Small-vessel vasculitis

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Abstract

Small-vessel vasculitis (SVV) refers to an inflammatory disorder of arterioles, venules and capillaries that leads to obstruction, ischaemia and infarction. The identification and management of SVV is a challenge for health professionals, with an accurate diagnosis requiring comprehensive evaluation of the clinical and pathological findings. Early diagnosis and aggressive management of the inflammatory process facilitate improved patient outcome. However, a lack of clinical trials means that treatment options vary according to the assessment, experts' advice and clinicians' experience.

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Aetiology and investigation of small-vessel vasculitis (SVV)

The term SVV describes the inflammation of arterioles, venules and capillary blood vessels, which produce vascular obstruction, tissue ischaemia and infarction [1-4]. Also known as leucocytoclastic, cutaneous necrotising or hypersensitivity vasculitis, SVV is typically confined to the skin and is more prevalent than systemic vasculitis, which encompasses collagen diseases, infectious disorders or malignancy or may involve organs [4-6]. The prevalence of vasculitic ulcers is approximately 2-7% of all leg ulcers [7].

Patients with SVV may present with flu-like symptoms in the initial stage of the disease, while other symptoms include fever, myalgias, arthralgia and malaise [2]. Occasionally, SVV affects medium and larger arterial vessels to produce systemic involvement of an affected tissue or organ [2]. Vasculitis occurs either as a primary disorder known as idiopathic vasculitis (generally self-limiting; resolves within 2-4 weeks), or as a secondary feature of another disease (requiring aggressive therapeutic management) [4, 6].

It is common for SVV to present as cutaneous leucocytoclastic angiitis lesions with palpable purpura and mild small dermal subcutaneous arteries necrosis which causes erythematous tender nodules, focal necrosis, ulceration and livedo reticularis [4, 7, 8]. Generally, the lower limbs are affected and the patient may occasionally present with infarction of the nail bed [5, 9]. Peripheral neuropathy, a common neurological symptom, occurs as a result of inflammation of the small epineural arteries, arteriole inflammation and neural ischaemia [2].

The aetiology of vasculitis is classified according to three broad categories [7]:

- Presenting as skin purpuric rashes.
- Immunopathological.
- Idiopathic.

Presenting as skin purpuric rashes

Some infections produce skin purpuric rashes. These infections may be caused by:

- Bacteria – meningococcus, mycobacterium leprae.
- Rickettsia – various spotted fevers.
- Spirochetes – syphilis, leprosy.
- Fungi – aspergillosis and mucormycosis.
- Viruses – hepatitis B and C, haemorrhagic fever, varicella-zoster [10].

Immunopathological

This category follows an immunopathological pathway which arises when immune complexes embed in the lower extremity blood vessel walls as a result of an increase in post-capillary venule hydrostatic pressure [7, 11]. Antigens may derive from exogenous or endogenous factors.

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Exogenous factors

These arise from:

- Infections – beta-haemolytic streptococcal, viral hepatitis, hepatitis C.
- Hypersensitivity:
  - Drugs – particularly antibiotics, NSAIDs, Dilantin, allopurinol and thiazide diuretics [7, 9, 12]. Thiazide diuretics are implicated in 10-24% of leucoclastic vasculitis [3, 12].
  - Food and food additives, particularly tartrazine [3].
  - Herbicides and insecticides [3].
  - Vaccines, anti-thymocyte globulin, intravenous and intra-coronary streptokinase [12].

Endogenous factors

These arise from:

- Allergic angiitis – urticarial vasculitis develops from inflammatory injury to the capillaries and postcapillary venules of the skin [4, 12].
- Antineutrophil cytoplasmic antibodies associated vasculitis – antibodies target endothelial antigens causing connective tissue disorders such as systemic lupus erythematosus, rheumatoid arthritis and cryogloulinaemia [4, 10, 12]. Collagen vascular diseases account for 10-15% of all vasculitis cases [13].
- Immune-complex vasculitis – in areas of reduced blood flow, antibodies and complement mediators may adhere to vessel wall and activate the complement cascade sequence as in leukocytoclastic vasculitis, Kawasaki disease or Goodpasture syndrome [4, 12]. Immunological involvement accounts for the majority of cutaneous vasculitis.
- T-cell-mediated hypersensitivity – granulomatous vasculitis occurs in Crohns disease, sarcoidosis, tuberculosis and lymphoproliferative disease [4, 12]. Malignancy occurs in <1% of vasculitic cases [7, 13].

Idiopathic

Idiopathic occurs in approximately 33%-50% of cutaneous vasculitis, including temporal arteritis and polyarteritis nodosa [3, 13].

Classification

Classifying vasculitis is a challenging clinical pathological process. The diagnosis needs to be determined from a multiplicity of investigations to ensure treatment is efficacious and to improve the prognosis. The diagnosis may be established from the appearance of the lesions, although a skin biopsy is generally required. Nonetheless, a biopsy rarely identifies the aetiology of vasculitis [14]. Kidney, nasal mucosal or lung biopsy may possibly identify underlying pathology and determine the extent of systemic involvement [3, 14]. Full blood tests are recommended to assess leucocytosis, liver and kidney function. Testing for immune complexes and anti-neutrophil cytoplasmic antibodies may indicate an autoimmune disorder [2, 5, 8]. Anti-streptococcal antibodies indicate recent streptococcal infection [5]. Hepatitis B serology identifies hepatitis, as SVV can occur during the acute phase of this illness [5]. Urine testing assesses protein or blood and identifies renal involvement [14].

Difference between SVV and large vessel vasculitis (LVV)

As vasculitis is a general term that refers to segmental inflammation and necrosis of blood vessel walls, it does not identify the type, location, size of involved vessel or manifestations of the vasculitis [3, 14]. The clinical and pathological features of vasculitis depend upon the location and type of blood vessels involved.

A review of the literature acknowledges the complexities and difficulties associated with the present vasculitic classification systems [3, 10]. The aetiology and pathogenesis of vasculitis are rarely identified, with clinical and histological features intersecting [3]. In 1990, the American College of Rheumatology devised a vasculitis classification system comprising of two categories: cutaneous SVV and large-vessel necrotising vasculitis [10].

In 1992, the Chapel Hill Consensus Conference proposed three categories:

- LVV – includes giant cell arteritis or Takayasu arteritis (skin lesions uncommon).
- Medium-sized vessel vasculitis – classic polyarteritis nodosa or Kawasaki disease (associated with mucocutaneous lymph node syndrome).
- SVV – encompasses Wegener granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis (polyarteritis), Henoch-Schonlein purpura, essential cryoglobulinemia vasculitis and cutaneous leucocytoclastic vasculitis.

The Chapel Hill nomenclature describes 10 vasculitic syndromes according to vessel size [15]. However, from a dermatological perspective, it is problematic as some cutaneous SVV demonstrate systemic involvement [16].

Cutaneous vasculitis may manifest as leucocytoclastic vasculitis, which describes the histopathological manifestation of endothelial swelling, segmental fibrinoid necrosis of vessel walls and neutrophil infiltration that disrupt and exude nuclear fragments [3-5]. Leucocytoclastic vasculitis occurs in many systemic and vasculitic syndromes [3]. Therefore, it is advisable that all cutaneous diseases with histopathologically leucocytoclastic vasculitis be examined to identify possible systemic involvement [16]. In addition, the Chapel Hill nomenclature does not address vasculitis where there are well-defined systemic autoimmune diseases such as Sjogren Syndrome [17].

Vasculitis of small-vessels involves venules, capillaries, arterioles and intra-parenchymal distal arterial radicals that connect with arterioles [18]. Medium-sized vessels refer to the main visceral arteries, for example the renal, hepatic, coronary and mesenteric arteries. LVV encompasses giant cell and Takayasu's arteritis. The latter condition is uncommon, affecting young adults as a non-specific illness and later causing pulselessness and claudication, principally of the upper limbs [5]. The term LVV refers to the aorta and the largest branches directed toward the major body regions, head and neck. As LVV does not involve vessels smaller than arteries, it is a serious and potentially life threatening condition, whereas SVV is a milder process [3].

Vasculitis initially manifests in the small to medium-sized vessels that supply oxygen and nutrients to the skin. Albeit the skin is the only structure identified, cutaneous vasculitis may signify a systemic process which is associated with the presence of circulating immune complexes [3, 19].

Clinical appearance of SVV

The skin manifestations of SVV intersect but generally comprise of papules, bullae, erythematous macules, nodules, ulcerations and pigmentary changes [5, 7]. Palpable purpuric lesions are primarily located in dependent areas below the knees or the hands [11]. Common signs and symptoms include fever, myalgias, arthralgias and malaise [2]. Lesions vary in number and size from a few millimetres to centimetres, while vesicles, pustules and plaques may lead to ulcerations [11].

Common clinical features of systemic vasculitis include fever, fatigue and loss of weight. Rarely are skin lesions (erythema, oedema, tender nodules, linear ulceration and alopecia) reported in large-vessel arteritis [4].

Differentiating between precipitating factors, association with other diseases and idiopathic factors

Vasculitis is an extremely complex disorder allied to various precipitating, associated and idiopathic factors that intersect. Management of SVV is dependent upon obtaining a correct diagnosis and the elimination and treatment of causal factors. As previous noted, precipitating factors include infection and immune complexes. Diseases associated with vasculitis include collagen disorders, infections, medications and inflammatory bowel [1]. Reports indicate an association between cutaneous vasculitis and haematological disorders such as anaemia, thrombocytopenia, leukopenia or leukocytosis [3]. Additionally, vasculitis may arise from chemotherapy, bone marrow transplantation or radiotherapy [3].

Malignancies such as lymphomas, leukaemia, myeloproliferative, lymphoproliferative, adenocarcinomas or myelodysplastic disorders may be associated with SVV [3, 8]. Therefore, any underlying infection, autoimmune disorder or malignancy requires thorough investigation before making a diagnosis [8]. Sepsis produces similar multi-system involvement, while specific diseases (such as atheroembolic disease and endocarditis which generate multi-system embolisation) need to be differentiated from SVV [5, 8]. Unfortunately, for nearly half of all cases of leucocytoclastic vasculitis, there is no known illness [10, 13]. Idiopathic vasculitis encompasses polyarteritis nodosa, Henoch-Schonlein purpura, Churg-Strauss disease, urticarial vasculitis and erythema elevatum diutinum [1, 20].

Management options

A literature review identifies enormous variation in management practices for vasculitic ulcers, with paucity in randomised controlled trials [7, 21]. However, for all patients with non-healing leg ulcers, a referral to a specialist is critical for diagnosing SVV and the initiating of appropriate treatment. Nevertheless, the literature review identifies six possible management options: primary treatment, systemic treatment, topical, surgical, physiotherapy and palliative.

Primary treatment

Primary treatment for hypersensitivity vasculitis involves identifying and eliminating causative agents such as drugs, infection, chemicals or food [4, 10, 11]. The disease process is self-limiting where causative agents are removed [7]. However, where there is systemic involvement of the kidneys, liver or central nervous system, the process is protracted and life threatening [3, 9, 12].

Systemic treatment

Systemic treatment is the principle option and includes long-term corticosteroids, non-steroidal-anti-inflammatories, cyclophosphamides, colchicine, dapsone, potassium iodide, antihistamines, fibrinolytic agents, aminocaproic acid, immunosuppressive and monoclonal antibodies [10, 6]. Systemic therapy varies according to the cause and extent of vasculitis and the clinicians' experience [11, 6].

Topical

Topical therapies are an adjuvant measure for SVV to alleviate allergic reactions, bacterial loading, inflammation and discomfort. They comprise of corticosteroids, antibiotics, antiseptics, zinc preparations, growth factors, cyclosporin A, chlorpromazin, indomethacin, acetylsalicylic acid or lidocaine [22].

Surgical

Surgical treatment includes the application of skin grafts and cultured epidermal cells. Autografts or allografts have been successfully applied to granulating non-infected vasculitic ulcers [22].

Physiotherapy

Physiotherapeutic procedures may include hyperbaric oxygen therapy, laser and whirlpool baths [22]. However, the efficacy of treatment is questionable due to a lack of supporting evidence.

Palliative

General palliative measures encompass comfort, bed-rest, elevation, simple analgesics, warmth and skin protection [23]. Patients need to avoid venous stasis and feeling cold, which enhance the deposition of immune complexes and aggravate the vasculitis. Therefore, compression therapy and gentle movement is advocated [7, 10, 13]. A broad range of dressing options are available to provide moisture balance, protection, thermo-regulation, bacteria balanced, exudate and odour control and autolytic debridement. A hypoxic environment stimulates angiogenesis, thus occlusive hydrocolloids dressings may be applied to low to medium exudating wounds [7].

Conclusion

SVV represents a diagnostic and management challenge for health professionals, with an accurate diagnosis requiring a comprehensive evaluation of all clinical findings. As this disorder often indicates a systemic disease, it is critical that associated factors are eliminated to make certain efficacious treatment is implemented. Early and aggressive management of the inflammatory process can help improve patient outcome. However, the lack of clinical trials means that treatment options are generally based on expert advice, previous experience and clinical evaluation.

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