Management of Deep Vein Thrombosis of the Upper Extremity

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Case 1: A 34-year-old previously healthy male office manager was admitted with acute onset of heaviness, pain, and functional impairment of his right arm. The arm was cyanotic and massively swollen (Figure 1). For the past weeks, he reported transient paresthesia of his right arm during overhead activities and was unable to perform repetitive or strenuous arm exercise. He had a fracture of the right clavicle after a ski accident 5 years previously. The fracture was managed conservatively. There was no personal or family history of thrombosis. Conventional phlebography confirmed axillary and subclavian vein thrombosis (Figure 2, top), and treatment with intravenous unfractionated heparin was started.

Case 2: A 55-year-old man with lung cancer presented with swelling, heaviness, and pain in his left arm 1 week after completion of chemotherapy administered via a left-sided indwelling central venous catheter. Axillary and subclavian vein thrombosis was confirmed by ultrasonography. Low-molecular-weight heparin (LMWH) was initiated, and the catheter was removed 3 days later because it was no longer functional. At 1 week, pain and functional impairment had not improved, and the circumference of the left upper arm had increased by 2 cm.

Case 3: A 65-year-old woman with metastatic ovarian cancer presented with swelling of the face and both arms, headache, shortness of breath, and confusion. Contrast-enhanced computed tomography showed a large mediastinal tumor mass compressing the superior vena cava (SVC) and thrombosis of both innominate and subclavian veins. Treatment with intravenous unfractionated heparin was initiated.

How should these 3 patients be further evaluated and managed?

Classification and Risk Factors

Upper-extremity deep vein thrombosis (UEDVT) accounts for ∼10% of cases of deep vein thrombosis. The prevalence appears to be increasing, particularly because of an increased use of indwelling central venous catheters.1,2 Proximal UEDVT is defined as thrombosis involving the axillary or more proximal deep arm veins. Axillary and subclavian veins are most frequently affected. Primary UEDVT is less common than secondary forms. The most common primary form is effort-related thrombosis, also called Paget-Schroetter syndrome. It usually occurs in otherwise healthy young men who report, before the onset of thrombosis, vigorous arm exercise such as lifting weights, playing badminton, pitching a baseball, or performing repetitive overhead activities such as painting or car repair. Most patients with effort-related UEDVT have an underlying venous thoracic outlet syndrome (VTOS). VTOS results in compression of the subclavian vein because of anatomic abnormalities within the anterior part of the thoracic outlet triangle, bordering the intersection of the clavicle and first rib with the subclavian muscle and the costoclavicular ligament anteromedially and the anterior scalene muscle posterolaterally. Repetitive microtrauma to the subclavian vein intima, with subsequent fibrosis and activation of the coagulation cascade, elicits effort-related thrombosis.

In patients with idiopathic UEDVT, no obvious risk factor or underlying VTOS can be identified. Thrombo-
philia testing is less often abnormal in patients with UEDVT than in patients with thrombosis of the lower extremity. However, patients with idiopathic UEDVT more often have positive test results than patients with effort-related or catheter-associated UEDVT. Catheter-associated UEDVT accounts for the vast majority of secondary forms, resulting mainly from indwelling central venous lines or port systems and less frequently from pacemaker or defibrillator leads. The rate of clinically overt UEDVT after central venous catheter placement varies between 5% and 28%. However, systematic screening revealed thrombosis in up to two thirds of cancer patients with central venous catheters. Patient-related risk factors include the presence of cancer, particularly ovarian or lung adenocarcinoma, presence of distant metastases, personal history of thrombosis, and thrombophilia. Catheter-related risk factors include subclavian venipuncture, technically difficult or left-sided catheter placement, location of the catheter tip not at the atroio caval junction, prior central venous catheterization, and large-lumen catheters. Implanted ports are associated with a lower risk compared with peripherally inserted central catheters. Treatment-related risk factors are radiation therapy of the chest, bolus chemotherapy, and parenteral nutrition.

Even in the absence of central venous catheters, cancer is often the cause of secondary UEDVT, with cancer-induced prothrombotic states or venous stasis resulting from vein compression or infiltration as contributing factors. Up to one quarter of patients who were thought to have idiopathic UEDVT are subsequently diagnosed with cancer (predominantly lung cancer and lymphoma). Other risk factors for secondary UEDVT are surgery on, trauma to, or immobilization of the arm; pregnancy; oral contraceptive use; and the ovarian hyperstimulation syndrome.

Any condition leading to obstruction of blood flow through the SVC may cause the SVC syndrome. Subsequent thrombosis of the innominate and subclavian veins may occur with severe SVC stenosis. The malignant SVC syndrome is caused by tumor infiltration or compression of the SVC with lung cancer, non-Hodgkin lymphoma, and thymoma accounting for the majority of cases. In the preantibiotic era, the nonmalignant SVC syndrome often resulted from fibrosing mediastinitis, syphilitic thoracic aortic aneurysms, tuberculosis, and other infections. Nowadays, most nonmalignant SVC syndromes are caused by indwelling central venous catheters or pacemaker leads.

Clinical Manifestations

Patients with UEDVT typically present with heaviness, discomfort, pain, paresthesia, and swelling of the affected arm.
Many patients with catheter-related UEDVT have no symptoms of venous obstruction, and the inability to draw blood from the catheter or fever caused by catheter infection may be the presenting problem. Physical examination may reveal pitting edema, redness, or cyanosis of the involved extremity; visible collateral veins at the shoulder or upper arm; and fever.

The severity of the SVC syndrome depends on the dynamics of SVC obstruction in relation to the recruitment of venous collaterals, which normally takes several weeks. Patients may present with acute symptoms when a rapidly invading malignancy obstructs the SVC before sufficient collateral flow has been established through the azygos and hemiazygous veins into the inferior vena cava. In contrast, symptoms develop over years in patients with fibrosing mediastinitis. Shortness of breath, facial swelling and head fullness, cough, hoarseness, nasal congestion, epistaxis, hemoptysis, and dysphagia are the most common presenting symptoms. Physical examination typically reveals edema and venous distension of the upper chest, neck, and face; facial plethora, conjunctival injection, upper-body cyanosis, and arm edema are less frequently observed. Severe SVC syndrome may cause life-threatening airway obstruction with stridor resulting from laryngeal and pharyngeal edema and confusion, coma, or death caused by cerebral edema.

**Complications**

UEDVT causes fewer complications than thrombosis of the lower extremities (Table). The risk of pulmonary embolism after UEDVT is very low. Lower rates of pulmonary embolism have been reported for primary UEDVT compared with catheter-associated UEDVT. The risk of recurrence after UEDVT is increased during the first 6 months, whereas in patients with lower-extremity thrombosis, late recurrence beyond 6 months is common. Risk factors for recurrent UEDVT are cancer, female sex, high body mass index, and possibly thrombophilia. Central venous catheter removal at the time of thrombosis is associated with a lower risk of recurrence compared with leaving the catheter in place. However, in case of catheter removal and immediate replacement in another site, the risk of new-site UEDVT is increased.

In contrast to the standardized Villalta scale for the assessment of the postthrombotic syndrome (PTS) of the lower extremities, no such standard exists for upper-extremity PTS. This might explain the large variation in PTS rate (7%–46%) reported in a recent systematic review. Quality of life is reduced in patients with PTS of the dominant arm; however, severe PTS with skin ulceration is rare. Catheter-associated thrombosis is associated with a low risk of PTS. The risk of developing PTS may be greater in patients with subclavian vein thrombosis and in patients with residual vein obstruction at 6 months. However, no association between ultrasound findings and the development of PTS was found in a recent study. In patients with thrombosis resulting from VTOS, up to 53% of patients treated with anticoagulation alone developed PTS at 5 years. Because of the high prevalence of cancer, the 3-month mortality rate is at least as high in patients with UEDVT as in patients with lower-extremity thrombosis.

**Diagnosis**

In contrast to lower-extremity thrombosis, no validated integrated diagnostic strategy exists for UEDVT that encompasses estimation of the clinical pretest probability, D-dimer testing, and imaging confirmation. A clinical prediction rule including 4 items (central venous catheter or pacemaker, +1; pain, +1; unilateral pitting edema, +1; and presence of an alternative diagnosis, −1) is available. However, in patients with a low probability score (≤0 points), 13% were diagnosed with UEDVT, suggesting that this score is too insensitive to be considered reliable. Similarly, D-dimer testing is not routinely recommended because most patients with suspected UEDVT have elevated D-dimer levels owing to comorbidities, recent procedures, or indwelling central venous catheters.

Whereas venography remains the gold standard for diagnosing UEDVT, it has been largely replaced by ultrasoundography as the initial diagnostic modality. In a recent review including 6 studies, compression ultrasonography had a sensitivity of 97% and a specificity of 96%. The use of color Doppler is helpful for the evaluation of the proximal subclavian and innominate veins, where compression is not possible because of overlying bony structures. An additional imaging test may be required if the physiological variability of the Doppler flow velocity with normal respiration or with the Valsalva maneuver is reduced or absent. Neither the safety of withholding anticoagulation treatment if ultrasonography is negative nor the diagnostic strategy with serial ultrasonography has been evaluated for patients with suspected UEDVT. Both contrast-enhanced computed tomography and magnetic resonance imaging are useful not only to confirm UEDVT but also to diagnose concomitant pathologies, including cancer, adenopathy, or anatomic abnormalities suggestive of the VTOS.

**Management**

Treatment aims to alleviate symptoms, to prevent progression of thrombosis,
and to reduce the risk of pulmonary embolism, recurrence, and PTS. Most recommendations for the management of UEDVT were derived from data of patients with lower-extremity thrombosis (Figure 3).10

Anticoagulation Therapy, SVC Filters, and Mechanical Therapy

Anticoagulation therapy should be undertaken with a once-daily regimen of LMWH or fondaparinux for at least 5 days, followed by vitamin K antagonists for at least 3 months.10 Compressions sleeves or bandages are not recommended in the acute phase but may be useful for the treatment of PTS.10

Unfractionated heparin instead of LMWH is recommended for patients with renal failure or for those treated with catheter-directed thrombolysis (CDT). According to a meta-analysis of 22 trials of lower-extremity thrombosis, LMWH reduced the rates of recurrence, major hemorrhage, and mortality compared with unfractionated heparin therapy.17 In contrast to idiopathic lower-extremity thrombosis, extended anticoagulation therapy beyond 3 months is generally not recommended after a first episode of idiopathic proximal UEDVT. In patients with cancer-associated UEDVT, extended LMWH monotherapy is preferred over the administration of vitamin K antagonists. Anticoagulation therapy should be continued as long as the cancer remains active if the thrombotic event was not related to a central venous catheter. After the first 3 to 6 months, anticoagulation therapy may be continued with LMWH or with vitamin K antagonists. In patients with catheter-associated UEDVT (with or without cancer), anticoagulation therapy can be discontinued after 3 months if the central venous catheter is removed; if the catheter is not removed, anticoagulation therapy should be continued as long as the catheter remains.10

Figure 3. Suggested algorithm for the management of acute upper-extremity deep vein thrombosis (UEDVT). Recommendations were adapted from the 2012 consensus guidelines of the American College of Chest Physicians10 with the levels of evidence graded as follows: Grade 1B indicates strong recommendation with moderate-quality evidence; grade 2B, weak recommendation with moderate-quality evidence; and grade 2C, low- or very-low-quality evidence. CVC indicates central venous catheter; LMWH, low-molecular-weight heparin; SVC, superior vena cava; and UFH, unfractionated heparin. *Includes vitamin K antagonist, LMWH, dabigatran, or rivaroxaban.
An SVC filter should be placed only in exceptional situations. Major complications include cardiac tamponade and aortic perforation in up to 4% of SVC filter insertions.

**SVC Syndrome**
The management of the SVC syndrome depends on the clinical severity and the underlying cause. First-line treatment for patients with severe symptoms is early stent placement for both malignant and nonmalignant SVC syndromes. When extensive thrombosis is present, CDT should be performed, followed by stenting if a mechanical obstruction persists. For the malignant SVC syndrome, current guidelines underscore the importance of an accurate histological diagnosis before specific therapy is started. An exception to this general approach is patients with life-threatening symptoms in whom immediate treatment with stenting and radiotherapy is required.

**Catheter Intervention**
Early thrombus removal and restoration of venous patency aim at reducing the risk of PTS. Catheter-based therapy is recommended for patients with proximal UEDVT of recent onset and severe symptoms, low risk for bleeding complications, and good functional status.

In a retrospective study of 30 UEDVT patients treated with CDT using recombinant tissue-type plasminogen activator, >50% clot lysis was observed in 97% of patients, with major bleeding complications in 9% and mild PTS in 21%. Pharmacomechanical thrombolysis is defined as CDT combined with a mechanical catheter intervention such as rheolytic thrombectomy with the AngioJet system. Ultrasound-assisted thrombolysis with the EkoSonic Endovascular System is another catheter intervention technique. Ultrasound alone cannot dissolve thrombus, but it facilitates CDT by disaggregating fibrin strands, increasing thrombus permeability, and dispersing thrombolytic drug through acoustic microstreaming effects. Compared with CDT, both pharmacomechanical thrombolysis and ultrasound-assisted thrombolysis may reduce thrombolytic infusion time, duration of hospital stay, and costs.

In the absence of VTOS, surgical therapy, including thrombectomy and venous bypass, should be reserved for refractory cases because these procedures are invasive, carry the risk of anesthesia, and may be complicated by phrenic nerve or brachial plexus lesions, lymphatic fistula, and hemopneumothorax.

**Paget-Schroetter Syndrome**
A multidisciplinary approach consisting of anticoagulation therapy, CDT, or pharmacomechanical thrombolysis and subsequent surgical correction of VTOS is the current standard of care. Physical therapy alone without surgical correction may reduce symptoms in patients with arterial or neurogenic thoracic outlet syndrome, but there is no firm evidence to support this approach in patients with VTOS. Surgical decompression involves resection of the first rib and costoclavicular ligation, anterior scalenectomy, and venolysis. The optimal timing of surgical decompression, ie, immediately after CDT compared with 1 to 3 months later, remains controversial. Although early decompression seems to be effective and safe with earlier return to previous activity, it is possible that a certain number of patients would be overtreated with this strategy. In patients who are managed with CDT and without immediate surgical decompression, the indication for surgery should be assessed during a follow-up visit at 1 to 3 months. If symptoms of venous obstruction persist (swelling, heaviness, or pain) with evidence of residual subclavian vein stenosis by positional venography, surgical decompression is warranted. It also remains controversial whether angioplasty with or without stenting should be performed routinely in cases in which residual venous stenosis persists after surgical decompression. Stenting of the subclavian vein at the costoclavicular junction without surgical decompression is not advised because of the high rate of stent fracture and reocclusion. Further study is needed to define the optimal combination and timing of the different treatment modalities.

**Catheter-Associated Thrombosis**
Whether a catheter should be removed in patients with UEDVT depends on several factors (Figure 3). If a catheter is occluded, an attempt to restore patency can be performed by instillation of thrombolytics, with 1 or 2 doses of 2 mg recombinant tissue-type plasminogen activator. If a catheter is still needed, functional, and well placed, it is safe to maintain the catheter. In a cohort study of 74 cancer patients with symptomatic catheter-associated UEDVT, 57% had a functional catheter at 3 months; the remaining 43% had the catheter removed but none because of catheter failure or recurrent thrombosis. The optimal timing of catheter removal has not been evaluated, but it is usually appropriate to remove the catheter after 3 to 5 days of anticoagulant therapy.

**Cases, Continued**
For case 1, pharmacomechanical thrombolysis (intraclot delivery of 10 mg recombinant tissue-type plasminogen activator via PowerPuls spray) was performed with the DVX AngioJet catheter device. Control venography showed restored patency of the right subclavian vein (Figure 2, middle). Symptoms and signs of UEDVT improved rapidly (Figure 1, right), and the patient was discharged on vitamin K antagonists. At 1 month, the patient was asymptomatic at rest but complained of persistent exertional discomfort and swelling of the arm. Positional venography confirmed residual venous stenosis at the level of the costoclavicular junction during arm abduction (Figure 2, bottom). Surgical decompression was complicated by a lymphatic fistula requiring reoperation. At 3 months, the patient was asymptomatic with normal ultrasonographic findings, and anticoagulation therapy was stopped.

For case 2, ultrasound-enhanced CDT (20 mg recombinant tissue-type plasminogen activator over 15 hours) was
performed. Venography demonstrated patency and residual stenosis of the left innominate vein, which was successfully treated with a self-expanding nitinol stent. At 3 months, the patient was asymptomatic with normal ultrasonographic findings. Anticoagulation therapy with LMWH was continued because of ongoing cancer chemotherapy.

For case 3, ultrasound-enhanced CDT (20 mg recombinant tissue-type plasminogen activator over 15 hours) resulted in successful thrombus removal from the innominate and subclavian veins. Residual severe stenosis of the SVC was treated with a self-expanding nitinol stent. Radiotherapy and chemotherapy were initiated later. At 3 months, the patient had no symptoms or signs of the SVC syndrome, and repeated contrast-enhanced computed tomography demonstrated venous patency and substantial shrinking of the mediastinal tumor mass. The patient continues to self-administer once-daily LMWH injections.

Disclosures
Dr Kucher reports being a consultant for EKOS Corp and MEDRAD and having received honoraria from Sanofi-Aventis, Boehringer Ingelheim, and Bayer. Dr Engelberger reports no conflicts.

References

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