Atypical Skull-Base Osteomyelitis

Subjects: Otorhinolaryngology | Surgery

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Atypical skull-base osteomyelitis is a rare but fatal disease that usually involves infection of the ethmoid, sphenoid, occipital, or temporal bones that form the skull base. Unlike typical (so-called otogenic), atypical skull-base osteomyelitis has no otogenic cause. Instead, some authors call atypical skull-base osteomyelitis sinonasal, since the infection most often originates from the nose and paranasal sinuses.

Keywords: osteomyelitis ; osteitis ; aspergillosis ; mucormycosis ; clivus ; sphenoid sinusitis

1. Introduction

Percival Pott first described osteomyelitis of the cranial bones in 1775 in a patient with a sub-pericranial abscess resulting from a frontal bone injury [1]. Later, it became known that the cause of such an infection was not an injury but the spread of infection from neighbouring structures, for example, paranasal sinuses. Meltzer and Kelemen first described skull-base osteomyelitis (SBO) in 1959 in patients with a burn injury and osteomyelitis of the external auditory canal [2]. Subsequently, it became known that SBO is not only the result of the progression of inflammation of the external auditory canal [3] but also inflammation of the face, nose, paranasal sinuses, oral cavity, and pharynx [4][5].

Atypical skull-base osteomyelitis (ASBO) is a rare but fatal disease and usually involves infection of the ethmoid, sphenoid, occipital, or temporal bones that make up the skull base. Unlike typical SBO, which is usually the result of advanced necrotising external otitis (so-called otogenic), ASBO does not have an otogenic cause. Some authors call ASBO sinonasal or non-otogenic SBO [4]. Other authors divide it into non-sino-rhino-otogenic and sino-rhino-otogenic, and the latter into SBO of the front (i.e., anterior), middle (i.e., central), and posterior cranial base (i.e., posterior SBO) [5].

2. Pathogenesis of Atypical Skull-Base Osteomyelitis

2.1. Causes and Routes of Disease Spread

ASBO can occur as a result of advanced or untreated infection of the deep tissues of the face, oral cavity, pharynx, or nasal and paranasal sinuses, usually the sphenoid (i.e., basisphenoid) and occipital bones (i.e., basiocciput) [4][6]. Rarely, the cause of the infection is hematogenous from a remote source, e.g., from the lung or spine [5][7].

The infection spreads along the soft tissues at the skull base, and when it invades the Haversian canals, it also begins to spread along the cancellous bone. Due to the spread of the infection, neurovascular structures are affected along their extracranial course, through their foramina at the skull base, and intracranially. Therefore, knowledge of the precise surgical anatomy of the skull base is necessary to understand the clinical picture of ASBO.

The most common cause of ASBO is an advanced paranasal sinus infection. From the sphenoid sinus, which is the centre of the skull base, the infection can spread in all directions, i.e., anterior, middle, or posterior cranial fossa, orbit, and adjacent paranasal sinuses. From the ethmoid cells, the infection first spreads to the adjacent paranasal sinuses (frontal, maxillary, and sphenoid sinus) and then across the borders of the paranasal sinuses to the orbit and, above all, to the intracranial space. From the maxillary sinus, the infection (e.g., odontogenic maxillary sinusitis) spreads through the pterygopalatine and infratemporal fossa into the middle cranial fossa, orbit, sphenoid sinus, and through the ostiomeatal complex, into the ethmoid cells and frontal sinus. Finally, the infection spreads through the posterior wall of the frontal sinus to the anterior cranial fossa. The occurrence of remote intracranial infection (e.g., intracerebral abscess, epidural abscess, subdural empyema) is possible due to the venous drainage of the face and paranasal cavities into the cerebral venous sinuses.

ASBO can also be iatrogenic, for example, after endoscopic surgery of the nose and paranasal sinuses [8]. The occurrence of SBO after bilateral transnasal endoscopic sphenopalatine artery cauterisation and sphenoidotomy has been described [9]. The occurrence of clival abscess or osteomyelitis after adenoidectomy [10][11] and epipharyngeal cyst excision [12] has also been described. Thornwaldt's cyst infection can also cause ASBO [13]. Injuries to the skull base, especially in the case of contaminated wounds (e.g., sharp or gunshot injuries), can lead to ASBO [5]. In patients after head and neck cancer radiotherapy, the tissue at the skull base is more susceptible to osteoradionecrosis and SBO [14].

In some cases, the cause of ASBO is unknown. Some authors also report otogenic ASBO without otoscopic signs of ear infection. The absence of signs is associated with regression of necrotising external otitis, but the progression of infection at the skull base spreads to the clivus [15][16].

2.2. Patients' Predispositions

Mostly, infection usually does not progress to ASBO, as certain patient predispositions or virulence factors of the microbe are also required [10][17]. Patients with diabetes and immune suppression are particularly susceptible [18]. Diabetes causes immunodeficiency and poor blood circulation due to damage to small (i.e., microangiopathy) and large vessels (i.e., macroangiopathy), which hampers tissue regeneration. Similarly, other diseases that cause vascular damage or poor oxygen delivery, e.g., post-irradiation changes, vasculitis, cancer, diseases of bone metabolism (e.g., osteoporosis, osteopetrosis, Paget's disease), malnutrition, anaemia, cardiovascular diseases, liver failure, kidney failure, smoking, obesity, chronic lung disease, and prolonged hospitalisation, predispose to the development of SBO [4][19]. Advanced age is an independent risk factor [5]. Risk factors for ASBO are rarely absent [4][20]. For that reason, they must be identified and controlled.

2.3. Causative Microbes of Atypical Skull-Base Osteomyelitis

ASBO is most commonly caused by *Staphylococcus aureus*, followed by *Pseudomonas aeruginosa* and atypical mycobacteria. *Pseudomonas aeruginosa* is less likely to cause ASBO than typical SBO. More commonly than typical SBO, ASBO results from a fungal infection, most commonly with *Aspergillus* spp., usually in patients with neutropenia. Less often, ASBO results from infection with *Candida* spp. [5], *Rhizopus* spp., and *Mucor* spp., the latter usually in patients with diabetic ketoacidosis, causing a clinical picture of acute fulminant invasive fungal rhinosinusitis [4][18][19][21]. In the literature, cases of ASBO due to infection with the *Streptococcus anginosus* group, *Eikenella corrodens*, *Serratia marcescens*, *Enterococcus faecium*, *Peptostreptococcus* spp., *Mycobacterium tuberculosis* [5][7], *Klebsiella pneumoniae* [14], *Propionibacterium acnes* [9], *Nocardia* spp. [22], *Morganella* spp. [23], and *Bacteroides* spp. [5] are described.

More often than in typical SBO, the results of microbiological tests are negative in ASBO, making the diagnosis even more complex [8].

3. Treatment of Atypical Skull-Base Osteomyelitis

Patients with ASBO are usually treated in the department of infectious diseases because of long-term antimicrobial therapy and poor general health. The infectious disease specialist leads the treatment and includes other specialists, including—an otorhinolaryngologist, neurosurgeon, radiologist, clinical microbiologist, and a pathologist. The mainstay of treatment for ASBO is antimicrobial therapy [18]. At the same time, managing all risk factors for developing ASBO is necessary, e.g., treating diabetes and immune deficiency [19].

3.1. Surgery

Surgical treatment has a role in ASBO as a complement to antimicrobial treatment. Often, it would not be possible to eradicate the disease surgically, or the procedure would be too risky. At the same time, patients are more susceptible to the surgical risks of extensive skull base surgery due to their generally poorer health status and proximity of the vital neurovascular structures (e.g., internal carotid artery, basilar artery, lower cranial nerves). The purpose of surgical treatment is tissue biopsy, decompression of vital neurovascular structures (e.g., transnasal endoscopic transodontoid decompression of the brainstem, optic nerve decompression), abscess drainage (**Figure 1**), drainage of the paranasal cavities, partial necrectomy, or sequestrectomy, to reduce the microbial load, to improve tissue perfusion, and consequently, for better penetration of antimicrobials. Nevertheless, indications for surgical treatment are still unclear [18][24][25].

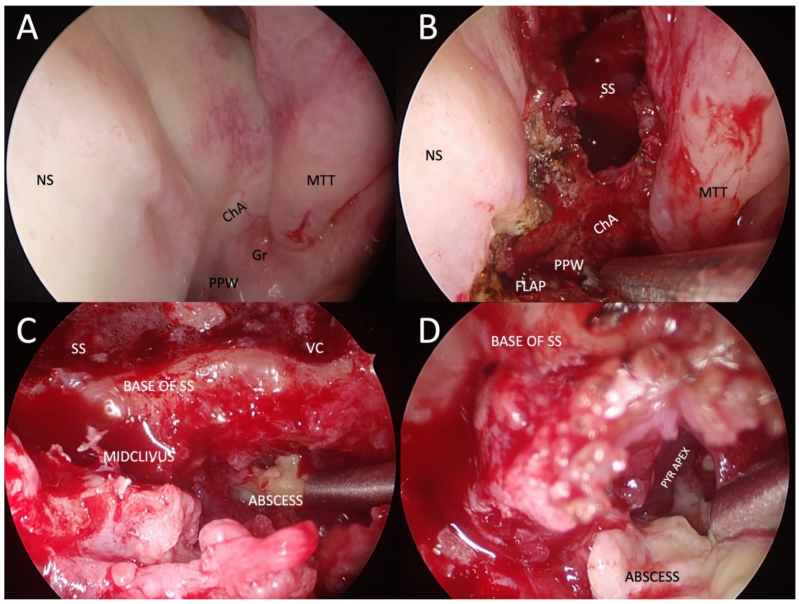

Figure 1. Example of transnasal endoscopic drainage of clival abscess in a patient with left-sided fungal atypical skull-base osteomyelitis. (**A**) Nasal endoscopy after decongestion, showing very subtle abnormalities, only a granulation tissue on the left side of the nasopharynx and a poorly defined choanal arch. (**B**) Paraseptal left-sided sphenoidotomy and elevation of nasopharyngeal flap pedicled on the inferomedial posterior nasopharyngeal wall. (**C**) Close-up view of the base of the left sphenoid sinus and mid-clivus after drilling to gain access to the abscess cavity. (**D**) Abscess cavity is drained with blunt dissection to visualise the tract under the pyramid apex. NS: nasal septum; ChA: choanal arch; MTT: middle turbinate tail; PPW: posterior pharyngeal wall; SS: sphenoid sinus; VC: an area of the Vidian canal; PYR APEX: pyramid apex.

3.2. Antimicrobial Treatment

Long-term pathogen-specific antimicrobial therapy remains the mainstay of treatment [18]. Early empiric therapy with broad-spectrum intravenous antibiotics should include coverage for *Pseudomonas aeruginosa* (e.g., antipseudomonal beta-lactam, a third-generation cephalosporin or carbapenem) and methicillin-resistant *Staphylococcus aureus* (e.g., vancomycin) [4][8][24]. A biopsy should be performed before initiating antimicrobial therapy to increase the microbiologic yield. Unless the patient's history, microbiological (culture/fungal markers), or pathology results suggest fungal infection, empiric broad-spectrum antifungal therapy is not indicated. However, it should be considered if there is no clinical improvement despite appropriate empiric antibiotics [14][18]. According to the literature, the optimal treatment duration is unknown. Based on case reports and case series, the suggested length of antimicrobial therapy is 6–20 weeks [4][8][18][24], started by intravenous antimicrobial therapy for a minimum of 6 weeks [8][18]. The final duration of antimicrobial therapy with a good treatment response should be based on clinical status and serial inflammatory markers, whereby a normalisation of ESR is a good indicator of infection resolution [15][18]. Long-term monitoring with CT or MRI is generally not helpful because radiologic abnormalities of the bone may persist for weeks to months despite clinical improvement [4][18]. However, radiologic imaging should be performed in case of clinical deterioration. The variable duration of treatment is highly based on the patient's immune status, the extent of the initial infection, the opportunity for source control procedures, the tolerability of antimicrobial therapy, and the risk of treatment failure [14]. Nevertheless, there is no evidence of an association between diabetes and the longer duration of antimicrobial therapy [18]. In patients with fungal infection (especially in immunocompromised patients), oral antifungal therapy is usually prolonged by up to 6–12 months, or even more, and depends on the patient's underlying disease, immune status, and response to therapy.

3.3. Hyperbaric Oxygen Therapy

Hyperbaric oxygen therapy is effective in some cases of ASBO. However, the research is insufficient, so routine use is not indicated. Nevertheless, this method has a role as a complementary treatment, especially in recalcitrant ASBO [5][18]. This treatment increases the partial pressure of oxygen in tissues, reduces tissue hypoxia, improves phagocytosis, and accelerates angiogenesis and osteogenesis. An example of a hyperbaric oxygen treatment regimen is a 90-min dive at a pressure of 2.5 atmospheres, 5 days a week, for 1 month [19].

4. Prognosis of Atypical Skull-Base Osteomyelitis

ASBO is a serious life-threatening condition with the possibility of severe complications. It presents with at least one cranial nerve dysfunction in 21–48% of cases. Although neurological improvement during treatment depends on the individual case and is not universal, paresis persists in approximately 30% of patients. Correction of paresis can occur due to nerve regeneration after a cured disease, decompression of neural structures, or compensation from the contralateral side. As such, surgical intervention does not directly contribute to improving neurological deficits. Post-operative deterioration may occur at the expense of radical resection of the affected bone, which surrounds the already damaged neural structures. The disease can be complicated by the spread of the infection to the surrounding soft tissues, and in rare cases, to the brain or meninges. Disseminated infection is associated with a higher risk of sepsis and increased mortality, despite surgical intervention and aggressive antimicrobial therapy [15][18][24].

Considering the relatively rare occurrence of the disease and the small set of studies, the predictive factors of the outcome of ASBO are not entirely clear. Associated diseases are generally the main prognostic factor, and worse disease outcomes have been described in elderly, male, diabetic, and immunocompromised patients, and patients with chronic ear disease [15][26]. The most important independent factor for a more favourable outcome is a multidisciplinary approach to the patient, with early and radical surgical removal of the focus of infection and adjuvant antimicrobial therapy. According to some studies, the treatment outcome is improved by the addition of hyperbaric oxygen therapy, which increases the partial pressure of oxygen and thereby reduces tissue hypoxia, and also improves phagocytosis and promotes angiogenesis and osteogenesis [19]. Clinical and radiological parameters, such as the resolution of the disease on imaging, the reduction of pain, and the improvement of cranial nerve paresis, speak in favour of a better outcome [24]. Other variables during treatment (e.g., duration of antibiotic therapy, number of repetitions of therapy) did not prove to be prognostically significant [18].

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