

Vasculitic leg ulcers – a review

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Summary

Vasculitic leg ulcers, although forming a small proportion of all leg ulcers seen at the specialised wound clinics, pose a significant challenge in terms of diagnosis and treatment. Cutaneous vasculitis may be associated with systemic involvement and occur as a result of hypersensitivity reaction with formation of immune complexes.

Obtaining a deep biopsy from the margin of the ulcer assists with making a definitive diagnosis of a vasculitic leg ulcer. The essential elements of treatment of vasculitic leg ulcers include treatment of the primary cause, providing moist occlusive dressings, protection from further trauma and, most importantly, relieving pain.

Introduction

The majority (70 per cent) of chronic leg ulcers are from chronic venous insufficiency (CVI), about 10 per cent of cases occur from occlusive disease of major arteries and, in another 10 per cent of cases, usually have mixed aetiology. About 2-7 per cent of all the leg ulcers that are diagnosed are vasculitic ulcers^{1,2}, a diagnosis which is, at best, beset with controversies about their exact pathogenesis and hence appropriate management.

Strictly speaking, vasculitis really should be defined as inflammation with destruction of the vascular wall. A perivascular infiltrate without wall destruction is not vasculitis³. Cutaneous vasculitis is a type of limited or focal vasculitis implying that the process is confined to the skin only, as opposed to systemic vasculitis indicating involvement of other organs. Cutaneous vasculitis is more common than systemic vasculitis and the spectrum of clinical presentation ranges from reticulated erythema to widespread purpura and finally necrosis leading to ulceration.

Aetiology

The aetiology of vasculitis can be grouped in three broad categories. Firstly, vasculitis can present as skin rashes

caused by infections. Responsible agents include bacteria (e.g. meningococcus, mycobacterium leprae), rickettsia (various spotted fevers), spirochetes (e.g. syphilis, leprosy), fungi (e.g. aspergillosis and mucormycosis) and viruses (e.g. varicella-zoster virus and other childhood exanthems).

The next group is immunologically mediated. The most common scenario here is immune complex formation. The antigen involved may be exogenous, such as infections and drugs, or endogenous, such as in connective tissue diseases (rheumatoid arthritis, SLE) and cryoglobulinemia. Less common immunological causes include direct antibody mediated, such as Kawasaki disease and Goodpasture syndrome. Among the drugs, the most common culprits are NSAIDs and antibiotics. Inflammatory bowel diseases and malignancy are also recognised causes of vasculitis.

Finally, a number of vasculitis cases have unknown causes. Diseases belonging in this group include giant cell arteritis, Takayasu arteritis and polyarteritis nodosa⁴.

Pathogenesis

Cutaneous vasculitis can occur with or without the formation of immune complexes. The immune complexes result from hypersensitivity due to the presence of autoantibodies or exposure to foreign antigens. The antibodies involved are usually IgG or IgM and the formed complexes circulate within the blood until they become deposited in the walls of blood vessels. This often starts in the legs because of the high hydrostatic pressure in the post-capillary venules due to gravity.

Subsequently, the Fc portion of the immunoglobulins activates the complement system, causing the chemotaxis of

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neutrophils. In attempts to phagocytose the complexes, the activated neutrophils release destructive proteolytic enzymes that result in inflammation and vessel wall destruction. This is essentially a type III hypersensitivity reaction³.

In the non-hypersensitivity related group, immune complexes do not play a central role. The inflammatory infiltrate is induced by unknown mechanisms, probably due to an abnormality of the immune system itself. The infiltrate may include lymphocytes, eosinophils or giant cells⁴.

Management of vasculitic leg ulcers

A careful and thorough history could provide clues to the causative agent. Table 1 shows a list of common drugs that has been known to induce vasculitis⁵. Although prescription drugs are important, food intake such as health foods, soft drinks (especially coloured and in large quantities) and intake of food, which the patient is known to be allergic, are equally important⁶.

Underlying disease processes should not be overlooked. Recent infections such as streptococcal sore throat, tuberculosis and leprosy or any history of recent flu like illness, cystitis, sinusitis, dental disease or vaccinations may be significant. One should also look for chronic illnesses such as diabetes mellitus, blood disorders, rheumatoid arthritis or other forms of collagen disease, chronic respiratory disease, disorders of the bowel or liver and malignancy. Undue exposure to extremes of temperature in the environment and recent surgery or pregnancy is also implicated in vasculitis⁶.

Table 1. Common drugs known to be responsible for inducing vasculitis⁵.

• Allopurinol	• Hydralazine
• Aminosalicilic acid	• Iodides
• Amiodarone	• Levamisole
• Amphetamine	• Methotrexate
• Ampicillin	• Penicillin
• Aspirin	• Phenacetin
• Captopril	• Phenothiazines
• Carbamazepine	• Phenylbutazone
• Cimetidine	• Phenytoin
• Coumadin	• Propylthiouracil
• Enalapril	• Quinidine
• Erythromycin	• Radiocontrast media
• Ethacrynic acid	• Sulphonamides
• Fluoroquinolone antibiotics	• Thiazides
• Frusemide	• Vaccination
• Griseofulvin	• Zidovudine

Generally, a triggering factor can be recognised in only about 50 per cent of cases diagnosed, of which 30 per cent are due to drugs. NSAIDs and antibiotics are the most common culprits⁷. In considering the treatment, removal of the triggering factor is of top priority; this may be a difficult decision in elderly patients on NSAIDs for osteoarthritis.

A careful, thorough physical examination is necessary to look for diseases such as pericarditis, scleritis, glomerulonephritis, polyarthritis and mononeuritis multiplex; the presence of any of them would enhance the diagnosis of the vasculitic ulcer. However, sometimes investigations for hypocomplementaemia, raised VIII related antigen, ANCA and rheumatoid factor may be necessary to confirm this⁸.

Histopathology of a deep biopsy from the margin of the ulcer to confirm the diagnosis is essential due to lack of reliable clinical signs or biochemical tests.

Treatment

Unfortunately, there are no randomised controlled trials to indicate the optimal treatment for vasculitic ulcers. Most of the information in the literature comes from case reports and uncontrolled trials⁹. However, one can conclude that the general management guidelines are: treat the primary cause, support healing, protect from further trauma, prevent contamination and relieve pain (Figure 1)¹⁰.

Treating the aetiology

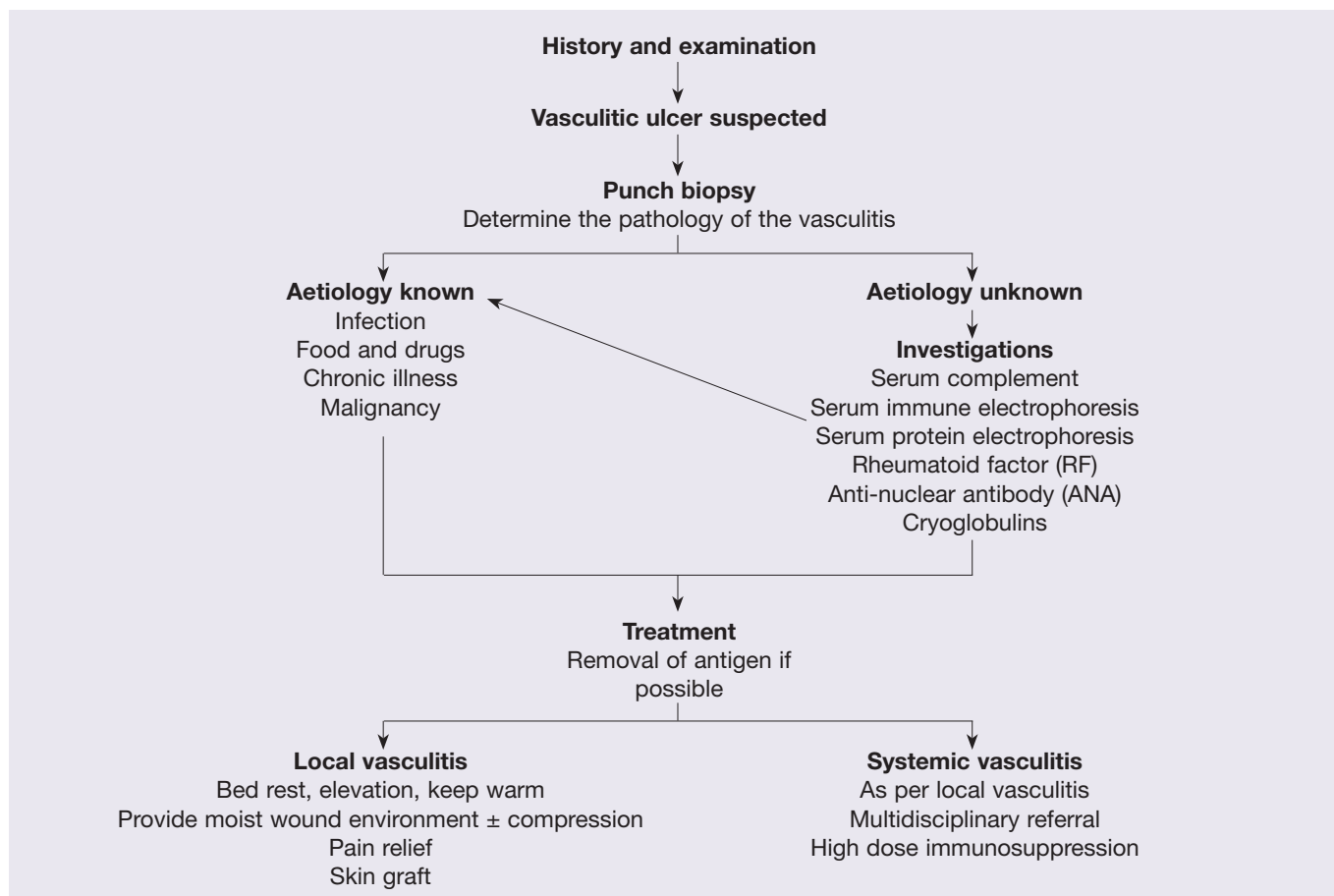
Hypersensitivity vasculitis is usually self-limiting following the removal of the inciting insult or antigen. Most infectious diseases are easily treatable. Bacterial infections should be treated with antibiotics. Viral infections are generally self-limiting¹¹.

If the antigen is suspected to be a drug, the management approach would be to discontinue all suspected medications and, if necessary, substitute them with chemically unrelated ones.

In malignancy, surgical removal of the primary tumour may sometimes help. Immunosuppressive therapy may be required in vasculitic ulcers due to autoimmune diseases and in inoperable malignancy. Immunosuppression can be achieved by intravenous cyclophosphamide and methylprednisolone¹², followed by meticulous monitoring of body organ functions.

On rare occasions, plasmapheresis has been reported to be helpful in fulminant hypersensitivity reactions¹⁰ and in ulcers due to cryoglobulinaemia¹³.

Figure 1. Approaches to a vasculitic leg ulcer.



Local support and dressings

Venous stasis and cold exposure are to be avoided, both tending to cause deposition of immune complexes. Simple measures such as bed rest, elevation of dependent parts, keeping warm and avoiding further trauma are essential parts of the treatment. Gentle frequent movements such as wiggling of the toes will further help venous return⁹.

The general goals of dressing the ulcer are to keep the wound moist, to protect from trauma and to create a mildly hypoxic environment¹⁰. Hypoxia has been shown *in vitro* to stimulate angiogenesis and hence promote healing¹⁴. Occlusive dressings are therefore recommended. Low-adherent dressings such as Melolin are good for superficial dry wounds while the more absorbent hydrocolloid dressings such as DuoDERM and Comfeel are suitable for deeper ulcers with medium exudate⁸.

In very slow healing ulcers, slow-releasing iodine dressings may be considered. Cadexomer iodine (Iodoflex) dressing was found to be very helpful in a case of vasculitic ulcer due to rheumatoid arthritis¹⁵. GammaGraft, a cadaveric skin product, may be used as a biological dressing¹⁶.

An often neglected treatment option is the use of compression bandaging. Although this is widely used for venous ulcers, most wound therapists would not think of compressing applying compression therapy to vasculitic ulcers. Compression can be very effective because it reduces venous stasis and hence further immune complex deposition¹¹.

Anti-inflammatory agents

Hypersensitivity vasculitis, not associated to NSAIDs, may be treated by NSAIDs as the first line of drugs before steroids. One such NSAID found to be useful is indomethacin (100mg daily)¹⁷. Another useful anti-inflammatory is colchicine (1.5mg daily)¹⁸. Dapsone (100mg daily) has also been found to be effective, especially in dermatitis herpetiformis¹⁹. A concomitant course of antihistamines is also of value in urticarial patterns of the disease⁶.

In more severe cases of hypersensitivity vasculitis or ones that do not show signs of healing, a mild immunosuppressive treatment is usually required. Prednisolone 20-40mg daily should be used initially and dosage reduced as soon as the

ulcer starts to heal. This should be followed up by colchicine or with Dapsone for 3-6 months²⁰.

In idiopathic vasculitis, where healing is unlikely with only local treatment, such as in polyarteritis nodosa and pyoderma gangrenosum, high dose systemic corticosteroids (100mg daily prednisolone) are required. In elderly and frail patients, a lower dose of prednisolone may be advisable. In most cases, this should be combined with azathioprine (100-150mg daily) for the glucocorticoid-saving effect¹¹.

Injection around the edge of the ulcer with Triamcinolone acetate (Kenalog 10mg/ml) 0.75-1ml for ulcer of 5cm diameter is also used [Prof A Hebert, personal communication] in recalcitrant vasculitic ulcers.

Much active research is being done in attempts to discover new therapeutic options. Various topical growth factors look promising, including platelet-derived growth factor²¹, epidermal growth factor²² and nerve growth factor (NGF)²³. It is believed that NGF works by promoting keratinocyte proliferation and vascular neoangiogenesis²³. There has also been a case report where intravenous infusion of prostacyclin in a patient with rheumatoid related ulcers caused a dramatic relief of pain and acceleration of healing¹².

Last but not least, one should never forget about pain relief. Vasculitic ulcers tend to be very painful and simple NSAIDs alone are generally ineffective. A combination of NSAIDs and opioid analgesics, such as codeine, is usually required. Topical application of Bupivacaine or Naropin has been found to be very effective where conventional analgesics failed to control pain.

Surgical options

Although not a common option, it should still be considered when conservative measures fail in large ulcers. Porcine skin grafting followed by split thickness skin grafts has been used successfully in rheumatoid patients²⁴. Use of split thickness skin grafts has also been recommended for recalcitrant pyoderma gangrenosum (combined with immunosuppression therapy)²⁰.

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Further reading

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