



DIAGNOSTIC CHALLENGES IN TWO CASES OF CUTANEOUS VASCULITIS

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Abstract. Objectives. To distinguish those cases of local cutaneous vasculitis in children very difficult to diagnose and classify in the absence of other clinical characteristic findings. **Materials and methods.** Two patients presenting with unusual cutaneous chronic vasculitis in children with early onset in the first decade of life are reported. **Results.** Clinical features (livedo reticularis), histopathologic changes (presence in the reticular dermis of fibrin in the wall of venules and thrombi within their lumen) and the evolution (healing with atrophie blanche) were necessary to identify the diagnosis in each case, in order to exclude other types of vasculitis. Complex laboratory investigations were done in order to do this. Finally, the diagnosis in both cases was livedoid vasculitis. **Conclusions.** Proper diagnosis of livedo reticularis with recurrent ulcers of the lower extremities that heal to leave hyperpigmentation and atrophie blanche is very important, because ulcers may result from a variety of small vessel vasculitis which do not require the same treatment. Patients with livedoid vasculitis may be associated with various systemic diseases including hypercoagulable states, so a complete evaluation is required.

Keywords: cutaneous vasculitis, livedo reticularis, children

Introduction

There are three major types of small-vessel vasculitis in skin: allergic (leukocytoclastic) vasculitis, septic vasculitis, and livedoid vasculitis. The livedoid vasculitis is the least common and the most enigmatic vasculitis because neither its cause nor its pathogenesis is known for sure [1].

Leukocytoclastic vasculitis and livedo vasculitis, as their names denote, are vasculitides that favor the lower extremities, but whereas a rule in livedo vasculitis is that only the legs are affected, in leukocytoclastic vasculitis any anatomic site may

be involved [2]. The important findings that enable histological differentiation of leukocytoclastic vasculitis from livedo vasculitis are the presence in leukocytoclastic vasculitis of abundant nuclear "dust" of neutrophils and often of many eosinophils, and the absence of thrombi. In contrast, livedo vasculitis usually displays no nuclear "dust" of neutrophils or eosinophils, but exhibits both fibrin in the wall of venules and thrombi in their lumen [2]. Livedoid vasculitis, also known as livedo reticularis with summer/winter ulcerations, is a rare distinctive type of cutaneous acute vasculitis, in particular, the type characterized histopathologically by the presence in the reticular dermis of fibrin in the wall of venules and a thrombus within their lumen. A mild infiltrate of inflammatory cells is also present, neutrophils predominating early, and lymphocytes later. Leukocytoclasia is not observed. Although livedo vasculitis has no urticarial stage,

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it does present itself as purpuric macules, papules, vesicles, and bullae. Lesions of livedo vasculitis ulcerate commonly and those defects are replaced by white scars, as a consequence of which the late stage of the disease has been named “atrophie blanche” [2]. That last change, combined with a thinned epidermis devoid of both discrete rete ridges and of melanin, presents itself clinically as white atrophic scars [1]. This is in fact the origin of an imprecise synonym for livedo vasculitis, known colloquially as “atrophie blanche”. Atrophie blanche is merely the end stage clinical lesion, which is characterized by irregular, white or ivory, depressed scars on the lower extremities [1,2]. It is mandatory to emphasize that the lesions of livedo vasculitis are not always truly vasculitic, because they may develop as a consequence of coagulation disturbances and are associated only with thrombi without remarkable infiltrates of inflammatory cells. The presence of fibrin within the wall or thrombi within the lumen of blood vessels, without inflammatory cells, does not qualify as vasculitis [1]. Thus, it is classified as mimickers of vasculitis (pseudovasculitis) [2]. There is no relationship between livedo vasculitis and livedo reticularis. The word “livedo” shared by both conditions means a bruise-like discoloration of the skin. Livedo reticularis is not a vasculitis, but a kind of ectasia that does not change perceptible in terms of its basic morphologic structure over time [1].

Cases presentation

Case No 1. 11 year-old girl. The past medical and family histories were non-contributory. The onset was at the age of 3 years with painless perimalleolar erythematous macules and palpable purpura, unilateral at the beginning. In the next cold season the lesions improved spontaneously, but soon recurred and spread around both ankles, persisting despite the treatment, until now. At the age of 9 years she was admitted for the first time in our hospital.

Physical examination: Normal temperature; Pulse: 80 bpm; Respirations: 18/min; BP: 95/50mmHg; Weight: 53 Kg; Height: 160 cm. General appearance: good state of nutrition and mental development. The patient had cold teguments with a bruise-like discoloration (livedo) on the dorsal aspect of the feet and around the ankles, with extended hyperpigmented confluent or ring-shaped

areas, hemorrhagic blisters and crusted ulcers at the same sites, without local itching and pain. No systemic signs were present (see fig. 1A, 1B).



Figure 1A, 1B. Hyperpigmentation and atrophic porcelain-white scars in a reticulate pattern over the ankles

Laboratory data. The usual screening exams were normal (CBC, acute phase reactants, urinalysis, chest radiograph). Renal and hepatic tests were also normal. Serum immunoglobulins, C3 and C4 fractions of serum complement were within normal limits, cryoglobulins were negative and so were the tests for B and C viral hepatitis. Rheumatoid factor (RF), anti-cyclic citrullinated peptide (CCP), anti-nuclear antibody (ANA), anti-dsDNA, anti-SmENA, anti-La, anti-RNP, anti-Scl70 and anti-centromere antibodies were negative. P-ANCA and c-ANCA were positive. Protein C, protein S, antithrombin III levels in the plasma were normal. An antiphospholipid syndrome was confirmed (see table I).

Periungual capillaroscopy: blood column fragmentation; normal capillary morphology with elongation of the afferent and efferent ansa; megacapillary with small shot shaped hemorrhage.

SaO₂: 100% in remission phase.

Skin biopsy (excisional biopsy): intermediate power showing vessels of the deep plexus involved

	27/04/2007	27/04/2007	06/09/2007	04/02/2008	05/05/2009
LA1 (sec)	53	121.7	41.85	84.45	26.5
ACL	negative	negative	negative	negative	negative
Anti-β2GP1	negative	negative	negative	negative	30 Eu/ml
APTT (sec)	21.7	17.7	18.80	19.90	27.2
PA (INR)	0.81	0.82	0.96	0.72	1.2

Table I. Antiphospholipid syndrome

Legend: LA1 = lupus anticoagulant (N:30-51 sec); ACL = anticardiolipin antibody; Anti-β2GP1 = anti-beta 2 Glyco-Protein1 (negative:<20 Eu/ml); APTT = activated partial thromboplastin time (N:26-36 sec); PA (INR) = prothrombin activity (N:0,9-1,2).

by fibrin, thrombi and perivascular mixed cell infiltrate; high power aspects illustrate fibrin in the wall of the vessel, thrombus in its lumen and perivascular mixed cell infiltrate – signs of vasculitis. (Original magnification: A, X50; B, X400; H&E stain) (see fig. 2A, 2B).

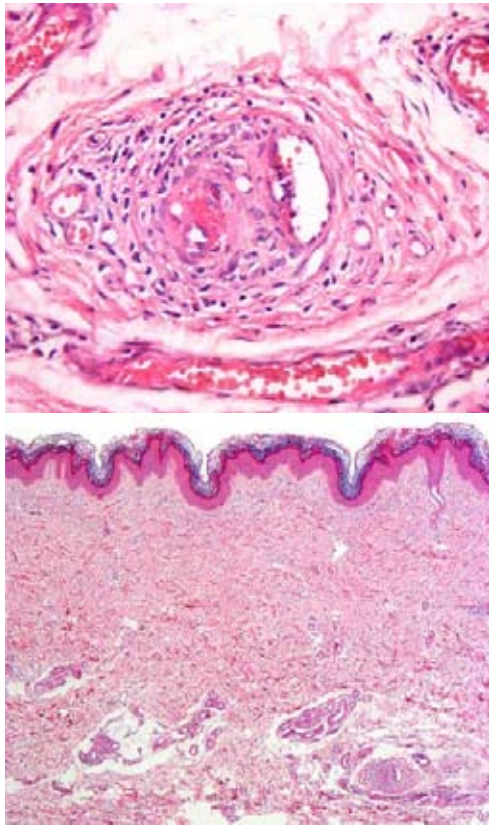


Figure 2A, 2B. Intermediate power showing vessels of the deep plexus involved by fibrin, thrombi and perivascular mixed cell infiltrate; high power aspects illustrates fibrin in the wall of the vessel, thrombus in its lumen and perivascular mixed cell infiltrate – signs of vasculitis. (Original magnification: A, X50; B, X400; H&E stain)

Treatment. In the first year after the onset, the patient received non-steroidal anti-inflammatory drugs (NSAID) and local antibiotics and/or steroids. The only improvement was noted, probably spontaneously, in the winter, but the lesions recurred in

the summer, despite the treatment. For the next 2 years the treatment consisted of prednisone (1mg/kg/day), and sulodexide, but the disease was refractory to these drugs. In the following year azathioprine (2.5mg/kg/day), hydroxychloroquine (6mg/kg/day), aspirin (75mg/day) and topical applications with heparin successfully cured the lesions and a complete remission was noticed after 3 months of treatment. After 18 months the patient remained asymptomatic, with hyperpigmented scars and *atrophie blanche* (fig.1), so the treatment was withdrawn. In the present, the remission is maintained.

Case No 2. A 14 year-old girl presented with persistent *livedo reticularis* and palpable purpura for the past two years in the legs, especially on the feet and gradually extending to the knees (fig. 3).

The patient was admitted in our hospital with crusted ulcers around painful ankles associated with cervical pain, fatigue and mild malar rash.



Figure 3. Reticulate hyperpigmentation, small superficial ulcers and white atrophic scars (atrophie blanche) in the vicinity of the ankles are characteristic clinical features of livedo vasculitis

Physical examination: Normal temperature; Pulse: 92 bpm; Respirations: 16r/min; BP: 115/60mmHg; Weight: 42Kg; Height: 153cm.

General appearance: good state of nutrition and

mental status; mild tiredness. Skin: palpable purpura on the feet (including plantar aspect) and around the ankles, some of these lesions being confluent; bilateral erythematous perimalleolar areas (placards) with relatively deep ulcerations and crusts (fig. 3); mild malar rash; mild swollen and painful left ankle; mild splenomegaly.

Laboratory data. CBC and acute phase reactants were within normal limits. Renal and liver tests were also normal. Serum immunoglobulins, C3 and C4 fractions of serum complement were normal. Tests for antiphospholipid syndrome (lupus anticoagulant/LAC, anticardiolipin antibody, anticardiolipin β 2GP1) were negative. Protein C, protein S, antithrombin III were all negative. The homocysteine levels in the plasma, and the IgG class of phosphatidyl-dependent anti-prothrombin antibody (anti-PS/PT) weren't studied. RE, c-ANCA and p-ANCA, ANA and ENA screen, anti-dsDNA, anti-Sm, anti-Ro, anti-La, anti-Jo1, anti Scl-70, anti-centromere were all negative. Creatinase (CK) and lactic dehydrogenase (LDH) were within normal limits. Proteinuria was absent.

Transcutaneous oximetry was in normal limits.

Skin biopsy (excisional biopsy): Classical histological features of livedo vasculitis: vasculitis affecting small vessels, with sparse perivascular infiltrate of lymphocytes and interstitial infiltrate of neutrophils, fibrin in the wall of some venules in the upper and lower parts of the dermis, thrombi occluding the lumen of other venules, fibrin and thrombi together in still others; numerous erythrocytes extravasated in the upper part of the dermis and the necrotic epidermis. (Original magnification: A, X50; B, X100; C, X400; H&E stain). Direct immunofluorescence to demonstrate the deposition of immunoglobulins IgA, IgM and C3 in the small vessel walls of the dermis was not done. (see fig. 4A, 4B)

Treatment. NSAID and vasodilating agents (nifedipine) administered in the first two years failed and then the patient received prednisone (1mg/Kg/day), but after one month of treatment any improvement was noted. Azathioprine (2.5mg/kg/day) for six months, and hydroxychloroquine (6mg/kg/day) for 18 months replaced prednisone. Nifedipine, pentoxifylline, sulodexide and local heparin completed the therapeutic strategy. After 6 months of treatment the patient became asymp-

tomatic and azathioprine was withdrawn. After 2 years, the remission continues under a maintenance treatment with aspirin, pentoxifylline, nifedipine, and hydroxychloroquine.

Discussion

While the etiology of livedoid vasculitis is not yet fully defined, there are many pathogenetic

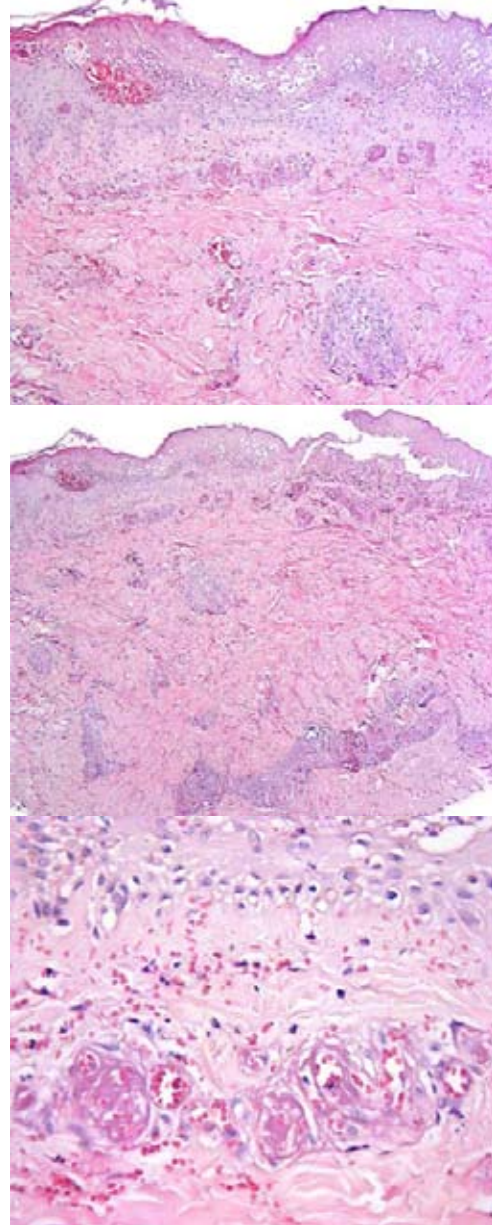


Figure 4A, 4B. Classical histological features of livedo vasculitis: vasculitis affecting small vessels, with sparse perivascular infiltrate of lymphocytes and interstitial infiltrate of neutrophils, fibrin in the wall of some venules in the upper and lower parts of the dermis, thrombi occluding the lumen of other venules, fibrin and thrombi together in still others; numerous erythrocytes extravasated in the upper part of the dermis and the necrotic epidermis. (Original magnification: A, X50; B, X100; C, X400; H&E stain)

hypotheses. The most probable is now considered a thrombogenic disorder [1,2,3]. The livedoid vasculitis has been linked with Factor V Leiden mutation, heterozygous protein C deficiency, and other inherited hypercoagulable states or thrombogenic factors. Hyperhomocysteinemia, which results in increased clotting, seems to play a role in livedoid vasculitis. Plasminogen activator inhibitor (PAI)-1 is an important inhibitor of the fibrinolytic system, and PAI-1 promoter 4G/4G genotype, in which PAI-1 is increased, has been linked to livedoid vasculitis [3]. Tissue-type plasminogen activator (tPA) levels are lower in patients with livedoid vasculitis, and some authors [4] reported a high incidence of defective release of tPA and increased levels of PAI and a high incidence of antiphospholipid antibodies. Livedoid vasculitis may be a manifestation of the antiphospholipid syndrome and screening for it is mandatory [5]. Otherwise, in our first case this syndrome was definite (table I). Sometimes, like in our second case, the detection of such responsible thrombogenic factors is not possible, suggesting that unknown thrombogenic factors are additionally related to livedoid vasculitis [6]. Regarding laboratory tests for antiphospholipid syndrome, not only LAC and anticardiolipin β 2GP1 antibodies but also PS/PT antibodies have recently been reported as possible thrombogenic factors. Anti-PS/PT antibodies were suggested as the antibodies against one of the major target antigens of LAC [7]).

The underlying mechanism of the development of livedoid vasculitis may be related to [1] the development of a fibrin cuff, [2] white cell trapping, [3] microthrombi, [4] a defect of endothelial cell plasminogen activator, [5] platelet dysfunction, and [6] enhanced fibrin formation [3].

Although the initial histopathologic diagnosis was that of leukocytoclastic vasculitis, the presence of fibrin deposition within both the wall and the lumen of affected vessels and the absence of a substantial perivascular infiltrate or leukocytoclasia argues against this kind of disease. The described epidermal infarctization is the consequence of vessels' occlusion with thrombi, but not an argument for LCV. The intraepidermal pustules without the presence of neutrophils also exclude LCV.

An intravascular coagulopathy is excluded by the presence of fibrin which is also an argument for livedoid vasculitis, but of course corroborating clinical signs and symptoms. Clinical features are recognizable in both cases: purpuric macules and patches around the ankles and

in their vicinity that in time become hemorrhagic blisters that ulcerate and heal with white, stellate scars (atrophie blanche). In case 2, the presence of pustules is observed. Once the process begins, it may resolve completely in a few years, or worsen and then remit episodically for a lifetime [1]. Both our cases had indeed a chronic or recurrent evolution: 8 years in the first case, and 2 years in the second. In both cases the onset was in the summer with livedo reticularis and ulcers, both suggesting a livedoid vasculitis.

Chronic periarteritis nodosa may be associated with painful ulcerations, but the absence of nodules differentiates it from livedoid vasculitis. Case 2 presented with a few extracutaneous manifestations along its chronic evolution of two years. Patients with systemic diseases, such lupus, rheumatoid arthritis can present also with skin ulcers and atrophie blanche-like lesions but they do not have livedoid vasculitis. In addition, laboratory tests for these diseases were in normal limits.

Livedoid vasculitis is an uncommon condition which can occur at any age but is extremely rare in childhood and this is one of the reasons for our presentation.

Treatment. In the beginning, the diagnosis was of leukocytoclastic vasculitis and the therapeutic modalities included anti-inflammatory drugs (prednisone) and local antibiotics (bacitracin or neomycin ointments), vasodilating agents (nifedipine) and pentoxifylline. Although systemic steroids (prednisone) initially seemed to be of benefit, the lesions relapsed. While we hoped at least that each case will have a self-limited evolution, this did not happen, so we had to administer anticoagulant agents (oral sulodexide, topic heparin) and immune-suppressing therapy with azathioprine associated with hydroxychloroquine. The indication for immunosuppression may be controversial, but the initial (wrong) diagnosis of leukocytoclastic vasculitis and the lack of any results with previous treatment, the extended uncomfortable lesions (still only cutaneous), and prolonged evolution (minimum 2 years, but 8 years in the first case) seemed to justify it at that time. The lesions healed indeed with ivory-white atrophic plaques and surrounding hyperpigmentation (fig.1).

If the good results with this treatment in these cases of livedo vasculitis are only a coincidence, it remains a question. No systemic approach has been universally successful, and this disorder is

notoriously difficult to treat [1]. While systemic steroids are initially of transient benefit, they do not represent a long-term solution to this problem [1]. Therapeutic strategy is aimed at treating the prothrombotic state [1,3,6,7]. The therapeutic prevention of additional vascular lesions is the therapeutic goal [1]. For the first steps the following agents have been employed with varying success: antiplatelet agents (aspirin, dipyridamol), vasodilating agents (nifedipine, nicotinic acid), pentoxifylline (enhances cutaneous blood flow), and anticoagulants (heparin subcutaneously twice daily or low molecular weight heparin) [1,3,7]. Warfarin was an useful and effective treatment for livedoid vasculitis associated with cryofibrinogenemia and hyperhomocysteinemia [8]. The combination of folic acid, vitamin B-12, and vitamin B-6 (cofactors of homocysteine metabolism) may be an effective treatment for hyperhomocysteinemia, hypercoagulability, and livedoid vasculitis [9].

In most cases, after the ulcerations resolve, some maintenance therapy is required. In refractory patients, oral androgens (danazol, oxandrolol) may be given in adults to enhance the deficient fibrinolytic factors [1,3,6]. Severe cases, especially those of livedoid vasculitis associated with plasminogen activator inhibitor-1 (PAI-1), may respond to tissue plasminogen activator infusions [1,3,6]. Intractable livedoid vasculitis was successfully treated with hyperbaric oxygen therapy 5 times/wk (range 2-5 weeks) [10].

Conclusions

Livedoid vasculitis is a very rare disease in children. This poses a great diagnostic and therapeutic challenge for the treating physicians.

Proper diagnosis of ankle ulceration is very important because ulcers may result from a variety of small vessel vasculitides which do not require the same treatment. Patients with livedoid vasculitis may have multiple defects in thrombolysis, so a complete coagulation workup is required.

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