Superior Vena Cava Syndrome

An update on causes and treatments.

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Superior vena cava (SVC) syndrome is the constellation of clinical symptoms resulting from the obstruction of blood flow through the SVC. Causes include tumor compression or invasion and intraluminal thrombosis. An estimated 19,000 cases occur every year in the United States,[1] with increasing frequency concomitant to the prevalence of indwelling catheters.[2] There has been difficulty in setting up prospective randomized studies because patients may be excluded from a treatment limb due to exclusion criteria such as previous radiation therapy, chemosensitive disease, or obstruction not amenable to stenting.[3] The current data are mostly based on case series and individual experience. For chemosensitive and radiosensitive malignancies, treatment of the tumor will often cause regression of the SVC obstruction and resolution of the symptoms, but the length of time for symptom resolution may be delayed, and there is a high recurrence rate.[4] Endovascular therapy is being increasingly used as a rapid response to treatment-resistant tumors, benign thrombosis, and recurrent obstruction.

PATHOPHYSIOLOGY

Obstruction results from thrombosis formation or tumor infiltration of the SVC. The resultant upstream cervical venous pressure may be increased from 2 to 8 mm Hg to between 20 to 30 mm Hg,[5] which causes clinical manifestations, including facial and arm edema. Bilateral occlusion of the brachiocephalic veins can also produce similar symptoms. Collateral pathways arising from the internal thoracic, paraspinous, and esophageal veins return blood via either the azygos vein or the inferior vena cava.[6] These collateral pathways dilate over several weeks to further accommodate the venous hypertension, which can decrease the clinical severity of SVC syndrome symptoms. However, when collaterals have not yet developed or the azygos arch is also obstructed, there is impairment of collateral return and rapid development of symptoms.[7]

ETIOLOGY

Since its first description in 1757 as a complication of an aortic aneurysm, the major causes of SVC syndrome have evolved.[8] Infectious causes, such as fibrosing mediastinitis from tuberculosis and thoracic aortic aneurysm from syphilis, comprised the majority of cases until the mid-1900s.[1] With the use of antibiotics and the increase in cancer prevalence, bronchogenic carcinoma was reported as the cause in more than 90% of reported cases up until the late 20th century.[8] In recent years, the use of indwelling catheters and pacing wires has increased the incidence of thrombotic causes.[2] In a series of 78 patients with SVC syndrome, as reported in 2006 by Rice et al, 60% of cases were due to malignancy, and nearly 30% were due to intravascular devices.[8] Recent unpublished data from our group involving 43 affected patients showed only 16% of cases due to direct tumor invasion and 77% due to central venous catheters.

The pathogenesis of thrombotic SVC syndrome is multifactorial, including catheter-induced endothelial injury with smooth muscle proliferation and eventual fibrotic stenoses and increased turbulent flow through an arteriovenous fistula or arteriovenous graft in dialysis patients, stimulating intimal hyperplasia. The placement of catheters within the subclavian vein or on the left side of the neck are further risk factors for SVC obstruction due to vessel tortuosity and smaller vessel diameter. The longer the catheter dwell time, the higher the risk of vascular obstruction.[9] SVC obstruction is reported in 1% to 3% of patients with central venous catheters[10] and in 0.03% to 0.2% of patients with pacing leads.[11]

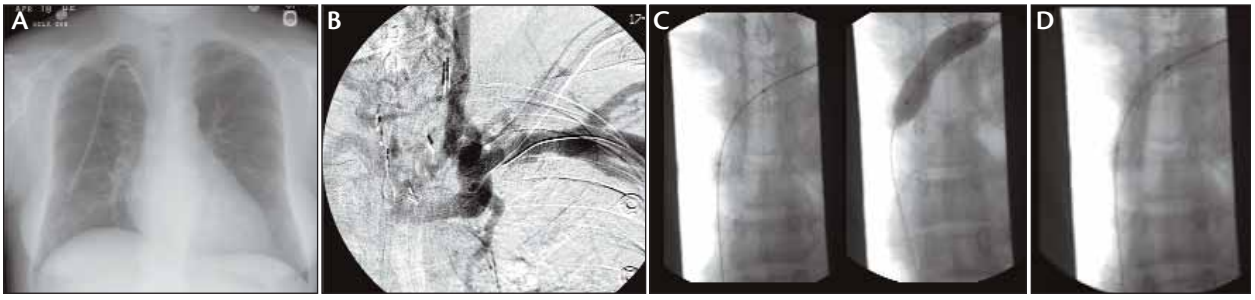

Figure 1. A patient with a history of multiple dialysis catheters who presented with head and neck swelling (A), occlusion of the left brachiocephalic vein and SVC (B), treatment with stenting and percutaneous transluminal angioplasty (PTA) (C), and good flow postprocedure (D).

CLINICAL PRESENTATION

The increase in venous pressure upstream from the SVC obstruction results in edema of the upper extremities, head, and neck. Facial swelling with periorbital edema and conjunctival suffusion may manifest as early signs and are most apparent in the morning.[6] Other common symptoms include dyspnea, cyanosis, and distension of the neck and chest veins, which can all be aggravated by lying supine or bending forward. Edema progressing to the larynx and pharynx is manifest by hoarseness, cough, and dysphagia and can be critical if the airway is compromised. Cerebral edema represents a more serious compromise and is manifest by headache, confusion, and obtundation; however, this is seen in < 10% of cases. Most patients develop symptoms progressively over the span of several weeks or longer, with some improvement as the collateral vessels develop.[1]

The diagnosis of SVC syndrome is based on these characteristics, and it is usually confirmed with computed tomographic (CT) imaging.[1,2] The presence of collateral vessels on contrast-enhanced CT is associated with a sensitivity and specificity of 96% and 92%, respectively, for SVC syndrome.[12] CT imaging also provides information regarding the extent, location, and etiology of the obstruction. Venographic confirmation is done at the time of endovascular intervention.

TREATMENT

The management of SVC syndrome has changed in recent years with advances in technology and a better understanding of the disease course. In the setting of malignancy, SVC syndrome was once considered a medical emergency that warranted urgent radiation therapy. However, it is now accepted that in clinically stable patients, a full diagnostic workup can be safely performed to assist in choosing an optimal therapy without worsening patient outcomes.[13] Endovascular therapy offers an effective, minimally invasive alternative with decreased mortality and morbidity rates. Thirty-day primary patency rates have been reported at 93% for both surgical and endovascular therapy. Periprocedural morbidity with surgical reconstruction has been reported as high as 19% to 30% when compared to 4% with endovascular therapy.[10,14] Patients often notice immediate clinical improvement while on the angiographic table after endovascular decompression, with complete resolution of symptoms within 24 to 72 hours.[15] The immediate increase in central venous return to the heart may predispose patients with underlying cardiac disease to cardiac failure and acute pulmonary edema after decompression. Periprocedural hemodynamic monitoring may help prevent this complication.

Medical and Surgical Management

Symptomatic maneuvers include elevation of the patient's head and administration of diuretics to reduce the venous load. Treatment-sensitive tumors, such as small-cell lung carcinoma, often respond to standard chemotherapy and radiation therapy and regress to the point of relief from SVC obstruction in 77% of cases treated with chemotherapy. Nonsmall cell lung carcinoma shows a response to chemotherapy in up to 60% of patients.[4] Recurrent stenosis is a common occurrence that is reported in 17% of patients treated with radiation and 19% of patients with radiation plus chemotherapy.[4] In addition, these modalities require 2 to 4 weeks for symptom resolution and include toxic effects such as nausea/vomiting, tumor necrosis, and radiation fibrosis. Due to the subsequent tumor hypoxia from the initial radiation therapy negatively affecting the effectiveness of further radiation, patients with recurrent symptoms are not candidates for repeat radiation.[16]

Historically, surgery has been the standard treatment for benign and refractory cases, including surgical bypass, recanalization, and venous grafting of the SVC. Case series of SVC reconstruction show patency rates of 80% to 90% with an operative mortality rate of approxi-

mately 5%.[1] However, the development of minimally invasive endovascular techniques has rendered surgical approaches less common. The limitation of surgical bypass is that it involves a radical surgery that includes a sternotomy, and its practice is now reserved for resistant cases.

In patients with obstruction secondary to intravascular devices, the first step is removal of the device with systemic anticoagulation to prevent thrombus propagation; there may be no need for further treatment if there is thrombus resolution. When further treatment is required, endovascular therapies have added to the selection of available treatment options, improving the overall outcomes.

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Endovascular Therapies

Endovascular repair has several advantages including decreased morbidity and shorter recovery times. Not only is it the fastest way to relieve symptoms in most patients, but it will also not affect the ability to administer subsequent radiation or chemotherapy. The principal endovascular therapies in use today include thrombolysis, PTA, and stenting (Figure 1). Depending on the presentation of the patient, any combination of these techniques may be employed in a single setting. These therapies provide rapid symptomatic relief with efficacies comparable to surgery and high patency rates for recurrent obstructions. Primary patency is defined as the length of time a vessel remains patent after initial therapy without the need for further intervention, whereas secondary patency signifies the length of patency in which repeated intervention was required to maintain or re-establish patency. Technical success for this technique is high, ranging from 88% to 95%.[10,17]

Thrombolysis. Thrombolysis is typically used as an adjunct to PTA and stents to decrease the amount of thrombus and embolic material and expose the underlying stenosis for subsequent intervention.[16] It is most effective when used during the acute phase of extensive thrombosis.[18] The tip of an infusion catheter is placed within the thrombus, and the thrombolytic agent is infused at a slow rate.[19] The typical regimen of thrombolysis involves an agent, such as tissue plasminogen activator, infused at a rate of 0.02 mg/kg/hour over 24 to 48 hours.[20] During the infusion, patients are systemically treated with intravenous low-dose heparin. Fibrinogen (maintain level > 100 mg/dL) and partial thromboplastin times (therapeutic levels should be avoided due to bleeding risk) are measured before infusion and monitored every 6 hours during therapy.[17] After the procedure, patients are treated with intravenous heparin until they are converted to oral warfarin, with the goal of an international normalization ratio of 2 to 2.5 for 4 to 6 months, then the regimen may be changed to an oral antiplatelet agent such as aspirin. Although low-dose anticoagulation has been used in attempts to prophylactically prevent clot formation, there is no clear consensus on the role of anticoagulation. However, in a prospective study by Bern et al, there was a significant reduction in the incidence of SVC syndrome when low-dose warfarin (1 mg/day) was implemented.[21]

An early series of 16 patients by Gray et al reported successful thrombolysis in seven of the eight patients treated < 5 days after the onset of symptoms.[22] After 5 days, however, success was seen in only two of eight patients. Clearly, the utility of thrombolysis as monotherapy is limited. In a subset of 26 patients treated with thrombolysis alone, Kee et al reported complete symptomatic relief in only 15%.[17] This low efficacy may be due in part to the fact that most cases of SVC syndrome are complicated by the presence of an underlying mechanical stenosis (due to fibrosis or mass) that is not amenable to thrombolysis. Given the potential bleeding complications, some investigators advocate thrombolysis only in the setting of extensive occlusion.[18] Percutaneous mechanical thrombolysis techniques are also in use but with limited outcomes data available.

PTA. Data regarding the use of PTA as monotherapy are sparse. A study by Rizvi et al included a subset of four patients treated with PTA alone and 19 patients treated with PTA followed by stenting showed improved secondary patency associated with PTA plus stenting at 3 years (88% vs 100%; $P = .02$).[10] This may be due, in part, to the elastic and fibrous nature of venous tissue, rendering it less amenable to long-term patency with angioplasty alone. For recurrent obstruction, PTA is often successful in secondary intervention for recurrent obstruction.

Endovascular stenting. Stenting is currently the first line of treatment in the setting of emergent symptoms and for recurrent obstruction after the use of chemotherapy and radiation.[17,23] Stents are often used in conjunction with thrombolysis and PTA in the cases of extensive thrombus or tight stenotic lesions. The technical success rate of endovascular stent placement is between 95% to 100%.[24] Symptomatic improvement

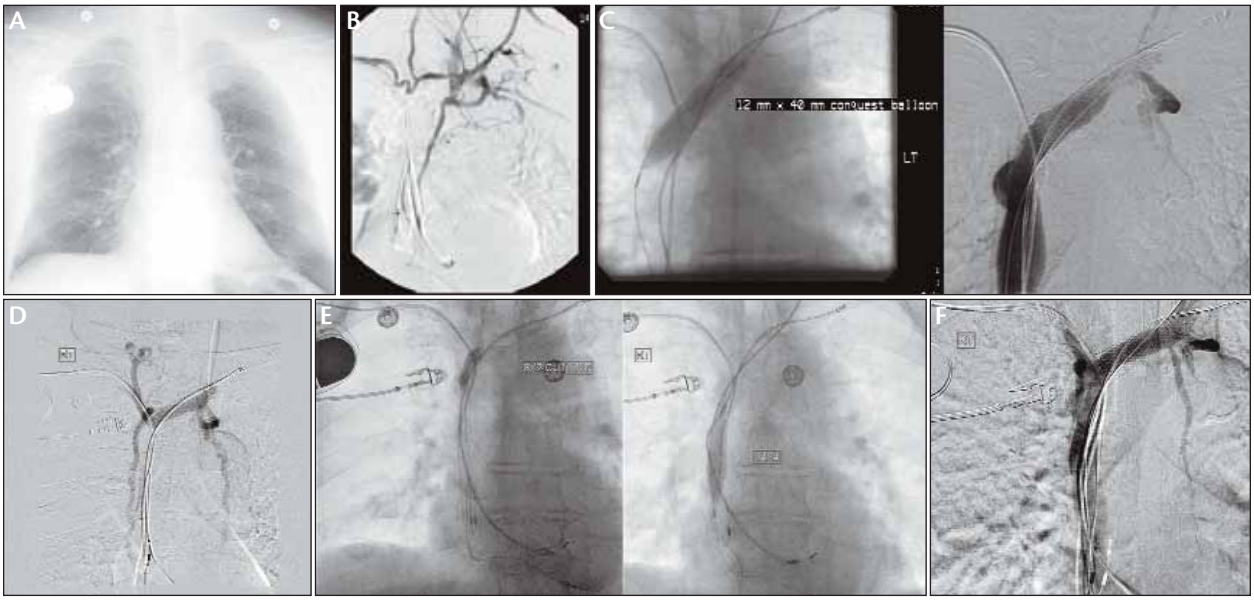

Figure 2. A patient with a history of pacemaker wire leads in the bilateral brachiocephalic veins who presented with thrombus and head pressure (A). A thrombolysis catheter at the confluence of the left brachiocephalic vein and SVC (B), successful PTA and stent implantation to recanalize the obstruction (Conquest, Bard Peripheral Vascular, Tempe, AZ) (C), recurrence of symptoms 2.5 years later (D), reintervention with PTA (E), and good flow postprocedure (F).

is typically seen within 48 to 72 hours.[1] Data from case series describe primary patency rates of 77% to 85% at 17 months.[18] In a systematic review, the relapse of obstruction for SVC stenting procedures was lower than with chemotherapy and radiation at a rate of 11%.[4] The majority of these recurrences are successfully treated with reintervention. Secondary patency rates are reported up to 85% to 91% at 17 months.[18]

With respect to bilateral brachiocephalic obstructions, placement of a unilateral stent has the advantage over bilateral stents that future access to the SVC can be obtained through the nontreated side. Unilateral stents have been found to relieve symptoms as effectively as bilateral placement while still allowing existing collaterals to continue to drain through the contralateral vein via the cervical and intracranial route. In addition, fewer complications, such as poor positioning or shortening of the stent, have been observed with unilateral stenting.[15,25]

The diameter of a stent is sized to be 10% to 20% larger than the normal vein in an attempt to avoid stent migration.[25] Stents are placed across an obstruction, spanning both above and below the obstruction. Multiple stents may be placed in series to bridge the stenotic area; this technique is used in 16% of cases according to one retrospective study.[26] Stents are divided into two types: self-expanding and balloon-expandable. The type of stent used is determined by the diameter, length, and location of the stenosis. Gianturco Z-stents (Cook Medical, Bloomington, IN) are large-diameter stents that have excellent radial expansile strength but have wide gaps between the stent wires, predisposing them to restenosis by tumor ingrowth. Palmaz balloon-expandable stents (Cordis Corporation, Warren, NJ) have high radial strength but are inflexible and short in length. Wallstents (Boston Scientific Corporation, Natick, MA) are self-expanding, stainless steel stents that have less radial strength but are flexible and longer in length. Nitinol self-expanding stents are placed easily and accurately but have a maximum usable size of 14 mm, which is often too small for the SVC. Stent effectiveness has been shown to range from 81% to 100% and is unrelated to the type of stent utilized.[27]

PROGNOSIS

Rizvi et al compared 3-year outcomes data for patients with SVC syndrome that were treated with either open-surgical reconstruction or endovascular repair that included a combination of thrombolysis, PTA, and stenting. The two techniques had equivalent efficacies, with primary and secondary patency rates at 45% and 75% for surgery and 44% and 96% for endovascular repair, respectively. Although endovascular intervention required a greater number of secondary interventions (typically within 6 months), recanalization was

successful in the majority of cases.[9] Complication rates for endovascular therapy are reported at 3% to 7% and include stent thrombosis, migration, infection, bleeding, pulmonary embolism, and rarely, perforation.[1]

Among the available endovascular interventions, there is no clear consensus on the efficacy of primary PTA versus primary stenting. The primary and secondary patency rates for primary stenting range from 11% to 70% and 71% to 100%, respectively, whereas the primary and secondary patency rates for primary PTA range from 12% to 29% and 73% to 100%, respectively.[14] There is also no agreement on whether thrombolysis before PTA or stenting improves long-term patency. In patients presenting with acute/subacute thrombosis (< 4 weeks), there may be a benefit in thrombolysis before PTA or stenting.[10] The endovascular treatment algorithm that is used is largely operator-dependent with no large-scale prospective studies available to identify significant differences in patency.

The morbidity and mortality rates associated with SVC syndrome are mostly a function of the underlying benign or malignant disease process. Serious side effects of SVC syndrome are unusual and are related to airway obstruction or cerebral edema. In a series of 1,986 patients with SVC syndrome, only one death was documented.[28]

CONCLUSION

SVC syndrome is a disease with shifting etiologies and expanding treatment options. As the use of central venous catheters has increased, so has the proportion of cases due to intraluminal thrombosis. Endovascular therapy is now considered appropriate first-line treatment for SVC syndrome, regardless of benign or malignant etiology.[10,15] It is a minimally invasive option with lower morbidity rates when compared to surgical therapy. Although multiple interventions are the rule, endovascular therapy is efficacious with high primary and secondary patency rates. Thrombolysis, PTA, and stenting are often utilized in combination approaches for effective and rapid relief of symptoms (Figure 2). ■

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