Blue (or purple) toe syndrome

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The blue (or purple) toe syndrome consists of the development of blue or violaceous discoloration of one or more toes in the absence of obvious trauma, serious cold-induced injury, or disorders producing generalized cyanosis. The major general categories are: (1) decreased arterial flow, (2) impaired venous outflow, and (3) abnormal circulating blood. Depending on its pathogenesis, the discoloration may be blanching or nonblanching. An accurate diagnosis is critical, because many of the causes threaten life and limb, but the patient's medical history, accompanying nondermatologic findings on physical examination, and a discriminating use of laboratory tests are usually more important than the nature of the cutaneous abnormalities in determining the cause. (J Am Acad Dermatol 2009;60:1-20.)

Learning objectives: After completing this learning activity, participants should be able to define the blue (or purple) toe syndrome, categorize the causes, and recognize the important historical, clinical, and laboratory findings that differentiate the causes and lead to the correct diagnosis.

In 1961, a report described six patients who developed painful, tender “purple toes” 3 to 8 weeks after beginning oral anticoagulation. Their prothrombin times were in the therapeutic range, and in all patients the bluish-purple color blanched completely on moderate pressure and faded with leg elevation. Biopsies were unrevealing, and the pathogenesis remained mysterious. Fifteen years later, the term “blue toe syndrome” (BTS) first appeared in a publication that defined the entity as the sudden onset of acute pain and cyanosis in one or more toes. The report described 31 patients, all with angiographic evidence of a proximal source of emboli in the vascular tree, primarily in the femoral or popliteal arteries, but also in aortic aneurysms and iliac vessels. The authors urged prompt excision of the vascular site of origin and restoration of arterial continuity, because among five untreated patients, four suffered further embolization within the subsequent 6 weeks, causing substantial ischemic loss of the forefoot in three cases.

Since then, numerous reports of BTS have appeared, and, although emboli remain a common.
crucial, because they often suggest or establish the diagnosis, rather than the dermatologic aspects, which are frequently nonspecific.

BLUE TOE SYNDROME FROM DECREASED ARTERIAL PERFUSION

Emboli

Emboli from atherosclerotic plaque (atheromatous or cholesterol crystal emboli). Material dislodged from ulcerated atheromatous plaques in the aorta and arteries of the lower extremities can occlude the small vessels of the feet, leading to BTS. Depending upon their site of origin, the emboli may affect other areas, including the eye, central nervous system, kidney, muscle, and gastrointestinal (GI) organs.

Table I. Causes of blue toe syndrome

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<td>Thrombotic thrombocytopenic purpura</td>
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<td>Cryofibrinogenemia</td>
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Predisposing factors, incidence, and pathogenesis

Atheromatous plaques (Fig 1) contain a necrotic core within the arterial intima, consisting of foam cells, debris, and lipids, including cholesterol crystals, all covered by a fibrous cap comprising endothelial cells, smooth muscle cells, and connective tissue. Spontaneous plaque hemorrhage or shear forces of the circulating blood can disrupt this protective cap and cause embolization of the cholesterol crystals. More commonly, however, such atheroemboli are iatrogenic complications, especially those caused by mechanical damage to the arterial walls from vascular surgery or invasive percutaneous procedures, such as angiography and angioplasty. Another predisposing factor is anticoagulant or fibrinolytic therapy, which can weaken the thrombi that, by overlying ulcerated plaques, help prevent the release of cholesterol crystals.

In routine autopsies, the incidence of spontaneous atheroembolism has ranged from 0.3% to 3.5%. In an examination of the skin and skeletal muscle of the lower extremities in 100 consecutive autopsies, the frequency was 4%. When advanced atherosclerosis is present, the incidence is between 4.3% and 31%. As expected, the frequency of atheromatous emboli found during routine postmortem examinations increases with the patient’s age. In one study examining atheroemboli to the kidneys, for example, the incidence in patients between 80 and 90 years of age was 11.8%.

After vascular procedures, the risk of atheroembolization is substantial. In patients dying shortly after cardiac surgery for valve operations or myocardial revascularization, 22% had atheroembolism, almost exclusively in those with severe atherosclerosis of the ascending aorta. Among 71 autopsies of patients who had recently undergone angiography, the frequency of atheroembolization was 30% following aortograms and 25.5%
after cardiac catheterization and coronary angiograms. Postmortem examinations of patients dying shortly after surgery for abdominal aortic aneurysms disclosed atheroemboli to the kidneys in 77.3%. In 1000 percutaneous catheterizations for coronary interventions, blood retrieved from the lumen of the guiding catheter, which scrapes the aorta during insertion, revealed atheromatous debris in 24% to 65% of the procedures, depending upon the catheter shape. Clinically apparent atheroemboli, however, are much less common. Retrospective studies of patients undergoing cardiac catheterization or aortic angiograms suggested incidences of about 0.1% to 0.2%. In a prospective study of 1786 patients 40 years of age or older undergoing cardiac catheterization, however, 25 (1.4%) had clinical evidence of cholesterol emboli.

### Clinical features

#### Skin findings
Cutaneous abnormalities are usually the earliest, and often the only, clinical findings of atheromatous emboli and may appear the very day of the provoking event or, more often, a few days later, but sometimes only after many weeks. A common finding, BTS, may affect only a single digit, but usually involves several and is typically bilateral if the origin of the atheroemboli is proximal to the bifurcation of the abdominal aorta. Peripheral pulses are characteristically well preserved, but if the small vessels become occluded, digital infarcts, ulceration, and gangrene may develop.

Another common cutaneous finding is livedo reticularis, which consists of macular reddish, blue, or violaceous connecting rings in a net-like pattern (Fig 2). This discoloration occurs when the cutaneous venousplexus becomes visible because of increased amounts of desaturated venous blood or because of venodilation. Its presence in atheroembolization arises when cholesterol crystals obstruct small arteries, decreasing vascular flow into the venous plexus and causing the blood there to stagnate and deoxygenate. Livedo reticularis blanches with pressure and disappears or fades with elevating the affected area, which explains why it is sometimes visible only when the patient is in the upright position. In atheroembolization, livedo reticularis is usually bilateral, is often quite extensive, and is most commonly seen on the feet and legs, but it may appear on the buttocks, trunk, or upper extremities, depending upon the origin of the cholesterol crystals.

Additional cutaneous findings include purpura, cyanosis, gangrene, and ulcerations in areas other than the feet, such as the leg, scrotum, and penis. An inflammatory reaction to the atheroemboli can cause nodules, which are typically firm, erythematous, and localized to the lower extremities. Splinter hemorrhages in the nail bed may also be a manifestation.

#### Renal involvement
Clinical kidney disease occurs in about 50% of reported cases of atheroembolism. In one series of 354 patients, iatrogenic causes, such as invasive vascular procedures, were responsible for about 75% of those with renal involvement, while approximately 25% occurred spontaneously. Nearly all the iatrogenic cases had at least a 50% reduction in glomerular filtration rate that was either acute or subacute, defined as an onset within 1 week or 2 to 6 weeks after the inciting event, respectively. These patterns suggest a sudden large shower of atheroemboli or repeated episodes of intense embolization over a short period of time, the latter probably explaining the stepwise decrease in renal function (periods of worsening alternating with periods of stability) often seen during the subsequent weeks of observation. Oliguria is uncommon. The spontaneous cases typically presented as stable chronic renal failure, with the pathogenesis probably being slow or intermittent release of fewer cholesterol crystals over a prolonged period of time. About half of all patients with renal involvement have severe, accelerated, or labile hypertension.

Urinalysis may disclose hematuria, casts (usually hyaline or granular), and pyuria. With the Hansel stain, eosinophiluria (eosinophils constituting ≥ 1% of the white cells in the spun urine), was present in 89% of nine patients. Proteinuria of >1+ on dipstick occurs in about 60% of cases, but only in a few has it been severe enough to cause the nephrotic syndrome. Hypocomplementemia develops in about 40% of patients. Approximately 35% require dialysis, and of these, only 20% to 30% improve enough to discontinue it.
Gastrointestinal involvement. About 15% to 20% of patients with systemic atheroemboli have involvement of one or more digestive organs. The most common features are abdominal pain, diarrhea, and GI blood loss. The mechanism of diarrhea is unclear, but probably arises from mucosal inflammation, malabsorption, and the purgative effect of blood in the gut. GI bleeding presumably develops from mucosal damage (including erosions, ulcerations, and infarcts) caused by bowel ischemia, which can also be a mechanism for the abdominal pain. Occasionally, bowel infarction and perforation occur.

Pancreatitis is a common complication. In one series of 16 cases, serum amylase levels were increased in 44% of patients, which is about the frequency of pancreatic involvement discovered at autopsy. Most patients are asymptomatic, but some develop clinically overt disease, which is occasionally fatal. Similarly, hepatic involvement is frequent on postmortem examination, and liver enzymes are often elevated, but patients rarely have symptoms.

Neurologic findings. Atheroemboli originating from the proximal aorta may travel to the eye and brain. They are sometimes visible on fundoscopy as bright yellow, orange, or copper-colored fragments lodged at bifurcations of the retinal arterioles. Called Hollenhorst plaques after the ophthalmologist who described them, these lesions more often arise from carotid arteries, but when bilateral, multiple, or associated with atheroemboli elsewhere, they are virtually diagnostic of the cholesterol crystal embolization syndrome (Fig 3). They usually produce no symptoms but do occasionally occlude vessels, resulting in visual loss. Emboli to the brain can cause transient ischemic attacks, strokes, confusional states, seizures, and gradual deterioration in cerebral function. Atheroemboli may travel to the spinal cord, but rarely cause symptoms. A peripheral neuropathy caused by cholesterol crystal emboli to peripheral nerves is also uncommon.

Other clinical features. Atheroemboli to the pulmonary vessels can cause diffuse alveolar hemorrhage with hemoptysis. Weight loss and fever may occur, probably from inflammation provoked by the cholesterol crystals. Myalgia is another non-specific symptom, caused by vessel occlusion within the muscles. The combination of constitutional features, multiorgan involvement, and skin lesions can suggest a systemic vasculitis. Some commonly abnormal laboratory results may contribute to that impression, including elevated erythrocyte sedimentation rates in almost all patients, anemia, and leukocytosis. A particularly important finding is blood eosinophilia, which occurs in about 60% to 80% of cases.

Diagnosis. The clinical features may be sufficiently compelling to allow a presumptive diagnosis of cholesterol crystal syndrome, but definitive evidence depends upon histologic examination of a sample from an affected organ. Premortem diagnosis has usually come from specimens of the skin, kidney, or muscle. Skin biopsies of a wide variety of lesions, including livedo reticularis, purpura, and cyanotic areas, have been positive in about 90% of cases. In paraffin-fixed biopsy or autopsy specimens, cholesterol crystals are dissolved and leave diagnostic acicular (needle-shaped) clefts within the lumen of blood vessels, most commonly in small arterioles with diameters of 100 μm.

The atheroemboli initiate a thrombotic process, and, by irritating the vessel wall, provoke a foreign body–type giant cell reaction or inflammation that resembles vasculitis and includes neutrophils, eosinophils, and mononuclear cells. Within the involved vessels, hyperplastic intimal proliferation occurs with variable fibrosis. The occluded vessel may recanalize but the cholesterol crystals seem permanent because they are insoluble in body fluids and impervious to phagocytosis.

Emboli from “coral reef” aorta

An unusual form of atherosclerosis consists of large, discrete, rock-hard, and gritty calcific intraplaque masses that resemble a coral reef. Pathologic examination of the masses demonstrates fibrosis of the intima and media, with a loss of the internal elastic lamina, focal intraplaque hemorrhage, and dystrophic calcification, sometimes with hyperplastic bone formation. The masses are most common in the suprarenal aorta alone or in both suprarenal and infrarenal locations, often primarily on the posterior vessel wall.
The disease is more frequent in women than men. Patients are usually in their fifties, most are smokers, and many have hyperlipidemia. The main manifestations are renovascular hypertension and lower extremity ischemia causing claudication or rest pain. A few have intestinal angina with postprandial pain and weight loss. In one case, a 45-year-old female had intermittently painful blue toes over the course of 3 months, at one time or another affecting all the digits. After undergoing an endarterectomy of an infrarenal coral reef aorta, no further episodes occurred. Presumably, she had emboli from the calcific mass.

Emboli from cardiovascular tumors

**Myxomas.** The most common primary heart neoplasm, a myxoma, arises in the left cardiac chambers in nearly 80% of cases—in the left atrium in about 75%, in the left ventricle in about 3%—and, from these locations, fragments of the tumor can embolize to various arterial vessels, including those of the foot. More common in females than males, they are most frequently discovered between the third and sixth decades of life. Most symptomatic patients have one or more of the classic triad of clinical features: (1) obstructive cardiac findings, (2) emboli, and (3) constitutional symptoms. When a left atrial myxoma occludes the mitral valve, patients may develop dyspnea from increased pulmonary venous pressure, syncope from impaired left ventricular filling and subsequent inadequate cerebral perfusion, or arrhythmias, which can be life threatening. Constitutional symptoms include fatigue, fever, weight loss, arthralgias, and myalgias. The myxomas may have a smooth surface or one that consists of fragile, gelatinous projections that tend to fragment, causing emboli, which occur in about 30% to 40% of patients. Clinically apparent emboli from

![Fig 4. Intimal aortic angiosarcoma is visible in the inferior aortic arch on the sagittal view of a computed tomography angiogram. The tumor emboli caused left arm ischemia, right homonymous hemianopsia, and blue toe syndrome.](image)

![Fig 5. Osler nodes in patient with bacterial endocarditis caused by Staphylococcus aureus.](image)

the left side of the heart most frequently involve the cerebral vessels, including the retinal arteries, causing transient or permanent visual or neurologic findings. Less commonly, they produce symptoms by obstructing peripheral, visceral, and renal arteries. Occasionally, the tumor fragments cause skin lesions, and biopsies may reveal myxomatous material obstructing a vessel. Cutaneous findings are acrocyanosis, including blue toes; erythematous, often tender, and usually acral macules and papules; petechiae; splinter hemorrhages; livedo reticularis; ulcers; reddish-violet malar flush; Raynaud phenomenon; and serpiginous and annular, violaceous non-blanching lesions.

**Intimal angiosarcoma of the aorta.** Intimal angiosarcoma of the aorta, a rare malignant tumor of endothelial origin arising in the vessel lumen, can affect the aorta at the arch, the upper abdominal portion, or, most frequently, the infrarenal segment (Fig 4). Its most common manifestation is an embolus to a peripheral or mesenteric artery. In one case, it caused bilateral foot pain, mottled purplish discoloration of both lower extremities, and cyanotic or gangrenous toes. Multiple erythematous macules also occurred on the legs and feet.

Emboli from cardiac vegetations

**Infective endocarditis.** In infective endocarditis of any duration, diverse cutaneous lesions can develop, including erythematous or purplish macules, papules, or nodules. They most commonly appear on the hands and feet, including the pads of the fingers or toes (Fig 5). Edward Janeway in 1899 and William Osler in 1909 described some of these skin findings, which are now commonly called Janeway lesions and Osler nodes, but with differing and often conflicting definitions. Perhaps the most widely adopted distinction characterizes Osler nodes as painful papules on the tips of the fingers and toes and Janeway lesions as painless macules on
the palms and soles. Skin biopsies or aspirates from several of these lesions have disclosed such features as neutrophilic inflammation (sometimes forming microabscesses), vascular occlusion, septic vasculitis, microemboli, and evidence of the infecting organism on stains and/or culture of the specimens.60-65 These findings indicate that at least some of the cutaneous manifestations of endocarditis represent infectious, rather than immunologic, complications and are probably caused by emboli from an infected valve.

Nonbacterial thrombotic (marantic) endocarditis

Nonbacterial thrombotic endocarditis consists of sterile platelet-fibrin thrombi on cardiac valves. The term is partly a misnomer, because infection is absent. Its prevalence at autopsy is about 1%, being present about three times more commonly in patients with malignancies than in benign disorders.66 The cancer is most frequently an adenocarcinoma of the lung, pancreas, or alimentary canal, but virtually any malignancy, including hematologic ones, can be present.67 Other associated disorders comprise a wide variety of illnesses, including acute infections and chronic, often debilitating, diseases, which led to the name of “marantic” (from Latin, marasmus: wasting) endocarditis. Patients may have disseminated intravascular coagulation or antiphospholipid syndrome. When associated with systemic lupus erythematosus (SLE), the valvular lesions are called Libman–Sachs endocarditis, but they do not differ histologically from other kinds of nonbacterial thrombotic endocarditis.67 These cardiac vegetations may be much more common than autopsy data suggest: echocardiograms have identified lesions compatible with nonbacterial thrombotic endocarditis in 32% of patients with primary antiphospholipid antibody syndrome, 63% with myeloproliferative diseases, 19% with solid tumors, and 43% with SLE.68,69

The vegetations are present on the mitral valve (on the atrial surface) in about 45% of cases, on the aortic valve (on the ventricular surface) in 35%, on both in 15%, and on the right-sided valves (tricuspid) much more often than on the pulmonic) in less than 5% of cases. They rarely alter valve function or produce cardiac murmurs. Most are less than 3 mm in diameter, and several vegetations can occupy a single valve. Because of their size, emboli usually occlude small arteries, most commonly in the spleen, kidney, and extremities, where they typically produce no symptoms or signs. Emboli become clinically evident most commonly in the cerebral vessels, causing focal findings (eg, aphasia or hemiparesis) or, with several emboli, either multifocal features (eg, left hemiparesis and focal seizures of the right arm) or diffuse cerebral dysfunction (eg, confusion or coma). Coronary artery occlusion can cause an acute myocardial infarction. Less common findings are hematuria from emboli to the kidneys, bowel infarction from occlusion of GI vessels, left upper quadrant pain from splenic infarct, and myalgia or weakness from obstruction of arteries to the muscles. Occasionally, emboli from nonbacterial thrombotic endocarditis can cause BTS.70

THROMBOSIS

Hypercoagulable states

Antiphospholipid syndrome. Antiphospholipid syndrome is an autoimmune disorder whose diagnosis requires both clinical and laboratory findings.71 The clinical features include: (1) thrombosis anywhere in the arterial or venous vessels confirmed by imaging techniques or histopathology and/or (2) pregnancy morbidity. The latter is defined by: (1) one or more unexplained deaths of a morphologically normal fetus at or beyond the tenth week of gestation; (2) one or more premature deaths at or before the thirty-fourth week of gestation because of severe preeclampsia, eclampsia, or placental insufficiency; or (3) three or more unexplained consecutive abortions before the tenth week of gestation. The laboratory abnormalities must include the presence of one or more of the following: (1) lupus anticoagulant, (2) immunoglobulin G (IgG) or IgM antiphospholipid antibodies in medium or high titers, or (3) anti–β2-glycoprotein I of IgG or IgM isotype at a titer more than the 99th percentile for the testing laboratory when assessed according to recommended procedures. These findings must be present on two or more occasions at least 12 weeks apart, because these antibodies can appear transiently in some healthy people and with certain illnesses, especially infections, but in those situations, the tests are rarely positive when repeated after 3 months or longer.71

Antiphospholipid syndrome may occur in the absence of other diseases or be associated with some disorders, especially SLE. The most common clinical feature of the syndrome is venous thrombosis, which can affect superficial vessels but more frequently involves deep veins, especially in the legs, often accompanied by pulmonary emboli.72 Neurologic manifestations are also common, most frequently in the form of ischemic strokes and transient ischemic attacks from occlusion of the cerebral arteries. Arthritis or arthralgias occur in more than half of patients.72 Cardiac manifestations include myocardial infarction, stenosis or regurgitation of the mitral or aortic valves, and the presence of
leaflet thickening or vegetations. Renal disease consists of acute or chronic renal failure, hypertension, proteinuria, and hematuria that result from either thrombosis of large veins or arteries or thrombotic microangiopathy affecting both arterioles and glomerular capillaries. Thrombocytopenia occurs in about 50% of cases, and hemolytic anemia in approximately 20% of cases.72

When sought carefully, dermatologic findings are detectable in about 50% of patients and are the presenting feature in approximately 30% of patients.73 Livedo reticularis is the most common cutaneous manifestation. In their criteria for diagnosing antiphospholipid syndrome, an international consensus group74 defined it as “violaceous, red or blue, reticular or mottled pattern [. . .] that may consist of regular unbroken circles (regular livedo reticularis) or irregular-broken circles (livedo racemosa [from Latin, *racemus*: grape bunch]).” The width of the branching lines can be large (≥10 mm) or small (<10 mm). The most frequent appearance is a fine, widespread, and irregular network in several areas, including the limbs, trunk, and buttocks. Other cutaneous findings include skin necrosis or gangrene, especially affecting the digits; superficial thrombophlebitis; leg ulcers, often consisting of painful, stellate lesions around the ankle; thrombocytopenic purpura; and anetoderma (circumscribed round or oval atrophic, wrinkled areas of slack skin, either bulging or depressed, caused by loss of elastic tissue). Patients can have blue toes from: acrocyanosis,74 purplish macules apparently provoked by systemic corticosteroid therapy,75 digital ischemia,76,77 nonblanching dusky network (unfading acral microlivedo),78 or nodules resembling pernio (chilblains).79 The cutaneous findings include livedo reticularis, ulcers, digital gangrene, purpura, multiple ecchymoses, and acrocyanosis.81 The last four conditions can cause blue toes.

The diagnosis of catastrophic antiphospholipid syndrome employs four criteria: (1) evidence of involvement of 3 or more organs, systems, or tissues; (2) development of manifestations simultaneously or in less than 1 week; (3) confirmation by histopathology of small-vessel occlusion in 1 or more organs or tissue; and (4) laboratory demonstration of antiphospholipid antibodies on 2 or more occasions 6 or more weeks apart. A “definite” diagnosis requires all four criteria, while a “probable” diagnosis entails: (a) all four criteria, but only two organs or tissues involved; (b) all four criteria, but the absence of at least two positive serologic tests; (c) 1, 2, and 4 above; or (d) 1, 3, and 4 above and the development of a third event between 1 week and 1 month after onset despite anticoagulation.82

Malignancy (paraneoplastic acral vascular syndrome)

The association of Raynaud phenomenon, gangrene, or acrocyanosis of the fingers and toes with neoplasias is called “paraneoplastic acral vascular syndrome.”83 About 60% of the reported underlying malignancies have been carcinomas of various histologies, most commonly adenocarcinomas affecting diverse organs, especially the lungs, ovaries, and stomach. About 20% have been hematologic malignancies, including leukemias, lymphomas, and plasmacytomas. The remaining 20% were sarcomas or cancers of unknown types. The cutaneous abnormalities appeared simultaneously with cancer detection in about 50% of patients, preceded the diagnosis in about 45% by a median interval of 3.5 months, and developed after discovery of malignancy in about 5% of patients.
The most common skin finding was acute digital gangrene in about 60% of cases, preceded by Raynaud phenomenon in about 50% of cases (Fig 7). Acrocyanosis occurred in about 25% of patients and Raynaud phenomenon alone in about 20% of patients. The fingers were affected in about 95% of patients, both fingers and toes in 30% of patients, and the toes alone in approximately 5% of patients. The histologic examinations of skin biopsies from 10 patients revealed fibrinoid necrosis of the vessels, intimal proliferation, and inflammatory cells in five cases and tissue necrosis with venous and/or arterial thromboses in the other five cases. In about 50% of cases, the digital ischemia regressed with successful treatment of the malignancy.83

Thrombotic thrombocytopenic purpura

In thrombotic thrombocytopenic purpura (TTP), which is primarily a disease of previously healthy adults, the major histologic feature is widespread occlusion of small arterioles by platelet plugs containing variable quantities of von Willebrand factor. It is clinically defined by the presence of thrombocytopenia and a microangiopathic hemolytic anemia without another cause, such as disseminated intravascular coagulation, malignant hypertension, malignancy, or severe preeclampsia.84,85 As in other forms of microangiopathic hemolytic anemia, the erythrocyte damage is not immune-related—the direct antiglobulin (or Coombs) test is negative—but instead is caused by the shearing of erythrocytes passing through vasculature partially occluded by microthrombi. The resulting fragmented red cells (schistocytes) are visible on a peripheral blood smear (Fig 8).

TTP affects women more than men, with an average age at onset of about 40 years. It has a nine-fold increased incidence among blacks. Most cases are idiopathic, but some have been associated with medications (eg, ticlopidine, clopidogrel, quinine, cyclosporine, or tacrolimus), infection with HIV, pregnancy or the postpartum period, and bloody diarrhea caused by enterohemorrhagic Escherichia coli.85

The earliest clinical manifestations are often non-specific symptoms, such as weakness, malaise, nausea, abdominal pain, and fatigue. Most patients develop neurologic findings that are typically transient or fluctuating, including confusion, headaches, focal motor or sensory abnormalities, seizures, visual symptoms, and coma. Fever is common but is often low-grade (<102°F [38.9°C]). Renal involvement is frequent, with proteinuria, microscopic hematuria, and mild to moderate depression of renal function being the predominant features. Clinically apparent bleeding is often the earliest sign, and the skin is, by far, the most common site of hemorrhage, evidenced primarily by petechiae and purpura. Digital ischemia occurs in some patients with TTP and begins with mottling of the fingers and toes that evolves into bluish discoloration and, eventually, gangrene86 (Fig 9).

The laboratory evidence for microangiopathic hemolysis includes markedly elevated serum lactate dehydrogenase (LDH), increased indirect bilirubin, decreased haptoglobin, elevated reticulocyte count, and anemia with the peripheral blood smear revealing increased polychromatophilic erythrocytes and fragmented red cells (schistocytes) representing more than 1% of the red cell population (usually ≥2 per microscopic field at ×100 magnification).85 Thrombocytopenia is usually severe, with average platelet counts being about 25,000 per μL.

A large percentage of patients with TTP unassociated with other disorders have a severe deficiency of ADAMTS 13 (the thirteenth of a group of proteases named by the acronym “a disintegrin and
metalloprotease with thrombospondin-1-like domains\(^5\)). This substance cleaves the large von Willebrand factors produced by vascular endothelial cells, and, when its levels are diminished, von Willebrand factor multimers accumulate and react with platelets, causing the disseminated platelet thrombi that are characteristic of TTP. The ADAMTS 13 levels are less than 5% to 10% of normal in many patients with TTP, depending on the definition of the disease, and usually the cause is an ADAMTS 13—binding IgG. Rarely, there is a hereditary deficiency of ADAMTS 13.\(^8\)

**Disseminated intravascular coagulation**

In disseminated intravascular coagulation (DIC), widespread activation of the clotting cascade and generation of excess thrombin results in intravascular fibrin formation and thrombotic occlusion of small and larger vessels, often causing organ failure.\(^8\) The consumption of clotting factors and platelets in the diffuse thrombotic process may deplete these hemostatic substances, leading to hemorrhage from various sites. The compensatory actions of natural anticoagulants, such as protein C and antithrombin, are decreased because of consumption, impaired synthesis, and increased degradation; fibrinolysis, although activated and resulting in increased fibrin degradation products, is inadequate to halt the clotting.

DIC is always secondary to another illness, most commonly the following: (1) diverse infections, but especially those with bacteremia; (2) severe trauma; (3) malignancy, including myeloproliferative and lymphoproliferative disorders, promyelocytic leukemia, and solid tumors; (4) obstetric complications, such as abruptio placentae and amniotic fluid emboli; (5) severe immunologic or toxic reactions, such as snakebites, transplant rejection, and transfusion reactions; and (6) fulminant hepatic failure.

The major clinical features may relate to the underlying disorder, but DIC, when acute, tends to cause bleeding, tissue ischemia, and a microangiopathic hemolytic anemia similar to that seen with TTP. Acute renal failure and hepatic dysfunction are common. Neurologic features, caused by thrombi, hemorrhage, or hypoperfusion, include delirium, coma, and transient focal signs.

The bleeding of DIC may be from mucosal surfaces, but most commonly involves the skin. The cutaneous findings include petechiae, macular or palpable purpura, hemorrhagic bullae, subcutaneous hematomas, and bleeding from areas of trauma, such as venipuncture sites or surgical wounds.\(^8\) Acrocyanosis in DIC is a gun-metal gray to purplish, sharply demarcated and symmetrical discoloration of the tips of the fingers or toes that may progress to gangrene. A distinctive finding, purpura fulminans, tends to occur with infections and consists of an extensive confluent purpura of explosive onset, frequently associated with hemorrhagic bullae and focal gangrene (Fig 10). The lesions can occur diffusely and anywhere on the body, but are usually symmetrical and involve the distal upper and lower extremities, tip of the nose, and genitalia.\(^8\)

The critical steps in diagnosis are to identify the underlying disorder that provoked the problem and to confirm the presence of DIC by laboratory studies that demonstrate evidence of both thrombin generation (eg, decreased fibrinogen) and compensatory fibrinolysis (eg, elevated fibrin-related markers). No single test establishes the diagnosis of DIC, but suggestive findings are: (1) thrombocytopenia; (2) elevated fibrin-related markers (eg, fibrin degradation products, D-dimer); (3) prolonged prothrombin time (PT); and (4) decreased fibrinogen. Often, serial coagulation tests are more helpful than single measurements.\(^8\)

**Warfarin-induced skin necrosis.** Skin necrosis occurs in an estimated 0.01% to 0.1% of patients taking warfarin, and the indication for anticoagulation in these cases is usually venous thrombosis rather than cardiac conditions, such as atrial fibrillation.\(^9\) It typically occurs in middle-aged, obese women, with the first cutaneous symptoms...
appearing 1 to 10 days (usually 3-6 days) after initiation of warfarin, although occasionally they develop more than 2 weeks later.91 Paresthesias, a sensation of pressure, and an evanescent flush may occur at the sites of involvement before the appearance of the skin lesions, which are usually painful and tender, well demarcated red or hemorrhagic plaques with an erythematous rim. They may have an edematous dimpled surface (peau d’orange). Hemorrhagic bullae develop within the lesions, and underlying necrosis then occurs. The most common locations are the breast, buttocks, and thighs, but the process can involve the feet, causing blue toes.91,92 Biopsies of the lesions demonstrate extensive occlusion of the dermal and subcutaneous capillaries with fibrin thrombi. The pathogenesis of warfarin skin necrosis remains unclear, but deficiency of protein C, a natural anticoagulant, is a major risk factor. In some cases, at least, the rapid decrease in protein C that normally occurs after warfarin initiation may remove an important anticoagulant in patients with low levels already, thereby encouraging thrombosis in the small cutaneous vessels.

**VASOCONSTRICTION**

**Acrocyanosis**

Acrocyanosis is transient or persistent bluish discoloration of the fingers and/or toes that may also involve the proximal surfaces of the hands or feet. It tends to lessen with elevation and become redder with dependency. Exposure to cold often intensifies the cyanosis, and warming the area can decrease or eliminate the discoloration. Its mechanism appears to be vasoconstriction of the small cutaneous arteries and arterioles, causing diminished blood flow, with engorgement of the capillaries and subpapillary venules.93

Sometimes, it is episodic. For unclear reasons, it occurs in patients with anorexia nervosa, especially those who are more severely ill, and improves with weight gain.94

**Perniosis (chilblains) and chilblain lupus erythematosus**

Perniosis or chilblains (Anglo-Saxon for “cold sores”) are red-purple patches, papules, or plaques that develop on acral areas in nonfreezing cold, damp conditions.95,96 They typically occur on the toes, fingers, and ears, usually bilaterally. Both acute and chronic forms exist. In the acute type, the lesions appear a few hours after exposure, causing intense pruritus, and often produce a burning sensation, especially after warming. Blisters, erosions, and ulcers may develop, but the lesions tend to resolve in 1 to 3 weeks.

In the chronic type, recurrent cyanotic papules, macules, plaques, or nodules form on the toes and fingers after repeated exposures to cold. Sometimes, the only manifestation is cyanotic toes.97 Most patients are women between 20 and 40 years of age, in whom these lesions develop each year during the cold months and typically resolve when the weather becomes warmer. In many patients, the disorder is idiopathic, but those with severe, protracted lesions often have clinical symptoms or laboratory findings of a concomitant rheumatologic disease.98 Occasionally, it is Sjögren syndrome, but usually SLE or cutaneous lupus erythematosus (discoid lupus) is present. The lesions commonly persist throughout the year, and in some of the patients, biopsies of the lesions do not reveal the features of usual chilblains (described below) but instead show the histopathologic and direct immunofluorescence findings typical of lupus erythematosus. This disorder, originally described by Hutchinson in 1888,99 has been called “chilblain lupus erythematosus.”100 Other cutaneous findings are often present, including Raynaud phenomenon, malar rash, photosensitivity, and discoid lupus.98,100-103 Serologic testing commonly reveals antibodies, less frequently anticardiolipin antibodies, or anti–SS-A or anti–SS-B. Proposed diagnostic criteria for chilblain lupus erythematosus are divided into two categories as follows: major criteria—(1) skin lesions in acral locations induced by exposure to cold or a drop in temperature; (2) evidence of lupus erythematosus in the skin lesions by histopathologic examination or direct immunofluorescence; and minor criteria—(1) the coexistence of SLE or skin lesions of discoid lupus erythematosus; (2) response to anti–lupus erythematosus therapy; and (3) negative results of cryoglobulin and cold agglutinin studies. Diagnosis requires fulfilling both major and one or more of the minor criteria.101

The pathogenesis of chilblains is unsettled, but the usual explanation is that intermittent or protracted cold-induced vasoconstriction causes ischemia and inflammation of vessels and surrounding tissue. The major histopathologic findings are dermal edema, keratinocyte necrosis, and a deep dermal lymphocytic infiltrate, which are especially prominent around vessels and eccrine glands.98,104,105 Vascular thrombi are sometimes present. Angiography in one patient disclosed narrowing and occlusion of several vessels.95

**Medication-induced vasoconstriction**

Some medications, such as amphotericin B deoxycholate,106 and imipramine,107 can cause acrocyanosis. A similar phenomenon occurs when local
anesthetic combined with epinephrine is injected as a nerve block for toe surgery.108 Systemic vasopressors also produce cutaneous vasoconstriction, which can lead to acrocyanosis, ischemia, and even gangrene. Such ischemic skin lesions occurred in 30% of 63 patients receiving continuous arginine vasopressin infusion for catecholamine-resistant vasodilatory shock109 and have developed from the intravenous administrations of dopamine,110 norepinephrine,111,112 and phenylephrine.113 Another cause is ergotism, now most commonly associated with ergot medications taken for migraines.114

INFECTIOUS AND NONINFECTIOUS INFLAMMATION, INCLUDING VASCULITIS

A patient with syphilis developed painful blue toes that on biopsy demonstrated a superficial and deep, tightly cuffed perivascular lymphohistiocytic and plasma cell infiltrate with endothelial cell swelling.115 The findings resolved with penicillin therapy.

Patients with localized pyogenic infection of the foot can develop blue toes, presumably from impaired arterial flow because of the pressure of accumulating pus compressing the vessels and/or from vasculitis causing vessel narrowing or occlusion (Fig 11).

A young girl with Behcet disease developed tender, purpuric papulondodular lesions on her toes and fingertips.116 A skin biopsy demonstrated a lymphocytic interface dermatitis and perivascular and intramural lymphohistiocytic infiltrates associated with endothelial prominence, mural edema, and erythrocyte extravasation. Other vasculitides can also cause BTS, but they have not been the subjects of reports (Fig 12).

OTHER VASCULAR OBSTRUCTION

Calcific vasculopathy (“calciphylaxis”)  
Ischemic skin lesions can develop when calcification of the small cutaneous vessels and intimal fibrosis cause narrowing or occlusion of the vasculature. It is most common in patients with end-stage renal disease, including kidney transplant recipients and those undergoing chronic peritoneal or hemodialysis.117-119 They often have evidence of secondary or tertiary hyperparathyroidism with an elevated serum calcium-phosphate product. It has also occurred, however, without end-stage renal disease in such disorders as cancer, autoimmune hepatitis, inflammatory bowel disease, rheumatoid arthritis, sarcoidosis, SLE, alcoholic liver disease, and primary hyperparathyroidism.117,118 In one series of 64 patients, for example, 23% were not undergoing dialysis, although most had some degree of renal insufficiency.118 Risk factors include obesity, liver disease, systemic corticosteroid use, and a calcium-phosphate product of greater than 70 mg²/dL.118 Called “calciphylaxis,” based on the dubious assumption that it is caused by a hypersensitivity reaction, this disorder has also been labeled “calcific uremic arteriolopathy,” “calcifying panniculitis,” “metastatic calcinosis cutis,” and “necrotizing panniculitis.”117 A more accurate name would be “calcific vasculopathy.”

Cutaneous lesions usually occur on either or both: (1) the distal extremities (below the elbow or, much more commonly, the knee) and (2) the proximal extremities, trunk, and buttocks.117,118 The skin abnormalities on the distal lower extremities may begin as livedo reticularis or acral cyanosis, including blue toes,120 but typically progress rapidly to ulceration and gangrene. In the proximal form, the cutaneous lesions tend to overlie thick adipose tissues of the abdomen, thigh, and buttocks and begin as erythema...

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Fig 11. A diabetic with a foot ulcer and infected distal foot developed a blue fourth toe. An amputation specimen of toe revealed purulence and extensive tissue necrosis, presumably from pus compressing the vessels and/or vascular inflammation occluding the vessel lumen.

Fig 12. Focal violaceous cutaneous infarcts and splinter hemorrhages in a patient with leukocytoclastic vasculitis.
that evolves into violaceous, indurated nodules or plaques. Hemorrhagic bullae may form, commonly followed by ulceration or necrosis with eschar formation. When the process involves both inner thighs, they are often in a symmetrical “kissing” pattern where the surfaces of the skin appose. Unusual sites include the neck, breast, and genitals. In all forms, intense cutaneous pain is common.

The diagnosis is often readily apparent in patients with chronic renal failure who have characteristic lesions. When the condition is atypical or occurs in the absence of end-stage renal disease, the diagnosis can be suggested by skin biopsy, although the biopsy site may heal poorly. The characteristic findings are calcification of the media, intimal proliferation, and endovascular fibrosis of the small vessels of dermis and subcutaneous fat. Vascular occlusion by thrombus or calcific obliteration of the lumen is often, but not necessarily, present.118,119 Acute and chronic panniculitis, with a predominantly septal pattern, may occur, and collagenous degeneration is frequent in early lesions. In advanced cases, dermal and subcutaneous necrosis with mixed acute and chronic inflammation is common.121

BLUE TOE SYNDROME FROM IMPAIRED VENOUS OUTFLOW
Ischemic venous thrombosis (phlegmasia cerulea dolens and venous gangrene)

Occasionally, extensive occlusion of the veins in an extremity causes tissue ischemia. Sometimes called phlegmasia cerulea dolens (“painful blue inflammation”) to distinguish it from the much more common nonischemic venous thrombosis phlegmasia alba dolens (“painful white inflammation”), it nearly always involves the legs.122 Many patients have predisposing factors for venous thrombosis, such as immobility, clotting disorders, pregnancy, and leg trauma. The most frequent underlying condition, however, is a malignancy, which is present in about 40% of cases. The most common cancer, by far, is bronchogenic, but others tumors have arisen from such sites as the pancreas, alimentary canal, gall-bladder, ovary, and uterus. The left leg is more commonly involved than the right, probably because the right iliac artery normally compresses the left iliac vein as it crosses over it, predisposing it to clotting in the presence of another condition promoting thrombosis.

Typically, the clots in phlegmasia cerulea dolens obstruct nearly the entire venous system of the affected extremity, inhibiting venous outflow and substantially elevating venous hydrostatic pressure. Marked edema forms from extravasation of fluid and its impaired absorption. The excessive fluid increases tissue pressure and diminishes arterial flow, to the point that it may cease, even though the arterial lumens remain patent. Cyanosis develops from the superficial venules becoming engorged with stagnant, desaturated blood.

The major clinical findings are unilateral pain, edema, and cyanosis, which begins in the toes but can ascend the leg and is sometimes associated with rubor. Hemorrhagic bullae may form over the toes, and gangrene develops in 40% to 60% of cases (Fig 13). Pulmonary emboli occur in about 15% to 40% of cases.123 The diagnosis is apparent on duplex Doppler ultrasonography.124

BLUE TOE SYNDROME FROM ABNORMAL CIRCULATING BLOOD
Paraproteinemia causing hyperviscosity syndrome

Viscosity is a measure of a fluid’s resistance to deformation, and in whole blood its major determinants are the plasma and the erythrocytes, whose viscosity depends upon their concentration (hematocrit), mechanical properties, and reversible aggregation.125,126 White cells contribute significantly only with marked leukocytosis. The primary factors affecting plasma viscosity are the levels of fibrinogen, albumin, and globulins. In adults, the most common cause of clinically significant increased viscosity (hyperviscosity syndrome) is substantially elevated serum globulins in the form of monoclonal immunoglobulins (paraproteins), whose viscosity depends upon their quantity, shape, and size. Because of its size, IgM increases viscosity the most, and in Waldenström macroglobulinemia, the hyperviscosity syndrome is fairly frequent, occurring
in 8% to 39% of patients. Because polymerization of the paraprotein commonly occurs in IgA myelomas, they are the second most common cause of the hyperviscosity syndrome. With multiple myelomas associated with an IgG paraprotein, symptoms of hyperviscosity arise in about 4% of cases. Less frequent causes of hyperviscosity syndrome are polyclonal hyperglobulinemia, erythrocytosis from polycythemia vera, and leukocytosis caused by acute or chronic leukemias. On peripheral blood smears, rouleau formation (red cells arranged in a row like a stack of coins; Fig 14) can be visible with multiple myeloma or Waldenström macroglobulinemia, which can also cause red cell agglutination (clumping of erythrocytes; Fig 15).

The major clinical manifestations of hyperviscosity syndrome are: (1) mucosal hemorrhage, from gingival, nasal, GI, or postoperative sites; (2) opthalmic abnormalities, such as blurring, visual loss, and fundoscopic findings of retinal hemorrhages and exudates, retinal vein thrombosis, and papilledema; and (3) neurologic abnormalities, such as headache, dizziness, hearing loss, and confusion. Some patients develop congestive heart failure. The main cutaneous findings, which arise from stasis of blood and vascular occlusion in the superficial vessels, include livedo reticularis, acrocyanosis, and digital ischemia, which can progress to gangrene.

Myeloproliferative neoplasms

Chronic myeloproliferative neoplasms are clonal hematopoietic stem cell disorders with bone marrow proliferation of one or more myeloid lineages (ie, granulocytic, erythroid, or megakaryocytic). Effective maturation of the cells leads to increased numbers of circulating erythrocytes, granulocytes, and/or platelets. The resultant diseases include polycythemia vera, chronic myelogenous leukemia, chronic neutrophilic leukemia, chronic eosinophilic leukemia, hypereosinophilic syndrome, primary myelofibrosis, mast cell disease, and essential thrombocythemia. Two of these—polycythemia vera and essential thrombocythemia—can cause BTS. The World Health Organization diagnosis of essential thrombocythemia requires fulfilling all four of the following criteria: (1) a sustained platelet count equal to or greater than $450 \times 10^9/L$; (2) a bone marrow biopsy whose major abnormality is increased numbers of enlarged, mature megakaryocytes; (3) the exclusion of other disorders that can cause thrombocytosis, such as chronic inflammation, previous splenectomy, underlying neoplasm, and other myeloproliferative diseases; and (4) demonstration of JAK2V617F or another clonal marker. The diagnosis of polycythemia vera requires meeting two major criteria and one minor one or the first major criterion and two minor ones. The major criteria are: (1) an elevated red cell mass more than 25% above the mean normal predicted value or a hemoglobin value greater than 18.5 g/dl in men or greater than 16.5 g/dl in women; (2) the presence of JAK2V617F or similar mutation. The minor criteria are: (1) bone marrow demonstrating proliferation of erythroid, megakaryocyte, and granulocyte precursors; (2) a subnormal serum erythropoietin level; and (3) endogenous erythroid colony growth in vitro.

When patients with these disorders develop BTS, the main initial feature is erythromelalgia, a burning erythema and swelling of the extremities that is exacerbated by heat, relieved by cold, and usually preceded by paresthesias. Without treatment, cyanosis and coldness of the toes may develop and progress to ulceration or gangrene. With aspirin, the symptoms and signs usually resolve within hours. In others, the normalization of platelet counts by cytoreductive therapy may be necessary to relieve
Cryofibrinogenemia

Cryofibrinogens are complexes present in the plasma, but not in the serum, which precipitate when the plasma is cooled to 4°C and dissolve at 37°C. They consist of fibrinogen, fibrin, fibronectin, and smaller amounts of other proteins. In some cases, no underlying disease coexists—primary or essential cryofibrinogenemia—but most patients have the secondary form, associated with such illnesses as infections, rheumatologic disorders, or cancer. Some patients have concomitant cryoglobulins, and they usually have an underlying disease. Although Raynaud phenomenon, arthralgias, fever, glomerulonephritis, and arterial or venous thromboses can occur, the main clinical features in symptomatic cryofibrinogenemia are cutaneous and include livedo reticularis, purpura or ecchymoses, ischemia, ulcers, necrosis, and gangrene. Blue toes from vasoconstriction may be present anywhere, but tend to develop in areas where the body temperature is low, including the hands, feet, ears, nose, and buttocks. Cooling these areas may provoke skin lesions. Biopsies of the cutaneous abnormalities reveal thrombi in the superficial and deep dermal vasculature that are eosinophilic with hematoxylin–eosin stain and purple-red with the periodic acid–Schiff preparation. They may partially or completely occlude the vessels. These findings are nonspecific, occurring in several thrombotic diseases, including TTP, DIC, monoclonal cryoglobulinemia, and antiphospholipid syndrome. Other abnormalities include dermal and epidermal necrosis and leukocytoclastic vasculitis.

Cryoglobulinemia

Unlike cryofibrinogens, which precipitate when the plasma is cooled, cryoglobulins precipitate with cooling of the serum. Blood is allowed to clot completely at 37°C for 30 to 60 minutes before centrifugation, and the supernatant is then stored at 4°C for the 1 to 7 days required for the cryoprecipitate to appear. Cryoglobulins are immunoglobulins of three major types. Type I consists of isolated monoclonal immunoglobulins, usually IgM or IgG. Types II and III are “mixed cryoglobulins,” composed of two immunoglobulins, one of which, usually IgM, has either monoclonal (type II) or polyclonal (type III) rheumatoid factor activity (anti-Fc) against a polyclonal component, usually IgG. In a few cases, there is an oligoclonal IgG or IgM and polyclonal IgG, and these have been called type II-III cryoglobulins.

Type I cryoglobulinemia occurs most commonly with lymphoproliferative disorders, such as Waldenström macroglobulinemia, chronic lymphocytic leukemia, or multiple myeloma. Most cases of type II and III cryoglobulinemia have underlying hepatitis C infection—in many series, the frequency is higher than 80%. Conversely, about 20% to 60% of patients with hepatitis C infection have cryoglobulinemia, although it causes symptoms in only about 10% to 30% of these. In some patients with cryoglobulinemia, no other disease is present (“essential cryoglobulinemia”), but in the secondary cases, other causes besides lymphoproliferative disorders and hepatitis C infection include: (1) rheumatologic diseases, such as SLE, rheumatoid arthritis, and Sjögren syndrome; (2) other inflammatory disorders, such as sarcoidosis, thyroiditis, and inflammatory bowel disease; and (3) viral, bacterial, fungal, or parasitic infections, such as HIV, Q fever, bacterial endocarditis, coccidioidomycosis, toxoplasmosis, and malaria. The major clinical manifestations of the cryoglobulinemias involve the skin, kidney, peripheral nerves, and the liver. In type I, the prominent findings are cutaneous and tend to be acrocyanosis, purpura, ulcers, and gangrene, which are sometimes precipitated by cold exposure. Extracutaneous features are much less common and include arthralgias, renal disease, and peripheral neuropathy.

In the mixed cryoglobulinemias, characteristic features are purpura, weakness, and arthralgias (also known as the Melzer triad). Purpura is present in most patients and may be preceded by a burning or itching sensation, most often on the lower extremities. The purpura may have an erythematous and papular
component, reflecting the presence of leukocytoclastic vasculitis or nonvasculitic inflammation commonly seen in skin biopsies.\textsuperscript{145} Showers of purpura lasting for 1 to 2 weeks may occur once or twice a month, with a minority of attacks provoked by cold exposure. Postinflammatory sequelae include hyperpigmentation, especially on the legs; ulcers, which characteristically appear above the malleoli; hemorrhagic crusts; and scarring.\textsuperscript{140,143} Raynaud phenomenon is common and may lead to digital necrosis. Livedo reticularis may also occur. Bullous or vesicular lesions are unusual.

Blue toes, which may be the major dermatologic finding of cryoglobulinemia,\textsuperscript{144} can develop from several mechanisms: acrocyanosis caused by vasoconstriction, vascular thrombosis, purpura from vasculitis or nonvasculitic inflammation, and ischemia.

About 20\% to 30\% of patients with mixed cryoglobulinemia have renal involvement, but it usually follows the onset of purpura by about 4 years.\textsuperscript{139} The major manifestations are proteinuria, sometimes leading to nephrotic syndrome (hematuria, proteinuria, and acute nephritic syndrome [hematuria, proteinuria, and rapid deterioration in renal function]. The most common histologic pattern, present in about 80\% of cases, is type I membranoproliferative glomerulonephritis. Most of the remaining patients have mild mesangial proliferative glomerulonephritis.\textsuperscript{139}

Peripheral neuropathy occurs in about 20\% to 60\% of patients and usually begins with symmetric or asymmetric sensory findings, including numbness and painful paresthesias in the distal extremities. Later, motor involvement may develop. Mononeuritis (mononeuropathy) multiplex, the discrete involvement of two or more individual nerves, can also occur.

Other common findings include hepatomegaly, splenomegaly, and increased liver enzymes. Many patients have arthralgias, which usually involve the small distal joints symmetrically and may follow cold exposure. Frank arthritis, however, is rare.

Cold agglutinins

Cold agglutinins are immunoglobulins, usually IgM, that agglutinate erythrocytes at temperatures below 37°C. They can be present in healthy people, but with titers less than 1:64 at 4°C and no activity at higher temperatures. Pathologic cold agglutinins occur in high titers at 4°C and frequently react at 28°C to 31°C.\textsuperscript{145}

In primary cold agglutinin disease, in which no other systemic disease is present, the responsible immunoglobulins are usually monoclonal IgMκ paraproteins, and the disease is typically a chronic, low-grade lymphoproliferative disorder occurring in older adults. Transformation to a clinically overt B-cell lymphoma is rare. In secondary cold agglutinin disease, the associated illness is usually an infection, especially from \textit{Mycoplasma pneumoniae} or Epstein–Barr virus (infectious mononucleosis) in children or young adults, and the IgM antibodies are polyclonal. The IgM in either situation fixes serum complement to the red cell surface, causing hemolysis when the mononuclear phagocytic system destroys the erythrocytes, mostly in the liver. The IgM is usually directed against the I antigen on the red cell surface with chronic cold agglutinin disease and against the i antigen with the acute, self-limited, postinfectious disorder. In addition to markedly elevated cold agglutinin titers, the laboratory findings include increased serum lactate dehydrogenase, elevated indirect bilirubin, and a positive Coombs test when employing polyspecific and anticomplement antiserum, but usually negative with anti-IgG.

In patients with chronic cold agglutinin disease, cold-induced circulatory symptoms are common, primarily acrocyanosis or Raynaud phenomenon, which are often precipitated by even very slight cold exposure.\textsuperscript{145,146} Rarely, gangrene can occur.\textsuperscript{147}

EVALUATING PATIENTS WITH THE BLUE TOE SYNDROME

\section*{History}

A critical component in determining the cause of BTS is a thorough history, which should particularly elicit information about several issues whose presence suggests certain specific diagnoses (listed in parentheses): (1) cold-induced skin lesions (pernio, cryoglobulinemia, cryofibrinogenemia, cold agglutinin disease, and acrocyanosis); (2) a recent invasive procedure involving the heart or a peripheral arterial vessel (atheroembolism); (3) the recent initiation of warfarin (atheroembolism and warfarin skin necrosis); (4) previous arterial or venous thromboses and/or pregnancy morbidity (antiphospholipid syndrome); (5) neurologic symptoms involving the brain (myxoma, aortic tumor, infective endocarditis, nonbacterial thrombocytopenic purpura, infective endocarditis, myxoma, TTP, and DIC); and (6) the presence of malignancy (nonbacterial thrombocytopenic purpura, infective endocarditis, paraneoplastic acral vascular syndrome, phlegmasia cerulea dolens, hyperviscosity syndrome, cryoglobulinemia, cryofibrinogenemia, and DIC).

\section*{Physical examination}

As with the history, the physical examination should be meticulous and specifically seek the following findings, whose presence suggests certain conditions (listed in parentheses): (1) fever (atheroemboli, infective endocarditis, myxoma, TTP, and DIC); (2)
Table II. Evaluation: Laboratory and imaging studies

<table>
<thead>
<tr>
<th>Routine</th>
<th>Liver tests</th>
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<tbody>
<tr>
<td>Complete blood cell count, with white cell differential count and peripheral blood smear</td>
<td>Renal function tests (serum creatinine and blood urea nitrogen)</td>
</tr>
<tr>
<td>Urinalysis, including microscopy (with eosinophil smear for suspected atheroemboli)</td>
<td>Coagulation tests (for suspected disseminated intravascular coagulation)</td>
</tr>
</tbody>
</table>

If routine tests are unrevealing or for specific diagnostic concerns, consider:

**Laboratory studies**

- Antinuclear antibodies
- Antiphospholipid antibodies
- Blood cultures (for suspected endocarditis or infection causing disseminated intravascular coagulation)
- Coagulation tests (for suspected disseminated intravascular coagulation)
- Cold agglutinins
- Cryofibrinogens
- Cryoglobulin
- Hemolysis evaluation (reticulocyte count, serum lactate dehydrogenase, indirect bilirubin, and haptoglobin)
- Hepatitis C tests (for suspected cryoglobulinemia)
- Serologic tests for syphilis
- Serum and urine protein electrophoresis and immunofixation

**Imaging**

- Chest radiograph
- Computed tomography angiogram or magnetic resonance imaging (for origin of suspected atheroemboli or aortic tumor)
- Computed tomography of chest and abdomen (for suspected occult malignancy)
- Echocardiogram (for suspected infective endocarditis, myxoma, and nonbacterial thrombotic endocarditis)
- Venous duplex of legs (for suspected phlebmasia cerulea dolens and antiphospholipid syndrome)

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