

UPPER EXTREMITY D.V.T: A REVIEW ARTICLE

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ABSTRACT: Upper extremity deep venous thrombosis (UEDVT) is also known as thrombosis of the axillary-subclavian vein, or Paget-Schroetter syndrome. It has primary and secondary varieties. Once considered rare, over the past decades U.E.D.V.T. has emerged as an increasingly important clinical entity. It makes up approximately 1-4% of all episodes of deep venous thrombosis (DVT) and carries a potential for considerable morbidity. Pulmonary embolism (PE) is present in up to one third of patients.

Primary UEDVT is still a relatively infrequent disorder of predominantly young, otherwise healthy people who participate in repetitive upper extremity activity. From an epidemiologic perspective, the general incidence of UEDVT remains low (approximately 2/100 000 persons per year), even though it is the most common vascular condition among athletes. Although early clinical recognition of UEDVT is important, diagnosis can be difficult due to its indeterminate cause and indistinct pathophysiology. PRIMARY (idiopathic) UEDVT is rare with controversial pathogenesis and treatment.

KEY WORDS; UEDVT, DVT, PE, LEDVT, SVC

REVIEW OF LITERATURE: Symptoms of UEDVT are nonspecific, ranging in severity, and may be position dependent. Occasionally, patients may be entirely asymptomatic. Most commonly, however, patient complaints include initial "heaviness" in the affected arm, as well as a dull ache and pain in the neck, shoulder, and/or axilla of the involved limb. The differential diagnosis is complex because patients typically display compressive signs usually associated with thoracic outlet syndrome. Other more dramatic signs may include ecchymosis and non-edematous swelling of the shoulder, arm, and hand; functional impairment; discoloration and mottled skin; and, distention of the cutaneous veins of the involved upper extremity.

Risk factors for UEDVT include central venous catheterization, strenuous upper extremity exercise or anatomic abnormalities causing venous compression, inherited thrombophilia, and acquired hypercoagulable states including pregnancy, oral contraceptive use, and cancer. Unexplained or recurrent UEDVT should prompt a search for inherited hypercoagulable states or underlying malignancy. In the present era the increased incidence is directly related to the increasing use of central venous catheters for chemotherapy, bone marrow transplantation, dialysis, and parenteral nutrition. . Pulmonary embolism (PE) is present in up to one third of patients with UEDVT (1). As high as 25 % of the patients with indwelling catheters can have UEDVT (2).

Kabani et al (3) a study of 1,275 patients admitted to the surgical ICU over a 12-month period found that the incidence of UEDVT was higher than that of LEDVT (17% vs. 11%;

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P=0.11) and scanning of all four extremities was able to diagnose more DVT than two-extremity scans (33% vs. 7%; P<0.001). Though most patients were symptomatic a significant proportion did not manifest any local DVT signs and symptoms in the form of swelling, erythema, paresthesias and collateral veins. While there is increased reference to UEDVT in recent literature, there is no consensus on its treatment. Recent American College of Chest Physicians (ACCP) guidelines addressed UEDVT treatment specifically and recommended analogous treatment to LEDVT with heparin and warfarin (4). The ACCP guidelines do not specifically recommend different treatment courses based on whether the UEDVT is catheter-related or not. Furthermore removal of a catheter hasn't been found to improve the outcome and there is no supporting data to reduce the treatment duration following catheter removal. UEDVT commonly implies thrombosis of the axillary and/or subclavian veins and is classified as primary or secondary on the basis of pathogenesis.

Primary UEDVT is a rare disorder (2 per 100 000 persons per year) (5). It includes effort thrombosis (Paget-Schroetter Syndrome) or idiopathic UEDVT. First described in the late 1800s, spontaneous primary thrombosis of the upper extremity, or Paget-Schroetter syndrome, accounts for approximately 20% of UEDVT (6). Paget-Schroetter Syndrome is a spontaneous UEDVT seen in young and healthy individuals, usually affecting the dominant arm following strenuous activity such as rowing, wrestling, and weight lifting. The heavy exertion causes micro trauma to venous intima which in turn activates the coagulation cascade. With repeated intimal insults especially if associated with mechanical venous compression, significant thrombosis may occur. (7)

In contrast to patients with Paget-Schroetter Syndrome, patients with idiopathic UEDVT have no known trigger or obvious underlying disease. Idiopathic UEDVT may, however, be associated with occult cancer. In one study, one fourth of patients presenting with idiopathic UEDVT were diagnosed with cancer (most commonly lung cancer or lymphomas) within 1 year of follow-up. Most of these cancers were discovered during the first week of hospital admission for the venous thrombosis. (8) Some hypothesize that effort-related thrombosis is related to a hypercoagulable state or anatomic abnormalities, although a specific cause, such as thoracic outlet syndrome, is found in only 5% of these cases. (9,10)

Compression of the neurovascular bundle (brachial plexus, subclavian artery, and subclavian vein) in thoracic outlet obstruction, may initially cause intermittent, positional extrinsic vein compression but later on repeated venous trauma causes dense, perivascular fibrosis with persistently vein compression. (11). Compression of the subclavian vein typically develops in young athletes used to do heavy weight lifting or complete abduction of arms. In addition cervical ribs, long transverse processes of the cervical spine, musculofascial bands, and clavicular or first rib anomalies can sometimes be found. Therefore, cervical spine and chest plain films should be obtained in all patients undergoing evaluation for thoracic outlet syndrome. (12)

The prevalence rate of hypercoagulable states in UEDVT is uncertain, observational studies have reported varying results. (13) Screening for coagulation disorders is controversial and not considered cost-effective. These tests should be considered in patients with idiopathic UEDVT, a family history of deep vein thrombosis (DVT), a history of recurrent unexplained pregnancy loss, or a personal history of a prior DVT. Tests for the rare causes of inherited thrombophilia-protein, Factor V Leiden, prothrombin gene mutation, hyperhomocysteinemia, and antiphospholipid antibodies can be undertaken in patients below 40 years of age. The

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optimal duration of anticoagulation for a thrombotic event associated with hypercoagulable disorders, such as abnormality of factor V Leiden or coexisting thrombophilia, is unknown. (14) Secondary UEDVT- Several endogenous or exogenous risk factors contribute to the causation of secondary UEDVT which accounts for most cases of UEDVT. Exogenous risk factors include CVC pacemakers, intracardiac defibrillators, malignancy, previous or concurrent LEDVT, oral contraceptives, some artificial reproductive technologies leading to ovarian hyper stimulation syndrome associated with increased hypercoagulability, trauma, and IV drug use (especially cocaine). In device insertion cases the vessel wall may be damaged during catheter insertion or during drug infusion, the catheter may itself impede the venous blood flow with resultant stasis. Incorrectly placed catheters are more prone to cause deep vein thrombosis. The catheter tips should be positioned in the lower third SVC or at the junction of the superior vena cava and right atrium because blood flow is most rapid in the SVC, which may sufficiently dilute the infusate and reduce the risk of thrombophlebitis (15).

Endogenous risk factors include coagulation abnormalities, such as antithrombin 3, protein C and protein S deficiencies; factor V Leiden gene mutation; hyperhomocysteinemia; and antiphospholipid antibody syndrome. (16, 17, 18)

SIGNS AND SYMPTOMS: UEDVT is frequently asymptomatic until complications ensue; when present the signs and symptoms are non-specific & may reveal low-grade fever attributable to thrombosis. Higher fevers may suggest septic thrombophlebitis or may be related to the underlying malignancy in patients with cancer. SVC syndrome reduces venous return to the heart and, like PE, may cause sinus tachycardia. Patients may have mild cyanosis of the involved extremity, a palpable tender cord, (17) arm and hand edema, supraclavicular fullness, jugular venous distension, and dilated cutaneous collateral veins over the chest or upper arm may develop. (1) If a central venous catheter is present, one or multiple ports may be occluded. (16) The same findings may also be seen in lymphedema, neoplastic compression of the blood vessels, muscle injury, or superficial vein thrombosis but in this subset of patients less than half will have imaging evidence of UEDVT. Therefore in such a scenario it is important to clinically confirm or exclude the diagnosis with objective testing before planning the imaging studies (1) and a high index of suspicion is required for patients with one or more risk factors for thrombosis in such situations.

INVESTGATIONS (19)

DUPLEX ULTRASOUND: Duplex ultrasound is the initial imaging test of choice for diagnosing UEDVT being noninvasive. It has high sensitivity and specificity for peripheral (jugular, distal subclavian, axillary) UEDVT. However the clavicle limits visualization of a short segment of the subclavian vein.

C.T.CHEST WITH VENOGRAM: CT is readily available and widely used. The thrombus is hypo attenuating compared with the hyper attenuating vein. In addition it provides excellent information about soft tissue structures (e.g. tumor, lymphadenopathy) surrounding the vein that may account for the thrombosis.

MAGNETIC RESONANCE ANGIOGRAPHY: Magnetic resonance angiography (MRA) is an accurate, noninvasive method for detecting thrombus in the central thoracic veins, such as the SVC and brachiocephalic veins. It correlates extremely well with venography and provides more

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complete evaluation of central collaterals, all central veins, including contralateral vessels, and blood flow. Being noninvasive it may be preferred for diagnosis, especially when contrast venography is contraindicated or impossible.

CONTRAST VENOGRAPHY: Venography provides excellent characterization of venous anatomy but has several drawbacks like difficulty in cannulating the vein in an edematous arm, need for an iodinated contrast agent, which may cause an allergic reaction, nephrotoxicity, or a chemical phlebitis that can worsen the preexisting thrombosis. It has been largely replaced by M.R. venography but is required as a prelude to interventions such as catheter-directed thrombolysis and angioplasty and may be used for post interventional follow ups.

Treatment Options for UEDVT

ANTICOAGULATION: The cornerstone of therapy is Anticoagulation which helps maintain patency of venous collaterals and reduces thrombus propagation even if the clot does not resolve fully. Typically, unfractionated Heparin has been used as a “bridge” to Warfarin. These days Low molecular weight Heparin has been found safe and effective for outpatient treatment and for reducing the duration of hospitalization. (20) Warfarin or other anti-vitamin K agents are typically continued for a minimum of 3 months, with a goal INR of 2.5 to 3.0 and for 6 months if a coagulation abnormality is detected.

THROMBOLYSIS: Thrombolysis is indicated in young and healthy patients especially with primary UEDVT, symptomatic SVC syndrome, for preservation of a mandatory central venous catheter because they can have significant long-term morbidity if treated with conventional anticoagulation alone. Thrombolysis restores venous patency early, minimizes damage to the vessel endothelium, and reduces the risk of post-thrombotic syndrome characterized by chronic arm and hand aching and swelling. Catheter-directed thrombolysis needs lower doses of medication to achieve higher rates of complete clot resolution and reduced risk of serious bleeding. Thrombolysis works best within several weeks of the onset of symptoms, later on progressive thrombus organization limits its effectiveness. (21) Contraindications include active bleeding, neurosurgery within the past 2 months, a history of hemorrhagic stroke, hypersensitivity to the thrombolytic agent, and surgery within the preceding 10 days.

Many case series of thrombolysis in carefully selected patients reported excellent outcomes and only minor bleeding complications (occasional hematomas or oozing at venipuncture or catheter sites. (23-26) however due to small size of these studies the risks of intracranial or gastrointestinal hemorrhage cannot be reliably estimated.

Heparin is usually given concurrently with the thrombolytic agent to prevent thrombus formation around the catheter (21). Venipuncture, intramuscular injections, and invasive procedures should be minimized.

No controlled trials have compared the different thrombolytic agents. Low-dose Urokinase and Recombinant tissue plasminogen activator (rtPA) are commonly used as thrombolytic agents. Streptokinase has a high rate of allergic reactions and may be ineffective if re-administered within months of a prior dose or streptococcal infection. The recombinant tissue plasminogen activator (rtPA) is currently the agent of choice for treating UEDVT, catheter-directed rtPA is usually administered as a continuous infusion of 1 to 2 mg/h for at least 8 hours. Serial venography is used to assess response to treatment. Delivery of rtPA over

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15 minutes via a pulse-spray catheter lodged in the obstructing thrombus has been found as effective as longer infusions and may carry a lower risk of bleeding. (27)

Percutaneous mechanical thrombectomy with devices such as the AngioJet is often used in combination with thrombolytics, as it can rapidly extract large quantities of thrombus, the dose and duration of thrombolytic therapy is reduced. (28)

CASE REPORT OF A PRIMARY UEDVT WITH HYPERHOMOCYSTEINAEMIA: A 50 year old, obese 70 kg muslim male presented to emergency room at on 4TH April 2013 at 10 pm. At 6 am on the day of admission he had noticed sudden swelling, pain and redness of left upper limb extending from the shoulder to the elbow on getting up from sleep. There was no history of recent strenuous activity involving the left upper limb. There was no antecedent trauma, insect bite, and exercise of any kind, fever. He was a past smoker and had retired from his occupation as welder for last 7-8 years due to recurrent exacerbations of chronic bronchial asthma. He had been on inhaled beta agonists and oral bronchodilator (Theophylline and Salbutamol) medications off and on. He was not on corticosteroids and had no history of Diabetes. For last 3 months he was on 5 mg Amlodipine for recently detected hypertension.

The physical examination revealed no fever, a regular radial pulse of 112 per minute , blood pressure of 140/90 mm. of mercury, respiratory rate 20 per minute and no pedal oedema. There was gross swelling of the left arm and forearm with redness, pitting edema and tenderness. All the arterial pulsations were palpable and there was no color change suggestive of gangrene. The respiratory system examination revealed an emphysematous chest, bilateral generalized rhonchi and crepitations; SP O₂ was 100% on room air. The C.V.S, C.N.S. and abdominal examinations didn't reveal any abnormality.



(A) UEDVT in left upper limb

His investigations showed hemoglobin 13.9 gram %, total R.B.C. count of 5.3 million/ cu.mm, total W.B.C. count of 16200/cu.mm with 80 % neutrophils and 18% lymphocytes, platelet count 2.56 lac /cu mm, blood Urea 27 mg %, serum creatinine 0.9 mg%, I.N.R. 1.4 .Random capillary glucose value was 210 mg % on admission and ranged between 122 to 171mg% during stay ,D-dimer was 0.15 mg/dl ,Serum Sodium 136 m.eq./dl .Potassium 4.0m.eq./dl, Chlorides 96 m.eq./dl. Arterial blood gas analysis was normal. Serum Homocystine was 20.72(3.72 - 13.9)umol/lit.

E.C.G. was normal, skiagram of chest, and all joints of the left upper limb were normal. A duplex sonography with color Doppler of left upper limb showed extensive venous thrombus extending into left jugular vein and from brachiocephalic to the ulnar vein with total absence of

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flow seen. C.T. Venogram confirmed the extensive venous thrombosis and in addition revealed a middle lobe segmental collapse on the right side with ground glass appearance and incidental left non-obstructive renal calculus.

Bronchoscopy and alveolar lavage revealed a narrowed opening albeit a patent middle lobe segmental bronchus, no endobronchial growth, purulent secretions were present. B.A.L. analysis was negative for fungus, tuberculosis and malignancies and sterile on culture. A biopsy could not be taken in view of 3 times rise in I.N.R on Warfarin.

TREATMENT : He was treated with inj. Enoxaparin 0.6 ml B.D, Warfarin 5-7.5 mg per day as per INR, oral Amoxicillin with Clavulanic acid 625 mg T.D.S., oral Doxophylline 400 mg b.d, nebulization with Salbutamol and Ipratropium, Tab. Metformin 500 mg B.D., tablets Chymotrypsin, Paracetamol, Diclofenac sodium, Amlodipin, Storvastatin, Methycobalamine , Pyridoxine and Folic acid.

PROGRESS: Patient was symptomatically better after anticoagulation at 2 weeks follow up after discharge. Warfarin is going to be continued for 3months or more and scrutiny for malignancy will be continued in view of right middle lobe collapse.



(a) Coronal and sagittal view of thrombus in left jugular , left subclavian & brachio-cephalic veins



(b) Collapse of right middle lobe and ground glass appearance

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