Unusual bleeds, unusual clots*

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Summary
Nine unusual bleeding and clotting disorders (or mimickers of such) are described in the format of case presentations, with focus on clinical history, images and diagnostic tests, followed by a discussion of the disease itself and a summarizing clinical teaching point. The disease entities discussed are acquired factor VIII inhibitor, acquired von Willebrand factor inhibitor, haemophilic pseudotumour, Gardner-Diamond syndrome, coumarin-induced skin necrosis, purple toe syndrome, brachiocephalic vein thrombosis with breast enlargement, and leg swelling due to nephrogenic fibrosing dermopathy and lymphoedema. The publication is meant to demonstrate the fascination of clinical coagulation.

Schlüsselwörter

Zusammenfassung

Ungewöhnliche Blutungen und Gerinnel
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Thrombotic and haemorrhagic disorders can be striking in their severity, rarity, or unusualness of clinical presentation and pathophysiology. This article describes some of such disorders. It is meant as a showcase of clinical coagulation, not as an all-inclusive report. The enjoyment of being a coagulationist is to be involved in the diagnosis and care of patients with a large variety of clinical presentations and to interact with medical professionals of many different specialties who care for these patients and consult the coagulationist for input into diagnosis and treatment. The enjoyment is also being able to use one’s understanding of the complex coagulation processes to order and interpret clinical coagulation tests, esoteric as some of them may be, to diagnose the coagulation disorders, and to make recommendations on the use of antithrombotic and prothrombotic therapies to prevent or treat bleeding and thrombosis.

The cases presented show patients with a variety of haemorrhagic and thrombotic disorders and hopefully transmit the fascination that clinical coagulation can have.

Bleeding disorders

Acquired factor VIII inhibitor
A woman (age: 78 years, nursing home resident) with no previous history of increased bleeding presented with large ecchymoses of both forearms and haematomas on the dorsum of both hands (Fig. 1) after attempted intravenous catheter insertions to give antibiotics for treatment of pneumonia. Her family reported that she had also had easy generalized bruising in the preceding four to six weeks.

Diagnosis
The history suggests an acquired bleeding disorder. Laboratory work-up showed a normal platelet count and prothrombin time (PT), but a prolonged activated partial thromboplastin time (aPTT) of 75.4 seconds (normal 27.0–36.5). 1:1 mixing with normal plasma led to shortening of the aPTT to 40.5 s, but not complete correction, and prolongation to 57.4 s after 60 minutes of incubation at 37º Celsius. These findings suggested the presence of an inhibitor. As the patient had a bleeding tendency, a specific factor inhibitor is most likely, particularly a factor VIII inhibitor, as it is the most common type of acquired coagulation factor inhibitor. Factor VIII activity was 5% (reference range: 84–216), factor VIII Bethesda inhibitor titer 5 BIA units (normal <0.4). A diagnosis of acquired factor VIII inhibitor was made.

The patient received recombinant factor VIIa before and after surgical evacuation of the hand haematomas and had good post-operative haemostatic control. No underlying aetiology for the inhibitor was clinically evident. No monoclonal protein was found in serum or urine. In view of the patient’s general poor health a decision with the patient and her family was made against further malignancy work-up. Three treatments with weekly Rituximab were given. Ten weeks later her factor VIII activity was 14% and an inhibitor titer 0 BIA. At 14 months follow-up no further bleeding had occurred and aPTT and factor VIII activity were normal.

* This article is dedicated to my father, Dr. Helmut Moll, paediatrician, Papenburg, Germany, to his 80th birthday. His clinical images of paediatric medicine are an inspiration for me and a guideline for excellence.
Discussion

Acquired factor VIII inhibitors are rare, with an incidence in the general population of ca. 1.5 in one million per year. However, they are the most common acquired coagulation factor inhibitors leading to a bleeding disorder. There is an equal gender distribution and the median age of patients is 70–80 years. In about 50% of patients an associated disease or triggering factor can be identified, mostly autoimmune disorders, cancer (solid or lymphoproliferative), skin disorders (pemphigus, epidermolysis), drugs (penicillin, interferon, and others), and postpartum state. Bleeds are typically into the soft tissues, such as the muscles, but may also be mucosal (gastrointestinal and nasal), uncommonly into the joints. While in patients with inherited factor VIII deficiency a factor VIII level of ≥5% is typically associated with only a mild bleeding disorder, the absolute factor VIII level in patients with acquired factor VIII inhibitors is not a good indicator of the severity of bleeding, as the kinetics of acquired factor VIII inhibitors are different to those of inhibitors in congenital haemophilia. Treatment options for the acute bleeding situation depend on the inhibitor titer and extent of bleed, and include activated prothrombin complex concentrates, recombinant factor VIIa, and porcine factor VIII concentrate. DDAVP or human factor VIII concentrate may be attempted for smaller bleeds in patients with low levels of inhibitors. Treatments for longer-term eradication of the inhibitor are immunosuppressants (steroids, cyclophosphamide, other alkylating agents), intravenous immunoglobulin, or immunomodulators (cyclosporine, Rituximab). A review of the literature and treatment guidelines have recently been published (1, 2).

Relevance

In the patient with a history suggestive of an acquired bleeding disorder, in whom the aPTT is prolonged, but the PT and platelet count are normal, an acquired factor VIII inhibitor should be considered. If confirmed and no associated condition is apparent (i.e. autoimmune disorder, postpartum state, drugs), full malignancy work-up is indicated.

Acquired von Willebrand factor inhibitor

A 64 year old man without prior bleeding history was admitted to the hospital with persistent severe rectal bleeding (Fig. 2) after a transrectal prostate biopsy, requiring transfusion of four units of packed red cells (3). He had had several surgical procedures in the past without increased bleeding: a herniorrhapsy 15 years earlier, multiple dental extractions, and multiple prostate biopsies on three separate occasions in the preceding two years. His only significant medical history was that of hypertension, obesity, and a chronically elevated prostate specific antigen without evidence of prostate malignancy. The patient had a large family with no history of a bleeding disorder.

Diagram

His admission platelet count and PT were normal; the aPTT was 46.6 seconds (reference range: 22.0–33.4). A 1+1 aPTT mix with normal plasma without incubation was 31.9 seconds. Factor VIII activity was 10% (reference range: 61–158) without inhibitory pattern on dilutional studies. A factor VIII Bethesda inhibitor assay demonstrated absence of a factor VIII inhibitor. Von Willebrand factor (VWF) activity was <10%, i.e. undetectable (reference range: 43–143), VWF antigen <10%, i.e. undetectable (reference range: 59–144), and VWF multimers showed absence of all multimer sizes. A diagnosis of severe von Willebrand’s disease was made. Due to the absence of previous bleeding and a negative family history of bleeding he was thought to have acquired von Willebrand’s disease.

Treatment with factor VIII concentrate high in VWF (Humate P®) led to no decrease in bleeding and no increase in VWF activity and antigen level eight hours after infusion, suggesting acquired von Willebrand’s disease due to a VWF clearing antibody or absorption of VWF to an abnormally expressed glycoprotein Ib receptor on
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Somatic tissue. Serum protein electrophoresis showed a small 0.8 g/dl IgG kappa monoclonal spike, but bone marrow biopsy and plain X-rays of skull and skeleton showed no evidence of multiple myeloma. A diagnosis of monoclonal gammapathy of undetermined significance (MGUS) was made. Malignancy work-up was negative (computer tomograms of chest, abdomen and pelvis; colonoscopy).

The acute bleeding stopped after treatment with recombinant factor VIIa and initiation of intravenous immunoglobulin (IVIG), which temporarily normalized VWF levels. However, undetectable levels were present again within four weeks (Fig. 2c). Treatment with steroids, Rituximab and subsequently oral cytoxan failed to increase the VWF activity. Over the following two years the serum M-spike remained minimal and stable, the VWF activity undetectable off treatment, but no bleeding occurred, except for one large prepatellar bleed after the patient accidentally hit his knee on a door frame (Fig. 2b, c: MRI scan). This episode was successfully treated with recombinant factor VIIa and intravenous immunoglobulin infusion.

Discussion

Acquired von Willebrand’s disease is a rare bleeding disorder, distinguished from congenital von Willebrand’s disease by age at presentation and absence of personal and family history of bleeding disorders. The mean age at diagnosis is 61 years. Most patients have a spontaneous or post-operative haemorrhage at presentation. Gastrointestinal bleeding and epistaxis are the most common spontaneous symptoms. Marked reductions in plasma VWF activity and antigen are found and VWF multimers are either diffusely decreased, completely absent, or lack the high molecular weight components. An inhibitor may or may not be demonstrable. Various pathogenetic mechanisms have been observed to lead to low VWF activity, such as
- Specific inhibitory antibodies against functional domains of VWF,
- Increased VWF proteolysis, and
- Decreased VWF synthesis.

Acquired von Willebrand’s disease can occur with a variety of associated disorders, such as plasma cell proliferative disorders (MGUS, Waldenstrom’s disease, and multiple myeloma), lymphoproliferative, myeloproliferative and autoimmune disorders, neoplasia, and drugs. As in acquired factor VIII inhibitors, the treatment has two components:
- Treatment of the acute bleeding event or prevention of bleeding in patients having invasive procedures, and
- Treatment of the underlying disease if identified.

Relevance

Awareness of the existence of acquired von Willebrand’s disease is essential for diagnosis and appropriate management.

Pseudotumour

A 31 year old man with severe congenital haemophilia A (factor VIII activity <1%) and low titer factor VIII inhibitor (Bethesda inhibitor 3.0 BIA units) presented with an expanding right lower extremity mass and right calf and heel skin ulcers (4) (Fig. 3). He had developed below the waist paraplegia at age three after a fall resulting in a spinal haematoma and cord compression. Two years prior to presentation he had developed spontaneous swelling around the right knee, but this had not been treated due to the lack of availability of coagulation factor products in the country where he had lived. Over several months prior to presentation, the lesion had markedly expanded to 24 cm in diameter.

Diagnosis

Clinical suspicion was that the right leg swelling (Fig. 3a) was due to a haemophilic...
pseudotumour. A plain radiograph revealed a large soft tissue mass with near complete destruction of the proximal right fibula. Since the size and weight of the pseudotumour and the recurrence of skin ulcers interfered with the patient’s activities of daily living, and since he was wheelchair bound and had no function of his legs, leg amputation was performed. Pathological examination confirmed haematoma, consistent with haemophilic pseudotumour.

**Discussion**

Patients with bleeding disorders may develop chronic bleeding into soft tissue, subperiosteum or bone that leads to cysts with a fibrous capsule and with blood-like material within them. Vascular neoformation may contribute to continued slow bleeding, and, thus, to expansion of this mass over weeks, months and years. The pressure onto surrounding tissues leads to destruction of bone and necrosis of adjacent tissue, giving the mass the growth pattern of an invasive tumour. Thus, the term pseudo-tumour. The clinical course varies, ranging from a dormant, asymptomatic lesion to acute expansion and bleeding. Complications include bone fracture, infection, and compression of adjacent nerves and vessels. Radiographic findings are often non-specific mass lesions with bone destruction, calcification, and ossification.

While most commonly seen in haemophilia, pseudotumours can occur with any kind of bleeding disorder, including chronic oral anticoagulant therapy. The prevalence is ca. 1.3% in patients with severe, 2.8% with moderate, and 1.3% with mild haemophilia A or B (5). Treatment options include chronic factor replacement, surgical resection, amputation, and external beam irradiation.

**Relevance**

Pseudotumours lead to a variety of different clinical presentations, depending on their anatomic location.

**Gardner Diamond syndrome**

A 48 year old woman with no previous bleeding problems presented with a one year history of spontaneous bruising on extremities and trunk of always the same pattern (Fig. 4): At first she experienced a localized stinging, popping, and pulsating sensation; then, the surrounding skin became very warm, diffusely red, and itched intensely, followed within minutes by an enlarging bruise, reaching maximal diameters over 20–30 minutes (6). Her symptoms subsided after two hours, and were followed by extreme exhaustion. The individual bruises disappeared after several weeks. The patient had multiple emotional stresses, including localized breast cancer diagnosed two years before the onset of bruising (free of disease after treatment), a pending medial law suit, loss of a job held for more than 20 years, and significant marital problems with a pending law suit for divorce. She saw a psychiatrist and was being treated for depression. There was no evidence of domestic physical violence.

**Diagnosis**

Physical examination was unremarkable except for the illustrated skin findings (Fig. 4). The images show a so-called bruise on the left lateral thigh, which had appeared 16 hours earlier. Petechiae and multiple ecchymoses are seen that were non-palpable, but
tender. Extensive workup for a bleeding disorder at the time of this acute bleeding episode was negative. A skin biopsy showed no evidence of vasculitis or amyloid infiltration. The patient was thought to have Gardner-Diamond syndrome, also known as psychogenic purpura and autoerythrocyte sensitization syndrome.

Reassurance was given to the patient that this type of bleeding disorder typically does not lead to internal or serious bleeding, and close follow-up with psychiatry was recommended. She was lost to hematologic follow-up.

Discussion

Gardner-Diamond syndrome is characterized by spontaneous bruising in patients who have significant psychological disturbances (7, 8). The occurrence of bruises often has a classical pattern of symptoms: A localized popping sensation is followed by skin erythema, warmth and itching, with rapid occurrence of a bruise; significant fatigue often follows. The lesions are not self-inflicted. It has been suggested that the bruises may be a localized allergic reaction against parts of the patient’s own extravasated red cells, hence the term autoerythrocyte sensitization syndrome, but this theory has not been substantiated. The pathogenetic mechanism of the disorder remains unknown.

Relevance

Gardner-Diamond syndrome should be considered in the differential diagnosis of purpura and ecchymoses, especially in patients with psychiatric problems and the description of a typical pattern of symptoms associated with the development of bruises. However, extensive work-up for an acquired bleeding disorder of the pro-coagulant and fibrinolytic systems and of platelet function is needed, and a skin biopsy to rule out vasculitis or amyloid infiltration may also be necessary, before giving the patient a diagnosis of Gardner-Diamond syndrome.

Thrombotic disorders

Coumarin-induced skin necrosis

A 29 year old woman presented with acute pulmonary embolism (9) (Fig. 5). Unfractionated heparin was started and a therapeutic aPTT achieved within eight hours. Warfarin was also started on day 1 (day +1). Within 48 hours the INR was supratherapeutic at 3.5 and heparin was discontinued (Fig. 5a). On day 5 the patient developed severe pain, purple discoloration and swelling of the right breast.

A diagnosis of coumarin-induced skin necrosis was made, warfarin discontinued, vitamin K given, and heparin restarted. Platelet counts did not decrease. Symptoms progressed over the next several days. Thrombophilia work-up revealed only heterozygous factor V Leiden. Protein C and S activities were normal. The patient was discharged on low molecular weight heparin.

Four weeks later the gangrenous part of her breast was well demarcated and two months later partial mastectomy was performed. After six months the breast was almost completely healed (Fig. 5e).

Diagnosis

The diagnosis of coumarin-induced skin necrosis is made on clinical grounds – gangrenous skin appearance in a patient initiated on a vitamin K antagonist. The suspicion for the disorder is heightened if

● high loading doses of a vitamin K antagonist were given,
● the overlapping parenteral anticoagulant was prematurely discontinued, i.e. given less than five days or discontinued before the INR was in the therapeutic range.
● Heparin-induced thrombocytopenia should be ruled out (10).
Coumarin-induced skin necrosis occurs in less than 0.1% of patients treated with oral vitamin K antagonists, mostly women, usually obese individuals. Symptoms occur within 3–11 days of starting the vitamin K antagonist and the process is complete within 2–3 days. Not uncommonly, the breasts are involved (11). It may occur with or without identifiable thrombophilia and is due to thromboses in subcutaneous vessels, leading to fat necrosis. Lowering of the natural anticoagulant protein C (half-life: 9 hours) leads to a hypercoagulable state upon initiation of the vitamin K antagonist, before lowering of prothrombin (half-life: 60 hours) leads to protective anticoagulation (12). High loading doses of the vitamin K antagonist and premature discontinuation of the overlapping parenteral anticoagulant predispose to the development of coumarin-induced skin necrosis.

The patient at risk is the one who is started on anticoagulants for acute thrombosis, as such a person is already in a procoagulant state with ongoing thrombin generation. However, the person who is started on a vitamin K antagonist without having an acute thrombosis, such as the patient with newly diagnosed atrial fibrillation, does not have active thrombin generation and is, therefore, at much lower risk for developing coumarin skin necrosis; overlapping parenteral anticoagulants upon initiation of vitamin K antagonist therapy is, therefore, typically not needed in that person.

**Relevance**

In the patient with acute thrombosis or with protein C or S deficiency who needs initiation of oral anticoagulation, parenteral anticoagulants need to be overlapped with vitamin K antagonists for at least five days and until the INR is above 2.0. Also, heparin induced thrombocytopenia needs to be considered and ruled out as an etiology of the skin necrosis (10).

**Purple toe syndrome**

A 63 year old woman presented with purple and painful feet. Five weeks earlier she had started warfarin for treatment of deep vein thrombosis. Within a few days she developed pain in her feet with patchy purplish discoloration, which slowly progressed over the next weeks (Fig. 6). She had similar, but less pronounced, non-painful discolorations in her hands. Peripheral blood eosinophil count was 0.5×10^6/µl (normal ≤0.4×10^6/µl); creatinine was 1.1 mg/dl, compared to 0.7 mg/dl five weeks earlier. Urine examination was negative for eosinophils. Chest CT and transesophageal echo demonstrated extensive calcification and atherosclerotic plaques of the ascending and descending aorta.

**Diagnosis**

Purple toe syndrome secondary to warfarin therapy was diagnosed. A skin biopsy was not performed. It is typically not needed. Warfarin was discontinued and low molecular weight heparin started. The symptoms in her feet did not change over the next four weeks, but then slowly improved. She died a few weeks later from complications of chronic obstructive pulmonary disease.

**Discussion**

Oral anticoagulants can, in rare instances, cause violaceous painful discoloration of
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the toes and the sides of the feet, referred to as the purple toe syndrome (13, 14). Occasionally, the hands are also involved and livedo reticularis occurs. This typically happens within the first few weeks of starting oral anticoagulation. The problem appears to occur mostly in elderly people and in people with arteriosclerosis. It is thought that bleeding into atheromatous plaques in the vessel wall or weakening of the fibrin mesh overlying atheromatous lesions leads to cholesterol embolization to feet, hands, skin, and sometimes internal organs, such as the kidneys. The problem may also occur on heparin.

Symptoms typically do not lead to gangrene, as only small vessels are involved. Biopsies may show intravascular cholesterol crystals (14). The treatment of choice is to stop the anticoagulant. This typically leads to complete recovery over a few weeks. If the anticoagulants cannot be stopped, one will have to wait and observe whether the symptoms disappear in spite of their continuation of anticoagulants.

Relevance

Painful purple toe syndrome can be a complication of anticoagulant therapy.

Left brachiocephalic vein thrombosis

A 69 year old woman presented with non-painful left breast swelling (Fig. 7) of approximately eight months duration. She had a history of renal failure due to hypertension and had been on haemodialysis for two years via a right arm brachiocephalic dialysis fistula. Stenosis of the right brachiocephalic vein had required angioplasty and stenting eight months ago, with the stent extending into the proximal superior vena cava (SVC) and partially covering the left brachiocephalic vein confluence with the SVC.

Around that time she noticed increasing swelling of her left breast and left arm. Bilateral mammograms and breast ultrasonics showed a significantly enlarged oedematous left breast with increased overall density, but no definite mass. Because of a concern for inflammatory breast cancer breast biopsy was performed. This only showed mild superficial perivascular chronic inflammation, but no malignancy.

Upper chest Doppler ultrasound and contrast venography demonstrated occlusion of the left subclavian and brachiocephalic veins and narrowing of the proximal SVC. The patient was started on anticoagulation. Over the next seven months the arm swelling improved but the breast swelling persisted.

Diagnosis

Figure 7a shows a markedly enlarged left breast, which, on palpation, was diffusely firm, with thickened and edematous skin. A chest magnetic resonance venography (MRV) showed left brachiocephalic and subclavian vein thrombosis and superior vena cava narrowing. Unilateral breast enlargement secondary to venous outflow obstruction was diagnosed.

Discussion

Venous drainage of the left breast is by three pathways:
● via the perforating veins through the pectoralis muscle into the left internal mammary vein (vena thoracica interna) in the anterior chest, which empties into the left

![Fig. 6 Purple toe syndrome secondary to warfarin therapy](image1)

![Fig. 7 Unilateral breast enlargement secondary to left brachiocephalic vein thrombosis](image2)
brachiocephalic vein (vena brachiocephalica sinistra),
● via the thoracoepigastric vein (vena thoracoepigastrica) which empties into the axillary vein, and
● via the intercostal veins to the hemiazygous vein in the posterior chest, which empties into the left brachiocephalic vein.

If the venous obstruction is proximal to the junction of the internal mammary and hemiazygous veins with the subclavian vein, venous outflow obstruction from the breast may lead to breast swelling. Such unilateral breast enlargement is rare, but has been described in subclavian and brachiocephalic vein thrombosis, as well as superior vena cava syndrome (15, 16).

Relevance

Unilateral breast enlargement can occur due to outflow obstruction in proximal arm DVT or superior vena cava syndrome.

Unilateral leg swelling

A 37 year old man presented with a history of deep vein thrombosis of the right leg presented with firmness and pain in the thighs (Fig. 8). He had been on haemodialysis for end-stage renal disease secondary to glomerulonephritis since the age of 26 and had a failed renal transplant at age 30. At age 35 he was diagnosed with right leg deep vein thrombosis (DVT) secondary to a central venous dialysis catheter. Because of the DVT and several dialysis graft occlusions he has been on oral vitamin K antagonists since that time. At age 35 he underwent abdominal magnetic resonance imaging (MRI) with gadolinium for evaluation of his kidneys. One year later he underwent another abdominal and pelvic MRI with gadolinium to evaluate his pelvic vessels prior to planned kidney transplant. Three months later he complained about increasing tightness of his legs and pain.

Physical examination showed diffuse thickening of the right thigh and pretibial area with woody induration and nonpitting oedema (Fig. 8a, b). The left leg was also affected, but less. Postthrombotic syndrome was considered in the differential diagnosis, but because of the extent of skin induration, the inability of the patient to fully extend his leg in the knee, and the rapidity of worsening of symptoms, nephrogenic fibrosing dermopathy was entertained as a diagnosis. A skin biopsy was performed.

Diagnosis

The biopsy showed thickened dermis with an increased number of spindled cells, connective tissue, and connective tissue mucin, with no significant inflammatory infiltrate. A diagnosis of nephrogenic fibrosing dermopathy was made. Over the next 12 months the patient’s symptoms of skin hardening worsened, involving both legs, hands and arms, leading him to be wheelchair bound. Figures 8a and 8b show his skin changes about 18 months after the onset of symptoms.

Discussion

Nephrogenic fibrosing dermopathy (NFD) is a rare fibrosing disorder that occurs in patients with renal failure. It was first reported in 2000. Recent reports have strongly correlated the development of NFD with exposure to gadolinium-containing MRI contrast agents (17). These agents should, therefore, be used in patients with renal failure only if clearly necessary (18).

NFD affects males and females in approximately equal numbers. Patients typically present with painful indurated plaques involving the limbs and trunk, with sparing of the face. It can be rapidly progressive leading to significant morbidity and mortality. Management of NFD remains anecdotal and unsatisfactory (17, 19). A detailed and frequently updated summary of the disorder is presented on the world wide web by the International Center for Nephrogenic Fibrosing Dermopathy Research (20).
Relevance

Nephrogenic fibrosing dermopathy in the early phase may be confused with post-thrombotic syndrome in a patient with a history of deep vein thrombosis. It is a relatively newly described disorder occurring in patients with renal failure. Clinicians should be aware of the disease entity.

Bilateral leg swelling

A 46-year-old man presented with significant chronic, stable, non-painful bilateral leg swelling up to the groins (Fig. 9) since the age of 5 or 6. His primary care physician had started him on oral anticoagulants three years prior to presentation because he concluded that previous bilateral deep vein thrombosis explained his leg findings. The family history was negative for thrombosis or leg findings similar to those of the patient.

Physical examination showed markedly swollen legs with hardened, thickened and dry skin (Fig. 9a, b). Venous Doppler ultrasound examination of both legs showed no evidence of acute or chronic DVT. There was bilateral popliteal vein reflux. A CT venogram of the pelvis was normal with no evidence of pelvic or inferior vena cava narrowing or thrombosis.

Diagnosis, discussion

A clinical diagnosis of primary lymphoedema was made (lymphoedema praecox) and oral anticoagulants discontinued.

The onset of symptoms of lymphoedema can occur at any age. It can be divided into primary and secondary lymphoedema (21).

Secondary causes are

- lymphatic obstruction due to malignancy,
- radiation therapy or infection,
- or lymphatic interruption due to surgery.

Primary lymphoedema occurs without an associated disease or disorder and is divided into

- congenital lymphoedema with onset of symptoms before age 1,
- lymphoedema praecox with presentation between age 1 and 35, and
- lymphoedema tarda, with symptom onset after the age of 35.

Primary lymphoedema is occasionally familial and then termed Milroy’s disease. More commonly, however, it is sporadic. In two thirds of cases symptoms are unilateral. The distal part of the leg is affected initially, with proximal progression occurring later. The initial symptoms are painless leg swelling and a feeling of leg heaviness. The onset of symptoms can be rapid, over a few weeks, or slowly over months. The former may suggest DVT and lead to misdiagnosis.

Early on in the clinical course physical examination shows pitting oedema, but over time fibrosis of the subcutaneous tissues occurs, leading to non-pitting oedema and thick and rough skin. Recurrent episodes of cellulitis and lymphangitis are common, skin ulcers may occur. Lymphoedema may lead to secondary impairment of venous return and venous reflux may, thus, be found on Doppler ultrasound.

The aetiology of lymphoedema is often unclear, but recently a variety of mutations in the vascular endothelial growth factor receptor 3 gene (VEGFR3) have been described in patients with familial or sporadic congenital lymphoedema (22).

Relevance

Not every leg swelling and venous insufficiency, uni- or bilateral, is due to a history of venous thromboembolism.

References