A 9-Year-Old Male With Fever, Proptosis and Hemodynamic Instability

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CASE

A 9-year-old previously healthy, fully immunized boy presented to the emergency department at a tertiary pediatric hospital with frontal headache for 8 days and right-sided eye pain and eyelid swelling of 2 days' duration. He had received oral amoxicillin/clavulanic acid from his general practitioner for possible tonsillitis over the preceding 10 days. No fever, coryza or pharyngitis was reported. On admission, he appeared miserable and was agitated, hyperventilating, pale and toxic. He had a temperature of 38.9 °C, respiratory rate of 36 breaths/min and oxygen saturation of 95% in ambient air and was hemodynamically unstable with blood pressure of 80/29 mm Hg, heart rate of 154 beats/min, weak peripheral pulse, prolonged capillary refill time (over 2 seconds) and cold periphery. A marked right-sided proptosis with painful eye movements and right periorbital swelling were noted on arrival.

His initial white blood cell count was 7.1 × 10^9/L with 80.9% neutrophils, 17.2% lymphocytes, 1.2% monocytes, 0.6% eosinophils and 0.1% basophils. His C-reactive protein level was 225 mg/L (normal: 0–10 mg/L). Chest radiograph did not show any evidence of consolidation, and transthoracic echocardiogram was normal.

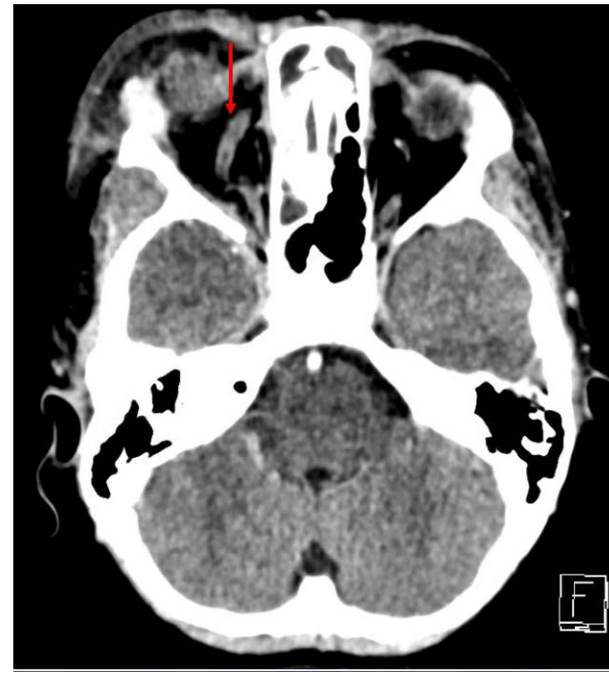

FIGURE 1. Orbital CT: axial image showing proptosis and soft tissue swelling of the right orbit and thrombus in right superior ophthalmic vein (arrow), which extends into the cavernous sinus. CT indicates computed tomography. full color online

Intravenous fluid boluses (total 40 mL/kg) and inotropes (epinephrine and dobutamine) were given in the first 24 hours of admission due to sepsis-induced hemodynamic compromise. Empiric therapy with intravenous cefotaxime, vancomycin, gentamicin and acyclovir was commenced. He was persistently febrile and developed worsening periorbital swelling and proptosis. Computed tomography imaging of the head with contrast was performed, which revealed both expected and unexpected findings (Fig. 1).

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DENOUEMENT

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Orbital cellulitis was suspected clinically and was confirmed by neuroimaging (Fig. 1), which revealed maxillary sinusitis and a superior orbital subperiosteal abscess. However, in addition, there was thrombosis of the superior ophthalmic vein extending into the cavernous sinus, a rare but serious complication of orbital cellulitis. No intracranial abscess or extra-axial collection was seen.

The child underwent emergency orbital exploration and functional endoscopic sinus surgery, with washout of the right superior orbital subperiosteal abscess and right maxillary sinus. After 48 hours of incubation, *Fusobacterium necrophorum* was isolated on anaerobic cultures of the intraoperative fluid specimens from both sites. The isolate demonstrated susceptibility to penicillin by Calibrated Dichotomous Sensitivity disc diffusion methodology.[1] Blood cultures obtained on admission and before commencement of intravenous (IV) antibiotics remained sterile, perhaps reflective of prior antibiotics received in the community. The child was transitioned to IV benzylpenicillin 60 mg/kg/dose every 6 hours and completed a 6-week course. He was commenced on anticoagulation therapy with IV heparin, later transitioning to warfarin to complete a 3-month course. The child recovered completely with no neurologic sequelae.

Clinical distinction between pre-septal and post-septal cellulitis is critical in management of infections in this region. Periorbital or pre-septal cellulitis is defined as infection and inflammation in the skin and soft tissues of the eye anterior to the orbital septum without involvement of the orbital septum and without impairment of ocular movements and function.[2] Orbital or post-septal cellulitis is infection and inflammation of the ocular muscles and fat lying posterior to the orbital septum and carries higher complication rates due to the more invasive nature of the infection with risk of extension into the central nervous system.[2] Compared with periorbital cellulitis, orbital cellulitis is more likely to present with striking symptoms, such as severe eye pain with eye movements, diplopia, proptosis and reduced visual acuity, as well as hemodynamic instability and/or central nervous system involvement. Clinician awareness of these "red flag" features of orbital cellulitis can reduce diagnostic delay and minimize associated morbidity and mortality.[3]

The "Chandler classification" is a commonly used framework to assess the severity of orbital infection and to guide appropriate management.[4] It divides the disease spectrum into 5 groups, including group 1: pre-septal cellulitis, group 2: orbital cellulitis, group 3: subperiosteal abscess, group 4: orbital abscess and group 5: cavernous sinus thrombosis.[4] The severity and extent of the infection is determined based on clinical and imaging (mainly computed tomography) findings, which enable tailored management decisions.

In the current era of widespread immunization against *Haemophilus influenzae* type b, pre-septal cellulitis (group 1) is usually caused by *Staphylococcus aureus*, *Streptococcus pneumoniae* or other streptococcal species and is treated with short courses (5–7 days) of oral β-lactam antibiotics guided by susceptibility data when available.[5] Surgical drainage is rarely necessary for drainage of pre-septal fluid collections.[5,6]

In contrast, cases assessed as Chandler groups 2–5 need thorough clinical evaluation and timely surgical and antimicrobial management as complications can be devastating. According to the literature, 77%–100% of children with orbital cellulitis (group 2) can be managed nonsurgically with appropriate antibiotic therapy.[6] Clinical deterioration while on antibiotics indicates progression of the disease with complications that warrant surgical intervention, including subperiosteal abscess formation (group 3), orbital abscess (group 4) and cavernous sinus thrombosis (group 5).

Cavernous sinus thrombosis (group 5), a rare but life-threatening complication of orbital cellulitis, represents the most advanced stage of disease in this classification framework and occurs secondarily to septic thrombophlebitis, usually extending from the ophthalmic vein.[4,7] Septic cavernous sinus thrombosis may be monomicrobial or polymicrobial in nature. The majority of cases are due to *S. aureus* and local data on prevalence of methicillin resistance must be considered when commencing empiric antibiotic treatment. Other common bacterial pathogens include *Streptococcus* spp., Gram-negative bacteria such as *Haemophilus* or *Pseudomonas* spp., and anaerobic bacteria such as *Bacteroides*, *Actinomyces* and *Fusobacterium* spp. Less commonly, *Corynebacterium* spp. and fungi such as *Aspergillus* species and Zygomycetes can also cause septic cavernous sinus thrombosis, particularly in the setting of immunosuppression.[4,8]

Children presenting with cavernous sinus thrombosis are at risk of developing significant complications including cranial nerve palsies, internal carotid artery thrombosis and cerebral infarcts.[6] Progression can be extremely rapid, particularly in cases involving *Fusobacterium* spp., with permanent neurologic sequelae including loss of vision developing within hours.[9] Therefore, timely management with surgical intervention and appropriate antibiotic therapy is crucial. Due to the rarity of cavernous sinus thrombophlebitis, no randomized control trials have been conducted on the optimal choice for empiric antibiotics, and therefore, treatment is guided by expert opinion along with individual risk assessment. Common empiric regimens include an antistaphylococcal agent, with or without coverage for methicillin resistance depending on the local antibiogram and a third-generation cephalosporin combined with metronidazole.[8] Isolation of a relevant pathogen from surgical specimens and/or blood culture allows further testing for antibiotic susceptibility and targeting of antibiotic treatment. However, oftentimes antibiotic coverage should remain broad due to the possibility of polymicrobial infection involving both oropharyngeal commensals and anaerobes. Although the optimal duration of treatment has not been assessed in randomized controlled trials, a prolonged course of parenteral antibiotics (typically 4–6 weeks) is often provided.[4]

The role of anticoagulation remains controversial in the management of cavernous sinus thrombophlebitis.[6,10] Most experts would suggest anticoagulation is warranted if the patient has no specific risks for hemorrhage. This is in line with a 2011 Cochrane review of 2 randomized controlled trials showing reduced mortality and morbidity with anticoagulation for cerebral venous sinus thrombosis in general.[10] The risk-benefit ratio must be assessed for each case, taking into account the risk of progression of the septic thrombus versus the possibility for intracerebral hemorrhage and/or need for further surgery.[10]

The early detection and appropriate management of cavernous sinus thrombosis can prevent associated complications such as meningoencephalitis, brain abscess formation and increased intracranial pressure that can lead to blindness, herniation and death. In the past, cavernous sinus thrombosis was associated with around 50% mortality. However, new case series report lower mortality rates of 0% to 25% but with high residual morbidity.[8] Permanent loss of vision has previously been reported with cavernous sinus thrombophlebitis.[9]

In the present case, *F. necrophorum*, a Gram-negative anaerobe, was isolated from all surgical specimens, and the isolate was proven susceptible to penicillin. *F. necrophorum* infections are usually treated with penicillin, a β-lactam/β-lactamase inhibitor combination, a carbapenem or

metronidazole, either alone or in combination.[11] *F. necrophorum* is well known to cause severe monobacterial infections in previously healthy children[11] and was thus considered the sole pathogen in the present case, justifying targeted antibiotic therapy. Due to previous reports suggesting clinical failure despite in vitro activity of penicillin in *Fusobacterium* infections,[11] de-escalation to IV penicillin was undertaken under close clinical observation. After a 6-week course of IV benzylpenicillin and 3 months of anticoagulation therapy, the child had recovered fully with no long-term neurologic sequelae.

We describe a previously healthy child with septic thrombophlebitis of the cavernous sinus due to *F. necrophorum* orbital cellulitis. Prompt treatment with a prolonged course of IV penicillin, anticoagulation and timely source control were integral to the positive outcome for this child. This case highlights a rare but potentially life-threatening complication of orbital cellulitis in children.

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