Warfarin-Induced Leukocytoclastic Vasculitis

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GOAL

To understand leukocytoclastic vasculitis (LV) to better manage patients with the condition

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Recognize the presentation of LV.
2. Explain the factors contributing to drug-induced LV.
3. Discuss treatments and preventive strategies for LV.

CME Test on page 348.

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Skin reactions associated with oral coumarin-derived anticoagulants are an uncommon occurrence. Leukocytoclastic vasculitis (LV) is primarily a cutaneous small vessel vasculitis, though systemic involvement may be encountered. We report 4 patients with late-onset LV probably due to warfarin. All 4 patients presented with skin eruptions that developed after receiving warfarin for several years. The results of skin lesion biopsies were available in 3 patients, confirming LV. Cutaneous lesions resolved in all patients after warfarin was

discontinued. In 2 of the 4 patients, rechallenge with warfarin led to recurrence of the lesions. LV may be a late-onset adverse reaction associated with warfarin therapy.

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Approximately 10% to 24% of leukocytoclastic vasculitis (LV) cases are drug-induced.[1] Cutaneous reactions from coumarin derivatives are not frequently encountered; however, several types of skin lesions associated with the coumarin anticoagulants have been reported, including hemorrhage related to prolongation of prothrombin time, skin necrosis,[2] gangrene, purple toe syndrome, and dermatitis.[3] Warfarin-induced necrosis was first reported in 1943[4]; since then, approximately 100 cases have been reported in the English literature.[5] Skin necrosis occurred in 0.01% to 0.1% of patients taking coumarin congeners.[6] There also have been several case reports of an LV resulting from coumarin derivatives, but the onset of these reactions have occurred within a relatively short time after initiation of coumarin therapy (Table 1).[7-15] This report describes 4 cases of LV that developed in patients on long-term warfarin therapy.

Case Reports

Patient 1—The first patient was a 57-year-old white woman with rheumatic heart disease and atrial fibrillation who had received warfarin therapy continuously for approximately 10 years following a mitral valve replacement with a Kay-Shiley prosthesis in May 1968. Additional medical history included an embolic cerebrovascular event in January 1976, frequent urinary tract infections, alcohol use, and allergy to penicillin. Her medications included aspirin, ferrous sulfate, acetaminophen, potassium chloride, diazepam, digoxin, furosemide, and warfarin.

In September 1978, the patient was admitted to our hospital for exacerbation of a nonpruritic maculopapular rash that had appeared intermittently since January 1978 with no apparent changes in her medications. She was afebrile and denied chills. The results of a skin examination revealed multiple discrete petechial lesions on her hands, upper thighs, lower legs, and feet bilaterally and in the suprapubic region. The results of a cardiac examination revealed that the patient was hemodynamically stable. Laboratory tests on admission included an excessive prothrombin-proconvertin test value of 6% (reference range, 10%–20%) and an elevated erythrocyte sedimentation rate. The results of blood cultures and workups for hematologic and collagen vascular diseases (CVDs) were negative. White blood count, platelet count, liver function, antinuclear antibody, hepatitis B and C viruses (HBV and HCV), complement, and rheumatoid arthritis latex function test results were either negative or within reference range. The results of a urinalysis revealed proteinuria and hematuria, and the renal ultrasound demonstrated no abnormalities. The results of a skin lesion biopsy were interpreted as LV.

During this time, all of the patient's medications except warfarin and digoxin were discontinued; warfarin was not considered to be a culprit. However, the skin lesions persisted, and warfarin was discontinued 6 days later. Anticoagulation was begun with subcutaneous unfractionated heparin, and improvement was noted in the patient's skin lesions during the course of her hospitalization. In mid October, she was discharged and restarted on all her previous medications, including warfarin. Five days later, the patient presented to the anticoagulation clinic with an increasing number of petechial lesions on her arms, legs, abdomen, and back. All medications except warfarin and digoxin were again discontinued. Subsequently, the patient continued to have flare-ups of her skin eruptions and hematuria, despite a series of medication changes including substituting furosemide with ethacrynic acid, changing to a dye-free warfarin tablet, and switching to a trial of dicumarol in place of warfarin.

On December 11, the patient was readmitted to the hospital for evaluation of persistent skin lesions. The results of a repeat skin lesion biopsy confirmed LV, and workup results for other systemic diseases, including endocarditis, were again negative. Dicumarol was discontinued, and unfractionated heparin was initiated. Within 7 days, the skin lesions improved. By December 19, the skin lesions were almost completely resolved, and yet another trial with warfarin was attempted. Eleven days after restarting warfarin therapy, a new set of nonpruritic petechial maculopapules reappeared on the extremities. Warfarin was again discontinued, and the patient was maintained on unfractionated heparin therapy while efforts were made to obtain anisindione, an oral anticoagulant belonging to the indanedione class. On January 11, 1979, anisindione therapy was initiated. No new cutaneous eruptions occurred during the subsequent 17 months of follow-up. Approximately 2 years after initiating anisindione, the patient developed pruritis but no skin lesions.

Patient 2—The second patient was a 49-year-old Hispanic man who began long-term warfarin therapy

in September 1982 following a peripheral vascular embolus. At that time, rheumatic mitral valve disease was diagnosed and a Starr-Edwards caged-ball prosthesis was implanted in October 1982. In 1983, he also was diagnosed with type 2 diabetes mellitus and was started on insulin treatment.

Two years after initiation of warfarin therapy, the patient was admitted to the hospital with a 10-day history of a pruritic rash that had developed over both lower extremities. He was afebrile and denied chills. His medications included warfarin, digoxin, and insulin. The patient denied any known drug allergies or any changes to his medication regimen. The skin showed multiple areas of coalescing violaceous maculopapular lesions with scattered ulcerated papules, few vesicles and bulla, plaques of lichenification, and postinflammatory hyperpigmentation. Multiple petechiae also were distributed on the extensor and flexor surfaces of the lower legs, groin, lower abdomen, and arms (Figure 1, A and B).

Laboratory evaluation included a urinalysis and 24-hour urine collection, results of which showed proteinuria and gross hematuria. The prothrombin-proconvertin test value was 24%. Laboratory test results for a complete blood count, erythrocyte sedimentation rate, C3, C4, antistreptolysin O titer, rheumatoid factor, HBV, and HCV were negative or within reference range. However, the patient's cryoglobulin level was elevated (7%), and the results of a skin lesion biopsy during this admission was interpreted as LV.

On September 18, one day after the patient's admission, warfarin was discontinued, and anticoagulation was begun with subcutaneous unfractionated heparin. By September 29, the skin lesions had improved, and warfarin treatment was restarted to "challenge" the patient; on October 3, the patient was discharged on his previous maintenance dose of warfarin, digoxin, insulin, and subcutaneous unfractionated heparin until the prothrombin-proconvertin test value was in the therapeutic range.

Table 1.

Literature Reports of Suspected Coumarin-Induced Reactions*

Reaction	Agent	Biopsy Confirmed	Onset	Positive With Rechallenge	Onset of Recurrence After Rechallenge
Leukocytoclastic vasculitis	Acenocoumarol[7]	Yes	21 d	Not done	NA
	Warfarin[8]	Yes	30 d	Not done	NA
	Warfarin[9]	Yes	10 d	Yes	6 h
Maculopapular and/or purpuric rash	Warfarin[10]	Not done	Weeks	Yes	5 d
	Warfarin[11]	Not done	12 h	Not done	NA
	Warfarin[12]	Not done	27 d	Yes	3 d
	Warfarin[13]	Not done	1 mo	Yes	NA
	Warfarin[14]	Not done	10 mo	Yes	3 d
	Warfarin[14]	Not done	3–4 mo	Yes	2 d
	Warfarin[14]	Not done	2 mo	Yes	2 d
	Warfarin[14]	Not done	5 mo	Yes	NA
	Warfarin[15]	Nonspecific perivascular inflammation	Several months	Yes	6 d

*NA indicates not applicable.

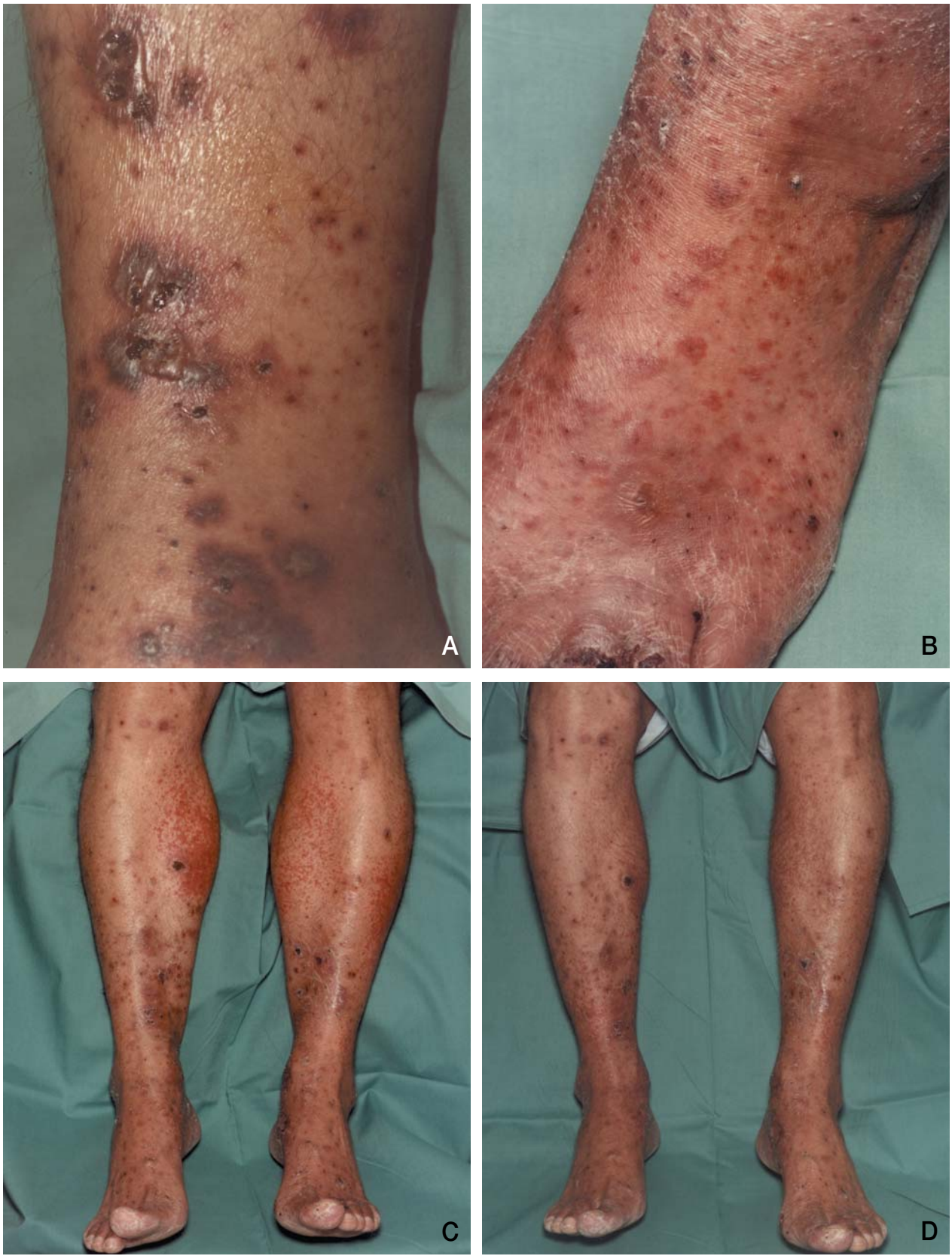

Figure 1. Patient 2 during the first hospital admission with skin lesions on the anterior pretibial region of the leg (A) and dorsal region of the foot (B). There was development of new skin lesions presenting 23 days after warfarin therapy was restarted (C). The skin lesions resolved 4 days after warfarin was discontinued (D).

On October 26, 23 days after warfarin was restarted, new petechial lesions were again observed over both lower extremities (Figure 1C); the patient was readmitted to the hospital. The results of several laboratory tests, including multiple blood cultures, C3, C4, antistreptolysin O titer, rheumatoid factor, hepatitis B surface antigen, antinuclear antibodies, and purified protein derivative, were either negative or within reference range. The results of a urinalysis revealed proteinuria and hematuria. The results of a second skin lesion biopsy during this admission confirmed LV; immunofluorescence was positive for immunoglobulin A (IgA), IgG, IgM, C3, and fibrinogen deposits.

During this admission, warfarin was discontinued, and intravenous unfractionated heparin was reinstituted. The cutaneous lesions resolved within 4 days (Figure 1D). Long-term anisindione therapy was begun with no appearance of new lesions during the subsequent 5 years.

Patient 3—The third patient was a 39-year-old Hispanic woman with a medical history of rheumatic heart disease, severe tricuspid and mitral regurgitation post–mitral valve replacement with a St. Jude Medical® mechanical heart valve and tricuspid valve commissurotomy, congestive heart failure, atrial fibrillation, and a hysterectomy. In January 1999, she was admitted to the hospital for heart failure and pruritic plaques on both lower extremities (Figure 2A). According to the patient, the plaques had begun appearing intermittently since 1997. She also described symptoms of swelling, erythema, palpable purpura, and tenderness from her knees to her feet.

The patient denied exposure to new drugs, new laundry detergent, insect bites, and poison ivy or oak. She was afebrile. Chemistry panel, hematologic profile, liver function, rheumatoid factor, antinuclear antibody, hepatitis B surface antigen, antibodies to hepatitis B core antigen, and anti-HCV test results were negative or within reference range. However, proteinuria and hematuria were present on urinalysis. The erythrocyte sedimentation rate was found to be elevated. Her international normalized ratio was 2.59.

The results of a skin lesion biopsy confirmed LV. On the patient's discharge from the hospital, captopril was added to her therapeutic regimen. During several follow-up appointments at the anticoagulation clinic, the skin lesions were found to have persisted with no improvement. Subsequently, a decision was made to discontinue warfarin and attempt a trial with anisindione. There were no further alterations to the patient's medications. During the next several months, while maintaining the patient's international normalized ratio goal with anisindione, the lesions gradually improved and resolved. She was subsequently followed through October 1999 with no further development of skin lesions (Figure 2B).

Patient 4—The fourth patient was a 48-year-old Hispanic woman with a history of rheumatic heart disease, post–mitral valve replacement with a St. Jude Medical mechanical heart valve, atrial fibrillation, hypothyroidism, and anaphylaxis to radio-contrast dye.

In April 1997, the patient was admitted to the hospital with a 6-day history of a nonpruritic maculopapular rash on her legs, feet, and chest. She was afebrile and denied joint pains or symptoms of nausea or vomiting. Her medications included warfarin, digoxin, and levothyroxine, all of which she had been taking since April 1994. There were no recent changes in the patient's medications. The results of a urinalysis taken on admission were negative for blood, protein, and bacteria. The results of tests for platelet counts, C3, C4, rheumatoid factor, HBV, HCV, antinuclear antibody, thyroid function, and serum creatinine were all negative or within reference range. Her prothrombin time and activated partial thromboplastin time were 16.9 and 28.0 seconds, respectively. The patient's erythrocyte sedimentation rate and cryoglobulin level were elevated. Her white blood count of 11,500 cells/mm^3 and neutrophil count of 84% were slightly elevated. LV was suspected; however, the patient was discharged home with a prescription of diphenhydramine as needed for pruritus, in addition to her previous medications.

On April 16, warfarin was discontinued, and anticoagulation was maintained with subcutaneous unfractionated heparin until anisindione was made available to the patient. The skin lesions improved within 5 days of discontinuing warfarin. Twelve days later, she developed proteinuria and hematuria while on unfractionated heparin. The results of a urinalysis revealed few bacteria and white blood cells, but no nitrites. Her antifactor Xa level and activated partial thromboplastin time at 6 hours postdose were 0.67 IU/mL and 54.9 seconds (ratio 1.82), respectively. The heparin dose was reduced secondary to hematuria.

On May 7, anisindione was initiated, and the patient's skin lesions resolved by May 28. However, proteinuria and hematuria persisted despite the change to anisindione therapy. Two months later, anisindione also was discontinued because of the concern of possible worsening of nephropathy with continued anisindione.[16] Self-injection with subcutaneous enoxaparin was recommended, but the

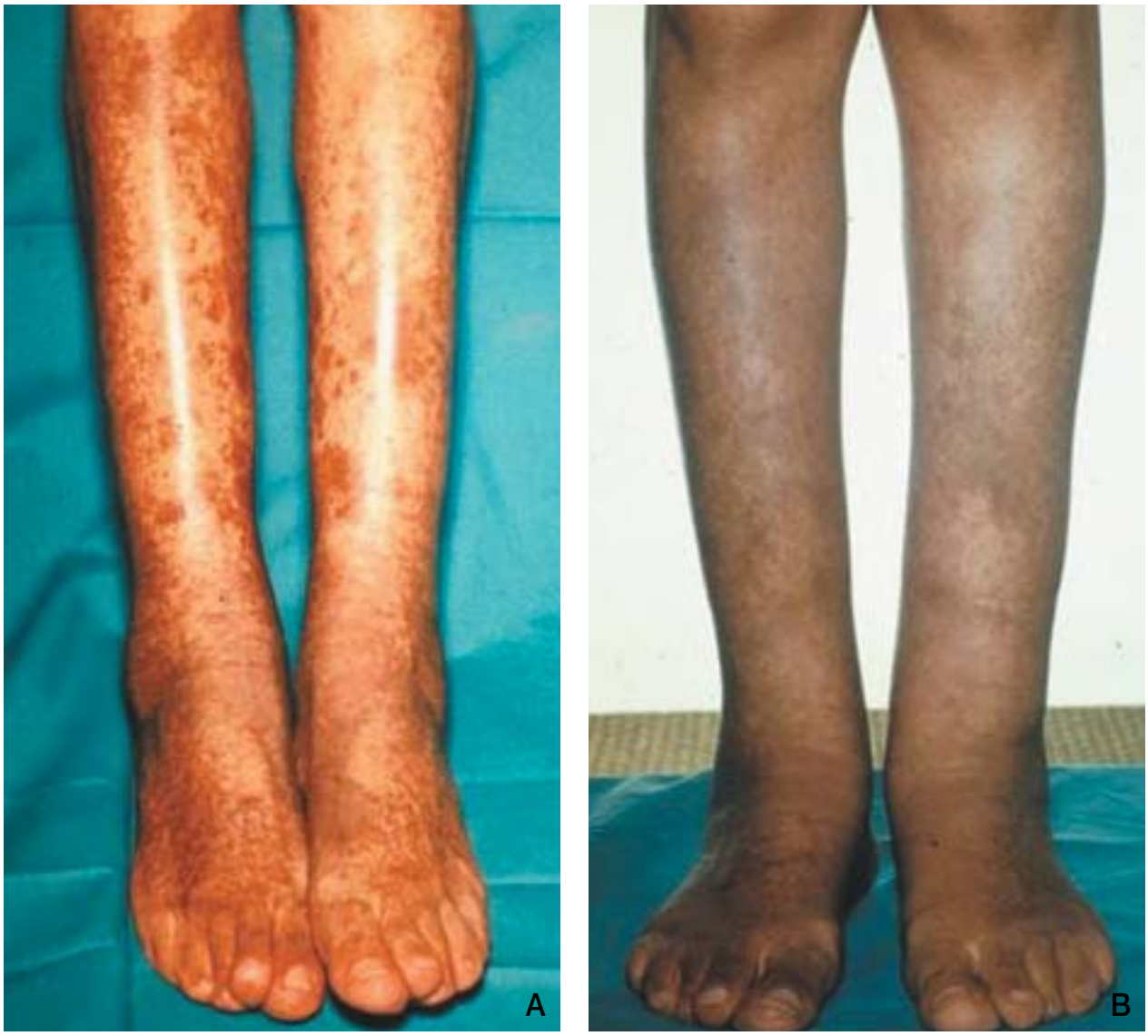

Figure 2. Leukocytoclastic vasculitis lesions in patient 3 (A), confirmed by biopsy results. Resolution of lesions several months after warfarin was discontinued (B).

patient refused. Proteinuria and hematuria persisted along with an increase in serum creatinine levels. Results of a renal ultrasound on May 29 revealed a right superior pole focal pyelonephritis. The patient continued to refuse treatment with low molecular weight heparin therapy and was lost to follow-up in July 1997. Although the patient was not actively followed by the cardiac/anticoagulation clinic, a more recent review of her hospital chart indicated that in August 1998, she returned to the medical center for a cystic pelvic mass. A hospital note also indicated that while in Ecuador in July 1998, the patient was restarted on warfarin therapy. Another follow-up note from December 1998 was unremarkable for any recurrence of cutaneous manifestations due to warfarin.

Comment

LV is an inflammatory disease involving the small vessels that usually presents as nonthrombocytopenic palpable purpura. Cutaneous lesions typically begin as asymptomatic localized hemorrhages that become palpable as blood leaks out of the vessels. Other cutaneous manifestations that may be encountered with LV include vesicles, nodules, hemorrhagic bullae, and superficial infarctions. The eruptions may be asymptomatic or associated with itching, burning, or edema. Although lesions are

commonly seen on the lower extremities, they may occur elsewhere, including areas under local pressure, such as the back in bedridden patients.[17]

It is reported that about half of the cases of LV have associated systemic effects that may involve the kidney; gastrointestinal tract; or pulmonary, cardiovascular, or central nervous systems (in addition to the cutaneous lesions).[17] Signs and symptoms may include general malaise, myalgia, arthralgia, abdominal pain, nausea, proteinuria, hematuria, and fever. In cases with severe systemic involvement, mortality has been reported.[17]

The differential diagnosis of LV encompasses a wide spectrum of diseases, including Henoch-Schönlein purpura, CVDs, and cryoglobulinemic vasculitis. LV-associated Henoch-Schönlein purpura presents as palpable purpura in the lower extremities and buttocks. The condition commonly manifests in children, especially in young boys. Henoch-Schönlein purpura usually follows an upper respiratory tract infection and is characterized by a tetrad of findings: palpable purpura, arthralgias or arthritis, abdominal symptoms, and renal failure.[18] The cutaneous lesions usually disappear in 10 to 14 days, though dapsone appears to be effective in clearing the cutaneous eruption and in shortening the duration of the disease.[19] Intravenous immunoglobulin therapy also has demonstrated some benefits.[20] The disease is self-limiting and generally has excellent prognosis in children. Characteristic histopathology features IgA deposition and neutrophilic predominance.[1]

LV-associated CVDs account for 15% to 20% of patients with vasculitis[18] and usually affect multiple organs. These CVDs include systemic lupus erythematous, rheumatoid arthritis, Sjögren syndrome, and Wegener granulomatosis.[1] Unlike drug-induced LV, which primarily targets small vessels, LV-associated CVD involves both small and medium vessels with multiple patterns of vascular injury.[1] LV-associated CVD is mediated by a type-2 immune mechanism in contrast to drug-induced LV, which is essentially a type-3 response. Depending on the particular CVD, the histopathology highlights different features: pauci-inflammatory, lymphocytic, neutrophilic, or granulomatous.[1] For LV associated with CVD, the goal is to treat the underlying condition.

Cryoglobulinemic vasculitis presents as lower extremity purpura precipitated by cold, prolonged standing, trauma, infection, or drug reaction.[1] A common cause of cryoglobulinemia is HCV, which accounts for approximately 80% to 90% of cases.[18,21-23] However, the overall incidence of LV induced by cryoglobulinemia is only 3%.[23] The hallmark of cryoglobulinemia is the presence of cryoprecipitates, which are composed of a mixture of monoclonal and polyclonal immunoglobulins. Neutrophilic and/or lymphocytic infiltrates with mural necrosis and thrombosis of vascular plexus are seen in the dermis.[18] In addition to cryoglobulin production, HCV also induces autoantibody production.[21-23] HBV reacts by a similar mechanism. Unlike HCV, HBV is associated with polyarteritis nodosa.[24] Interestingly, the histopathology of hepatitis B and C is distinguished from that of other vasculitis in that there is deposition of IgM and fibrinogen but absence of IgA deposition.

The treatment of choice of LV associated with HCV is interferon alfa, which has been shown in randomized trials to improve dermatologic, renal, and joint manifestations, as well as to reduce cryoglobulin levels.[25-27] For cryoglobulinemic vasculitis not associated with HCV, other agents such as colchicine, cyclosporine, melphalan, and intravenous immunoglobulin have been tried.[25,28-30] For hepatitis B vasculitis associated with polyarteritis nodosa, nonsteroidal anti-inflammatory drugs, acetylsalicylic acid, and high-dose corticosteroids have been used.[31-32]

Drug-induced LV is the final major etiology; in fact, LV also is known as hypersensitivity vasculitis, allergic vasculitis, or allergic angiitis resulting from various endogenous antigens and exogenous factors associated with connective tissue diseases, malignancies, infections, and chemicals or drugs.[17] LV also has been reported to be associated with prolonged exercise,[33] radio contrast media,[34] dyes,[35] food additives,[36,37] and various medications (eg, sulfonamides components, antibiotics, nonsteroidal anti-inflammatory drugs.).[17] Drug-induced LV presents as palpable purpura confined to the lower extremities. The mechanism for the development of drug-induced LV is postulated to involve a cascade of immune complex formation and complement activation. The onset of LV typically occurs 7 to 10 days after contact with the antigen responsible for the reaction but may occur as early as several hours and as late as several months after exposure.[11,17] The histopathology of drug-induced LV shows confinement to superficial vascular plexus, infiltration of vessel walls with neutrophilic leukocytes and nuclear dusts, lymphocytes, erythrocyte extravasation, and fibrinoid necrosis.

At the onset of the reaction, in patients with a history of taking medications, one study reported the presence of extravenular eosinophils in 33% of patients diagnosed with a hypersensitivity vasculitis compared with none in patients with Henoch-Schönlein purpura.[38] The timing of the biopsy also is

Table 2.

Suspected Warfarin-Induced Leukocytoclastic Vasculitis (Late Onset)*

Patient	Onset, y	Biopsy Confirmed	Positive With Rechallenge	Onset of Recurrence After Rechallenge	Lesions Despite Dye Change
1	10	Yes	Yes	5 and 11 d	Yes
2	2	Yes	Yes	23 d	NA
3	10	Yes	NA	NA	NA
4	3	Not done	NA	NA	NA

*NA indicates not applicable.

significant because early lesions are more likely to demonstrate positive immunofluorescence for IgM, IgG, and C3 near the vessel wall. IgA and fibrinogen are reported to be less commonly found. The optimal lesions on which to perform a biopsy are those that are 18- to 24-hours old.[17]

After the diagnosis of LV is confirmed with clinical presentation and a biopsy result of an involved lesion, the cause is determined by the patient's history and various laboratory testing. An effort is made to remove or treat the underlying infectious, inflammatory, or neoplastic etiology. Medications have been reported to cause about 10% to 24% of the cutaneous manifestations of LV.[1,17] Mild forms of LV may not require further treatment other than removal of the causative agent. Pharmacologic treatments include topical and systemic corticosteroids, immunosuppressants,[17] antihistamines,[12,17] and nonsteroidal anti-inflammatory drugs,[17] all of which have been used with varying degrees of efficacy. Systemic corticosteroid therapy and immunosuppressants are indicated in patients with rapidly progressing vasculitis or in severely ill patients with renal disease.[17]

Retrospective evaluation and comparison of case reports of LV and cutaneous eruptions associated with coumarin derivatives (Table 1) are difficult because some reports are purely descriptive and lack laboratory and biopsy data. The morphology and distribution of skin lesions in our patients were similar to previously reported LV cases. Timing of the drug reaction is an important issue in our 4 patients considering that 2 to 10 years elapsed between initiation of warfarin and the onset of the cutaneous manifestations. To our knowledge, there have been no other reports of LV occurring years after initiating warfarin therapy. Another notable difference in our patients was the long period between initiation of warfarin and the onset of the lesions during rechallenge (Table 2). Recurrence of lesions has been reported from 6 hours to 6 days after rechallenge (Table 1). In our patients, recurrence of the lesions occurred 5, 11, and 23 days after rechallenge.

It also may be possible that other events or factors may have contributed to LV reactions in our patients, as it can be argued that elevated cryoglobulins (patients 2 and 4) may have had an association. Although the possibility exists, it seems unlikely to have been the primary cause because LV associated with cryoglobulins is more likely a long-term and persistent reaction rather than a reaction that resolves with cessation of a drug.[39] Additionally, cryoglobulins involved in immune complex reactions have frequently been found in patients with hypersensitivity vasculitis.[39]

Infection did not seem to be a likely culprit in at least 3 of our patients. In patient 1, who had a history of recurrent urinary tract infections, the reaction resolved with the withdrawal of warfarin therapy. There was no evidence of an infection around the time of the reaction. In patient 4, an increased neutrophil count was noted, and a case could be made for the possibility of an underlying infection as a contributing factor. However, the patient was found to have a urinary tract infection after the warfarin was discontinued while skin lesions were improving.

Patients 1, 2, and 3 were eventually managed successfully on anisindione, an alternative to warfarin therapy, for a period. Approximately 2 years after initiating anisindione, patient 1 developed

pruritis but no skin lesions. Whether the patient's complaints of pruritis were associated with anisindione was unclear.

In summary, we present 4 patients with late-onset LV suspected to be due to a delayed reaction to long-term warfarin therapy. The skin manifestations in all 4 patients resolved with warfarin withdrawal, and in 2 out of 4 patients, recurrence occurred on rechallenge (patients 1 and 2). With an increasing number of patients being prescribed long-term warfarin therapy, it is important to alert clinicians to this rare and perplexing complication. We also encourage accurate documentation of future cases so that the clinical presentations can be accurately described and pathologic mechanisms elucidated.

At the time of this publication, it is not clear whether anisindione is still available. The unavailability of this agent further adds to the challenge of managing future patients who develop this complication and still require long-term anticoagulation therapy.

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