the sphenoid, occipital, and/or temporal bones; AND
3. Nasal endoscopy showing direct visualization of mucosal breakdown between the naso/oropharynx and the skull base; OR clinical and/or radiographic evidence for otic, paranasal, or odontogenic infection with suspicion for contiguous spread of infection to the skull base; AND
4. Treating providers prescribed systemic antimicrobials with the intention of treating SBO.

For patients with multiple episodes of SBO, data were collected for the first episode of SBO. Any patient who was retreated for SBO with systemic antimicrobials during follow up based on clinical symptoms, nasal endoscopy, and/or imaging was reported to have *recurrent* infection. Any recurrent infection that occurred within 9 months of discontinuing antimicrobial therapy would be classified as *relapsed* infection. Patients were deemed to have SBO *cure* if the presenting clinical symptoms of infection remained quiescent, and if patients did not receive additional systemic antimicrobials for the purposes of treating SBO during the period of follow up.

3 | RESULTS

3.1 | Patient characteristics

The demographics of the study patients are largely reflective of the population of patients with HNC. The mean age of patients at the time of SBO diagnosis was 62 years (+/− standard deviation [SD] 11 years). The majority of patients were male (17/23, 73.9%), Asian (13/23, 56.5%), and had nasopharyngeal carcinoma (18/23, 78.3%). A substantial portion of patients (8/23, 34.8%) had T4 staging at the time of cancer diagnosis (Table 1).

Patients were diagnosed with SBO a median of 9.3 years (Interquartile Range, IQR 7.9 years) following their initial diagnosis of HNC. The majority of patients were without evidence of malignancy at the time of the SBO diagnosis (17/23, 73.9%) (Table 1). Thereby, diagnosis of SBO was a median of 8.4 years (IQR 10.9 years) following the last cycle of chemotherapy, and 7.3 years (IQR 8.9 years) following the last dose of radiation therapy. Ten of 23 patients had surgical intervention for management of HNC, and the last surgery occurred a median of 1.7 years (IQR 3.8 years) prior to the diagnosis of SBO. Osteoradionecrosis seems to be a major risk factor for the development of SBO. Nearly all patients diagnosed with SBO received prior radiation therapy (22/23, 95.7%), and the majority of the patients had known osteoradionecrosis at the time of SBO diagnosis (17/23, 73.9%) (Table 1).

3.2 | Diagnosis of skull base osteomyelitis

For assistance with diagnosis and management of SBO, Infectious Diseases consultants were involved in the care of 17/23 (73.9%) patients.

At the time of SBO diagnosis, the most common presenting clinical symptoms were facial/neck pain (occurring in 11/23, 47.8%%) and headache (10/23, 43.5%), and only a minority of patients developed fever (4/23, 17.4%). Other presenting symptoms included otalgia (5/23, 21.7%), hearing loss (3/23, 13.0%), halitosis (3/23, 13.0%), increased nasal/oral mucosal secretions (3/23, 13.0%), weight loss (3/23, 13.0%), and otorrhea (2/23, 8.7%).

MRI was the most commonly used imaging modality to aid in the diagnose of SBO (15/23, 65.2%). Representative MR images are shown in Figure 1. CT and nuclear medicine studies were less commonly employed—CT in 21.7% (5/23), positron emission tomography (PET) in 4.3% (1/23), and tagged white blood cells scans in 8.7% (2/23) patients. The majority of patients had nasal endoscopy showing

TABLE 1 Patient characteristics

Patient ID	Age (years)/ sex/race	Cancer/comorbidities	TNM Staging at time of cancer diagnosis	Total Gy to primary tumor bed	Status of HNC at time of SBO dx	Time from HNC dx to SBO dx, yr	Time from last surgery to SBO dx, yr/last surgical intervention performed	Time from last chemo to SBO dx, yr	Time from last radiation to SBO dx, yr
1	60/M/White	NPC/ORN	T1N0M0	70	NED	1.1	0.5/Endoscopic resection of tumor in nasopharynx	NA	0.8
2	72/M/Asian	NPC/ORN/DM (A1C 8.2%)	T1N2M0	Received unknown Gy	NED	18	NA	17.7	17.7
3	70/F/Asian	NPC/ORN	T4N2c M0	Received unknown Gy	NED	14.3	NA	13.3	13.3
4	63/M/Asian	NPC	T2N0M0	Received unknown Gy	Active	7.6	0.2/Transpalatal nasopharyngectomy	NA	6.1
5	52/M/Asian	NPC/ORN/recurrent sinusitis	T4N0M0	76	NED	11.5	NA	11.3	11.3
6	62/M/Asian	NPC/ORN	T4N2M0	75	NED	18	NA	17.5	17.7
7	60/F/Asian	NPC/ORN	T2aN0M0	93	NED	10.1	NA	NA	9.8
8	43/M/Asian	NPC/ORN	T4N0M0	Received unknown Gy	NED	10.3	2.8/Extensive fulguration of nasopharynx	1.8	5.5
9	60/M/White	NPC/ORN	T2N1M0	66	NED	12	NA	11.5	10.8
10	66/F/Asian	NPC/ORN	T3N1M0	70	NED	9.3	NA	8.4	8.4
11	77/F/Asian	NPC/ORN	T1N0M0	122	NED	7.9	4.6/Neck dissection	4.0	3.8
12	69/M/Asian	NPC/ORN	T4N0M0	74	NED	12.6	NA	12.1	12.3
13	27/M/White	NPC/ORN	T3N3M0	68	NED	12.3	12.3/Tonsillectomy and lymph node dissection	11.8	12.0
14	52/M/Asian	NPC/DM (A1C unknown)	T4N2M0	74	Distant metastasis	1.8	1.8/Sinus surgery, not otherwise specified	0.5	1.5
15	61/M/White	Sinus squamous cell carcinoma/ORN	Stage group IV, TNM not specified	Received unknown Gy	NED	11.9	11.8/Ethmoidectomy, sphenoidectomy, maxillary antrostomy	11.7	11.6
16	60/M/White	NPC/ORN	Not documented	Received unknown Gy	NED	22.2	NA	19.3	19.3
17	76/M/White	NUT carcinoma/ chronic middle ear effusion	T4N1M0	66	NED	1.7	1.6/Sinonasal mass resection, R eye exenteration, R neck dissection and flap reconstruction	1.4	1.4
18	59/M/Black	Tonsil squamous cell carcinoma/ORN	T4N2M0	70	Active	4.9	0.3/Endoscopic resection of tumor at skull base	0.0	4.3
19	71/F/Unknown	NPC/ORN	Stage group IIB, TNM not specified	188	NED	6.1	NA	4.5	1.3
20	78/M/White	Parotid adenocarcinoma	T2N2M0	No XRT	Active	0.1	0.1/Excisions of parotid tumor, neck dissection, flap reconstruction	NA	NA

(Continues)

TABLE 1 (Continued)

Patient ID	Age (years)/ sex/race	Cancer/comorbidities	TNM Staging at time of cancer diagnosis	Total Gy to primary tumor bed	Status of HNC at time of SBO dx	Time from HNC dx to SBO dx, yr	Time from last surgery to SBO dx, yr/last surgical intervention performed	Time from last chemo to SBO dx, yr	Time from last radiation to SBO dx, yr
21	70 yo/M/Asian	Nonsmall cell lung cancer with metastasis to parotid extending to skull base/DM (A1C 8.0%)	Stage group IV, TNM not specified	40	Distant metastasis	3.7	NA	0.7	2.8
22	63 yo/M/White	NPC	T3N1M0	70	NED	0.8	NA	0.2	0.3
23	59 yo/F/Asian	NPC/ORN	T1N0M0	105	Active	6.3	NA	0.0	3.9

Abbreviations: DM, diabetes mellitus; Dx, diagnosis; F, female; HNC, head and neck cancer; M, male; NA, not applicable; NED, no evidence of disease; NPC, nasopharyngeal carcinoma; ORN, osteoradionecrosis; SBO, skull base osteomyelitis; yr, year.

breakdown of the mucosal barrier between the naso/oropharynx and skull base (17/23, 73.9%). The remaining patients (6/23, 26.1%) had other identified infections in the head/neck, for which contiguous spread of infection was believed to result in SBO (Table 2).

Specimens for pathology were obtained in nine patients. Two specimens had nondiagnostic pathology evaluation. Seven specimens showed inflammatory cells, but only four of these cases had specimens that contained bone. In two patients, pathology identified gram-positive filamentous bacilli with sulfur granules suggestive of *Actinomyces*, which did not grow in cultures (Table 2).

Specimens for microbiology were obtained in 18/23 (78.3%) patients (Table 2). Because nasal endoscopy is minimally invasive, it was the most commonly used means of obtaining specimens (13/18 patients) from the site of breakdown between the naso/oropharynx and skull base (Table 2). In the remaining patients with microbiology data, three patients had cultures obtained from more invasive operative interventions, and two patients had cultures obtained from superficial sites of purulence (one from purulent ear drainage, and another from purulent drainage at a retro-auricular surgical site). Although cultures obtained from superficial sources may not reflect the pathogens causing SBO, organisms recovered from these cultures were frequently targeted as part of the antimicrobial therapy.

Based on culture data, the majority of the infections were polymicrobial (16/18, 88.9% patients), mostly reflective of naso/oropharyngeal flora, such as *Streptococci*, *Staphylococci*, and anaerobes (Table 2). Gram-negative bacteria resistant to antibiotics used for typical coverage of nasopharyngeal flora were isolated from cultures in seven patients (five of which had *Pseudomonas aeruginosa*), and MRSA was isolated from culture in only one patient (Table 2). Only five patients had cultures suggestive of fungal involvement—four patients with suspected *Candida* spp. and one patient with *Aspergillus* spp.

3.3 | Treatment of skull base osteomyelitis

When culture data were available, antimicrobial therapy targeted isolated organisms, and usually included coverage of naso/oropharyngeal flora (Table 3). The majority of patients received an intravenous antimicrobial (19/23, 82.6%) for initial therapy, and 10/19 (52.6%) patients ultimately stepped down to oral antimicrobials to complete therapy (Table 3). The total duration of antimicrobial therapy was highly variable—ranging 28–387 days, with a mean of 117 days (+/− SD 94 days), and median of 105 days (IQR 116 days) (Table 3). In this cohort, one patient was prescribed lifelong antimicrobial therapy for suppression given persistently exposed skull base bone to the nasopharynx; this patient was excluded from the analysis of total duration of antimicrobial therapy. The patient with *Aspergillus* spp., and two patients with *Candida* spp. received systemic antifungal therapy during the treatment course.

As an adjunct to antimicrobial therapy, a minority of patients (7/23, 30.4%) underwent surgical debridement as an effort to achieve source control, and only one patient underwent soft tissue coverage of exposed bone (Table 3). Additionally, a minority of patients (5/23,

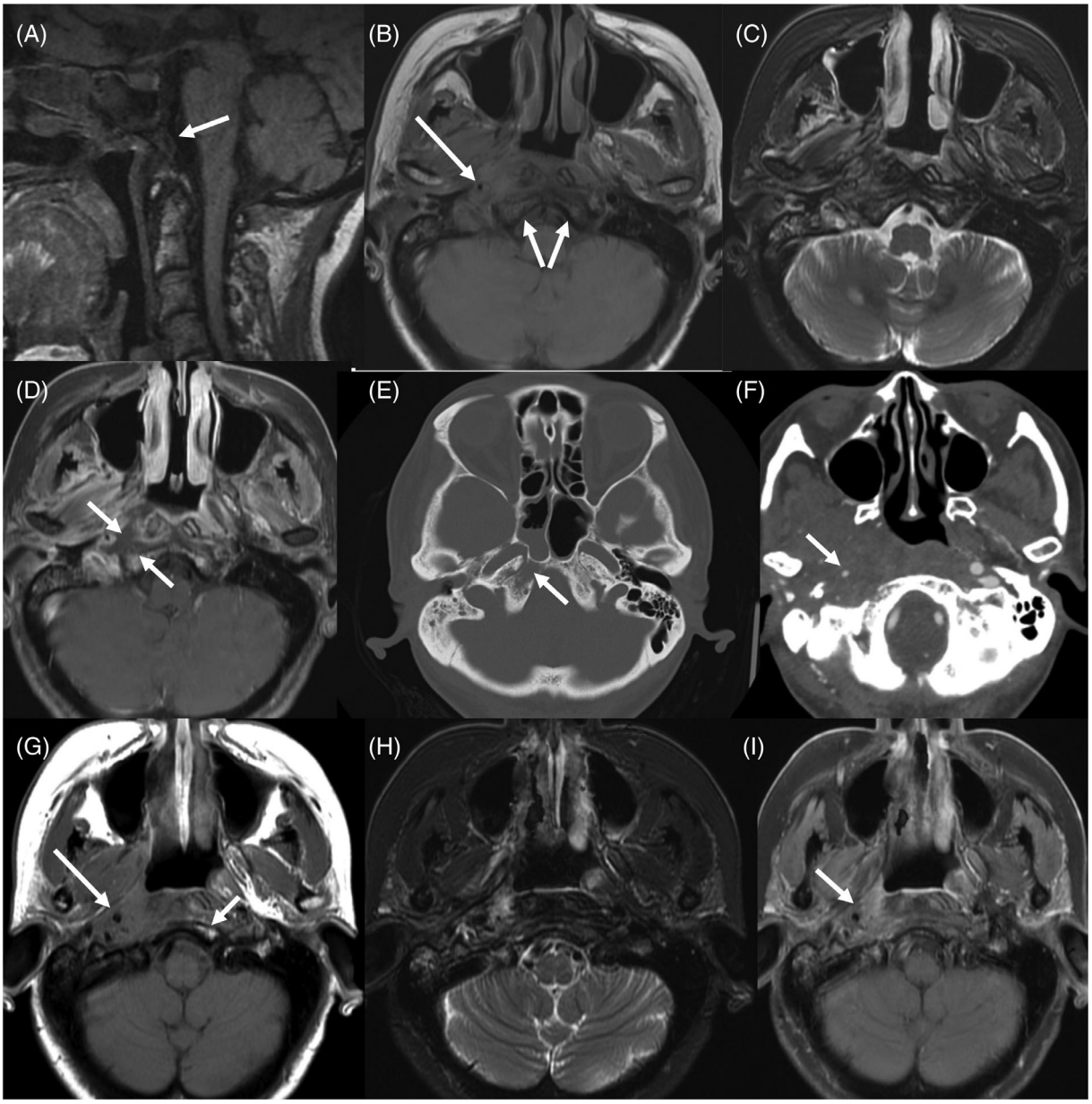

FIGURE 1 Representative MR images. 59-year-old female with nasopharyngeal carcinoma, treated with chemoradiation complicated by osteoradionecrosis, presented with worsening right ear and jaw pain, followed by otalgia and otorrhea, found to have skull base osteomyelitis (patient #23). (A) Sagittal T1-weighted image shows diffuse marrow hypointensity in the clivus (white arrow), which can be seen with tumor, osteoradionecrosis, and/or osteomyelitis. (B) Axial T1-weighted image shows diffuse loss of fatty marrow signal in the clivus (short arrows), as well as diffuse soft tissue thickening involving prevertebral, retropharyngeal, and parapharyngeal spaces, more so on the right. There is also marked narrowing of the flow void of the right internal carotid artery (long arrow). These findings are all suggestive of skull base osteomyelitis with adjacent soft tissue abnormalities. (C) Axial T2-weighted image with fat suppression also shows diffuse soft tissue and osseous signal abnormality without a focal mass, a finding that also supports infection rather than tumor recurrence. (D) Axial T1-weighted image, post gadolinium and with fat suppression, shows irregular nonenhancement consistent with infection and necrosis in the preclival soft tissues, again consistent with infection and radiation necrosis, which often go hand in hand. (E) Axial CT slice in bone algorithm shows focal erosion of the right side of the clivus (arrow), as well as fluid in the right sphenoid sinus and in the right mastoid and middle ear. (F) Axial image from a CT angiogram shows marked narrowing of the right internal carotid artery (arrow) as well as again demonstrating diffuse thickening of the preclival soft tissues and subtle right clival erosion. (G) Axial T1-weighted image from a follow up MR obtained almost 2 years later shows marked improvement in prevertebral soft tissue thickening, clival marrow (short arrow indicates fatty marrow signal in the left clivus), and improvement in the caliber of the right internal carotid artery (long arrow). (H) Axial T2-weighted image with fat suppression shows near resolution of the previously seen diffuse soft tissue thickening and edema. (I) Axial T1-weighted image, post gadolinium and with fat suppression, shows resolution of the areas of previously identified soft tissue necrosis. Only mild residual enhancing tissue remains (arrow), which is nonspecific and may represent granulation tissue, fibrosis, and scar. Though the presence of residual viable tumor is difficult to exclude, there are no findings to specifically point to tumor recurrence or active infection

TABLE 2 Culture data

Patient ID	Confirmed or suspected source for SBO	Culture data obtained	Source of culture data	Culture result	Pathology obtained/result
1	Mucosal breakdown between pharynx and skull base	Yes	Nasal endoscopy	Normal nasopharyngeal flora	No
2	Mucosal breakdown between pharynx and skull base	Yes	Operative debridement	*Streptococcus anginosus*, *Enterococcus faecalis*, *Klebsiella pneumoniae*, *Corynebacterium amyculatum*, mixed anaerobes	Yes, contained bone/ showing inflammatory cells
3	Mucosal breakdown between pharynx and skull base	Yes	Nasal endoscopy	MSSA, *Enterobacter cloacae*, *Serratia marcescens*, *Morganella morganii*, *Prevotella bivia*	Yes, no bone/ showing inflammatory cells
4	Mucosal breakdown between pharynx and skull base	No	NA	NA	No
5	Chronic sinusitis/mucosal breakdown between pharynx and skull base	Yes	Operative debridement	MSSA, Group B Streptococcus, *Enterobacter cloacae*, *Pseudomonas aeruginosa*, *Candida* spp.	Yes, no bone/ showing inflammatory cells
6	Mucosal breakdown between pharynx and skull base	Yes	Nasal endoscopy	*Streptococcus anginosus*, *Klebsiella pneumoniae*	No
7	Sinusitis/mucosal breakdown between pharynx and skull base	Yes	Nasal endoscopy	Normal flora	No
8	Mucosal breakdown between pharynx and skull base	Yes	Operative debridement	Beta-hemolytic Streptococcus (Pathology consistent with Actinomyces)	Yes, contained bone/ showing inflammatory cells
9	Mucosal breakdown between pharynx and skull base	No	NA	NA	No
10	Mucosal breakdown between pharynx and skull base	Yes	Nasal endoscopy	*E. coli*, normal flora; subsequent operative cultures 3 months later in treatment showing *Candida* spp.	No
11	Mucosal breakdown in sphenoethmoid recess and between pharynx and skull base	Yes	Nasal endoscopy	MSSA, *Streptococcus anginosus*, normal flora (Pathology consistent with Actinomyces)	Yes, no bone/ showing inflammatory cells
12	Mucosal breakdown between sphenoid sinus and skull base with abscess in sinus	Yes	Nasal endoscopy	MSSA; Gram stain showed polymicrobial flora with GPC/GNR/GPR	Yes, contained bone/ showing inflammatory cells
13	Mucosal breakdown between pharynx and skull base	Yes	Nasal endoscopy	MSSA; Gram stain showed polymicrobial flora with GPC/GNR/budding yeast	Yes, no bone/ no evaluation for inflammation
14	Chronic sinusitis	No	NA	NA	No
15	Mucosal breakdown between pharynx and skull base	Yes	Nasal endoscopy	MSSA, *Enterobacter aerogenes*	No
16	Infection of masticator space	Yes	Nasal endoscopy	*Pseudomonas aeruginosa*, lactose fermenting GNR, normal resp flora	No
17	Mastoiditis	No	NA	NA	No
18	Mucosal breakdown between pharynx and skull base	Yes	Nasal endoscopy	*Streptococcus constellatus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, lactose fermenting GNR, normal flora	No

TABLE 2 (Continued)

Patient ID	Confirmed or suspected source for SBO	Culture data obtained	Source of culture data	Culture result	Pathology obtained/result
19	Mucosal breakdown between pharynx and skull base	Yes	Nasal endoscopy	*Streptococcus* spp., *Enterococcus* spp., *Pseudomonas aeruginosa*, lactose ferment GNR, mixed anaerobes, *Candida* spp.	Yes, contained bone/ showing inflammatory cells
20	Surgical site deep space infection from parotid tumor resection, neck dissection, flap reconstruction	Yes	Superficial wound culture of purulence from surgical site	MRSA, *E. coli* (also had MRSA bacteremia concurrent with diagnosis of SBO)	Yes/ insufficient sample for any pathology evaluation
21	Otitis	Yes	Superficial wound culture of purulent ear drainage	*Aspergillus fumigatus*	No
22	Mucosal breakdown between pharynx and skull base	Yes	Nasal endoscopy	*Pseudomonas aeruginosa*	No
23	Otitis	No	NA	NA	No

Abbreviations: GPC, gram-positive cocci; GNR, gram-negative rod; GPR, gram-positive rod; MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; NA, not applicable; SBO, skull base osteomyelitis.

21.7%) underwent hyperbaric oxygen therapy to complement other treatment strategies (Table 3).

3.4 | Outcomes of skull base osteomyelitis

During the treatment course of SBO, no deaths occurred that were directly attributable to SBO. Infectious and noninfectious complications occurred in a minority of patients. Only one patient stopped antimicrobial therapy prematurely due to rash attributed to piperacillin-tazobactam, and another patient switched antimicrobial therapy due to adverse gastrointestinal side effects. During the SBO treatment course, three patients required gastrostomy tubes for dysphagia; two patients had evidence of cranial nerve palsy; one patient had an unstable cervical spine; and one other patient developed an oro-nasal fistula.

The duration of follow up with reported cure of SBO versus recurrent infection was variable. Complete chart data for follow up was available for 21 patients. Eleven of 21 patients (52.4%) with reported cure of SBO were followed for a median time of 121.6 weeks (IQR 95.6 weeks), range 13.1–530.3 weeks. The other 10 patients (47.6%) suffered from a recurrence of SBO and their follow up was documented until the first episode of recurrent SBO. For eight patients, the median time from completion of antibiotics to relapsed infection was 7.4 weeks (IQR 11.8 weeks), range 0–35.4 weeks; two patients were excluded from this calculation because of a very delayed presentation of repeat skull base infection (5.6 years) in one patient, and missing data regarding duration of antimicrobials in another. Among the eight patients with relapsed infection (i.e., occurring within 9 months of discontinuing antimicrobial therapy) and complete chart data, one patient developed worsening infection whereas on caspofungin monotherapy and 22.6 weeks after stopping meropenem.

In patients with relapsed SBO, cure was difficult to achieve. Among the seven patients with relapsed infection that developed off antimicrobials, four patients had repeat cultures from either operative debridement or nasal endoscopy. Two patients' cultures grew typical naso/oropharyngeal flora, and the other two patients' cultures grew *P. aeruginosa* that had become resistant to the antibiotic used to treat the first episode of SBO. Except for the two patients with *P. aeruginosa* isolated in cultures, the other five patients were re-treated with a single antibiotic targeting bacterial oropharyngeal flora (using ampicillin-sulbactam, amoxicillin-clavulanate, or moxifloxacin). Despite re-treatment with appropriate antibiotics, all seven patients suffered from multiple recurrences of SBO, and required a combination of suppressive systemic antibiotics, topical antibiotics, and serial debridements with nasal endoscopy. At the time of last documentation, four patients continued to receive therapies for SBO, one patient died from carotid artery rupture, and two patients were referred for hospice.

One patient in our cohort had a superficial culture from ear drainage that grew 10 colonies of *Aspergillus fumigatus* (no corresponding pathology). This patient presented with otitis complicated by mastoiditis and extension of infection into the skull base. Given the uncertainty as to whether *Aspergillus* reflected colonization versus infection, this patient was treated with voriconazole and empiric piperacillin-tazobactam, and subsequently underwent a subtotal petrosectomy 2.5 months following the diagnosis of SBO. Operative cultures did not demonstrate any fungi by staining or growth. (Histological staining for fungi was not performed on corresponding specimens.) The patient was then treated with a course of therapy targeting at naso/oropharyngeal bacterial flora with SBO cure.

TABLE 3 Skull base osteomyelitis treatment and outcomes

Patient ID	Source control surgical intervention	Antimicrobial regimen	Total duration of antimicrobial therapy, days	Treatment with hyperbaric oxygen	Endoscopic appearance of pharynx abutting skull base at completion of antimicrobials	Duration of follow up with cure or until repeat infection, weeks	Recurrent infection	Duration of time from completion of antimicrobials to recurrent infection, weeks
1	No	(1) TMP/SMX + ciprofloxacin × 56 days	56	No	Mucosal erythema and crusting	304	Yes	292
2	Yes—endonasal odontoidectomy	(1) Ampicillin-sulbactam × 9 days (2) Ertapenem + vancomycin × 51 days (3) Amoxicillin-clavulanate × 59 days	119	No	Resolved	57	No	
3	No	(1) Piperacillin-tazobactam × 3 days (2) Ertapenem × 118 days (3) Levofloxacin + amoxicillin-clavulanate × 54 days	175	No	Endoscopy not repeated	231	No	
4	No	(1) Clindamycin × 42 days	42	No	Residual exposed bone—5 mm exposed bone in nasopharynx	Chart data incomplete		
5	Yes—debridement of sinuses and necrotic skull base bone	(1) Piperacillin-tazobactam × 39 days	39	No	Mucosal erythema and crusting	39	Yes	30
6	No	(1) Levofloxacin × 12 days (2) Ertapenem × 96 days	108	Yes, 40 dives	Mucosal erythema and crusting	104	No	
7	No	(1) Amoxicillin-clavulanate × 28 days	28	No	Residual exposed bone with purulent drainage—patient was asymptomatic	530	No	
8	Yes—bilateral sphenoidotomy with debridement of sinuses and necrotic bone at skull base	(1) Penicillin IV × 52 days (2) Penicillin PO × 240 days, with concurrent benzathine penicillin IM qWeek × first 4 weeks	292	Yes, 40 dives	Mucosal erythema and crusting	56	Yes	13
9	Yes—6 months following SBO diagnosis, C1 osteotomy and C1-2 bone graft with ongoing exposed bone in oropharynx	(1) Vancomycin + ceftriaxone × 141 days (2) Amoxicillin-clavulanate planned for indefinite therapy, with TMP/SMX × first 405 days	Indefinite	No	Residual exposed bone	122	No—remained on antimicrobials at last follow up	
10	Yes—3 months following SBO diagnosis, skull base debridement	(1) Piperacillin-tazobactam × 86 days (2) Moxifloxacin × 55 days, with voriconazole × last 28 days	141	Yes, 40 dives	Mucosal erythema and crusting	26	Yes	6

TABLE 3 (Continued)

Patient ID	Source control surgical intervention	Antimicrobial regimen	Total duration of antimicrobial therapy, days	Treatment with hyperbaric oxygen	Endoscopic appearance of pharynx abutting skull base at completion of antimicrobials	Duration of follow up with cure or until repeat infection, weeks	Recurrent infection	Duration of time from completion of antimicrobials to recurrent infection, weeks
11	No	(1) Piperacillin-tazobactam × 4 days (2) Ceftriaxone × 103 days (3) Amoxicillin-clavulanate × 280 days	387	Yes	Endoscopy not repeated	92	Yes	35
12	Yes—bilateral sphenoidotomy, skull base debridement, pedicled nasoseptal flap	(1) Ertapenem × 11 days (2) Moxifloxacin × 31 days	42	No	Nasoseptal flap healing	130	No	
13	No	(1) Amoxicillin-clavulanate × 10 days (2) TMP/SMX × 50 days	60	No	Endoscopy not repeated	139	No	
14	No	(1) Amoxicillin-clavulanate × 42 days	42	No	NA	13	No	
15	No	(1) Vancomycin + ampicillin-sulbactam × 4 days (2) Cefazolin × 41 days (3) TMP/SMX × 60 days (4) Moxifloxacin—then lost to follow up	105, minimum before lost to follow up	No	Mucosal erythema and crusting	122	Yes	Unknown, lost to follow up whereas completing antimicrobials, and presented with repeat infection 2 years after lost to follow up
16	No	(1) Meropenem × 158 days	158	No	NA	31	Yes	5
17	No	(1) Vancomycin + cefepime + metronidazole × 43 days (2) Ciprofloxacin + doxycycline × 14 days	57	No	NA	17	No	
18	No	(1) Daptomycin + meropenem × 57 days (2) Voriconazole × 63 days (overlap with regimen #1 by 4 days)	116	No	Residual exposed bone	22	No	
19	No	(1) Daptomycin + meropenem × 69 days with caspofungin continued throughout duration of antibiotic therapy and additional 158 days	227	Yes	Significant mucosal erythema and crusting—occurring at time of recurrent infection	35	Yes	0—recurrent infection occurred whereas on caspofungin

(Continues)

TABLE 3 (Continued)

Patient ID	Source control surgical intervention	Antimicrobial regimen	Total duration of antimicrobial therapy, days	Treatment with hyperbaric oxygen	Endoscopic appearance of pharynx abutting skull base at completion of antimicrobials	Duration of follow up with cure or until repeat infection, weeks	Recurrent infection	Duration of time from completion of antimicrobials to recurrent infection, weeks
20	No	(1) Vancomycin + meropenem × 9 days (2) Ertapenem—planned for 6–8 weeks, but lost to follow up		No	NA	Lost to follow up, and then reported death due to pneumonia		
21	Yes—2.5 months following SBO diagnosis, subtotal petrosectomy	(1) Piperacillin-tazobactam + voriconazole × 51 days (2) Ampicillin-sulbactam × 22 days (3) Amoxicillin-clavulanate × 98 days	171	No	NA	122	No	
22	No	(1) Piperacillin-tazobactam × 57 days	57	No	Mucosal erythema and crusting	17	Yes	9
23	No	(1) Ertapenem × 41 days	41	No	NA	13	Yes	6

Note: NA, not applicable given initial nidus for SBO not due to breakdown between naso/oropharynx and skull base; TMP/SMX, trimethoprim/sulfamethoxazole.

Although limited by small sample size, patients infected with *P. aeruginosa* were more likely to have recurrent SBO (4/5 with recurrent SBO vs. 1/5 with cure). Patients who underwent a therapeutic surgical intervention were neither more prone to cure nor recurrent infection (4/11 had surgery in cure group vs. 3/10 had surgery in recurrent infection group). There was no difference in the duration of antimicrobial therapy for patients with cure or recurrent SBO ($p = .2$, using paired, two tailed *t*-test).

3.5 | Monitoring treatment of skull base osteomyelitis

During the treatment course, in conjunction with monitoring clinical symptoms, some patients had serial inflammatory markers, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), serial imaging, and repeat nasal endoscopy to help guide the duration of therapy.

Twelve patients had inflammatory markers trended over time. Two of these patients had normal inflammatory markers throughout the duration of SBO diagnosis and treatment. Only 3/10 patients had complete normalization of inflammatory markers at the end of antimicrobial therapy, whereas 6/10 patients had a down trend in inflammatory markers without normalization, and the remaining 1/10 patients had elevated inflammatory markers that remained stable. The median ESR and CRP at the time of SBO diagnosis were 87 mm/h (IQR 64 mm/h) [ESR reference range < 20 mm/h] and 1.9 mg/dl (IQR 16.1 mg/dl) [CRP reference range < 1.0 mg/dl], respectively. The median ESR and CRP at the completion of antimicrobial therapy were 32 mm/h (IQR 23 mm/h) and 0.5 mg/dl (IQR 0.8 mg/dl), respectively. The majority of patients had improvement in inflammatory markers regardless of SBO cure versus recurrent infection (among those with down trend of initially elevated inflammatory markers, 5/6 had cure vs. 4/4 had recurrent SBO).

Twelve patients had repeat imaging with MRI, CT, and/or nuclear medicine studies (PET, gallium scan, tagged white blood cell scan) during the treatment course to help guide the duration of antimicrobial therapy. These patients had an average of 2.25 (range 1–7) follow up imaging studies during the treatment course. All follow up imaging studies showed ongoing abnormalities of the skull base. Only 3/12 patients stopped antimicrobials within 3 weeks of the last imaging study based on improved or stable radiographic inflammatory changes at the skull base. The other 9/12 patients continued antibiotics for at least 1 month following the last imaging study. An equal number of patients with SBO cure versus recurrent infection had repeat imaging (6 vs. 6 patients).

Among the 17 patients, who at the time of SBO diagnosis had nasal endoscopy showing breakdown of the mucosal barrier between the naso/oropharynx and skull base, 14 had follow up nasal endoscopies at the time of completing antimicrobial therapy. Only 2/14 patients had complete resolution of mucosal barrier breakdown, and these two patients went on to have SBO cure. The majority of patients (12/14) had residual mucosal defects abutting the skull base

at the time of completing antimicrobial therapy, and four of these patients had residual exposed bone. One patient was then put on life-long antibiotics for suppression, and one patient was lost to follow-up. Seven of the remaining 10 patients with ongoing mucosal abnormalities abutting the skull base developed recurrent SBO.

4 | DISCUSSION

Our study shows that osteoradionecrosis is a major risk factor for SBO, with SBO developing a median 7.3 years (IQR 8.9 years) following the last dose of radiation therapy. Similar to HNC patients who develop osteoradionecrosis of the jaw and then superimposed osteomyelitis of the jaw,[13,14] SBO likely results from superinfection of devitalized soft tissue and/or bone at sites of osteoradionecrosis in the skull base.[7–10] Clinicians should therefore have a low threshold to evaluate for SBO in symptomatic patients with osteoradionecrosis.

Regarding the diagnosis of SBO in HNC patients, this study demonstrates the importance of obtaining clinical specimens for cultures and pathology. Although the majority of SBO was caused by polymicrobial infection from naso/oropharyngeal flora, 50% of patients with microbiology data were found to have resistant or atypical pathogens that would not be covered by antimicrobials targeting the naso/oropharyngeal flora alone. Therefore, identification of these pathogens is crucial for informing antimicrobial choice beyond routine coverage of naso/oropharyngeal flora.

A minority of patients in our case series were treated for fungal SBO. *Candida* species are normal commensals of oropharyngeal flora and were noted in four cases either by culture or Gram-stain. Among these four patients, only two patients received antifungal therapy, and both developed recurrent SBO, one of which occurred while the patient was still receiving caspofungin, suggesting *Candida* spp. was not the primary driver of infection. For the two patients not treated with antifungal therapy, one patient had SBO cure, and the other patient had recurrent SBO. One other patient with SBO cure received voriconazole empirically (negative culture for fungus and no pathology obtained). Although these numbers are small, our experience suggests that therapy targeting *Candida* is unlikely a primary factor to influence treatment outcome, and empiric antifungal treatment is unnecessary.

Given that there are no published treatment guidelines for management of SBO, drawing some parallels between SBO and osteomyelitis at other anatomical sites may be of relevance. In HNC patients, both SBO and jaw osteomyelitis often develop in sites of osteoradionecrosis and are commonly polymicrobial due to inoculation with naso/oropharyngeal flora. Although there are no widely accepted guidelines for the treatment of jaw osteomyelitis, primary principles are procedural source control (i.e., incision and drainage, sequestrectomy, mandibular resection) and culture-directed antimicrobial therapy.[15]

SBO additionally shares some similarities with native vertebral osteomyelitis given that both infections have limited opportunities for surgical debridement. The Infectious Diseases Society of America (IDSA) published guidelines for the management of native vertebral osteomyelitis in 2015,[16] and some of these guidelines may be applicable to SBO. For instance, the IDSA guidelines suggest monitoring serial inflammatory markers (ESR and CRP) given that patients with poor clinical response to therapy and persistently elevated inflammatory markers may be at risk for treatment failure.[16] Additionally, the IDSA guidelines for native vertebral osteomyelitis do not recommend routine repeat imaging unless there is concern for poor clinical response to therapy; and when repeat imaging is obtained, it is cautioned that bony structures show slow response to therapy, and interval changes in soft tissue structures likely provide better correlation with clinical response and treatment outcomes.[16]

Regarding treatment of SBO, in our case series only a minority of patients underwent hyperbaric oxygen (HBO) therapy as an adjunct to other treatment modalities. Overall, there are scarce data describing HBO specifically for the treatment of SBO.[17] Studies describing HBO for the management of osteoradionecrosis of the jaw show mixed results.[18] The most robust relevant literature describes HBO for the treatment of necrotizing otitis externa, but even in this population, there are no randomized trials to evaluate HBO.[19] Taken together, the literature does not provide enough data to make recommendations for or against HBO in the treatment of SBO.

Regarding antimicrobial treatment of SBO in HNC patients, our case series shows the total duration of antimicrobial therapy was highly variable and averaging 16.7 weeks +/− 13.4 weeks. Our treatment duration is consistent with other case series of SBO in all comers, showing the average antimicrobial treatment duration ranging from 6 to 21 weeks.[20–24] It is likely that the highly variable treatment duration is based on individual patient factors, such as comorbidities, extent of initial infection, opportunity for source control procedures, tolerability of antimicrobial therapy, and risk of treatment failure. The optimal treatment duration is unknown, but akin to vertebral osteomyelitis guidelines,[16] it is likely that most patients require a minimum of 6–12 weeks of antimicrobial therapy. Given the complexity of HNC patients with SBO, however, it is likely that treatment durations will have to be highly individualized.

Despite prolonged antimicrobial therapy, nearly half of the patients in our case series had multiple episodes of recurrent SBO. Infection with *P. aeruginosa* and persistent defects in the naso/oropharyngeal mucosal abutting the skull base were associated with recurrent SBO. The low SBO cure rate is likely influenced by the unique challenges of surgical source control at the skull base, which requires both adequate surgical debridement and successful coverage of bone by vascularized tissue. The anatomic constraints of debriding the skull base are reflected by the risks of potential injury to cranial nerves, great vessels, and intracranial structures. Moreover, coverage of exposed bone with vascularized flaps is particularly challenging in HNC patients, given the often compromised tissue integrity and vascularity resulting from surgical resection and/or radiation.[6] Whereas surgical treatment of chronic osteomyelitis is a mainstay when more accessible sites are involved,[13,25] in our case series, a minority of patients (7/23, 30.4%) underwent surgical debridement, and only one patient underwent soft tissue coverage of exposed bone. Although not directly comparable, other case series of SBO in all comers show a

TABLE 4 Recommendations for evaluation and treatment of skull base osteomyelitis in patients with head and neck cancer

1. Evaluation for possible SBO
   a. Evaluate for possible concurrent infection of head/neck (i.e., otitis, sinusitis, dental infection)
   b. Obtain MRI with and without contrast (if renal function allows) to evaluate for inflammatory changes of the skull base and other possible signs of head/neck infection.
   c. Perform nasal endoscopy to evaluate for mucosal barrier breakdown between the naso/oropharynx and skull base. At time of nasal endoscopy, obtain clinical specimens to send for pathology, aerobic and anaerobic bacterial cultures, and fungal cultures.
      i. Pathology can aid in evaluating for recurrent malignancy.
      ii. Culture data can provide microbiologic information to guide antimicrobial choice (i.e., Are there pathogens that require broader coverage than naso/oropharyngeal flora alone?).
2. Diagnose with SBO if clinical signs and symptoms, radiographic findings, nasal endoscopy findings, cultures, and/or pathology support diagnosis.
3. Is it possible to surgically optimize source control of SBO?
   a. Yes—proceed with surgical intervention, including debridement and coverage of exposed bone with vascularized flap if surgically feasible.
   b. Obtain clinical specimens to send for aerobic and anaerobic bacterial cultures, fungal cultures, and pathology.
4. Therapy based on culture and pathology data (if obtained).
   a. Antimicrobial coverage for bacterial naso/oropharyngeal flora is usually indicated[a]. If culture or pathology results reveal "atypical" or highly resistant organisms, consultation with Infectious Diseases is strongly recommended.
   b. Unless patient history or cultures/pathology are suggestive of fungal infection, empiric antifungal therapy is not necessary.
5. During treatment course, recommend monitoring based on clinical status, serial inflammatory markers (ESR and CRP), and repeat nasal endoscopy (especially if initial nasal endoscopy was diagnostic). If there is concern for poor response to treatment, consider repeat imaging with MRI to evaluate evolution of changes, especially in soft tissue structures.
6. The optimal treatment duration is unknown, but anticipate providing antimicrobial therapy for minimum 6–12 weeks, with final duration to be determined based on individualized patient factors.
7. Closely monitor patients' clinical symptoms after stopping antimicrobial therapy given significant risk of recurrent infection.
8. For patients with recurrent SBO and/or persistently exposed skull base bone to the naso/oropharynx, possible approaches may include: repeat antimicrobial therapy as needed for flares of SBO signs/symptoms, long term suppressive antimicrobial therapy[b], antibiotic nasal rinses, serial debridements of devitalized soft tissue and bone with nasal endoscopy, and/or coverage of exposed bone with vascularized flap if feasible.

[a]Commonly used antibiotics to target naso/oropharyngeal flora include ampicillin-sulbactam, amoxicillin-clavulanate, ertapenem, clindamycin, moxifloxacin.
[b]Noted there are no conclusive data to support the efficacy of long-term suppressive antimicrobial therapy, and potential risks of such therapy may include drug toxicities as well as selection of resistant pathogens.

higher proportion of patients managed with surgical debridement (range ~ 40%–80%).[22,23] Given that the skull base bone is more likely to remain exposed even after debridement of SBO, clinicians need to remain vigilant for recrudescent infection after completion of antimicrobial therapy owing to the continued exposure of bone to oral and nasal flora.

5 | CONCLUSIONS

Diagnosis and management of SBO in HNC patients is difficult and complex. It is best managed as part of a multidisciplinary team including consultation with Infectious Diseases, Otolaryngology, Oncology, and Radiology services. Based on our clinical experience and review of available literature, we propose recommendations for the evaluation and treatment of SBO in HNC patients (Table 4).

CONFLICT OF INTEREST

All authors declare that there are no conflicts of interest.

ORCID

Mary M. Czech https://orcid.org/0000-0002-8986-5419

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