ORIGINAL ARTICLE

Septic Cavernous Sinus Thrombosis: An Unusual and Fatal Disease

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Background: Septic cavernous sinus thrombosis (CST) is a rare and fatal disease. Clinical presentations in the early stage are nonspecific, and the sensitivity of cranial axial computed tomography (CT) with thick section is low. This study analyzed the clinical manifestation and neuroimaging findings in patients with septic CST in a medical center in Taiwan.

Methods: This retrospective case series included nine patients with septic CST who had typical symptoms and clinical course, evidence of infection, and imaging studies which demonstrated cavernous sinus lesion, and who were treated between 1995 and 2003 at National Taiwan University Hospital.

Results: Seven (77.8 %) patients were more than 50 years old. Five (55.6%) had diabetes, and three (33.3%) had hematologic diseases. All cases were associated with paranasal sinusitis. The most frequent initial symptom was headache (66.7%), followed by ophthalmic complaints (diplopia or ophthalmoplegia, 55.6%; blurred vision or blindness, 55.6%), and ptosis (44.4%). Initial cranial images failed to identify CTS in all patients. Subsequent magnetic resonance imaging (MRI) or coronal contrast-enhanced CT (CECT) with thin section confirmed the diagnosis. Fungi were the most common pathogens (55.6%). The inhospital case-fatality rate was high (44.4%).

Conclusion: Due to the high case-fatality rate and low yield rate of blood cultures, fungal CST should be suspected in an immunocompromised patient with ophthalmic complaints that progress from one eye to the other. Coronal thin-section CECT may be a useful alternative to MRI as a diagnostic modality for this condition. [*J Formos Med Assoc* 2006;105(3):203–209]

Key Words: cavernous sinus thrombosis, diabetes, sinusitis, zygomycosis

Septic cavernous sinus thrombosis (CST) was first described by Duncan in 1821.[1] It is a rare infective disease, and had up to 80% mortality and 75% residual morbidity in the pre-antibiotic era.[2] Mortality (13.6%) and morbidity (23%) have remained high in the modern era due to delay in diagnosis.[3] Imaging studies such as contrast-enhanced computed tomography (CECT), magnetic resonance imaging (MRI) and venography have had a significant impact on the diagnosis of CST in recent decades.

Septic CST is an uncommon and fatal disease. Early diagnosis and aggressive treatment are very important. With the increasing prevalence of immunocompromised patients, the clinical features and pathogens of septic CST should be re-evaluated. The present study retrospectively analyzed the clinical features of septic CST in patients treated over a 9-year period.

Methods

This study was a retrospective case series. National

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Taiwan University Hospital (NTUH), a major teaching hospital in Taiwan with 2200 beds, provides both primary and tertiary medical care. The medical records and images of 149 patients hospitalized at NTUH from 1995 through 2003 with the discharge diagnosis of thrombophlebitis of intracranial venous sinuses were reviewed. Those with clinical diagnosis alone, no imaging study or spontaneous resolution of symptoms were excluded. Only cases with typical symptoms (such as fever, headache, facial pain, blurred vision or blindness, diplopia, and ophthalmoplegia) and clinical course, evidence of infection, and imaging studies that demonstrated cavernous sinus lesion were included in this study. Ophthalmologists or otolaryngologists were consulted to exclude fulminant sinusitis or ophthalmitis. Age, gender, underlying diseases, initial presentation, laboratory and microbiologic data, treatment courses and complications were recorded and analyzed.

Results

Septic CST was diagnosed in a total of nine patients (2 women; 7 men) during the study period. The median age was 62 years (range, 16–79 years). Seven (77.8%) patients were older than 50 years, and the remaining two younger patients had hematologic malignancy (cases 2 and 3; Table 1). Five patients had diabetes and three had hematologic diseases (Table 1). None of the patients had a recent history of steroid use. Pain was the most common initial presentation (Table 2), including either headache or facial pain in five (55.6%) patients and orbital pain in one (11.1%). The interval between onset of pain and diagnosis of septic CST ranged from 3 to 60 days (median, 17 days). All patients had ophthalmic complaints which began in the left eye (6 patients, 66.7%), right eye (2 patients, 22.2%), or both eyes (1 patient, 11.1%). Progression from one eye to the other occurred within 10 days in three (33.3%) patients. The most frequent ophthalmic complaints were blurred vision/blindness or diplopia/ophthalmoplegia. The diagnosis of septic CST was confirmed within 1–16 days of the first ophthalmic complaint (median, 4.5 days). Case 6 was referred from another hospital; he died quickly and the duration between ophthalmic complaint and diagnosis of septic CST was unknown.

Imaging studies revealed acute or chronic paranasal sinusitis in all nine patients with ethmoid (66.7%) and sphenoid (44.4%) sinuses most frequently involved. The causative pathogens of septic CST were identified from blood cultures in three patients with Gram-positive bacteremia (33.3%). Fungi were identified from sinus biopsy in five (55.6%) cases, which included zygomycete (3 patients), *Aspergillus* (1) and unidentified fungus (1). One patient died rapidly but no infectious etiology was identified. Case 8 underwent lumbar puncture and culture of cerebrospinal fluid was negative.

When severe headache or ophthalmic symptoms appeared, imaging studies were performed, which included cranial axial CECT in five (55.6%) patients, MRI in two (22.2%), and sinusal/orbital coronal CT without contrast in two (22.2%). However, none of these images focused on cavernous sinuses because CST was not initially suspected. Progression of symptoms and signs led to the performance of secondary imaging study, which confirmed the diagnosis of CST in seven patients, based on MRI in five patients, axial CECT in one, and coronal CECT with thin section (3-mm-thick sections) in one. Filling defects in the cavernous sinus and abnormal signals of cavernous sinuses on CT or MRI (identified in 8 of 9 patients) were the most common imaging findings (Table 2; Figures 1 and 2).

The inhospital case-fatality rate of the nine patients with CST was 44.4%. Three patients died within 5–16 days after the diagnosis of CST, and another patient died suddenly of unknown cause after recovery from the infection. Of the five patients who survived, two (40%) had sequelae of blindness or blurred vision. Case 4 developed ophthalmic symptoms after initial response to antibiotic therapy and operation for left frontal abscess, but recurrent septic CST with symptoms

Table 1. Clinical characteristics of nine patients with septic cavernous sinus thrombosis

Case	Age (yr)	Gender	Underlying diseases/ conditions	Initial presentations (delay between onset and diagnosis, d)	Primary foci of infection	Pathogens/ Isolated from	Outcome, complications/ Interval between diagnosis and death, d	Cause of death
1	62	M	Diabetes mellitus	Left facial pain (10), blurred vision (4), ophthalmoplegia (2)	Paranasal sinusitis	Zygomycete/ Sinus biopsy	Died (status post surgery and amphotericin B)/14	Sepsis
2	45	M	Chronic myeloid leukemia, allogenic stem cell transplantation, graft-versus-host disease	Left eye blindness (1)	Paranasal sinusitis	*Staphylococcus simulans*/blood	Survived, left blindness	–
3	16	F	Acute myelogenous leukemia, febrile neutropenia	Headache (3); left eye pain, eyelid swelling, ptosis and ophthalmoplegia (3)	Paranasal sinusitis	–	Died/5	Sepsis and persistent febrile neutropenia
4	71	M	Diabetes mellitus	Left proptosis and ophthalmoplegia (16)	Paranasal sinusitis	Fungus, unidentified/ sinus biopsy	Survived (status post surgery and amphotericin B)	–
5	57	M	Asthma	Headache, bilateral ptosis and right proptosis (15)	Paranasal sinusitis	*Peptostreptococcus micros*/blood	Survived	–
6	59	M	Diabetes mellitus	Left blindness and right facial palsy (unknown)	Paranasal sinusitis	Zygomycete/ sinus biopsy	Died/Unknown	Unknown
7	76	M	Chronic myeloproliferative disease	Right orbital pain (5); limited eye movement, blurred vision, ptosis and ophthalmoplegia (3)	Paranasal sinusitis	Zygomycete/ sinus biopsy	Died (status post amphotericin B)/16	Sepsis
8	79	M	Diabetes mellitus, atrial fibrillation	Headache (10); right ptosis, chemosis and ophthalmoplegia (5)	Paranasal sinusitis	*Streptococcus constellatus*/ blood	Survived, blurred vision	–
9	62	F	Diabetes mellitus, hypertension	Headache (60); acute loss of left eye vision (2)	Paranasal sinusitis	*Aspergillus*/ sinus biopsy	Survived, blurred vision (surgery, amphotericin B, oral voriconazole)	–

in the other eye developed 1.5 months after the previous episode.

Discussion

This study demonstrated several unique features of host factors as well as the etiologies of septic CST compared to previous reports. Patients in this study were older and more likely to be immunocompromised than in early reports.[4,5] Diabetes is a risk factor for many infectious diseases,[6] and was the most common underlying disease in this series. In contrast, diabetes was not emphasized as a risk factor for septic CST in other studies.[4,5,7] Fever was a very common presentation of septic CST (> 90%) in a recent review,[7] but only 33.3% of our patients had fever in the early stage. These

Table 2. Symptoms, signs and imaging findings in nine patients with septic cavernous sinus thrombosis

	n (%)
Symptoms/Signs	
Headache or facial pain	5 (55.6)
Diplopia or ophthalmoplegia	5 (55.6)
Blurred vision or blindness	5 (55.6)
Ptosis	4 (44.4)
Fever	3 (33.3)
Periorbital swelling or exophthalmos (proptosis)	2 (22.2)
Facial palsy or numbness	2 (22.2)
Photophobia	1 (11.1)
Orbital pain	1 (11.1)
Initial ophthalmic complaints: right/left/both	2 (22.2)/6 (66.7)/1 (11.1)
Progressed from one eye to the other	3 (33.3)
Imaging findings	
Orbital cellulitis or exophthalmos	5 (55.6)
Engorged ophthalmic veins	3 (33.3)
Sinusitis or sinus lesions	
Ethmoid	6 (66.7)
Sphenoid	4 (44.4)
Maxillary	3 (33.3)
Frontal	2 (22.2)
Filling defect in cavernous sinus	4 (44.4)
Contrast-enhanced and high-signal lesions on MRI	4 (44.4)
Increased density in cavernous sinus on CT	1 (11.1)
Abnormal finding in cavernous sinuses: right/left/both	2 (22.2)/3 (33.3)/3 (33.3)

CT = computed tomography; MRI = magnetic resonance imaging.

findings may be due to the greater number of immunocompromised patients and the older age in this series.

In this study, fungi, rather than Gram-positive bacteria, were the main pathogens. In previous studies, however, the most frequently isolated pathogen was *Staphylococcus aureus* from facial infections and paranasal sinusitis.[3,8] Other bacteria (such as streptococci, Gram-negative bacilli or anaerobic bacteria), fungi (such as zygomycetes or *Aspergillus*) or mixed infection were less frequently reported in septic CST.[3,5,9–11] The predominance of fungal infection in this study may have been due to the higher percentage of immunocompromised patients. Pathogens were isolated from blood in 70% of patients in a previous study[12] but in only 33.3% of patients in this series. The predominance of molds, which are seldom isolated from blood,[13] may explain this difference. The high inhospital case-fatality rate (44.4%) in this study illustrates the great importance of performing invasive diagnostic procedures early in immunocompromised patients in order to guide their management based on the findings. The higher rates of immunocompromise and zygomycosis seemed to contribute to the higher case-fatality rate in this series. All three patients with zygomycosis and one patient with acute myeloid leukemia with febrile neutropenia died.

Headache, including in the retro-orbital area, and ophthalmic symptoms (periorbital edema, chemosis, proptosis, ptosis and diplopia) are common initial complaints in patients with septic CST. Thus, early septic CST is not easily distinguishable from intrabulbal diseases, intraorbital lesions such as orbital cellulitis, or vasodysformation in

the cavernous sinus such as an aneurysm or arteriovenous fistula. Septic CST should, however, be highly suspected in the presence of sepsis, cranial nerve palsies and bilateral eye problems.[4,9,14,15] Rapid progression of symptoms to the opposite eye is an important distinguishing characteristic.[8] In this study, all patients had ophthalmic complaints. Initial bilateral involvement occurred in one patient and progression from one eye to the other occurred within 10 days in three. None of our patients had hypopituitarism, a rare complication of septic CST.[14]

Since septic CST is a rare condition with nonspecific initial presentation, it is often missed, underestimated, or diagnosed late. In this study, correct diagnosis was not made until a second imaging study was performed in seven of nine patients. Orbital and retro-orbital pain were the most common initial presentations. However, these symptoms are not pathognomonic for septic CST. This may explain why the diagnosis of CST was delayed from 3 to 60 days after onset of headache in this study.

The results of this study demonstrated the limitations of traditional CT with sections of 5–8 mm, which was not diagnostic for septic CST in five patients. Two cases received CT that only focused on the orbital cavity or sinuses, so cavernous sinus was not seen on the images. Only one case was diagnosed by traditional CT with 5–8-mm sections, and another did not receive CT at all. Traditional CT is often used as a rapid study for intracranial lesions, but failed to detect lesions in the cavernous sinuses in many cases.[8,16] Thin-section CECT (sections < 3 mm) is superior to traditional CT in evaluating the cavernous sinuses.[8,16] The axial scan shows indirect signs such as straightness of the lateral boundary of the cavernous sinuses, widening of the cavernous sinuses and engorged ophthalmic veins (Figure 1A).[16–19] Coronal scan is more sensitive for the detection of direct signs such as irregular filling defects, volume expansion or bulging of the lateral boundary of the involved cavernous sinuses. It is also easier to compare both cavernous sinuses and to evaluate intracavernous neural or vascular structures (Figure 1B).[19,20] Septic CST was diagnosed by MRI in most of our patients. MRI is more sensitive than CT in detecting septic CST because it can reveal vasography and more multiplanar sections.[17–19] Direct signs of CST on MRI include changes in signal intensity and in the size and contour of the cavernous sinuses; indirect signs include dilatation of the tributary veins, exophthalmos, and increased dural enhancement along the lateral border of the cavernous sinuses (Figure 2).[18] CECT with three-dimensional reconstruction can also reveal

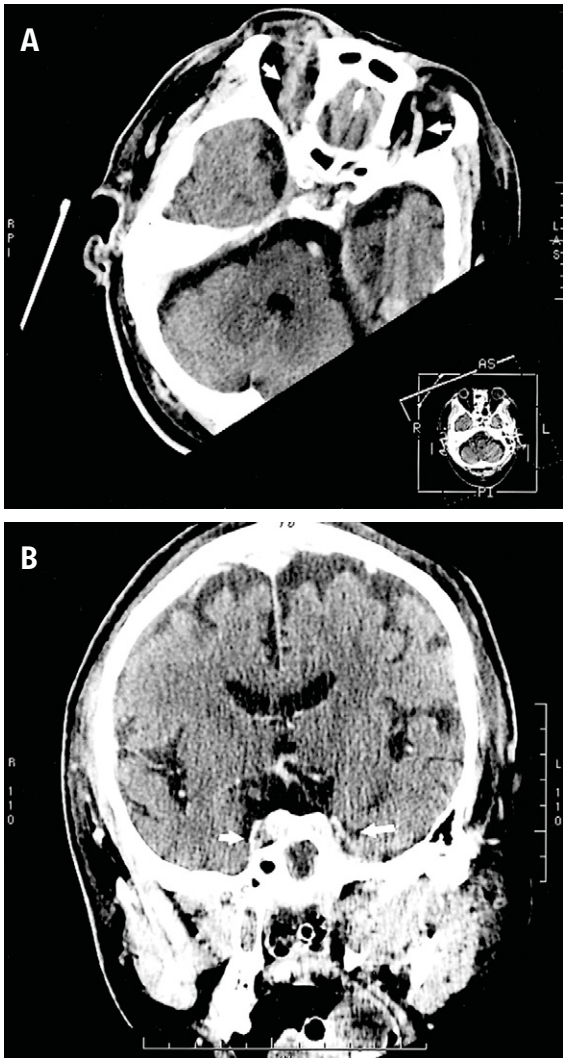

Figure 1. Case 8: (A) contrast-enhanced computed tomography (CT) with thin section (3-mm thick section) and three-dimensional reconstruction in the axial view reveals indirect signs of cavernous sinus thrombosis, including bilateral enlarged superior ophthalmic veins (arrows) and soft tissue in the right retrobulbar region, but does not show direct signs of abnormal cavernous sinuses; (B) coronal contrast-enhanced CT with thin section (3-mm thick section) reveals filling defects and bulges at bilateral cavernous sinuses (arrows).

vasography[21] and more multiplanar sections, as in case 8 of this series (Figure 1A), and may thus be a useful alternative to MRI.

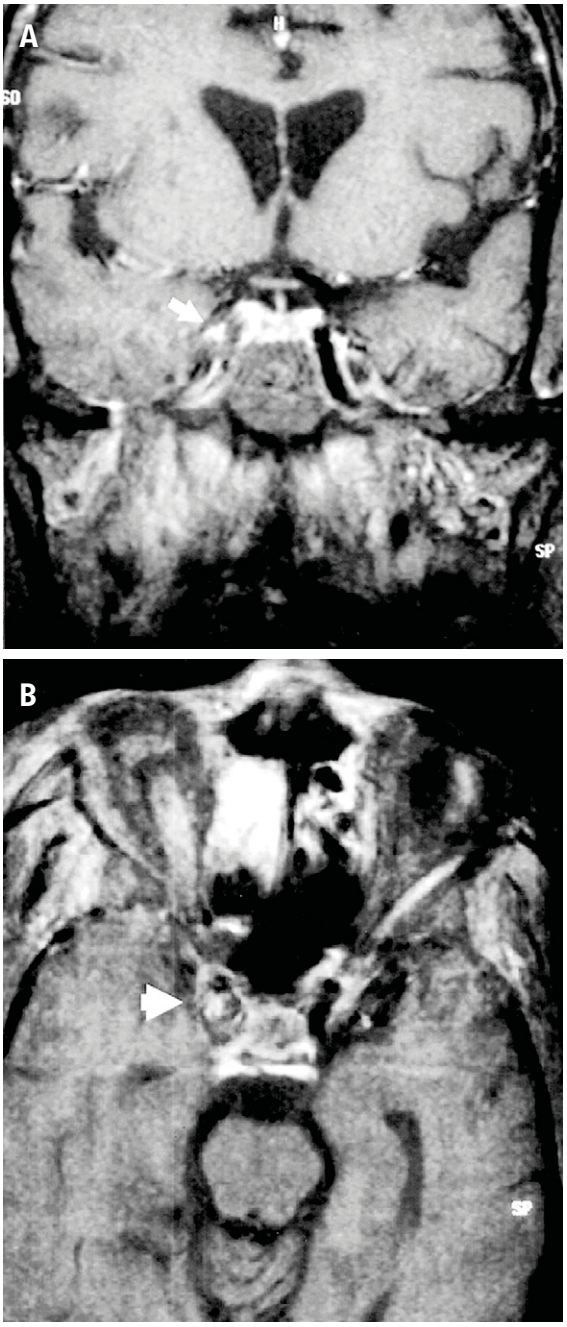

Figure 2. Case 7: (A) coronal T1-weighted magnetic resonance imaging (MRI) (TR/TE: 980/14) with Gd-DTPA contrast enhancement demonstrates diminished caliber and flow-void of the distal portion of the right internal carotid artery at the cavernous sinus segment (arrow). The right cavernous sinus discloses mild enlargement with abnormal enhancement. (B) Axial T1-weighted MRI (TR/TE: 980/14) with Gd-DTPA contrast enhancement shows abnormal signal intensity and enlargement at the right cavernous sinus, diminished caliber and flow-void of the distal portion of the right internal carotid artery at the cavernous sinus segment (arrowhead) and thickening mucosa and fluid collection in the right ethmoid sinus.

This study confirmed previous findings that sinusitis is the most frequent focus and that sphenoid and/or ethmoid sinuses are most frequently involved.[7,22] Dental infections, especially from maxillary teeth, and other infective foci, such as meningitis, otic or orbital infection, or tonsillitis, have been reported,[7,23,24] but there were no such cases in this series. With antibiotic treatment and surgical removal of the primary foci, septic CST secondary to these sites has become rarer.[7,8,23,24]

This study had several limitations. First, because only cases with a diagnosis of CST were included, and only image-confirmed cases were analyzed, the clinical importance of septic CST may have been underestimated in this retrospective study. Second, the small case numbers in this study cannot provide conclusive results concerning this rare disease. Third, as neurologists were consulted in less than half of the patients, the neurologic findings in Table 1 might have been underestimated. It was also difficult to confirm the diagnostic benefit of CT and MRI because these imaging modalities were not used simultaneously.

Conclusion

This study showed that fungi were the main pathogens of septic CST, typically occurring in immunocompromised patients, and were associated with a high case-fatality rate and a low yield rate from blood cultures. Thus, fungal CST should be considered in the differential diagnoses in immunocompromised patients presenting with headache and painful ophthalmoplegia. Progression of ophthalmic symptoms from one eye to the opposite eye is an important clue to the presence of septic CST. Coronal thin-section CECT (sections < 3 mm) may be a useful alternative when MRI is not available. Invasive diagnostic procedures, such as endoscopic sinus surgery or biopsy, may be necessary to allow early etiologic diagnosis and guide antimicrobial therapy, particularly in immunocompromised patients who have paranasal sinusitis.

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