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Review

Polyarteritis Nodosa Reviewed in 2023: Old Disease, New Etiologies

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Abstract: Polyarteritis nodosa (PAN), also known as panarteritis nodosa, represents a form of necrotizing vasculitis that predominantly affects medium-sized vessels, although it is not restricted to them and can also involve smaller vessels. The clinical presentation is heterogeneous and characterized by a significant number of patients exhibiting general symptoms including asthenia, fever, and unintended weight loss. Although PAN can involve virtually any organ, it preferentially affects the skin, nervous system, and the gastrointestinal tract. Orchitis is a rare but specific manifestation of PAN. The absence of granulomas, glomerulonephritis and ANCA serves to distinguish PAN from other type of vasculitis. Major complications consist of hemorrhagic and thrombotic events occurring in mesenteric, cardiac, cerebral, and renal systems. Historically, PAN was frequently linked to hepatitis B virus (HBV) infection, but this association has dramatically changed in recent years due to declining HBV prevalence. Current epidemiological research often identifies connection between PAN and genetic syndromes as well as neoplasia. This article provides a comprehensive review of PAN, specifically focusing on the progression of its clinical manifestations over time.

Keywords: PAN; polyarteritis nodosa; panarteritis nodosa; monogenic; VEXAS; DADA2

1. Introduction

PAN was first described in 1866 by Kussmaul and Maier. They reported an "intermittent nodular appearance affecting arteries throughout the body sparing large vessels (the aorta and its branches), small vessels (arterioles, capillaries and venules) and pulmonary vessels" [1]. The distinct "pearl necklace" pattern led to the naming of this condition as polyarteritis nodosa. In 1952, pathologist Pearl Zeek laid out the first classification of PAN, distinguishing between hypersensitivity vasculitis, allergic vasculitis, PAN, and temporal arteritis, now respectively known as urticarial vasculitis, eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), PAN, and giant cell arteritis (Horton's disease) [2]. A pivotal development came in 1982 when autoantibodies directed against neutrophil cytoplasm antigens (ANCA) were identified in 8 patients with clinical characteristic of vasculitis, introducing ANCA-associated vasculitis (AAV) as a distinct category of vasculitis separate from PAN [3]. The most recent definition of PAN came from the 2012 Chapel Hill Consensus Conference (CHCC) where the disease is described as "necrotizing arteritis of the medium or small arteries without glomerulonephritis or vasculitis of arterioles, capillaries or venules and without ANCA" [4–6]. Over the past two decades, the medical community's understanding of PAN has significantly evolved. While initially described as a either primary vasculitis or Hepatitis B virus

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(HBV)-related, current understanding recognizes PAN as a disease often secondary to genetic syndromes and malignant hematologic disorders [7].

2. Epidemiology

Due to the lack of serum markers, heterogeneity in classification criteria, and numerous predisposing causes, estimating the overall prevalence of PAN is challenging. The prevalence of PAN varies greatly across different countries, ranging from 2 to 31 per million inhabitants in Europe [8,9]. There is notable North-South and seasonal gradient in the occurrence of the disease. Historically, PAN was frequently linked to Hepatitis B Virus (HBV) infection. With the advent of the HBV vaccine, the incidence of PAN has seen a significant decline, turning it from one of the most common vasculitis in the 1990s to one of the least common today [8,10]. In addition, the improvement of laboratory techniques for the detection of ANCA in the 1980s led to the reclassification of certain vasculitis that were initially diagnosed as PAN [11].

In the cohort from Pagnoux et al., which included 348 patients enrolled between 1963 and 2005, with a mean age of 51 ± 17 years old and a male to female ratio of 1.7 [12]. More recently, Rohmer et al. described 197 patients who were diagnosed with PAN between 2005 and 2019 and who had a mean age of 53.6 ± 18 years and a gender distribution with a male predominance of 1.5 [13].

3. Physiopathology

PAN is typically characterized by a segmental, necrotizing, and transmural inflammation, predominantly involving small to medium-sized arteries, although any arterial size could theoretically be susceptible. The disease most commonly impacts the visceral and muscular arteries, including their branches. In patient biopsies, it is common to observe co-existing lesions of diverse stages of inflammation and scarring within a single sample [14]. Because of the arterial inflammatory process, fibrinoid necrosis may develop, leading to the formation of microaneurysms. Over time, these complications can progress to chronic stages, characterized by fibrous scarring and vascular aneurysms, which can rupture and lead to severe bleeding [15,16]. During the acute phase, the cellular infiltrate, composed of macrophages, T lymphocytes, neutrophils, and eosinophils, is generally observed in the tunica media, but can also invade the tunica interna and tunica externa [17]. One distinctive feature of PAN, compared to other vasculitis is the absence of granulomas. This lack of granuloma formation provides a contrasting characteristic that aids in distinguishing PAN from other forms of vasculitis. This disease is also characterized by the coexistence of different stages of vascular inflammations at the same time.

The pathophysiology of PAN, not yet fully understood, may vary depending on the disease's specific etiology. Serum cytokine profile analysis in PAN patients has revealed an elevation of interferon-alpha (IFN-α), interleukine-2 (IL-2), Tumor necrosis factor- (TNFα) and IL-1-ß compared to healthy individuals and those with Granulomatosis with Polyangiitis (GPA) [18]. Immunohistochemical studies of muscle and nerve biopsies from patients showed the presence of macrophages (41%) and mostly CD4+ T lymphocytes (41%) [19]. Most of these studies, however, primarily focuses on PAN associated with HBV.

Viral infections remain a common a trigger of PAN and should be excluded in all cases. With PAN associated with HBV, the HBs antigen is responsible for the formation of immune complexes [20,21], as suggested by animal models of hepatitis B antigen-associated PAN, which show an accumulation of immune complexes in blood vessels [22,23]. Hepatitis C virus (HCV) has also been linked to PAN, with HCV-associated PAN tending to present more severe and acute symptoms [24,25]. However, this only concerns 5% of patients with PAN and the distinction with cryoglobulinemic vasculitis can sometimes be challenging [26]. HIV infection has been associated with PAN, though HIV-associated PAN is generally less aggressive than HBV-associated PAN. The classical manifestation is mononeuritis multiplex and can occur at any stage of HIV infection [27]. Although parvovirus B19 has been associated with PAN, a study using PCR tests found no higher prevalence of this infection in people with PAN compared to those without [28–31].

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More recently, vasculitis has been associated with SARS-CoV-2 infection, but to date, no cases of PAN have been reported [32,33]. Covid-19 vaccines have been associated with PAN manifestations [34–36]. Similarly to other vasculitis, PAN can be induced by the use of certain drugs, such as minocycline [37]. The association between PAN and neoplasia is well established, especially for hematological malignancies, such as hairy T cell leukemia or, more recently, myelodysplastic syndrome (MDS) [38–42]. In a study by Roupie et al., out of 70 patients with MDS and vasculitis, 9% presented with PAN. MDS is associated with a pro-inflammatory state in 10–30%, which also tend to present with autoimmune and inflammatory disorders. MDS and certain chronic inflammatory diseases share common genetic markers (such as HLA-B27) and polymorphisms (such as IL-1) [43,44].

More recently, genetic forms of PAN have been described. In the early 2000s, cases of PAN-like vasculitis were described in patients with Familial Mediterranean Fever (FMF) [45,46]. In a nationwide study in Turkey, PAN prevalence in patients with FMF was 0.9% [47]. FMF is caused by mutations in the MEFV gene that encodes for pyrin/marenostrin, which result in unregulated production of IL-1, leading to recurring inflammation, fever, and sometimes, autoimmune manifestations [48]. Patients with PAN associated to FMF present a higher incidence of perirenal hemorrhages and elevated levels of inflammation [49–52]. Another condition related to genetic forms of PAN is STING-associated vasculopathy, with onset in infancy (SAVI), which is a type I interferonopathy. This condition is caused by mutations in TMEM173 gene that induce inflammation of endothelial cells in children. It often presents PAN-like symptoms in affected children [53]. A monogenic syndrome resulting from a deficiency in Adenosine Deaminase 2 (DAD2) has been described in familial cases of necrotizing vasculitis that resemble PAN [54]. Since 2014, over 60 bi-allelic loss-of-function mutations in the ADA2 gene have been documented [55,56]. Vascular inflammation in DAD2 patients is believed to be cause by an imbalance in macrophages, favoring the M1 type over M2 type. To date, more than 200 cases of this condition have been recorded [57,58]. In 2020, Beck et al. published a cohort of 25 men exhibiting a somatic mutation affecting methionine-41 (p.Met41) in the UBA1 gene. Located on the X chromosome, this gene encodes for a critical enzyme involved in the initiation of ubiquitination. The syndrome associated with this mutation is known as VEXAS, an acronym for Vacuoles, E1 enzyme, X-linked, Autoinflammatory and Somatic. Although PAN-like features were initially reported in 12% of these patients, more recent studies suggest a lower incidence [59,60] (Figure 1).

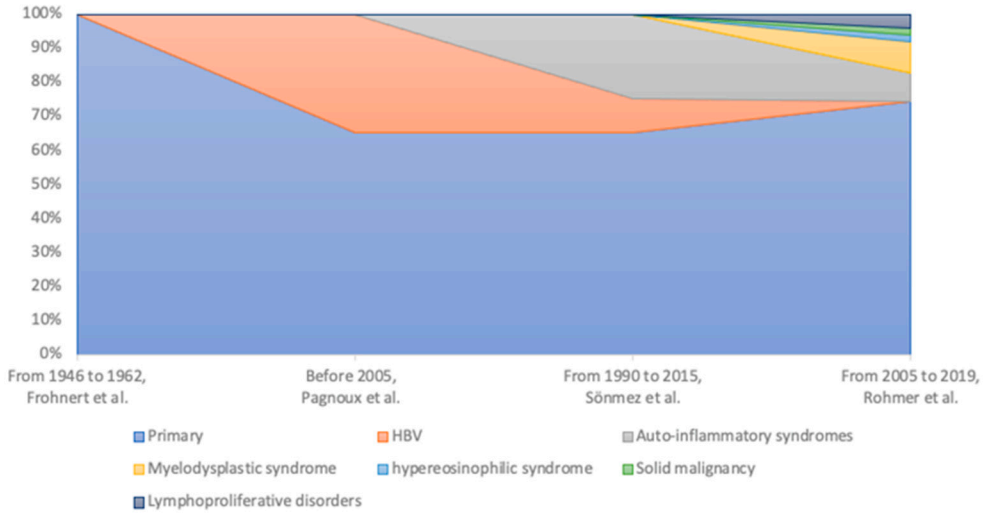

Figure 1. Comparison of various etiologies of PAN across different cohorts over distinct time periods.

4. Clinical manifestations

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Signs and symptoms of PAN result from damage to the vascular walls, potentially affecting all organs. This section provides an overview of organ systems that can be impacted in PAN patients. Unless otherwise stated, the percentages and specifics of the manifestations come from the cohorts shown in Table 1.

Table 1. Characteristics of PAN patients reported in different cohorts (PNP: peripheral neuropathy, CNS : central nervous system, FFS : Five Factor Score, 1996). Results are expressed in percentage.

Characteristics	Pagnoux et al. (1963 to 2005)	Sönmez et al (1990 to 2015)	Rohmer et al. (2005 to 2019)	Georgin-Lavialle et al. (VEXAS)	Meyts et al. (ADA2)
General symptoms	93.1		85	95.7	
Fever	63.8	53.7	54	64.6	50
Loss of weight	69.5	53.7	50	54.5	
Myalgia	58.6	46.2	50		
All cutaneous	49.7	67.2	59	83.6	75
Nodules	17.2				14
Purpura	22.1				
Livedo	16.7	17.9			50
Panniculitis			7.5	12.9	
Renal	50.6	47.7			
Hematuria	15.2		20	9.5	
Proteinuria	21.6				
Hypertension	34.8	41.7			21
Orchitis	17	14.9	16		4
Neurologic	79.0				
PNP	74.1	43.2	59	5.2	9
Mononeuritis	70.7			2.6	
CNS	4.6				53
Digestive	37.9			13.8	33
Abdominal pain	35.6	22.3	28	8.6	12
Bleeding	3.4	37.3		0.9	
Perforation	4.3			0.9	2
Cardiovascular	22.4				
Pericarditis	5.5		39	4.3	
Distal necrosis	6.3				
Thrombo-embolism		13.5		35.3	22
Ophtalmic	8.6				
Retinal vasculitis	4.3			40.5	
Pulmonary				49.1	
Cough	5.7	2.9	8		
Lung infiltrate	3.4			40.5	
Pleural effusion	3.4			9.5	
Chondritis				36.2	
Arthralgia		58.2		28.4	
Arthritis		17.9			

4.1. General symptoms (85-93%)

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General, non-specific symptoms such as asthenia, fever, weight loss, myalgia and arthralgia are frequently the initial symptoms of PAN. They are present in over 9 out of 10 patients.

4.2. Neurologic (59-79%)

Neurologic manifestations occur in more than two-thirds of patients, most commonly as motor and sensory mononeuritis multiplex of the peripheral nerves [61,62]. Peripheral neuropathy is typically distal, asymmetric, and can be rapid onset, often associated with localized skin edema. Of note, deep sensation is rarely affected. Foot drop, an important and disabling complication, may be the initial presentation [63]. Cranial nerves are affected in less than 1% of patients. Central manifestations such as strokes occur in 2 to 10% of patients, typically in the later stages of the disease [61,64,65]. Compared with classic PAN, DADA2 patients more frequently present with central neurologic manifestations, particularly stroke, usually at a young age.

4.3. Cutaneous (50-59%)

Skin lesions, including nodules, purpura, necrotic ulcers, and livedo reticularis are present in half of the patients [66]. In case of cutaneous manifestations suggestive of vasculitis, a skin biopsy is recommended. The biopsy should be deep enough to include the dermal layer where medium-sized arteries are located. A subset of PAN, known as cutaneous PAN (CPAN), is confined to the skin and requires different management [67,68].

4.4. Renal (15-75%)

Kidney involvement is typically characterized by stenosis and aneurysm, primarily affecting renal and interlobar arteries, less frequently the smaller arcuate and interlobular arteries [69,70]. This can manifest as hypertension (up to 35% of patients), micro or macro hematuria, mild proteinuria, and renal infarct [62,70,71]. Despite up to 75% of patients experiencing renal involvement, renal insufficiency occurs in only 15% of cases [62,72]. Glomerular involvement is infrequent [73]. Severe complication such as ruptured aneurysm and spontaneous perirenal hemorrhage, which require embolization or nephrectomy, are infrequent but can be life-threatening [74–77].

4.5. Gastrointestinal (22 to 38%)

Gastrointestinal manifestations of PAN are common, affecting up to 50% of patients. Abdominal pain is reported by one out of three patients [78,79]. Vascular inflammation in mesenteric arteries can be severe, leading to intestinal ischemia, perforation, and hemorrhage [80,81]. Reports have also shown gallbladder involvement, malabsorption with loss of weight and pancreatitis in patients with PAN [82,83]. In rare but severe instances, hepatic aneurysm can occur, potentially triggering acute liver failure and resulting in high mortality [84–88]. Gastrointestinal manifestations are associated with a poor prognosis; the mortality rate is around 25% for patients with such involvement [62,80]. This association with high mortality is supported by a retrospective study from 1988, which found that digestive complications contributed to the death of 16 % of PAN patients [89,90]. Diagnosing mesenteric arterial involvement in PAN can be challenging, and conventional angiography may be valuable, especially in patients with minimal clinical evidence of extraintestinal manifestations.

4.6. Genital (15 to 17%)

Manifestations such as testicular pain, with or without orchitis, have been described as potential symptoms specific to PAN, although similar symptoms have been noted in Behcet's patients. Testicular biopsy can be useful for diagnosis [91]. Interestingly, there are reports of ovarian artery dissection associated with PAN in women [92].

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4.7. Cardiovascular (7 to 78%)

Cardiac involvement predominantly affects the myocardium due to coronary artery vasculitis. The left anterior descending, circumflex branches and right coronary arteries are most affected. Pericarditis are relatively rare, often resulting from pre-existing myocardial involvement [93–95]. Myocardial infarction due to coronary infarction is also unusual [96]. Celiac artery involvement and new-onset hypertension are potential risk factors for coronary involvement [97]. Heart failure often presents during initial stages of the disease. Hypertrophic cardiomyopathy, which may be a result of uncontrolled hypertension, could trigger serious condition like ventricular tachycardia and syncope. Mild diffuse interstitial myocarditis can be caused by focal necrosis [98]. Among pediatric patients with PAN, cases of hemopericardium have been described [99–101]. In terms of vascular manifestations, large vessels can be affected due to necrosis of the vasa vasorum [102]. Symptoms of arterial claudication can be indicative of stenosis or ischemia in the lower extremities [103–105].

4.8. Other manifestations

Ophthalmic complications, including retinal vasculitis, are observed in PAN [106–108]. Unlike other forms of vasculitis such as granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA) or microscopic polyangiitis (MPA), pulmonary lesions are notably absent in PAN. However, an autopsy study revealed bronchial artery damage in 7 out of 10 patients, despite the absence of symptoms [109]. Muscular manifestations in PAN can vary from nonspecific myalgia to paresis, and muscle biopsy shows inflammation related to PAN in up to 50% of cases [110].

VEXAS Syndrome presents general symptoms like fever or weight loss in 96% of patients, skin manifestations such as neutrophilic dermatosis or tender plaques (84%), pulmonary infiltrates (49%), chondritis (36%), and deep vein thrombosis (35%) [111]. Hematologic manifestations include macrocytic anemia (96%) and vacuoles in bone marrow myeloid and erythroid cells found all patients [60]. The vascular manifestations of VEXAS mimic small to large vessels vasculitis [60,112]. In the inaugural study of 25 VEXAS patients, 12% were diagnosed with PAN [60]. A recent literature review showed that among 9 cases of medium vessel vasculitis found, all were men with macrocytic anemia and skin lesions, 6 of whom had passed away prior to the article's publication [113]. Patients with DADA2 exhibit vasculitis, immunodeficiency, and hematological manifestations. Vasculitis appears as mucocutaneous manifestations in 75% of cases, including livedo reticularis (50%), PAN-like skin lesions with non-granulomatous necrotizing inflammation of medium-sized arteries (34%), digital necrosis (22%), nodules (14%), Raynaud phenomenon (8 %) and aphthous ulcers (7%). Neurological manifestations occur in 51% of cases and may include ischemic strokes (27%), cranial nerve palsy (27 %), hemorrhagic strokes (12%) and polyneuropathy (9%). General symptoms such as fever elevated erythrocyte sedimentation rate or CRP are present in half of the patients. Immunodeficiency manifests as hypogammaglobulinemia (22%), low IgM (18%) or IgA (12%), and infections (20%). Viral infections (11%) are more frequent than bacterial ones (7%). Hematological diseases manifest as anemia (13%), neutropenia (7%) and thrombocytopenia (6%) due to bone marrow failure or autoimmune cytopenia. Lymphoproliferative symptoms (32%) including splenomegaly and lymphadenopathy are common in patients with DADA2. Most symptoms and signs appear (85%) occur before the age of 12 [114,115] (see Table 1).

5. Treatments

The treatment recommendations for PAN are primarily based on weak empirical evidence and are often drawn from recommendations for other forms of vasculitis, with modifications according to the disease severity. Mild PAN, characterized by non-life or organ-threatening manifestations like constitutional symptoms, arthritis, or skin lesions, is differentiated from moderate to severe PAN, which involves more severe complications, such as arterial stenosis—particularly those involving the renal arteries and aorta—and ischemic complications that affect the heart, peripheral nervous system, and gastrointestinal system [116]. To aid in risk stratification, the 1996 version of the Five-Factor Score

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(FFS) can be used. This score assigns +1 point for each: proteinuria greater >1 g/day, serum creatinine >140 μmol/L, cardiomyopathy, severe gastrointestinal involvement, and CNS involvement [117].

Treatment for mild PAN (FFS of 0) may include glucocorticoids (GC) only. The clinical benefit of supplementing glucocorticoids with an immunosuppressive agent is not definitively established, but it could potentially offset the high 40% relapse rate and function as a steroid-sparing strategy [116,118]. Guidelines, however, show divergence in recommendations. The French protocol typically prescribes glucocorticoids as standalone treatment, introducing immunosuppressants such as methotrexate or azathioprine only in instances of resistance or intolerance. In contrast, the ACR's 2021 guidelines advocate for a combined approach right from the beginning, recommending the incorporation of azathioprine (administered orally at 2–3 mg/kg/day) or methotrexate (preferably given subcutaneously at 0.3 mg/kg/week) with glucocorticoids [110, 113, 116,118]. Moderate to severe PAN (FFS >0) is treated with intravenous (IV) GC in conjunction with an immunosuppressive agent, preferably cyclophosphamide [116,117]. The start of treatment marks the induction phase, lasting 3 to 6 months, aimed at achieving disease remission, defined by American College of Rheumatology (ACR), as a complete absence of clinical manifestations, with or without immunosuppressive treatment [116]. Initial treatment strategies recommend starting with at least 1 mg/kg/day of prednisone equivalent, capped at 60 mg/day. In patients with severe manifestations requiring rapid intervention, IV boluses of methylprednisolone are recommended. If remission is incomplete, the duration of cyclophosphamide therapy may be extended, although it is recommended not to exceed a period of 6 months given its potential toxicity [119].

Alternative therapies, including rituximab, mycophenolate mofetil, tocilizumab, anti-TNF-alpha, JAK inhibitors, IV immunoglobulins or plasma exchange, have not been well studied and their application is only reserved for certain refractory or relapsed patients [30,120–126]. A recent European retrospective study analyzed 42 patients treated for relapsed and/or refractory PAN. Tocilizumab, TNF inhibitors and rituximab achieved complete remission in 50%, 40% and 33% of cases, respectively, with a comparable safety profile. The induction phase is followed by the maintenance phase, with the objective of preventing relapse. Patients treated with cyclophosphamide with a complete remission may be switched to azathioprine or methotrexate for 12 to 18 months [117]. In secondary forms of PAN, the therapeutic approach focuses on the underlying etiology. In the context of HBV-associated PAN, antiviral therapy is used as the primary intervention [117]. When PAN is concomitant with MDS, interventions targeting the MDS are often effective in attenuating the vasculitic manifestations [39]. From this perspective, Mekinian et al. showed that azacytidine successfully treated autoimmune manifestations in 9 of 11 patients with MDS [127]. In the case of DADA2-associated PAN, numerous treatments have been explored (azathioprine, cyclosporine, tacrolimus, cyclophosphamide, methotrexate) with mitigated results. The ACR 2021 guidelines have now approved the use of steroids and anti-TNF -agents (etanercept, infliximab or adalimumab) following demonstration of their efficacy in PAN associated with DADA2 [116]. Hematopoietic stem cell transplantation (HSCT) has been reported to treat cytopenia [128]. Regarding VEXAS syndrome, several drugs have been tested with mixed results [129]. GC in combination with azacytidine (possibly supplemented by HSCT) seem most effective for patients with MDS features. For those without myelodysplasia, JAK inhibitors or tocilizumab may be suitable [130,131]. Finally, vasculitis associated with primary immunodeficiency can be managed with biotherapies, HSCT, or IV immunoglobulin therapy [48].

6. Conclusions

Over the past two decades, our understanding of PAN has undergone a significant evolution. While historically viewed through the binary lens of primary vs HBV-related PAN, the landscape has expanded. We now recognize a spectrum of PAN, from those linked to infections and paraneoplastic syndromes, to novel classifications associated with DADA2, interferonopathies, and the VEXAS syndrome. Interestingly, these auto-inflammatory related PAN variants present distinct clinical manifestations. For instance, VEXAS syndrome has heterogenous manifestations, with heightened general symptoms, cutaneous, ophthalmic and thromboembolic manifestations, unique chondritis,

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and frequent but mild pulmonary involvement. DADA2, which mainly affects children and young adults, shows a deviation from traditional PAN symptoms. It presents fewer general symptoms, lacks orchitis, and its neurological manifestations predominantly target the central nervous system. Identification of potential secondary causes of PAN is critical, as it can significantly influence treatment decisions. While conventional immunosuppressants such as cyclophosphamide are often the standard of care for primary PAN, secondary forms may benefit from more specific agents: anti-TNF-alpha for DADA2, JAK inhibitors for VEXAS, and targeted MDS treatment for PAN associated with MDS. Overall, despite the emergence of new forms of PAN, the important decrease in HBV prevalence due to vaccination has contributed to a decreased overall incidence of PAN.

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