To understand the events associated with livedo reticularis, it is necessary to be familiar with the anatomy and physiology of the cutaneous blood vessels. The skin, like any organ, receives its blood supply via the arteries, which branch into arterioles at the junction between the dermis and the subcutaneous cellular tissue to form the deep vascular plexus, which runs parallel to the epidermis. This plexus is formed by the feeding artery and a network of arterioles measuring 100 µm in diameter; the walls of these vessels consist of 2 outer layers of muscle, an elastic lamina, and internally, the vascular endothelium. Smaller, communicating arterioles arise from the deep plexus and run perpendicularly to the epidermis to reach the upper dermis, where they form the superficial vascular plexus, which also runs parallel to the epidermis. The arterioles here are very small (diameter, 10 µm); their walls only have a single muscle layer and the internal elastic lamina is absent. The superficial plexus gives rise to capillaries that supply blood to the papillae; the blood then drains through the postcapillary venules into larger...
venules, which follow a path that is parallel but inverse to the afferent vessels. This entire structure forms a 3-dimensional network that acts as a single unit. Nonetheless, the clinical repercussions of vascular lesions vary according to the characteristics of the affected vessels and their location within the layers of the skin.

While a reduction of blood flow in the arterioles can cause livedo reticularis, a complete interruption of this flow due to blockage of the lumen can cause hemorrhagic infarcts. Infarcted areas initially present as reticular purpuric lesions (retiform purpura) that can become visibly ecchymotic and eventually form more or less extensive areas of necrosis and secondary ulceration. Accordingly, necrotic lesions and ulcers caused by arterial or arteriolar occlusion tend to have reticular, stellate margins. Intense inflammatory reactions of the vascular wall and perivascular dermis cause painful subcutaneous nodules, which are often located either in the same area as the reticular lesions or along the path of the vessel.

Diagnosis

The diagnosis in a patient with livedo reticularis on the legs requires a search for associated subcutaneous nodules, retiform purpura, necrosis and secondary ulceration (Table 2). Some authors distinguish between livedo reticularis (network pattern with complete, regular rings) and livedo racemosa (network pattern with incomplete, irregular rings) and consider that the latter is always secondary to organic rather than functional disorders (Figure 1). A detailed history can provide invaluable information and should include drugs (coumarins, sedatives, ergotamine), known associated diseases (such as renal failure, arteriosclerosis, systemic autoimmune diseases, and monoclonal gammopathy), recent surgery (catheterization, angioplasty), and history of spontaneous abortion. It is also essential to determine the course of the disease (chronic, acute, or fulminant), explore associated symptoms (fever, dyspnea, arthralgia), and analyze clinical findings (such as murmurs, signs of pneumonitis, and neck stiffness) however associated fever may suggest the presence of an infectious process, it can also be due to a generalized inflammatory process—almost always serious—such as an exacerbation of systemic lupus erythematosus or systemic vasculitis.
Laboratory tests should include a complete blood count, coagulation studies, evaluation of kidney function, urinary sediment, proteinuria, antinuclear antibodies, complement levels, antineutrophil cytoplasmic antibodies (ANCAs), cryoglobulin and cryofibrinogen levels, antiphospholipid antibodies, and hepatitis B and C serology. It is sometimes necessary to conduct a more comprehensive study of coagulation factors such as protein C and S levels, factor V Leiden mutations, prothrombin G20210A gene mutations, homocysteine levels, and the C677T mutation of the methylenetetrahydrofolate reductase gene.3,4

When faced with a case of livedo reticularis with purpura, necrosis, or subcutaneous nodules, a skin biopsy should be taken from the erythematous-violaceous or purpuric areas, the margin of a necrotic lesion, or a nodule; the biopsy should include the full thickness of the skin (reaching the hypodermis). A tissue sample obtained by punch biopsy may be sufficient if the biopsy site is chosen correctly. Punch biopsies are the method of choice for avoiding difficult-to-heal ulcers. Pathologic analysis will reveal whether or not the lesion is of inflammatory origin (Figure 2). If there is inflammation, it is important to determine the size of the affected vessels and to identify the types of cells of the inflammatory infiltrate (polymorphonuclear neutrophils, mononuclear cells, or giant cells). If there is no inflammation, the biopsy findings will help to identify the cause of vessel obstruction (eg, clot, cholesterol crystals, calcium, endothelial proliferation, hyalinization). On the basis of these data, further investigations will be indicated to determine possible causes and initiate appropriate treatment; in patients with severe symptoms, urgent treatment may be required.

Arteriolar Spasm

Arteriolar smooth muscle can respond to different stimuli, triggering vasoconstriction; this may be physiological, such as the response to cold in an attempt to maintain body temperature, or may be a response to certain drugs. It is well known that ergotamine and other alkaloids derived from rye ergot—once used to induce postpartum uterine contraction—can cause vasoconstriction. The constrictor response in such cases is so strong that it can cause severe necrosis in the limbs. Other drugs known to cause vasoconstriction are cocaine, amphetamines, and ephedrine. Ischemia can also affect blood vessel walls, leading to thrombosis and secondary inflammation, which may cause confusion with vasculitis.

Inflammation of the Blood Vessels

Vasculitis

Vasculitides that affect the arterioles of the skin include systemic and cutaneous polyarteritis nodosa, Wegener granulomatosis, Churg–Strauss syndrome, microscopic polyangiitis, polyangiitis associated with systemic diseases such as systemic lupus erythematosus and rheumatoid arthritis, and certain types of vasculitis induced by drugs such as thiouracil.

The skin manifestations in these cases include livedo reticularis, inflammatory subcutaneous nodules, palpable purpura, necrosis, and secondary ulceration (Figure 3). General signs and symptoms may be severe and vary according to the underlying disease and the organs affected, meaning that systemic examination will reveal key diagnostic clues. Skin biopsy will help determine the type of blood vessels affected and the nature of the inflammatory infiltrate.5 Polyarteritis nodosa almost exclusively affects the deep plexus while the other conditions can affect both the deep and superficial plexuses. The involvement of the small superficial, caliber vessels explains the clinical presence of palpable purpura in Wegener granulomatosis, Churg–Strauss syndrome, and polyangiitis. Inflammatory infiltrates in the superficial plexus are formed of
polymorphonuclear neutrophils, with evidence of leukocytoclasis, while those in the deep plexus vary according to the underlying disease. In polyarteritis nodosa, microscopic polyangiitis, and polyangiitis associated with systemic lupus erythematosus, rheumatoid arthritis, or drugs, the inflammatory infiltrate is formed of polymorphonuclear neutrophils, while in Wegener granulomatosis and Churg–Strauss syndrome, it has granulomatous features, with macrophages and lymphocytes. In Churg–Strauss syndrome, there are also numerous eosinophils and a strong tendency to develop tissue necrosis.

Although skin lesions are common and can aid diagnosis, inflammatory vascular diseases are characterized by extensive systemic involvement that affects the patient’s general health and causes serious and sometimes fulminant organ dysfunction (above all affecting the lungs and kidneys). It is therefore essential to reach an early diagnosis and initiate treatment rapidly. Consequently, when there is clinical suspicion of systemic vasculitis, it is crucial to request urgent ANCA determination to confirm or rule out the presence of serious disease without delay.

Antimyeloperoxidase ANCAs predominate in microscopic polyangiitis and Churg–Strauss syndrome, while antiproteinase 3 ANCAs predominate in Wegener granulomatosis. Complementary studies should include cryoglobulin levels and hepatitis B and C serology.

**Blood Vessel Inflammation Due to an Underlying Infection**

Inflammation of the blood vessels can also be caused by infectious diseases with hematogenous dissemination of bacteria. Skin involvement is involved in of the septic process and is characterized by the appearance of erythematous, purpuric, or pustular papules. Infectious processes generally affect the vessels of the superficial plexus, causing thrombosis and a polymorphonuclear infiltrate of neutrophils.
infiltrate and resulting in a clinical picture that can be confused with small vessel vasculitis.

Lucio's phenomenon is a necrotizing reaction that occurs in untreated diffuse lepromatous leprosy. Patients develop recurrent necrotic lesions, with irregular, stellate borders, which subsequently ulcerate; these lesions mostly affect the legs but can also be found on the arms and trunk. They are caused by inflammation of superficial and deep dermal vessels, with thrombosis, endothelial proliferation, an inflammatory infiltrate formed of macrophages, and the presence of acid-fast bacilli in the vessel walls. It is a serious condition with major health consequences and poor prognosis.

Vascular Obstruction in the Absence of Inflammation

The symptoms of noninflammatory vasculitic disorders (also known as pseudovasculitis) and vasculitis can be very similar but it is important to differentiate between them as drugs used to treat vasculitis (corticosteroids and immunosuppressants) can seriously worsen conditions caused by vascular obstruction of noninflammatory origin. Although vascular obstruction has many causes, the vascular endothelium appears to play a central role in its pathogenesis. In the absence of inflammation, livedo reticularis is found in association with signs of hemorrhagic infarction (retiform purpura), necrosis, and the subsequent formation of ulcers with reticular or stellate margins corresponding to areas of infarction.

Thrombosis

Hypercoagulable states can cause thromboembolic events in the arterioles of the skin, giving rise to livedo reticularis and extensive skin necrosis. The causes are many and the accompanying symptoms depend on the origin of the thrombotic process and on whether there is organ or multisystem involvement.

Antiphospholipid syndrome is an acquired autoimmune thrombophilic state characterized by the presence of antiphospholipid antibodies, thrombotic events affecting the arteries and veins (thrombophlebitis, pulmonary thromboembolism, cerebrovascular accidents), and recurrent spontaneous abortion. The antibodies responsible for the syndrome are lupus anticoagulant, anticardiolipin antibodies, and anti-β2 glycoprotein I antibodies. The presence of stable, generalized livedo reticularis that does not disappear in a warm environment is the most common sign of the disease and is significantly associated with other manifestations of arterial involvement. Patients may also present purpura, necrosis, superficial venous thromboses, chronic ulcers on the legs, atrophic blanche, acrocyanosis, perniosis, subungual hemorrhage, and digital infarcts. While antiphospholipid syndrome may be a primary disorder, it is often associated with systemic lupus erythematosus and other autoimmune diseases.

Sneddon syndrome is characterized by generalized livedo reticularis in association with thromboembolic events; it is clinically indistinguishable from antiphospholipid syndrome. The presence of antiphospholipid antibodies, however, is highly variable in Sneddon syndrome, affecting between 0% and 80% of patients depending on the series.

Livedoid vasculopathy is characterized by livedo reticularis and outbreaks of painful purpuric, necrotic lesions with stellate margins on both legs simultaneously, mainly in the malleolar region and on the soles of the feet. Lesions heal leaving atrophic scars with telangiectasias and pigmented borders (atrophic blanche) (Figure 4). There have been no reports of organ involvement, although the condition has on occasions been associated with Raynaud’s phenomenon, acrocyanosis, signs of peripheral venous insufficiency, and collagen vascular diseases (primarily systemic lupus erythematosus and scleroderma). Livedoid vasculopathy has found in association with carcinomas, lymphoma, and myeloma. Pathology findings include thrombosis and hyalinization of dermal vessels with no evidence of vasculitis (Figure 5). It is noteworthy that many patients with livedoid vasculopathy have coagulation disorders, with a predominant role attributed to procoagulant factors and mechanisms such as antiphospholipid antibodies, cryofibrinogen, decreased antithrombin III activity, heterozygous factor V mutations, protein C deficiency, increased platelet aggregation, cryoglobulinemia, and increased levels of plasminogen activator inhibitor-1.
In type I cryoglobulinemia, there is an accumulation of monoclonal immunoglobulin G or M. This dysproteinemia is associated with B-cell lymphoproliferative disorders such as myeloma, B-cell lymphoma, and macroglobulinemia. Why these immunoglobulins tend to precipitate in the cold is unclear because they do not appear to differ structurally from normal immunoglobulins. Intravascular precipitation of immunoglobulins causes arterial occlusion; the precipitates are visualized as amorphous, eosinophilic material within the vascular lumen, with no evidence of inflammation (Figure 6). The main organs affected in this type of cryoglobulinemia are the skin, kidneys, liver, and nervous system. Skin lesions can be one of the first signs of the disease, manifesting as acrocyanosis, distal necrosis of the legs, and Raynaud's phenomenon.

Generalized livedo reticularis, without vasculitis or thrombosis, can also occur in systemic lupus erythematosus and rheumatoid arthritis. In such cases, the condition may be secondary to a slowing of the blood flow (due to increased viscosity or thrombophilic states), to an intense vasoconstrictor reaction induced by cold, or to a combination of both mechanisms.

Disseminated intravascular coagulation is a very serious, acute condition (purpura fulminans) characterized by the appearance of extensive areas of hemorrhagic necrosis during or immediately after an infectious process (meningococcus, group A streptococcus, staphylococcus, pneumococcus) or other serious clinical conditions such as multiple trauma, obstetric conditions, and toxic syndromes. It is caused by the sudden intravascular activation of coagulation mechanisms resulting in a depletion of platelets and various coagulation factors such as fibrinogen, prothrombin, factor V, factor VIII, and protein C. Skin involvement is generalized, with well-demarcated, stellate, hemorrhagic and necrotic plaques (Figure 7); livedo reticularis is not common.

One of the possible complications associated with the use of coumarins is the appearance of extensive areas of stellate ecchymoses and necrotic skin lesions with well delimited borders occurring symmetrically on the chest, buttocks, thighs, and arms. A biopsy performed at the edge of lesions will show thrombosis of the dermal vessels but no inflammation. The condition is rare and occurs in subjects with congenital or acquired protein C deficiencies.

Sickle cell anemia is caused by homozygosity for hemoglobin S, which has a lower affinity for oxygen than other forms of hemoglobin and distorts the shape of red blood cells. It is a serious disease whose clinical manifestations are caused by the occlusion of microvessels by sickle-shaped red blood cells; it can affect all organs and occurs in young individuals. The disease causes highly persistent, chronic ulcers in the malleolar region that do not tend to heal.

There are reports of livedo reticularis, nodules, and necrotic lesions caused by the coadministration of
diphenhydramine and the sedative pyrithyldione. These complications, however, have not been observed when either of the 2 drugs has been administered separately. The manifestations are secondary to massive thrombosis of the dermal vessels and there is no evidence of vasculitis. The coadministration of diphenhydramine and pyrithyldione at high doses over a long period can cause hypercoagulability, which, in predisposed individuals with an autoimmune disorder, can cause the symptoms described.

There have been reports of very painful necrotic lesions and secondary ulcers with atrophic, fibrous borders in the malleolar region of the legs or on the feet of patients with myeloproliferative diseases receiving long-term treatment with hydroxyurea. Although perivascular inflammation and fibrin deposits have been observed in some cases, the pathogenesis of these lesions remains unclear. The resulting ulcers are difficult to treat and only heal once medication has been withdrawn.

**Emboli**

Emboli originating from atrial myxomas or atheromatous plaques can obstruct peripheral arteries or arterioles, causing livedo reticularis and necrosis. There have also been reports of similar processes following the accidental intraarterial injection of cement during a vertebroplasty or of polydadcinol.

Myxomas are benign tumors that originate in endothelial cells and are most commonly found in the left atrium. Tumor fragments can break off, causing distal emboli and characteristic symptoms such as livedo reticularis, necrosis, distal cyanosis, and splinter hemorrhages. Patients with atrial myxomas often have general symptoms such as fever, arthralgia, and weight loss, which, if considered in combination with the skin lesions, can lead to an erroneous diagnosis of systemic vasculitis or systemic lupus erythematosus. A skin lesion biopsy will reveal obstruction of the arteriolar lumen by an amorphous, basophilic material, whose myxoid composition becomes evident following staining with Alcian blue or colloidal iron.

Cholesterol emboli are caused by the rupture of atheromatous plaques in the aorta or other great arteries, either spontaneously or as the result of surgical procedures, catheterization, angioplasties, angiography, or following initiation of treatment with anticoagulants or thrombolytic agents. Skin lesions secondary to the presence of emboli in skin arteries and arterioles are very common and tend to be the first sign of cholesterol embolization. The lesions manifest as livedo reticularis (which becomes accentuated when the patient is standing), a bluish discoloration of the feet, a faint reticular pattern on the soles of the feet, retiform purpura, necrosis, ulcers, nodules, and cyanosis (Figure 8).

Cholesterol embolization can be confirmed by skin biopsy, which will reveal occlusion of the arteries and arterioles of the deep plexus; the lumen of the vessels contains needle-shaped biconcave spaces, formerly occupied by the crystals inside the embolism (Figure 9). Another possible finding is an inflammatory infiltrate consisting of neutrophils, eosinophils, and lymphocytes in the early stages and of giant cells in the late stages. Patients with cholesterol emboli often have leukocytosis with eosinophilia, thrombocytopenia, elevated levels of C reactive protein, high erythrocyte sedimentation rates, and signs of secondary acute inflammation. Embolization can occur in the blood vessels of different organs. Examination of the retina, for example, may reveal yellow cholesterol crystals in the retinal vessels. Kidney blood vessels are commonly affected, complicating the prognosis.

**Vessel Wall Disorders**

Disorders of calcium and phosphorus metabolism in patients with advanced renal failure and secondary hyperparathyroidism can cause metastatic calcifications in the arteries, soft tissues, joints, and organs. Calciphylaxis refers to the calcification of
the media of arteries and can result in the sudden appearance of livedo reticularis, hemorrhagic infarcts, necrosis, ulcers, and violaceous plaques on the limbs; the plaques are well delimited and extremely painful and sometimes have an orange-peel skin appearance (Figure 10). The condition is very serious and often fatal. There is a high risk of calciphylaxis when the calcium–phosphorus product is greater than 65 mg/mL. Diagnosis hinges on the identification of calcium in the walls of the superficial and deep dermal vessels (Figure 11). The cause of calciphylaxis is not clear but it has been suggested that it requires the combination of an increased calcium–phosphorus product and vessel wall disorders secondary to renal failure. Some patients have been found to have a protein C deficiency, which might act as a predisposing factor or as a marker for other disorders responsible for triggering the disease.

Primary hyperoxaluria is an autosomal recessive hereditary disease caused by a deficiency of either of the following liver enzymes: a) alanine-glyoxylate aminotransferase (type I hyperoxaluria or glycolic aciduria) or b) D-glyceric dehydrogenase (type II hyperoxaluria or L-glyceric aciduria); these deficiencies increase the levels of calcium oxalate in the body, causing crystal precipitation in the joints, kidneys, heart, eyes, and skin. The disease can affect children, adolescents, and adults; most individuals will have renal failure and some will have had kidney stones. Vascular complications manifest on the skin as livedo reticularis, retiform purpura, necrosis, ulcers, and acrocyanosis. Skin biopsy will reveal aggregates of yellowish–gray crystals in the dermis, subcutaneous tissue, and walls of blood vessels. Dilated vessels, thrombosis, and foci of necrotic fatty tissue may also be seen. Because primary hyperoxaluria occurs in patients with renal failure, the differential diagnoses must include calciphylaxis.29

**Treatment for Livedo Reticularis on the Legs**

We have described the many and varied causes of livedo reticularis of the legs, a condition in which subcutaneous nodules, necrosis, and ulcers are common. Treatment options should be carefully assessed and tailored to each case, as...
inappropriate treatment carries a high risk of serious consequences. Systemic vasculitis should be treated with corticosteroids and immunosuppressants; doses and combinations will vary according to the clinical condition of the patient and the extent of organ involvement. Serious organ dysfunction requires the use of corticosteroids and cyclophosphamide pulse therapy. Combining low doses of corticosteroids with methotrexate or azathioprine is a good option for maintenance treatment, and cotrimoxazole is recommended for maintenance in Wegener granulomatosis to treat lung dysfunction. There is no effective treatment for generalized livedo reticularis in antiphospholipid syndrome or Sneddon syndrome. Skin lesions due to thrombosis can be treated with low doses of aspirin or antiplatelet therapy, although some cases may require coumarin anticoagulants.

Patients with livedoid vasculitis or disorders secondary to thrombophilia are advised first of all to quit smoking or to use nicotine patches or gum. Appropriate drug treatment involves the use of aspirin, pentoxifylline, diprydamole, and hyperbaric oxygen. Some authors have indicated that better results will be achieved when these drugs are combined with immunosuppressants or intravenous immunoglobulin. Hydroxychloroquine is the treatment for livedo reticularis in patients with antiphospholipid syndrome. Danazol or stanozolol can be prescribed to patients with cryofibrinogenemia, and coumarins or low molecular weight heparin may be indicated for certain hypercoagulable states. Patients with methyleneetrahydrofurolate reductase mutation can be treated with folic acid while those with plasminogen-activator inhibitor-1 promoter homozygosity (4G/4G) treated successfully with tissue plasminogen activator.

There are no clearly effective treatments for embolic diseases, calciphylaxis, or hyperoxaluria, all serious conditions whose most severe complication is obstruction of the renal arteries and subsequent renal failure, which requires specific treatment. Systemic corticosteroids should be recommended treatment for cholesterol emboli as they appear to halt the secondary inflammatory cascade that can have fatal consequences.

Conflicts of Interest
The authors declare no conflicts of interest.

References


