CASE REPORT

Cavernous sinus thrombosis due to ipsilateral sphenoid sinusitis

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SUMMARY

We report a case of septic thrombosis of the right cavernous sinus in a diabetic woman in her late 70's due to ipsilateral sphenoid sinusitis. The diagnosis was delayed and made only after the abrupt and dramatic appearance of the manifestations of sinus thrombosis. The patient developed, among the other symptoms, right peripheral facial palsy, which is a very rare manifestation in cavernous sinus thrombosis (CST). She was treated with broad-spectrum antibiotics and enoxaparin. The day of the scheduled drainage of sphenoid sinus—24 hours after the initiation of anticoagulation—she developed fatal subarachnoid haemorrhage. Our case demonstrates the difficulty of timely diagnosis of acute sphenoid sinusitis which has emerged as the most common primary infectious source potentially leading in CST. It also underscores the uncertainty concerning the use of anticoagulation in cerebral sinus thrombosis of infectious origin.

BACKGROUND

Septic cavernous sinus thrombosis (CST) is a rare but life-threatening thrombophlebitic process resulting from the spread of an infection of a tissue adjacent or drained by the cavernous sinus. The paranasal sinuses are the most common primary source of infection leading to septic CST. Failure to recognise and treat the primary infection in a timely manner leads to the abrupt appearance of the characteristic symptoms of CST. These are due to venous obstruction and nerve involvement, and reflect the numerous anatomic relationships of the sinus. Favourable outcome depends on prompt broad-spectrum antibiotic treatment and recognition and surgical control of the primary focus. Despite the widespread use of CT and MRI, which facilitate the diagnosis, septic CST carries a significant mortality and morbidity. Anticoagulation treatment—while widely used—is not without risks and its role in improving outcomes remains a subject of debate.

CASE PRESENTATION

A woman in her late 70's was brought to the emergency department of our hospital because of hyperglycaemia. Two days before admission the patient presented frontal headache which was not alleviated despite the use of acetaminophen and progressively worsened. A finger-stick glucose test showed a glucose level of 520 mg/dL and the patient was transferred to the emergency department. She had a history of coronary artery disease and diabetes mellitus and her medications included clopidogrel, irbesartan, metformin and sitagliptin. At the emergency

department, the patient was alert and fully oriented to person, place and time. Her vital signs and temperature were normal; however the finger-stick glucose test showed a level of 645 mg/dL. On further questioning, she reported having urinary urgency for the last 2 days. Physical examination, including neurological examination, was normal. Laboratory studies showed a white cell count (WBC) of $18.6 \times 10^9/L$ with 89.6% neutrophils, a haemoglobin level of 146 g/L, creatinine level of 1.5 mg/dL, sodium of 127 mmol/L and C reactive protein (CRP) of 5.5 mg/dL (reference range <0.5 mg/dL). Chest radiography was normal, while microscopic examination of urine revealed pyuria (>100 WBC per field) and bacteriuria without haematuria or ketones.

The patient was admitted in our department with a presumptive diagnosis of pyelonephritis and hyperglycaemic hyperosmolar state. Blood and urine cultures were obtained and empiric antibiotic treatment with ampicillin-sulbactam was initiated, along with crystalloid fluids and insulin. Within 36 hours, renal function and blood glucose levels returned to normal. Urine culture revealed *E. coli* susceptible to ampicillin. Nevertheless, the patient continued to experience frontal headache, and she became febrile and somnolent while inflammation markers continued to rise. Three days after her admission, her level of consciousness deteriorated (Glasgow Coma scale 13/15, E3V4M6) and she developed right exophthalmos with chemosis, right ophthalmoplegia with extraocular movements limited in all directions of gaze, obliteration of the right corneal reflex, fixed and dilated right pupil and a right peripheral facial nerve palsy (figure 1).

INVESTIGATIONS AND TREATMENT

Laboratory studies showed a WBC of $2108/10-6/L$ and CRP of 21.5 mg/dL. CT of the brain and paranasal sinuses revealed signs of inflammation of all paranasal sinuses with opacification of the right sphenoid sinus (figure 2) and was otherwise normal. A lumbar puncture was performed and analysis of cerebrospinal fluid revealed pleocytosis (114 white cells/ μL) with neutrophilic predominance of 90%, 50 erythrocytes/ μL , glucose 123 mg/dL and total protein 59 mg/dL. Gram stain revealed no microorganisms. Based on these findings a diagnosis of septic CST resulting from infectious sinusitis was suspected. A new set of blood cultures was obtained and the antibiotic treatment was modified with the initiation of vancomycin, meropenem and metronidazole. In addition, anticoagulation was started with enoxaparin 60 mg twice daily subcutaneously.

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Figure 1 Anterior view of the right eye of the patient showing exophthalmos, chemosis and a fixed and dilated right pupil.

MRI of the brain showed total opacification of the right sphenoid sinus, a dilated right superior ophthalmic vein and fullness of right cavernous sinus (figure 3).

OUTCOME AND FOLLOW-UP

After consultation with the otolaryngology department of our hospital, drainage of the sphenoid sinus was scheduled. Unfortunately, the morning of the operation, 24 hours after the initiation of the anticoagulation, the patient presented a sudden loss of consciousness and she was intubated. Emergency CT of the brain revealed subarachnoid haemorrhage (SAH) and intraventricular haemorrhage. The patient was transferred to the intensive care unit where she died 12 hours after admission. Blood and CSF cultures revealed no microorganisms.

Figure 2 CT scan showing total opacification of the right sphenoid sinus and signs of inflammation of the ethmoidal and opposite sphenoidal sinuses.

Figure 3 MRI showing opacification of the right sphenoid sinus, dilated right superior ophthalmic vein and fullness of right cavernous sinus (arrows).

DISCUSSION

In contrary with the numerous aetiologies of the thrombosis of the cerebral sinuses (CS), in which a prothrombotic condition is almost always present, it seems that isolated CST is nearly always infectious in origin.¹ The primary focus of infection is the face, orbit, tonsils, teeth, ears and paranasal sinuses.

Knowledge of the regional anatomy is necessary for understanding the physiopathology and clinical manifestations of septic CST. The cavernous sinuses are narrow compartments situated on the lateral aspect of the sella turcica and receive blood from the ophthalmic veins, the superficial middle and inferior cerebral veins and the sphenoid sinuses. They drain in turn into the pterygoid plexus, the petrosal and sigmoid sinuses and ultimately into the internal jugular vein. In addition, the emissary veins establish communication between the cerebral sinuses and the veins draining the skull and the face. All these venous connections have no valves and vascular flow can occur in both directions, permitting the retrograde and anterograde spread of an infection. The abducens (VI) nerve, the internal carotid artery and its sympathetic plexus run within the cavernous sinus, whereas the oculomotor (III), trochlear (IV) and the superior two branches of trigeminal nerve (V1,V2) run within its lateral dural wall. In addition, the cavernous sinuses are situated just superolateral to the sphenoid air sinuses; they are separated from them by thin bone or sometimes only by soft tissue, if the bone is not fully formed.^{2,3}

The latency period for the development of septic CST varies from 5 to 15 days.⁴ Patients are usually toxic and febrile. Signs and symptoms occur abruptly with the appearance of exophthalmos, chemosis and orbital oedema due to venous obstruction. Cranial nerve involvement results in pupillary dilatation, complete ophthalmoplegia and hypoesthesia in the distribution of trigeminal nerve with obliteration of corneal reflex. Involvement of the facial nerve—as in our patient—is an extremely rare manifestation of septic CST in the absence of otogenic infection.⁵ It is presumed that is due to the elevated pressure in the nerve's satellite vein provoking transient neurapraxia.⁶ The progression to bilateral orbital symptoms in the course of septic CST is not common but is reported⁷ to be pathognomonic for CST, as the two cavernous sinuses are interconnected by the intercavernous sinuses that encircle the pituitary gland. Further extension of infection to adjacent structures may result in visual loss, hypopituitarism, meningeal irritation or true meningitis, brain abscess, epidural and subdural empyemas and finally coma and death. The diagnosis of CST is made on clinical grounds and can be confirmed by radiology studies with MRI being the best imaging method.

Due to the widespread use of antibiotics which are commonly prescribed for infections of the ear, face and teeth, the most common source of infection in CST nowadays is the paranasal

sinuses, with the sphenoid sinus reported as being the most common^{2,8} either alone or in the context of pansinusitis.⁹ Diagnosis of isolated sphenoid sinusitis requires a high index of clinical suspicion due to its rarity—representing about 1%–3% of all acute bacterial sinusitis cases¹⁰—and the anatomical location of the sphenoid sinus which prevent its direct examination. At the early stages of infection the nasal symptoms may be absent whereas headache is the only presenting feature.^{3, 10} Therefore there is often a significant delay in the diagnosis which is suspected only after the development of complications. This may explain the reported poorer prognosis of septic CST due to sphenoid sinusitis as well as the more extensive cavernous sinus involvement at the time of diagnosis.¹⁰ That was the case in our patient in whom the presence of bacteriuria—common in diabetic patients—provoked further delay, as a presumptive diagnosis of pyelonephritis was made in admission.

Before the antibiotic era, septic CST was ultimately fatal. Nowadays, even with the availability of imaging techniques facilitating the diagnosis, it still carries a significant mortality, reported as 30% with more than 50% of the patients experiencing residual cranial neuropathies.⁴ The cornerstone of treatment is the early initiation of broad-spectrum antibiotics and the surgical intervention at the primary source of infection with incision and drainage of the involved sites as soon as possible.

Once septic CST is suspected by clinical findings, blood cultures should be obtained and empiric antibiotic treatment should be initiated based on the common pathogens involved, depending on the primary infection. *S. aureus* is the most commonly identified organism, followed by *Streptococcus* spp, gram negative organisms and anaerobes. Fungal infection should be suspected in immunocompromised patients. Blood cultures are positive in 70% of cases while CSF cultures in nearly 20%, in the absence of previous antibiotic treatment.¹¹ The duration of antibiotic therapy is at least 3–4 weeks in accordance with other intravascular infections.

Antibiotic therapy must be accompanied by drainage of the primary source of infection, especially in the case of paranasal sinusitis where the focus is in a non-draining site. Although in some reports surgical intervention is reserved for the cases of septic CST with clinical deterioration despite antibiotic treatment, the presence of sinusitis must lead to urgent surgical exploration and drainage^{8,9} which clearly improves outcome. In particular, septic CST due to sphenoid sinusitis is associated with significant mortality without surgical intervention.^{3, 10}

Although anticoagulation is the standard of care in cases of aseptic CS thrombosis, its role in the management of thrombosis of infectious origin is still debated. Due to the rarity of the situation, a randomised control trial (RCT) to determine its efficacy is difficult to take place. The data concerning aseptic thrombosis of the CS cannot be easily extrapolated in case of infection due to the different pathophysiology. Even in cases of aseptic CS thrombosis, there is no consensus regarding the timing, type, dose and duration of anticoagulation. It is known that CS thrombosis per se is a haemorrhagic risk factor; in 50% of the patients venous infarcts occur which are often haemorrhagic or may transform into large and eventually lethal haemorrhages. A Cochrane meta-analysis¹² (including only two small RCT of CS thrombosis irrespective of aetiology) concluded that anticoagulation is safe and may improve outcome, but the average time to the initiation of anticoagulation was 4 weeks and 10 days, respectively. A recent analysis of the subgroup of patients with septic CS thrombosis¹³ included in the largest prospective cohort study on adult CS thrombosis showed that the vast majority received anticoagulation

‘in the acute phase’ but the clinical outcome did not differ as compared with the patients who did not. Also, all patients with a new intracerebral haemorrhage were treated with anticoagulation. On the other side, a recent review of 88 cases of septic CST⁸ showed that a greater number of anticoagulated patients made a full recovery and fewer died, nevertheless without difference in morbidity. Interestingly, the question if patients with septic CS thrombosis should be screened for potential prothrombotic conditions after cure remains open. In a series of paediatric patients with septic CST, 62% had one or more prothrombotic factors.¹⁴

In our patient fatal SAH and intraventricular haemorrhage occurred 24 hours after the initiation of anticoagulation. SAH seems to be exclusively a complication of the anticoagulation treatment, although there are rare case reports of SAH as presenting sign of aseptic CST.¹³ Retrospectively, taking into consideration the age of the patient, the significant delay in establishing the diagnosis of septic CST, the previous use of antiplatelet agents and the scheduled operation, the haemorrhagic risk was high and the initiation of anticoagulation should have been deferred.

Learning points

- ▶ Septic cavernous sinus thrombosis (CST) is a life-threatening condition that requires early recognition and management, which includes broad-spectrum antibiotic treatment and incision and drainage of the primary focus of infection.
- ▶ Paranasal sinusitis is the most common source of infection leading to septic CST.
- ▶ Sphenoid sinusitis is difficult to diagnose until complications occur and drainage of sphenoid sinus is indispensable part of the treatment.
- ▶ The use of anticoagulation in septic CST is not without risks and the decision to its initiation should be taken in individual basis.

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Reminder of important clinical lesson

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