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Review

# Polyarteritis nodosa: A contemporary overview

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ABSTRACT

Polyarteritis nodosa (PAN) is a systemic necrotizing vasculitis predominantly targeting medium-sized arteries. PAN is a rare form of vasculitis, and the precise frequency of this disease is difficult to determine. The major environmental factor associated with PAN is HBV infection.
The pathogenesis of "idiopathic PAN" remains enigmatic, although the clinical responses to immunosuppressive therapy support the concept that immunological mechanisms play an active pathogenic role.
The spectrum of disease ranges from involving a single organ to polyvisceral failure. Any organ might be affected; however, for reasons that are not understood, PAN does not affect the lungs. In addition to the systemic idiopathic form, called "idiopathic generalized PAN," there are 2 clinical variants of this disease: "cutaneous PAN" and "hepatitis B virus (HBV)-associated PAN".
Diagnosis requires the integration of clinical, angiographic, and biopsy findings. The overall prognosis of this disease has been improved in recent decades, primarily reflecting early diagnosis and more effective treatments.
Idiopathic generalized PAN should be treated with a combination of glucocorticoids and cyclophosphamide. The treatment of HBV-associated PAN involves a different approach, centered on the use of an antiviral agent to control the infection. The therapy for cutaneous PAN requires a less aggressive approach based on the administration of non-steroidal anti-inflammatory drugs over short periods of time.



**Contents**



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## 1. Introduction

Polyarteritis nodosa (PAN) is a systemic necrotizing vasculitis that predominantly targets medium-sized arteries [1,2]. Small arteries may also be involved, but small vessels, including arterioles, capillaries, and venules, are not [1].

The first complete macroscopic description of PAN was provided from K. Rokitansky in 1842. This pathologist described the presence of aneurysms without microscopic examination; therefore, the inflammatory nature of this disease was not recognized [3].

In 1866, A. Kussmaul and R. Maier provided a clinical description of a patient, including a post-mortem histological examination, arriving at a diagnosis of vasculitis [4]. Kussmaul and Maier introduced the term "periarteritis nodosa" to describe the nodules observed in intermediate-sized vascular arteries. These nodules resulted from aneurysm formation secondary to the involvement of all layers of the artery; therefore, the term was changed to "polyarteritis nodosa" [5,6]. However, it was not until 1931 that Lindberg first recognized PAN limited to skin [7]. In 1970, Trepo and Thivolet reported the association of PAN with hepatitis B virus (HBV) infection [8], and it soon became obvious that a substantial part of PAN cases were associated with HBV.

Since the first description, the term "polyarteritis nodosa" has generically been used to describe any form of systemic vasculitis of unknown cause. The lack of an understanding of this disease, which has been described for nearly 150 years, reflects the fact that there is no uniform definition of PAN associated with a condition exhibiting protean and overlapping clinical manifestations, and no specific serologic diagnostic tests have been developed.

## 2. Epidemiology

Although PAN has become an even more uncommon disease and a rare form of vasculitis, the precise frequency of this disease is difficult to determine. While a true change in PAN epidemiology cannot be excluded, there is little doubt that the current rarity of PAN largely reflects the gradual narrowing of the spectrum of systemic vasculitides.

In European countries, the incidence of PAN ranges from 0 to 1.6 cases per million, and the prevalence of this disease is approximately 31 cases per million [9].

PAN affects men more frequently than women and occurs in all ethnic groups. The average age at onset is approximately 50 years, and the peak incidence occurs in the 5th–6th decades of life [10,11].

The major environmental factor associated with PAN is HBV infection, and one of the highest rates reported for PAN was observed in an area endemic for HBV infection (Alaskan Indians) [12]. With the development of a vaccine for HBV, the percentage of patients with HBV-associated PAN has decreased from 36% to less than 5% [13,14].

## 3. Etiopathogenesis

The pathogenesis of "idiopathic PAN" remains enigmatic, although the clinical responses to immunosuppressive therapy suggest that immunological mechanisms play an active pathogenic role.

As in other forms of vasculitis, the presence of impaired endothelial function could reflect direct endothelial cell activation and damage resulting from primary inflammatory vasculitis or proinflammatory cytokines or antibodies (*i.e.*, anti-endothelial cell antibodies) [15,16]. Activated endothelial cells could perpetuate and potentiate the inflammatory milieu through the production of cytokines and adhesion molecules.

Elevations in the serum levels of interferon-γ and interleukin (IL) 2 and increased serum levels of IL-8, a potent chemo-attractant and activator of neutrophils, have been documented in PAN [17]. Moderate increases in tumor necrosis factor (TNF) α and IL-1β have also been detected [12]. However, elevated levels of circulating soluble adhesion molecules, including intercellular adhesion molecule 1 (sICAM-1), vascular cell adhesion molecule 1 (sVCAM-1), and E-selectin, which originate in activated endothelial cells from inflamed vessels, have been observed [18].

Tumor necrosis factor-α and interferon-γ increase the expression of class I major histocompatibility complex (MHC) antigens and induce MHC class II expression, resulting in antigen presentation to T cells [19].

Immunohistochemical studies on biopsied perineural and muscle vessels showing macrophages and T cells, primarily CD8 + cells, suggest a role for T cells in the pathogenesis of PAN [12].

In HBV-PAN, at least two general mechanisms have been determined. First, virus replication might induce the direct injury of the vessel wall [20]. Second, vascular lesions result from the deposition and/or the in situ formation of circulating immune complexes. These factors activate the complement cascade, which in turn attracts and activates neutrophils [12]. The immunological process responsible for PAN is typically observed within 6 months of HBV infection. During periods of active HBV-PAN, the serum levels of complement are low, consistent with complement consumption through immune complex deposition. Cases of PAN have been described in association with other infectious agents, such as group A streptococcus, hepatitis C virus, human T cell leukemia virus 1, cytomegalovirus, HIV, Epstein–Barr virus, and parvovirus B19, but consistent evidence of a role for any specific microbial pathogen in classic PAN is lacking [21].

## 4. Clinical manifestations

The disease spectrum ranges from involving a single organ to polyvisceral failure. The progression from one end of the spectrum to the other is uncommon. Virtually, any organ might be affected; however, for reasons that are not understood, PAN does not affect the lungs [12,19,22–24].

The occlusion or rupture of inflamed arteries might produce tissue ischemia or hemorrhage in a variety of organs and systems. Consequently, PAN might generate a wide constellation of clinical manifestations, including non-specific constitutional manifestations, such as malaise, weight loss, fever, arthralgia, and myalgia, and symptoms derived from the dysfunction or damage of target organs, in a high proportion of patients [25–27].

The peripheral nervous system and the skin are the most frequently involved territories [25,27]. The main neurological manifestation is mononeuritis multiplex, which presents with wrist or foot drop, although symmetrical polyneuropathy might also occur. Cutaneous features, including purpura, livedoid lesions, subcutaneous nodules, and necrotic ulcers, have also been observed [25,27].

The gastrointestinal tract and kidneys are frequently involved. Gastrointestinal tract manifestations are among the most serious expressions of PAN, and in one-third of the cases, this disease manifests as an acute surgical abdomen [21]. Renal involvement in PAN comprises tissue infarction or hematoma, typically produced from the rupture of renal microaneurysms [27,28]. Kidney infarcts might be clinically silent or produce micro- or macrohaematuria and mild to moderate proteinuria. PAN does not cause glomerulonephritis, and hypertension secondary to intrarenal artery involvement is frequently observed [25–27].

Although rarely the first manifestation of this disease, orchitis is the most characteristic symptom of PAN. Orchitis is typically unilateral and is observed as a consequence of testicular artery ischemia [12].

Hearing loss has commonly been reported as an otological manifestation of PAN [29,30,31]. The nature of hearing loss in PAN is most often sensorineural, and in rare instances, hearing loss has been the presenting symptom of this disease [32,33]. The sensorineural hearing loss is typically bilateral and symmetrical, with sudden onset [32,34] or a rapidly progressive course [30,35].