Atrophie Blanche: Is It Associated with Venous Disease or Livedoid Vasculopathy?

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This continuing education activity will expire for physicians on November 30, 2015.

PURPOSE:
The purpose of this learning activity is to provide information about the etiology and treatment of atrophie blanche.

TARGET AUDIENCE:
This continuing education activity is intended for physicians and nurses with an interest in skin and wound care.

OBJECTIVES:
After participating in this educational activity, the participant should be better able to:
1. Discuss the pathophysiology of atrophie blanche.
2. Explore treatment options for livedoid vasculopathy.
ABSTRACT
Atrophie blanche (AB) is a porcelain-white scar that may be seen at the base of a healed ulcer or in association with livedoid vasculopathy (LV). The term AB originally had been used synonymously with LV, whereas LV is a noninflammatory thrombotic condition presenting as either a primary or secondary event (often associated with coagulation).
KEYWORDS: atrophie blanche, venous disease, livedoid vasculopathy

INTRODUCTION
Atrophie blanche (AB) is a common clinical sign in patients with leg ulcers, which may be a consequence of venous hypertension with local involvement or part of a livedoid vasculopathy (LV). It presents as atrophic porcelain satellite scars with peripheral telangiectasia and hyperpigmentation. Atrophie blanche is a morphological feature that is commonly seen following a healed ulcer with venous stasis and other etiologies. In cases of AB associated with LV, the morphologic feature of AB presents as a primary lesion and in locations such as the dorsum of the foot and may precede ulceration. The terms hyalinizing vasculitis, AB, and LV have been used synonymously in the literature, whereas LV is a disease process with characteristic histology, and AB represents a morphological healing pattern that is the result of several different pathological processes including venous leg ulcers. Thus, the 2 forms of AB: (1) the AB-LV complex and (2) AB in the context of chronic venous insufficiency, are unrelated and require separate diagnostic and therapeutic approaches. This continuing education article focuses on the literature to clarify the misnomer of AB as a disease and review LV as a thrombo-occlusive disorder.

CASE 1
A 60-year-old female retired teacher presented with a long history of varicose veins, vein stripping, and recurrent leg ulcers. On physical examination, she had a painful area of scarring on the medial ankle surrounded by white atrophic patches of AB (Figure 1).

History of Atrophie Blanche
Atrophie blanche was originally described in 1929 by Milian as a particular form of cutaneous atrophy called “AB en plaque” presenting as a smooth, ivory-white, plaque-like area on lower extremities surrounded by a hyperpigmented border and telangiectatic blood vessels. He associated the lesions with syphilis and tuberculosis, but Gonin linked 70% of cases to vascular disorders. Gougerot and Hamburger postulated the lesions are a result of capillaritis and concluded that AB is a variant of stasis dermatitis. In 1950, Nelson described AB with fibrinous histological occlusion of blood vessels.

Pathogenesis
The pathogenesis of AB involves small-vessel thrombosis of the subpapillary vascular plexus. Following the thrombosis, megacapillaries (red dots) may arise within a white area of AB as a repair mechanism. This is seen as a common finding in not only a subset of patients with chronic venous insufficiency, but also in those with other entities.

CASE 2
A 56-year-old woman presented to the clinic with a leg ulcer on the lateral ankle extending to the dorsum of the feet. Her history is significant for 2 episodes of deep vein thrombosis and recurrent leg ulcers. On physical examination, the patient had small pinpoint ulcers and areas of white atrophic patches in the periwound areas with associated telangiectasia (Figure 2).

History of Livedoid Vasculopathy
Livedoid vasculopathy has been given multiple names in the literature including livedo vasculitis, segmental hyalinizing vasculitis, livedo reticularis with summer ulceration, Milian white atrophy, AB en plaque, and PURPLE (painful Purpuric Ulcers with Reticular Pattern of Lower Extremities), among others. Early descriptions of LV with the designation of livedoid vasculitis and
Pathogenesis of Livedoid Vasculopathy

Livedoid vasculopathy is a thrombo-occlusive disorder associated with several biochemical defects that may resolve with ivory white scars or AB. The occlusion of blood vessels by fibrin thrombi is a primary event in this context. Several cases have been reported in association with other conditions, such as with the lupus-type anticoagulant, hyperhomocysteinemia, increased levels of anticardiolipin, protein C deficiency, cryoglobulinemia, factor V Leiden mutation, plasminogen activator inhibitor 1 promoter mutation, and antithrombin III deficiency. There is evidence for a decrease in fibrinolytic activity and an increase in thrombogenic activity in patients with LV. Increased platelet expression of P selectin is linked to abnormal platelet function in patients with LV. Hyperhomocysteinemia is considered to be a thrombophilic condition that has been seen in association with LV. Overall, LV is mainly a thrombo-occlusive vasculopathy, and the thrombotic event may be due to multiple mechanisms.

CLINICAL PRESENTATION: ATROPHIE BLANCHE VS LIVEDOID VASCULOPATHY

An association of AB with venous insufficiency is the most common association because of the high prevalence of venous disease. Patients with chronic deep venous insufficiency of the short saphenous vein can develop AB on the dorsal foot, often at the base of the second to fourth toe. However, the involvement beyond bilateral malleoli, extending to the dorsal aspect of the feet and toes, is consistent with the secondary form of LV.

The estimated incidence of LV has been reported as 1:100,000 with female predominance. The initial appearance of telangiectatic purpuric papules and plaques (Figure 2) is followed by the formation of crusted ulcers and subsequently residual white atrophic stellate scars (Figure 3). The ulcers are painful, often bilateral, may be slow to heal, and often recur. The common locations for these ulcers are primarily in the medial ankle region and less commonly on the dorsum of the feet (Figure 3).

Hairston et al documented the lower extremity was involved in all patients, with lesions on the following locations: lower leg 80%, ankle 66.7%, and foot 62.2%. The white ivory scars or AB was seen in 71% of LV patients, and this clinical pattern has been reported either without previous ulceration, or following a painful ulcerative stage. Of the 45 patients, 19 showed associated comorbid conditions, including collagen vascular disease (6) and malignancies (5).

In patients with LV, the association with numerous heterogeneous coagulation abnormalities has been reported in more than 50% of cases. These abnormalities include factor V Leiden mutation (heterozygous), decreased activity for protein C or protein S, prothrombin G20210A gene mutation, anticardiolipin antibodies, elevated homocysteine level, and lupus anticoagulant.
Fifty percent of patients had no identifiable association with a coagulation disorder, a coagulopathy, or a vasculitis. Di Giacomo et al demonstrated pro-coagulable laboratory abnormalities in 52% (18 of 34). Among the laboratory abnormalities, a mutation in factor V Leiden was detected also in 17.64%, antiphospholipid antibody in 17.64%, protein C deficiency in 8.82%, and hyperhomocysteinemia in 5.88%. These findings emphasize the need for thrombophilic factor investigations in all patients with clinical and pathological features of LV. In a retrospective study of 70 Asian patients with LV, the association with collagen vascular disease (3%) and venous insufficiency (6%) was lower than Western studies.

HISTOPATHOLOGY OF LIVEDOID VASCULOPATHY
Histopathologic changes of LV are segmental and vary with the age of the lesion. The biopsy of an uninvolved segment may not demonstrate the histological features. The 3 typical LV blood vessel histological features include intraluminal thrombosis, endothelial proliferation, and subintimal hyaline degeneration. In the histopathology of these patients, nearly all (97.8%) demonstrated dermal blood vessel thrombosis. Direct immunofluorescence was positive for fibrin > C3 > immunoglobulin M (IgM) in 86.1% of samples.

In the early stage, the lumen of small blood vessels in the upper and mid dermis demonstrate hyaline thrombi with the vessel walls containing fibrinous material. In the presence of ulceration, infarction of the superficial dermis is seen. Extravasated red blood cells may present in the upper dermis. A nonspecific papillary dermis increase in small blood vessels is a common biopsy finding. Biopsies from partially developed lesions demonstrate a thickening and hyalinization of vessel walls in the superficial dermis with some endothelial edema and proliferation. This is similar to the nonspecific change at the base of leg ulcers.

In older lesions, dermal sclerosis and scarring with some dilated lymphatic vessels are often associated with epidermal atrophy. Immunofluorescent stained skin biopsies may demonstrate fibrin in vessel walls in early lesions and immunoglobulins (IgG and IgM) and complement (C3) in the later lesions. The immunologic reaction is most likely a secondary rather than a primary event related to the pathogenesis of this vasculopathy.

EVALUATION OF ATROPHIE BLANCHE VS. LIVEDOID VASCULOPATHY
In the presence of venous hypertension and distribution of lesions around the corresponding malleolus, no primary workup for coagulation disorders and inflammatory disorders is required (Table 1). The finding of white satellite scars on the lower legs with or without ulceration is sufficient to prompt a workup to assess the inflammatory and noninflammatory differential diagnoses (Figure 2). A thorough evaluation with a focus on personal or family history of hypercoagulable disorders, fibrinolytic

<table>
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<th>Characteristics</th>
<th>AB Associated with Healed Venous Ulcer</th>
<th>AB Associated with Livedoid Vasculopathy</th>
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<tbody>
<tr>
<td>Location</td>
<td>Most commonly on medial ankle</td>
<td>Medial and lateral ankle</td>
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<tr>
<td>History</td>
<td>Usually follows an ulcer</td>
<td>May precede, occur at the same time, or follow an ulcer</td>
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<td>Morphology</td>
<td>White atrophic scar with areas of megacapillaries</td>
<td>White atrophic scar with areas of megacapillaries plus livedo reticularis</td>
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<tr>
<td>Coagulopathy</td>
<td>Occasional</td>
<td>More common (up to 50%)</td>
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<tr>
<td>Associations</td>
<td>Varicose veins, Lipodermatosclerosis</td>
<td>Has 2 forms of primary and secondary (the secondary form is associated with connective tissue disease, hematologic disorders, and paraproteinemia)</td>
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<tr>
<td>Management</td>
<td>Compression therapy</td>
<td>Anticoagulants</td>
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<td>Medical intervention including pentoxifylline</td>
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<td>Surgical intervention</td>
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disorders, and inflammatory disease is also required. A skin biopsy for regular histology and immunofluorescence may be useful in determining the diagnosis of LV. A sufficient skin biopsy should include the ulcer marginal epithelium to avoid a nonspecific histology with granulation tissue or inflammatory cells. Ideally, it should be a deep punch or excisional biopsy. Further laboratory investigation depends on the presence of any associated clinical features. Extensive coagulation screening can exclude potential prothrombotic conditions. Laboratory investigations are focused on the exclusion of the 5 primary types of underlying diseases (remember with the mnemonic Fibrin CHIP):

- **Fibrinolytic disorders**
- **Collagen vascular disease**
- **Hypercoagulable states**
- **Infectious associations**
- **Paraproteinemia**

Based on the authors’ experience, LV must be distinguished from other conditions that produce similar cutaneous lesions on the legs, including cutaneous polyarteritis nodosa, true small and medium vessel cutaneous vasculitis (connective tissue diseases and antineutrophil cytoplasmic antibody–related vasculitis), pyoderma gangrenosum, cryoglobulinemic vasculitis, warfarin–induced cutaneous necrosis, and cutaneous ulcers due to primary antiphospholipid syndrome. One of the main differential diagnoses for the reticulate ulcerative stage is polyarteritis nodosa, which may present with purple lesions, livedo racemosa (irregular broken circles), reticulate (net-like) ulcers, subcutaneous nodules, and scars similar to AB.

To confirm a diagnosis of cutaneous polyarteritis nodosa, a deep wedge skin biopsy of a nodule including dermis and subcutaneous fat is required. The main pathology is located at the dermal subcutaneous junction with the arterioles demonstrating transmural neutrophils acutely or mononuclear perivascular infiltrates in the chronic stages.

### TREATMENT OF ATROPHIE BLANCHE

The association of varicose veins in 20% to 75% of patients with AB highlights the need for compression therapy in the management of these patients. Treatment of associated edema is important. Multiple studies demonstrated the role of compression therapy in fibrinolysis. Allenby et al demonstrated that the antithrombotic properties of the intermittent compression were due to fibrinolytic enhancement caused by the intermittent venous compression. Pain control is another essential part of the management. The pain is due to multiple factors including local ulcer formation, vascular occlusion, and coexisting venous disease.

Ulcer-related pain is often localized in the wound margin and may be maximal at the 3 stages of dressing change (dressing re-

moval, with cleansing or debridement). Using silicone adhesives instead of acrylates will help with pain and trauma on dressing removal. Surgical debridement is more painful than autolytic methods with calcium alginate hydrogels or hydrocolloids. Mechanical irrigation should be replaced with compresses. A compress consists of dipping a gauze in saline and ringing out the gauze prior to application to the wound surface. This process results in an astringent action (coagulates protein) with a net movement of fluid or exudate from the wound surface to the gauze. A soak can move fluid from a saline soaked gauze that is not squeezed to remove the excess fluid but applied dripping wet. The net movement is from the gauze to the wound surface and results in the hydration of a dry wound surface. The AB associated pain is usually due to vascular occlusion and represents a combination of nociceptive (stimulus dependent: gnawing, aching, tender, throbbing) and neuropathic components (spontaneous: burning, stinging, shooting, stabbing). This pain is best managed using the World Health Organization ladder for nociceptive pain: acetaminophen, paracetamol, ibuprofen, nonsteroidal anti-inflammatory drugs, short- and long-acting narcotics. Treatment of the neuropathic component starts with tricyclics (amitriptyline or anti-noradrenaline–specific agents—nortriptylene or desipramine with less drowsiness) given as a single dose at night starting with 10 to 30 mg. If these are unsuccessful or not tolerated, gabapentin, pregabalin, or carbamazepine can be added in increasing but divided daily doses.

Coexisting venous disease requires compression. In the absence of arterial disease, high compression can be used (palpable pulse and ankle brachial pressure index >0.8); however, compression should be modified for values between 0.6 and 0.8. In general, if pain is an issue from venous edema, utilizing nonelastic systems will have less pressure at rest and lower level of associated pain. As edema and pain control is achieved, elastic systems can be gradually introduced.

### TREATMENT OF LIVEDOID VASCULOPATHY

Management of LV remains controversial. The evidence for the efficacy of the commonly used therapeutic modalities is limited. Antiplatelet drugs and antithrombotic agents (fibrinolytic and anticoagulant medications) have been used with some success. There is no consensus on the dose of anticoagulants in LV, but most studies administered the dose for prevention of deep vein thrombosis.

Other treatments include stanozolol, danazol, sulfasalazine, nicotinic acid, intravenous immunoglobulin (IVIg), psoralen and UV light therapy (PUVA), hyperbaric oxygen, doxycycline, and cyclosphorine. Callen suggested cessation of smoking, low-dose aspirin, oral pentoxifylline, and oral dipyridamole. Recent studies have demonstrated that anticoagulants are a well-tolerated, effective therapeutic option for patients with LV.
The role of pentoxyfylline in the treatment of venous and arterial leg ulcers has been supported by several studies. The hemorheological effects of pentoxyfylline include the improvement of local hyperviscosity and hyperaggregability of erythrocytes or platelets, erythrocyte fluidity, and hypercoagulability, all of which may result in improved skin oxygenation. Pentoxyfylline has also been ordered for the treatment of LV with success, probably due to different mechanisms including a reduction of blood viscosity, increase in the flexibility of blood cells, and increase in inflow perfusion. Although the mode of action of IVIG is not completely understood, it induces modulation of cytokine production, neutralization of pathogens, and inhibition of complement-mediated damage and blockage of Fas receptors. The role of IVIG in vasculitis includes neutralizing circulating antibodies and tissue deposited immune complexes. Multiple case studies have demonstrated the response of patients with LV to IVIG with minimal complications. Cessation of smoking may also be beneficial.

CONCLUSIONS

Patients with AB commonly present in wound care clinics either following a healed ulcer or without preceding ulceration. Atrophic blanche is a morphologic pattern of tissue damage with scarring, and LV is thought to be a clinicopathologic entity caused by a variety of underlying conditions, not all of which have been identified. Clinicians must be alert to possible systemic associations. A multiprofessional approach for the management of these patients including pain control is optimal.

REFERENCES


PRACTICE PEARLS

- AB or white atrophic scars are associated with both venous disease and LV.
- AB associated with venous disease is often localized above the medial malleoli.
- AB associated with LV is more extensive with lesions extending over the malleoli bilaterally and radiating to the dorsum of the feet.
- LV is a thrombo-occlusive condition often associated with abnormalities in fibrinolysis or CHF disorders (collagen vascular disease, hypercoagulable states, infections, paraproteins).
- Thrombophilia screening may have limited direct therapeutic impact but may be useful for genetic counseling.
- Antiplatelet, antithrombotic, fibrinolytic, and anticoagulant medications have been used with success in the management of AB and LV.
- A multiprofessional approach to the management of patients with lividoid vasculopathy is required.

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