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An In-depth Review of Cutaneous Necrotizing Venulitis: Clinical and Pathological Perspective

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ABSTRACT

Background: Cutaneous necrotizing venulitis (CNV) is a complex multisystem disorder primarily affecting small skin vessels, particularly postcapillary venules. **Objective:** This article aims to provide an in-depth analysis of the pathogenesis, clinical manifestations, diagnosis, and treatment strategies of CNV. **Methods:** This article is based on a literature review of various relevant scientific sources, including journals and books accessed through PubMed, ScienceDirect, and Google Scholar. **Discussion:** CNV usually manifests as palpable purpura on the skin and may also involve multiple organ systems, including the kidneys, gastrointestinal tract, pericardium, and nervous system. The etiology of CNV remains incompletely understood but is often associated with infections, drug reactions, systemic inflammatory diseases, and malignancies. Clinical manifestation of CNV is mainly palpable purpura, which is red purpura that does not disappear when the skin is pressed. Other lesions such as erythematous macules, papulonodular lesions, urticaria, angioedema, pustules, hemorrhagic vesicles and bullae, necrosis, ulcers, subcutaneous edema and livedo reticularis can also be found in CNV cases. **Conclusion**: Cutaneous necrotizing venulitis (CNV) is a complex disease primarily affecting the skin and mucous membranes. Diagnosis of CNV involves clinical evaluation and histopathological examination. Treatment strategies of CNV aim to address underlying triggers, manage systemic involvement, and suppress inflammatory responses using topical and systemic therapies such as corticosteroids, NSAIDs, and immunosuppressive agents. Treatment strategies of CNV aim to address underlying triggers, manage systemic involvement, and suppress inflammatory responses using topical and systemic therapies such as corticosteroids, NSAIDs, and immunosuppressive agents and CNV often exhibits a favorable prognosis with appropriate management.
Keywords: cutaneous necrotizing venulitis, necrotizing angiitis, vasculitis, venulitis

ABSTRAK

Latar Belakang: *Cutaneous necrotizing venulitis* (CNV) adalah gangguan multisistem yang kompleks, terutama menyerang pembuluh darah kecil di kulit, khususnya venul postkapiler**. Tujuan:** Artikel ini bertujuan untuk memberikan analisis mendalam mengenai patogenesis, manifestasi klinis, diagnosis, dan strategi pengobatan CNV**. Metode:** Artikel ini didasarkan pada tinjauan literatur dari berbagai sumber ilmiah yang relevan, termasuk jurnal dan buku yang diakses melalui PubMed, ScienceDirect, dan Google Scholar**. Pembahasan:** CNV biasanya bermanifestasi sebagai purpura teraba pada kulit dan dapat melibatkan berbagai sistem organ, termasuk ginjal, saluran gastrointestinal, perikardium, dan sistem saraf. Etiologi CNV masih belum sepenuhnya dipahami, tetapi sering dikaitkan dengan infeksi, reaksi obat, penyakit inflamasi sistemik, dan keganasan. Manifestasi klinis utama CNV adalah purpura teraba, yaitu purpura berwarna merah yang tidak menghilang saat kulit ditekan. Lesi lain yang dapat ditemukan pada kasus CNV meliputi makula eritematosa, lesi papulonodular, urtikaria, angioedema, pustula, vesikel dan bula hemoragik, nekrosis, ulkus, edema subkutan, serta livedo reticularis**. Kesimpulan:** Cutaneous necrotizing venulitis (CNV) adalah penyakit

kompleks yang terutama mempengaruhi kulit dan selaput lendir. Diagnosis CNV melibatkan evaluasi klinis dan pemeriksaan histopatologi. Strategi pengobatan CNV bertujuan untuk mengatasi pemicu yang mendasari, mengelola keterlibatan sistemik, serta menekan respons inflamasi menggunakan terapi topikal dan sistemik, seperti kortikosteroid, NSAID, dan agen imunosupresif. CNV umumnya memiliki prognosis yang baik dengan penanganan yang tepat.

Keywords: angiitis nekrotikans, vaskulitis, venulitis, venulitis nekrotikans kutan

1. Introduction

Vasculitis can affect small or medium-sized blood vessels of the skin. Vasculitis affecting small blood vessels of the skin (e.g. arterioles, capillaries, post-capillary venules) tends to cause lesions such as purpura, petechiae and possibly superficial ulcers. Necrotizing angiitis or necrotizing vasculitis comprises a diverse group of disorders that combine inflammation with necrosis of blood vessels. Vascular damage in these diseases can be caused by both immunologic and inflammatory processes. Clinical symptoms are based on criteria that include gross and histopathological features of vascular lesion changes, caliber of affected blood vessels, frequency of specific organ involvement, and laboratory abnormalities. Necrotizing vasculitis is a primary disease that develops as a feature of a systemic disorder, or may be idiopathic. Although there is no standardized classification of vasculitis, the classifications of the American College of Rheumatology and International Chapel Hill Criteria are widely used.[1,2] Cutaneous necrotizing venulitis (CNV) is often misdiagnosed due to its similarity to other forms of vasculitis, making this article essential for improving diagnostic accuracy and treatment approaches.

Cutaneous necrotizing venulitis (CNV) is a clinical disorder consisting of skin lesions that usually present as palpable purpura. The skin is often the only organ that appears to be involved. Clinically, however, relevant systemic involvement may occur and the skin may only represent the early signs of systemic vasculitis and/or a different underlying disease. CNV is an inflammatory disease affecting the cutaneous vasculature characterized histologically by transmural inflammation of the blood vessel wall with fibrinoid necrosis. Associated histological features include endothelial swelling and leukocytoclasia, known as necrotizing angiitis. Although all sizes of blood vessels can be affected, in the majority of cases the inflammation involves postcapillary venules and thus can be referred to as cutaneous necrotizing venulitis. CNV represents a diverse spectrum of diseases from cutaneous small vessel vasculitis (CSVV) to rapidly progressing systemic vasculitis. [2, 3] While CNV has been explored in several studies, a comprehensive understanding of its subtypes and the most effective treatment approaches is still lacking. Thus, this article aims to discuss CNV in depth, exploring the clinical and pathological aspects of the disease.

2. Methods

This article was written by reviewing book and articles which are obtained from several search engines such as Pubmed, Science Direct, and Google Scholar. The search was conducted using keywords such as 'Cutaneous necrotizing venulitis,' 'Necrotizing Angiitis,' and 'Venulitis,' with filters applied based on the abstract and publication year. The selected articles are written in English, published mainly within the past 10 years, and focuses on the diagnosis or treatment of CNV. Articles were screened for relevancy from abstract and the information are mostly focused on the pathophysiology, diagnosis, and treatment of CNV.

3. Discussion

3.1 Definition and Classification of Cutaneous Necrotizing Venulitis

Cutaneous necrotizing venulitis (CNV) is a complex multisystem disease that affects the skin and mucous membranes and is usually accompanied by clinical signs and symptoms of other organ disorders such as renal, gastrointestinal, pericardial, and neurological. Cutaneous necrotizing venulitis (CNV) is a clinical disorder consisting of skin lesions, which usually present as palpable purpura, characterized by angiocentric segmental inflammation, endothelial cell swelling and fibrinoid necrosis of the vessel wall. The skin is often the only organ that appears to be involved. Although blood vessels of various sizes can be affected in systemic vasculitis, CNV usually occurs in small venules (postcapillary venules).[3]

Cutaneous necrotizing venulitis (CNV) has several subtypes based on its etiology, epidemiology and clinical manifestations. Some of the subtypes of CNV include:[2,4]

Table 1. Subtypes of CNV[2,5,6,7,8,9]

	Epidemiology	Manifestations	Histopathological Findings	Treatment
IgA Vasculitis	75% of CNV in children 25% of CNV in adults	History of recent upper respiratory tract infection and involvement of skin, synovia, GI tract, and kidneys	Mesangial, capillary and subendothelial IgA deposits and neutrophilic infiltration	● Angiotensin-converting enzyme inhibitors (ACE-i) ● Corticosteroids ● Plasmapheresis or plasma exchange ● Immunosuppressants
Urticarial Venulitis	Women most often affected; may be associated with other disease such as and malignant conditions, or idiopathic	Erythematous, indurated wheals with a foci of purpura and persists for as long as 5 days, may be chronic and recurrent	Fibrinoid changes of the vessel walls, inflammatory infiltrate in the vessels walls generally composed of neutrophils, eosinophils, and/ or lymphocytes	● Oral antibiotics ● Colchicine ● Dapsone ● Hydroxychloroquine ● Nonsteroidal anti-inflammatory drugs ● Immunosuppressants
Nodular Vasculitis	More common in women between 30 - 40 years of age; may be associated with *M. tuberculosis* infection (Erythema induratum)	Tender, red, subcutaneous nodules over calves without systemic manifestations; may be recurrent	Lobular panniculitis with granulomatous and lymphocytic inflammatory infiltrates, fibrosis with thickened subcutaneous septa	● Topical and systemic steroids ● Antitubercular therapy ● Immunosuppressants
Livedoid Vasculopathy	More common in women; may occur in association with connective tissue disorders, malignancies	Chronic recurrent episodic exacerbations; arteriosclerosis or stasis of the lower extremities	Thickening or hyalinization of superficial dermal vessels along with intraluminal fibrin deposits	● Pain management (NSAIDs, tricyclic antidepressants) ● IVIG ● Anticoagulants ● Anti-platelets
Eosinophilic Vasculitis	Idiopathic	Pruritic, purpuric papular skin lesions, urticarial plaques, and angioedema	Eosinophilic infiltration, necrotizing vasculitis, and extravascular granuloma	● Corticosteroids ● Immunosuppressants ● Biological agents

a. Immunoglobulin A Vasculitis

It is the most recognized idiopathic subtype of CNV previously known as anaphylactoid purpura and Henoch-Schönlein purpura. It accounts for 75% of CNV cases in children and 25% of CNV in adults. History of upper respiratory tract infection, involvement of skin, synovia, gastrointestinal tract, kidneys. Complaints such as abdominal pain, melena, arthralgia and hematuria can be found in this subtype.[2]

b. Urticarial Venulitis

This is a form of necrotizing venulitis that occurs in patients with serum sickness, connective tissue disorders, hematologic disorders, other malignant conditions, infectious urticaria and physical urticaria. This subtype occurs after administration of various therapeutic agents and as an idiopathic disorder.[2]

c. Nodular Vasculitis

Nodular vasculitis presents as soft, red, subcutaneous nodules in the lower extremities, especially the calves, without systemic manifestations. Occasionally, lesions develop on the thighs, buttocks, trunk, and arms, and ulcerated nodules may be found. Recurrent episodes are common. It is more common in women and has a peak incidence in individuals aged between 30 and 40 years. This subtype is often associated with Mycobacterium tuberculosis infection.[2]

d. Livedoid Vasculopathy

This type is more common in females and may be associated with connective tissue disorders, malignancy, hypercoagulation disorders and thrombophilia. Livedoid vasculopathy occurs as recurrent, painful ulcers of the lower extremities associated with persistent livedo reticularis (livedo racemosa) that is often dark purple in color. Healing results in sclerotic pale areas surrounded by telangiectasis called atrophie blanche.[2, 4]

e. Eosinophilic Vasculitis

Eosinophilic vasculitis is described as an idiopathic syndrome in individuals with recurrent pruritus and purulent papular skin lesions, plaque urticaria, and angioedema. Skin biopsy specimens show an infiltrate composed of eosinophils expressing CD40 and vascular cell adhesion molecule (VCAM)-1 on the endothelial cells of the involved blood vessels.[2]

3.2 Etiology of Cutaneous Necrotizing Venulitis

The cause of cutaneous necrotizing venulitis (CNV) is unknown or idiopathic. Some theories suggest that CNV is associated with several diseases. About 60% of CNV cases are idiopathic. Cutaneous necrotizing venulitis (CNV) can be triggered by bacterial, viral, or fungal infections, drug ingestion, chronic systemic inflammatory diseases, rheumatic diseases, lymphoproliferative malignancies, and solid tumors. The most commonly known infectious agents are *hemolytic streptococcus*, *Staphylococcus aureus*, *Mycobacterium leprae*, and hepatitis B and C viruses. Cutaneous necrotizing venulitis (CNV) is also often associated with connective tissue diseases, especially rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus (SLE), and purpura hypergammaglobulinemia. [2,3]

3.3 Pathogenesis of Cutaneous necrotizing venulitis

The pathogenesis of cutaneous necrotizing venulitis (CNV) is a very complex process. Experimental animal models and observations in humans suggest that the main pathogenetic mechanism of the leukocytoclastic form is represented by immune reactions between antigens and antibodies under conditions of moderate antigen overload, with subsequent deposition of immune complexes in the vessel wall, as demonstrated by immunofluorescence and ultrastructural techniques. Lymphomonocytic vasculitis is usually the final phase of leukocytoclastic vasculitis or the result of a lymphocyte mediated immune reaction.[2,3]

The accumulation of immune complexes activates the classical complement and alternative cascade with the production of anaphylatoxins (C3a, C5a) that induce mast cell degranulation and attract neutrophils to the lesion area. Neutrophils can phagocytose and degrade deposition of immune complexes, release lysosomal enzymes and produce oxygen free radicals that can damage the vascular endothelium. Local production of inflammatory agents, such as leukotriene B4, histamine, thrombin, interleukins (IL1, IL6), tumor necrosis factor-alpha (TNF-a) and interferon are also released. These mediators will increase neutrophil chemotaxis into the lesion area and will induce the synthesis and expression of adhesion molecules to various endothelium, thus maintaining the inflammatory process. Immune complexes can also interact with lymphocytes via their Fc receptors and provoke the release of cytokines.[3]

3.4 Diagnosis of Cutaneous necrotizing venulitis

Skin lesions in CNV cases are polymorphic. The typical main lesion most often found in CNV is palpable purpura, which is red purpura that does not disappear when the skin is pressed. Other lesions such as erythematous macules, papulonodular lesions, urticaria, angioedema, pustules, hemorrhagic vesicles and bullae, necrosis, ulcers, subcutaneous edema and livedo reticularis can also be found in CNV cases. Skin eruptions are often found on the lower extremities and frequently stressed areas such as the back and buttocks and are usually symmetrically distributed. The predilection of the lower extremities is due to the increased hydrostatic pressure and the twisting of blood vessels at these locations which may trigger more distortion and turbulence of the blood flow pattern. Skin lesions can also be found on the face, palms, soles of the feet/heels, and mucous membranes but this is rare. Clinical lesions are episodic and may recur within weeks or years. [2, 3, 10]

Palpable purpura can last from 1 to 4 weeks and will disappear slowly with transient hyperpigmentation and or atrophic scars. Clinical symptoms that can be felt by patients with CNV are itching or burning and pain that

can be felt in the skin lesions. Symptoms such as fever, malaise, arthralgia or myalgia can also be found in CNV patients and are usually symptoms that accompany the systemic disease underlying the CNV case. [2]

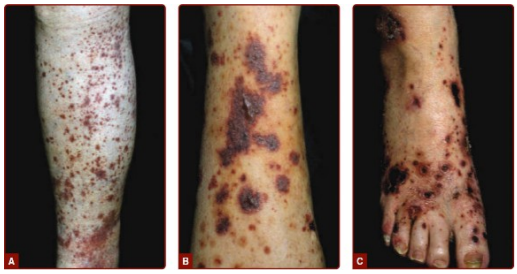

Figure 1. Clinical manifestations of CNV: palpable pupura, hemorrhagic and bullous, ulcus and multiple necrosis.[2]

Supporting examinations that can be performed in helping to confirm the diagnosis of CNV are laboratory examinations such as complete blood tests, urine tests, rheumatoid factor tests, immunoelectrophoresis tests, and histopathological examinations. [2]

On complete blood examination, elevated ESR and other abnormalities such as leukocytosis, anemia and thrombocytosis can be found, especially in idiopathic cases. On direct immunofluorescence examination, fibrin deposition in venules is routinely identified in biopsy specimens, while deposition of immunoglobulins and complement proteins is highly variable. IgG, IgM, and IgA may also be detected. In one study, IgA deposits were related to the absence of autoimmune and inflammatory disorders and IgM deposits were related to the presence of autoimmune and inflammatory disorders. IgA is deposited around blood vessels in the skin, gut, and kidneys in IgA vasculitis and has become an immunopathologic marker in this condition. In the skin with IgA vasculitis, IgA1 is the predominant subclass deposited. C3 is the most frequently detected immunoreactant in CNV.[2,3]

Vasculitis in large blood vessels and small blood vessels presents a different histopathologic picture. In small vessels such as venules, the vessels appear elongated with a single layer of endothelial cells, surrounded by connective tissue stroma (tunica externa). The two main cellular forms of CNV described are the leukocytoclastic form (with a predominance of neutrophils over lymphocytes) and the lymphocytic form (where lymphocytes are predominant over neutrophils). Skin biopsy specimens of palpable purpura and urticaria will be stained with hematoxylin and eosin. Histopathologic criteria required for the diagnosis of CNV include necrosis of blood vessels with deposition of fibrinoid material and cutaneous cellular infiltrates composed of neutrophils with mononuclear cell debris and extravasated erythrocytes. Cutaneous inflammatory infiltrates vary in intensity and are usually perivenular, but may be widespread. [2,11,12]

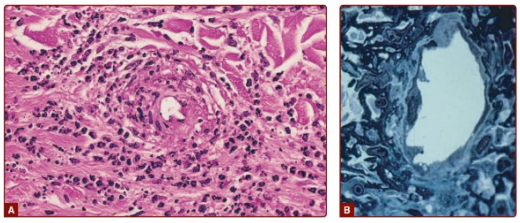

Figure 2. Histopathologic findings of CNV: Perivenular infiltrate of neutrophils with fibrin deposition and endothelial cell necrosis of a venule with perivenular fibrin and neutrophils.[2]

3.5 Treatment of Cutaneous necrotizing venulitis

The principle therapeutic approach in CNV may consist of removing antigens, treating the underlying disorder, treating the CNV case itself and removing all triggers such as food, drugs, infections, or chemicals. The therapeutic approach in the treatment of necrotizing vasculitis consists of prevention of immune complex deposition, suppression of the inflammatory response, modulation of the underlying immunopathologic mechanism, and administration of local therapy. When the eruption is associated with a precipitating event, cessation of medication or treatment of the infection will result in resolution of the skin lesions. If there is a coexisting chronic disease, treatment of the underlying disease may be associated with improvement of the cutaneous vascular lesions. In many cases, CNV is a self-limiting condition. In most cases, CNV will be

followed by rapid resolution of the skin and/or systemic lesions and no other treatment is required if the principle therapeutic approach is implemented promptly. When CNV is dependent on systemic disease, often treatment of the underlying disease can be associated with improvement of the cutaneous vasculature of the lesion. If this does not occur, local and/or systemic treatment of local and/or systemic treatments becomes necessary.[1,2]

Topical therapy consists of topical corticosteroids or antibiotic creams that can be given along with gradient support stockings in patients with lesions involving the lower limbs. Systemic therapy can also be given along with reducing the risk of local trauma, avoiding cold stasis in the limbs, and preventing lower limb oedema. [5]

Systemic treatment of Cutaneous necrotizing venulitis (CNV) depends on the extent of the lesions on the skin and also on the toxicity and side effects of the therapeutic agents. H1 antihistamines (hydroxyzine 25 mg alone or combined with H2 antihistamines i.e. ranitidine 150 mg/twice daily) can be used in patients with purpura to alleviate the symptoms of the lesions and to reduce tissue deposition of circulating immune complexes. NSAIDs such as acetylsalicylic acid 1-3 g or indomethacin 25-50 mg/three times daily can be used in patients with persistent or necrotic lesions. Administration of NSAIDs can be combined with H1 antihistamines in cases of CNV. Administration of colchicine 0.6 mg twice a day can be given as a substitute therapy for patients who have certain therapeutic reactions to the administration of NSAIDs and H1 antihistamines and is preferred in chronic CNV cases. In addition to the above therapy, systemic therapy in CNV can also be given hydroxychloroquine sulfate (200 mg, 1x/day), dapsone (50-200 mg), systemic corticosteroids. In refractory cases, immunosuppressive agents such as azathioprine, methotrexate, cyclosporine A, and cyclophosphamide can be given. Administration of potassium iodide, aminocaproic acid, fibrinolytic agents, intravenous gammaglobulin, monoclonal antibodies, and plasmapheresis can also help therapy in CNV.[1,2,3]

4. Conclusion

Cutaneous necrotizing venulitis (CNV) is a complex disease primarily affecting the skin and mucous membranes, characterized by angiocentric inflammation and vessel wall necrosis. While skin lesions such as palpable purpura are common, CNV can also involve various organ systems, indicating systemic vasculitic involvement. The disease encompasses several subtypes with distinct clinical features and underlying causes, including Immunoglobulin A Vasculitis and Urticarial Venulitis.

Diagnosis relies on clinical presentation and histopathological examination. The treatment strategy of CNV includes identifying triggering factors, managing systemic involvement, and suppressing the inflammatory response with topical or systemic agents like corticosteroids and immunosuppressants. This article highlights the importance of accurate histopathological diagnosis to differentiate CNV from other forms of vasculitis. Further studies are needed to evaluate the effectiveness of new therapeutic agents such as new immunomodulatory agents in the treatment of CNV.

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