Timely and Conservative Anticoagulation in Septic Cavernous Sinus Thrombosis: A Case Report

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ABSTRACT

Background: Cavernous Sinus Thrombosis (CST) is a rare and life-threatening condition with antibiotics as the mainstay of therapy for those due to infection. While controversy exists, recent retrospective reviews using anticoagulation reveal potential mortality reduction with a low risk of adverse events such as intracranial hemorrhage (ICH). The optimal timing and duration of treatment are unknown.

The Case: We report a 32-year-old female who presented with fever, headache, complete bilateral ophthalmoplegia, cellulitis, and a cranial MRV diagnostic of CST. She received antibiotics targeted to MRSA organisms isolated from eye and blood specimen. Further, into the course, the patient had an onset of aphasia and right-sided hemiplegia. Workup revealed multiple cranial infarcts with narrowing of the left internal carotid artery, likely representing thrombus as the source of embolism. The decision to anticoagulate was reevaluated and subsequently started. The patient was reassessed clinically after two months to have improved motor strength and speech return; thus, anticoagulation was discontinued.

Discussion: Although data are lacking, most recent reports favor the use of anticoagulation. Some authors recommend initiation in patients with deteriorating neurologic status despite antibiotics and hydration. The higher frequency of ICH in anticoagulated CST patients with CNS infection is a basis for some authors to withhold treatment. The treatment duration varies with different studies, generally ranging from several weeks to three months or more.

Conclusion: Further studies are needed to define the exact role of anticoagulation, particularly its timing and duration. Nevertheless, timely identification of the condition and constant re-evaluation are critical to early patient recovery.

Keywords: Septic Cavernous Sinus Thrombosis, Anticoagulation, Treatment Duration

INTRODUCTION

Cavernous sinus thrombosis (CST) is a rare, life-threatening condition with an annual incidence of 0.2 to 1.6 per 100,000 population, which may be due to either infection or non-infectious causes[1]. A majority is due to infection, and antimicrobial therapy is the mainstay of treatment. In the absence of guidelines and prospective clinical trials, the role of anticoagulation remains controversial. Most experts recommend anticoagulation as retrospective reviews reveal potential mortality reduction, favorable outcomes, and low risk of adverse events such as hemorrhage[1-3]. However, the optimal timing and duration of anticoagulation are unknown. While features and pathophysiology of CST overlap with cerebral venous thrombosis (CVT), many authors follow studies and guidelines on CVT, suggesting three months of treatment in thrombosis with a transient risk factor[3-5]. In other studies, the duration was variable, generally ranging from 2 to 6 weeks, two weeks to several months, to and three months or more.[2,3,6]

Furthermore, there is no consensus with regards to the discontinuation of treatment. Most reports rely on clinical or radiographic evidence of resolution of thrombus as a basis to terminate anticoagulation. In general, evidence regarding the timing and duration of anticoagulant use in CST is lacking.

THE CASE

We report a case of a 32-year-old female who developed orbital cellulitis initially involving the left eye. After two days, orbital cellulitis progressed to affect both eyes (*Figure 1*). Other manifestations included fever(38°C), tachycardia (115 bpm), headache, retroorbital eye pain, and complete bilateral ophthalmoplegia. Aside from bilateral orbital cellulitis, there were no external facial wounds or signs of infection. However, nasal drainage was absent in the history but with mild nasal congestion without discharge on otoscopy. Sinuses were non-tender. Additional pertinent findings include intact tympanic membranes and external auditory canals in

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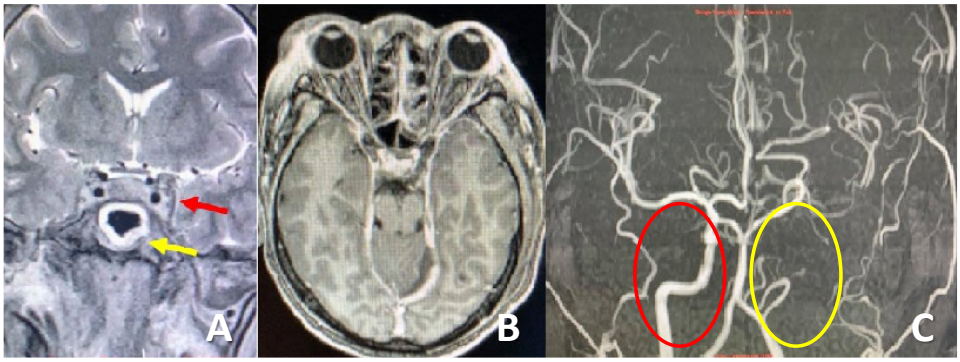

Figure 1 MRV and MRA findings: A.T2 hyperintensities representing areas surrounding the thickened and dilated cavernous sinus, more on the left (Red arrow), thickening of the mucosal lining of paranasal sinuses (Photo: sphenoid) – Pansinusitis (Yellow arrow) B. T1 axial post-contrast showing meningeal enhancement C. MRA revealing luminal flow void on the left ICA (yellow) as compared to normal on the right (red)

Figure 2 Resolution of bilateral orbital cellulitis. A. Bilateral ptosis, chemosis, and proptosis with bilateral discharges. B. Resolving of signs on the right eye, still with persistent cellulitis and discharges on the left. C. Resolution of discharges left eye with residual ptosis.

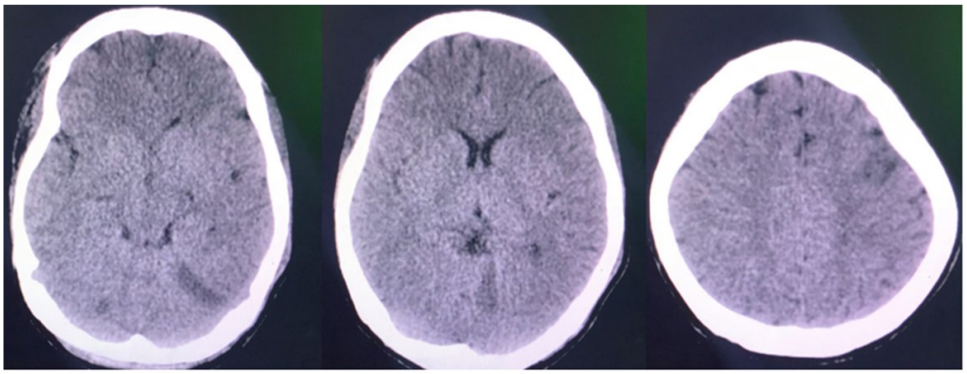

Figure 3 Computed tomography scan of the brain (Plain): Acute infarcts on left frontoparietal lobes and both cerebellar hemispheres

both ears. On neurologic examination, the patient was awake and oriented with no peripheral motor deficits. Pertinent findings include bilateral proptosis, chemosis, impaired ocular motility in all directions, and decreasing visual acuity. Headache and nuchal rigidity were also present. Leukocytosis (22 × 10^9 /L) with neutrophilic predominance (98%) on complete blood count. With the typical symptoms of fever, headache, and retroorbital pain accompanied by the classic signs of ptosis, chemosis, and extraocular dysmotility, the diagnosis of septic cavernous sinus thrombosis was considered. The patient was admitted and managed in the intensive care unit.

The differential diagnosis of CST includes rare conditions that may involve the cavernous sinus and present with ophthalmoplegia and retroorbital eye pain such as cavernous carotid fistula, lytic bone lesions near the Sella turcica, meningioma, superior orbital fissure syndrome, and Tolosa-Hunt syndrome[1]. These conditions usually do not present with sepsis and typically have a subacute to the chronic course. Cranial magnetic resonance venography (MRV), considered the test of choice, was done as this modality could also detect and rule out other possible differentials. MRV revealed irregular enhancement, thickening, and dilation, representing inflamed cavernous sinuses consistent with CST (*Figure 2*). Other findings included inflammation of periorbital tissues, enhancement of the basal cisterns, and pansinusitis. With an acute onset of the clinical picture and the presence of orbital cellulitis, fever, leukocytosis, and neutrophilic predominance, infection was the most likely etiology. Ceftriaxone, metronidazole, and vancomycin were started empirically and were later shifted to vancomycin monotherapy when blood culture specimen isolated Methicillin-Resistant Staphylococcus Aureus (MRSA).

The intimate anatomic relationship of the cavernous sinus with several important cranial structures and its valveless venous connections explains the tendency for local spread of infection, which most commonly occurs from facial infections, acute sinusitis, and periorbital infections[1]. Thus, despite cellulitis being present in our patient, an active effort to exclude other possible sources, including MRSA colonization sites were essential. Although with findings of sinusitis, reflected by nasal congestion on examination, and pansinusitis on MRV, the nasopharyngeal swab was negative for any organism. Cerebrospinal fluid cultures (CSF) analysis revealed elevated opening and closing pressures (>40cmH2O), high protein (1166mg/dL), and low glucose (36mg/dL), which were suggestive of bacterial meningitis. Lymphocytic pleocytosis (29/uL) and negative CSF cultures were attributable to CSF's possible sterilization with the empiric antibiotics. Because of prominent eye

involvement with positive cultures of eye discharges consistent with blood isolates and negative nasopharyngeal specimen and CSF, orbital cellulitis was considered the main cause of the entire clinical picture. It may have led to sinusitis and meningeal involvement through the local spread of infection.

Aside from antimicrobial therapy, supportive management included corticosteroids (dexamethasone), antipyretics, and intravenous hydration. Based on previous reports, anticoagulation in the presence of central nervous system infection may increase the tendency to hemorrhagic complications[7]; and with this in mind, anticoagulation was not given, especially with the patient clinically improving—the initial manifestations of septicemia (fever, tachycardia resolved early in the course. However, during the 5th hospital day patient was noted to have deteriorating neurological status. Upon assessment, the patient was awake, aphasic, follows commands, with right-sided paralysis having a motor strength of 0/5 in both right upper and lower extremities. Motor strength on the left upper and lower extremities was 5/5. There were no new cranial nerve deficits, reflexes were intact, and there were no cerebellar signs. Computed tomography (CT) scan of the brain revealed multiple small intracranial infarcts in both cerebellar hemispheres and left frontoparietal lobes (Figure 3). Embolic stroke was considered, and a search for a possible source was done. Magnetic resonance angiography revealed an absence of flow void in the intracavernous segment of the left internal carotid artery, denoting thrombosis and representing the most likely source for embolic stroke. An electrocardiogram, echocardiogram, and 24-holter monitoring to rule out possible cardiac sources of embolism were performed. Workup was negative for vegetation, thrombi, and rhythm disorders. Hence, the decision to start anticoagulation was reevaluated. With the resolution of sepsis and meningitis signs, the new neurologic deficit, and documentation of embolism and a thrombotic source, Low Molecular Weight Heparin (LMWH) was started. Enoxaparin was given subcutaneously at a dose of 1mg/kg twice a day. There were no adverse events during the whole duration of anticoagulation. The patient was noted to have slowly improved neurologic status. LMWH was given for two weeks and was shifted to warfarin upon discharge, with INR targeted at 2-3. Anticoagulation was given for a total of eight weeks, and the patient continued her physical rehabilitation.

DISCUSSION

While antimicrobial therapy has been the established mainstay of therapy, anticoagulation in CST remains controversial as there has been no clinical trial conducted because of the rarity of the disease. Guidelines are unavailable, and anticoagulation, particularly its initiation and duration, is based on expert opinion.[1] Data on earlier reviews have been conflicting.[8,9] The study by Southwick et al., which reviewed 86 cases of CST, suggested a reduced mortality rate in patients treated with heparin (14%) vs. those not treated with heparin (36%).[8] Levine et al., on the other hand, did not find conclusive evidence on mortality reduction.[9]

Several recent studies have seen a trend towards reduced mortality with anticoagulation.[2,3] One study reviewed 88 cases of CST and found fewer deaths, with a considerably more significant number of anticoagulated patients achieving full recovery.[2] A case series by van der Poel et al. also noted no mortality in 7 out of 11 patients treated with anticoagulation and complete or near-complete recovery among them.[8] In most studies, mortality was lower in patients in whom anticoagulation was given.[2,3,8]

The decision to start anticoagulation requires careful evaluation and consultation with a neurologist. Despite considerable overlap and differences in the two entities' pathophysiology, studies and guidelines in CVT management have been relied upon by many authors to treat CST.[1,3] Among these studies, a meta-analysis by Coutinho et al. (Cochrane Collaboration) showed a clear benefit of anticoagulation without bleeding complications.[4] The EFNS guidelines recommend using LMWH or low-dose intravenous heparin to manage CVT in patients without contraindications.[5] Nevertheless, it is important to consider that cavernous sinus thrombosis and septic thrombosis were not included in these trials.[3,5]

Many authors refrain from using anticoagulant therapy in the presence of meningitis[3,10]. In one study, a higher frequency of new intracerebral hemorrhage was found in anticoagulated patients in whom CNS infection was present or suspected[7]. A possible mechanism is dysregulation of coagulation and fibrinolytic pathways leading to massive clotting and depletion of coagulation factors, increasing the tendency to hemorrhage.[11] In our patient, the presence of clinical signs of meningitis and suggestive CSF findings served as the basis to withhold anticoagulation at least initially.

The timing and duration of anticoagulation in CST are areas less well-defined in the literature. Southwick et al. suggested that early administration of heparin may prevent the spread of thrombosis to the other cavernous sinus and the inferior and superior petrosal sinuses and that anticoagulation should only be considered if there is no evidence of cortical venous infarction clinically or by CT scan.[8] Therefore, imaging is required before even considering starting anticoagulation. Other sources recommend anticoagulation in venous thrombosis if there is neurologic deterioration despite antimicrobial therapy and intravenous fluids.[10] In our patient, the decision to anticoagulate was reconsidered with the onset of new neurologic deficits.

The optimal duration of anticoagulation is unknown. The EFNS recommends three months of treatment for CVT with transient risk factors such as infection.[5] In the case series by van der Poel et al., the majority of anticoagulated patients were also treated for 3 months.[3] In another recent review, the therapy duration was variable but shorter and generally ranged from 2-6 weeks, with a small proportion receiving treatment for three months or more.[2] Van der Poel et al. observed that

discontinuing anticoagulation in most patients was made clinically without repeat imaging.[3] In another literature review, some authors used either clinical or radiological evidence of thrombus resolution.[6] The thrombus resolution time was unknown but has been observed to be possibly less than three months in anticoagulated patients. They concluded by stating that long-term anticoagulation is unnecessary as long as there are no persisting factors for thrombosis in these patients[6]. In one report, evidence of radiographic resolution of thrombus has been described at six weeks of anticoagulation in patients with sinogenic CST.[12] Our patient received anticoagulation for a total of 8 weeks, at which time the patient was clinically stable and noted to have a steady resolution of neurologic deficits. The patient was further managed in conjunction with rehabilitative medicine.

CONCLUSION

With timely identification, CST treatment may be instituted promptly, and clinical improvement may be observed early. With knowledge of its potential advantages and risks, anticoagulation may be initiated. It may be given for less than the suggested three months, as long as clinical signs are resolving and the patient's neurologic status is improving. Hence, an advantage in minimizing both complications of the condition and potential toxic effects of therapy, particularly the risk of hemorrhage, may be seen. However, in the absence of prospective clinical trials and guidelines, further studies are needed to determine the optimal therapy for this condition

Informed Consent: The patient has authorized the use of this material. Informed consent was obtained after a thorough explanation of the patient's condition, the relevance of the case, and publication.

Declaration of Interests: The author declares there is no conflict of interest regarding the publication of this paper.

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