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POLYARTERITIS NODOSA NEUROLOGICAL MANIFESTATIONS

Hubert de Boysson, MD¹ and Loïc Guillevin, MD²

¹ Department of Internal Medicine, Centre Hospitalier Universitaire de Caen, Caen, France.

hubertdeboysson@yahoo.fr

² Referral Center for Rare Autoimmune and Systemic Diseases: Vasculitides and Scleroderma, Department of Internal Medicine, Hôpital Cochin, Université Paris Descartes, Paris, France

Correspondence: Loïc Guillevin, Referral Center for Rare Autoimmune and Systemic Diseases: Vasculitides and Scleroderma, Department of Internal Medicine, Hôpital Cochin, 27, rue Fg Saint-Jacques, 75679 Paris Cedex 14, France. E-mail: loic.guillevin@aphp.fr

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Key Points:

- Peripheral neuropathy is often the most frequent and earliest symptom of PAN.
- Peripheral neuropathy does not impact survival but can be responsible for severe functional sequelae.
- Central nervous system involvement is rare in PAN but outcome of CNS manifestations can be lethal.
- Treatment varies according to aetiology (HBV+ or not, DADA2) and severity: corticosteroids and sometimes immunosuppressants in the absence of HBV infection; corticosteroids, then antiviral treatment and plasma exchanges in case of HBV-PAN; anti-TNF in DADA2 patients.

SYNOPSIS

Polyarteritis nodosa (PAN) is a necrotizing vasculitis affecting medium-sized vessels whose main manifestations are weight loss, fever, peripheral neuropathy, renal, musculoskeletal, gastrointestinal tract and/or cutaneous involvement(s), hypertension and/or cardiac failure. Peripheral neuropathy is one of the most frequent and earliest symptoms, affecting 50–75% of PAN patients. Central nervous system involvement affects only 2–10% of PAN patients, often late during the disease course. Treatment relies on combining corticosteroids and an immunosuppressant (mainly cyclophosphamide) in patients with poor prognoses. In patients with hepatitis B virus-related PAN, plasma exchanges and antiviral drugs should be combined with corticosteroids.

Polyarteritis nodosa (PAN), first described by Küssmaul and Maier, is a necrotizing vasculitis mainly manifested by weight loss, fever, asthenia, peripheral neuropathy, renal, musculoskeletal and/or gastrointestinal (GI) tract involvement(s), cutaneous lesions, hypertension and/or cardiac failure.¹ Peripheral neuropathy is often the most frequent and earliest symptom of PAN. Central nervous system (CNS) manifestations are less frequent.^{2,3} In light of its potential etiologies, primary and secondary forms of PAN can also be distinguished; notably PAN can be the consequence of hepatitis B virus (HBV) infection (HBV–PAN).⁴ That etiology was frequent in the 1980s but is becoming extremely rare since the implementation of the anti-HBV vaccination and enhanced blood-transfusion safety and hygiene procedures. Herein, we review the clinical PAN manifestations, focusing on the peripheral nervous system (PNS) and CNS symptoms.

DEFINITIONS, CLASSIFICATION AND DIAGNOSIS

Vasculitides are mainly defined based upon their histological features. However, more recently pathogenic mechanisms and the presence or absence of immunological markers have also been considered.⁵ PAN is a necrotizing vasculitis, whose histological characteristics include fibrinoid necrosis of the artery media, perivascular inflammatory infiltrates and vessel thrombosis following intima infiltration. Lesions progress to fibrotic scar replacement causing tissue ischemia and damage.

Vasculitic lesions are segmentally distributed, with a predilection for arterial bifurcations. Early inflammatory infiltrates contain lymphocytes, plasmocytes, histiocytes and some neutrophils. Fibrinoid necrosis of the artery media leads to thrombosis development. Segmental necrosis of medium-sized vessels may also give rise to microaneurysms.⁶ Because PAN activity consists of successive flares, different histological stages may be seen in the same tissue sample. Arterial lesions are ubiquitous and can be present in all medium-sized

arteries. Some unusual localizations have been described, e.g., fibrinoid necrosis in a temporal artery mimicking the clinical symptoms of giant-cell arteritis.⁷ Granulomatous inflammation in biopsied tissue excludes PAN; it is mainly characteristic of granulomatosis with polyangiitis (GPA) or eosinophilic granulomatosis with polyangiitis (EGPA). The latter two vasculitides affect small-sized vessels, while medium-size vessels are the predominant sites of PAN.

The 1990 American College of Rheumatology classification criteria are no longer useful for PAN because they do not separate PAN and microscopic polyangiitis (MPA), a small-sized vessel antineutrophil cytoplasm antibody (ANCA)-associated vasculitis.⁸ The 1994 and 2012 Chapel Hill Consensus Conference Nomenclature versions^{9,10} provide a precise definition of PAN (Table 1).

Table 1. Definition of PAN adopted by the 2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides

Medium-vessel vasculitides: vasculitis predominantly affecting medium-sized arteries, defined as the main visceral arteries and their branches. However, any size artery may be affected. Inflammatory aneurysms and stenoses are common.

Polyarteritis nodosa: necrotizing arteritis of medium- or small-sized arteries, without glomerulonephritis or vasculitis in arterioles, capillaries or venules, and not associated with ANCA.

Adapted from Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013;65:1-11; with permission.

Specific guidelines have also been elaborated by the Peripheral Nerve Society to diagnose and classify vasculitides affecting peripheral nerves.¹¹

Diagnosis of vasculitis theoretically requires histological proof. However, because tissues

from sites easy to biopsy may show only non-specific inflammation or may be normal, the diagnosis can be based on a combination of clinical, immunological and radiological findings. ANCA-negativity and angiography-detected stenoses or microaneurysms are useful for diagnosis. Immunofluorescence- and/or enzyme-linked immunosorbent assay (ELISA)-detected ANCA should be considered an exclusionary criterion for PAN diagnosis. The angiograms of approximately two-thirds of PAN patients investigated visualize celiomesenteric and renal angiographic findings, e.g., multiple 1–5-mm diameter microaneurysms or irregular stenoses.¹² Although highly suggestive, those findings are not absolutely specific. Visceral artery aneurysms are also found in thrombotic thrombocytopenic purpura, mycotic infections, fibromuscular dysplasia, atrial myxoma, malignant hypertension and rare patients with small-vessel vasculitides.¹³ Our group established diagnostic criteria for PAN comprising positive and negative items which, when combined, are relevant for diagnosis (Table 2).⁵

Table 2. PAN diagnostic or exclusionary criteria

PAN criteria	Comment
Diagnostic	
Poor condition and/or weight loss	Present for several weeks or months, with loss of appetite
Myalgias and/or arthralgias	Proximal or distal muscle pain without deficit, inflammatory arthralgias with or without arthritis
Testicular tenderness	With or without concomitant orchitis; no infectious cause found
Mononeuritis multiplex	Recent, not attributable to metabolic or toxic cause
Hypertension	Recent-onset arterial hypertension not related to an organic cause other than a vasculitic process
Renal insufficiency	Recent-onset renal insufficiency or acute impairment of renal function
Replicating HBV	Should occur less than 24 months before vasculitis onset; replication proven by viral DNA- and hepatitis Be antigen (HBeAg)-positivity

Exclusionary

Glomerulonephritis	Suggested by hematuria and proteinuria, without renal insufficiency; histologically proven
Alveolar hemorrhage	Hemoptysis with alveolar pneumonia or positive bronchoalveolar lavage Golde test
Asthma	Severe and recent asthma onset with hypereosinophilia or history of asthma with recent worsening
ANCA+	Identified by immunofluorescence and confirmed by ELISA
Cryoglobulinemia	Mixed type II or III cryoglobulinemia

PAN may develop in a setting of infection, mainly HBV and rarely human immunodeficiency virus (HIV) or other viruses.¹⁴ When HCV is found, it is more frequently an HBV co-infection than a specific cause of PAN. In the late 1980s, HBV was responsible for one-third of the PAN cases.⁴ HBV–PAN is no longer observed in developed countries. The last rare cases we observed were the consequence of a probable reactivation of a dormant non-replicating HBV.

A cat eye syndrome critical region protein-1 (*CECRI*) mutation, responsible for a deficit of adenosine deaminase-2 (*DADA2*) was recently described in children. *DADA2* usually becomes manifest in childhood, with 24% of reported patients consulting before 1 year of age, and 77% before the age 10 years.¹⁵ It is the first molecularly described monogenic vasculitis syndrome. Patients carrying this mutation have PAN symptoms, with stroke(s) occurring more frequently than in other PAN forms.^{15–18} Systemic symptoms are comparable to those of PAN but *DADA2* is more severe.¹⁵ Patients can be siblings, sometimes twins. This new form of PAN demonstrates that PAN etiologies are probably multifactorial.

EPIDEMIOLOGY

No recent data on PAN prevalence and incidence are available. In a study on biopsy-proven

forms, the annual PAN incidence and prevalence were, respectively, 0.7 and 6.3 per 100,000 inhabitants.¹⁹ Estimates of the annual PAN-type systemic vasculitis incidence in the general population range from 4.6 per 1,000,000 in England, 9.0 per 1,000,000 in Olmsted County, MN, to 77 per 1,000,000 in a hepatitis B hyperendemic Alaskan Eskimo.^{20,21} PAN affects men and women with a male predominance, all racial groups, at every age, usually starting between 40 and 60 years, but can develop in children and patients over 65 years old.⁴ Based on follow-up of our vasculitis cohort, PAN is now extremely rare, even though we have seen its recrudescence in the two past 2 years but we cannot provide precise data on its frequency, which might have been biased by our referral center's specialty and tertiary nature. HBV–PAN has almost completely disappeared in the French population. In France, vaccination is strongly encouraged for teenagers and populations at risk. Blood transfusion is safe, with specific polymerase chain reaction detection of viruses (HBV, HCV and HIV) and the hospital hygiene measures implemented nationwide including systematic single-use of materiel.

EXTRANEUROLOGICAL MANIFESTATIONS

Two-thirds of PAN patients are in poor general condition, with anorexia and weight loss occurring early during the course of the disease, and perhaps being the sole manifestations. Patients may be febrile. They usually complain of myalgias and arthralgias, most often affecting the major joints: knees, ankles, elbows and wrists. Pain can be localized to nerve territories.

Renal Manifestations

Vascular nephropathy can lead to renal insufficiency of variable intensity, which, in turn, can cause severe or malignant arterial hypertension as a complication.²²

Acute renal failure can be an early manifestation or occur at the time of a flare. Some patients

may require renal dialysis early or at some later time, when renal insufficiency progresses as a consequence of chronic worsening of renal ischemia. However, the outcome of renal insufficiency is not predictable and improvement may occur.

Angiograms of patients with renal involvement show renal infarcts, multiple stenoses and/or microaneurysms of digestive and renal artery branches. Renal infarcts are responsible for renal insufficiency.

Orchitis

Non-infectious orchitis, attesting to testicular artery involvement is rarely the first sign of PAN but it is characteristic. With rapid initiation of corticosteroids, orchitis may regress.^{6,12}

Skin Manifestations

Vascular purpura is frequent in PAN. Because the skin contains medium-sized vessels, nodules can form in the dermis and hypodermis, and predominately on the legs. They appear and disappear within a few days. Livedo racemosa or reticularis can be observed. Post-inflammatory ischemic leg ulcers can develop and are recognized by their topography. They must be differentiated from cholesterol crystal emboli in patients with atherosclerosis.^{6,12}

Peripheral Vascular Manifestations

Distal digital gangrene can result from arterial obstruction. Angiography can demonstrate the presence of stenoses and/or microaneurysms. Raynaud's phenomenon, when present, can remain isolated or be complicated by necrosis.^{6,12}

Gastrointestinal Involvement

GI-tract involvement is one of the most severe PAN manifestations,²³ especially HBV–PAN.²⁴ Abdominal pain occurs in one-quarter to one-third of the patients and can be the first symptom. A majority of patients has ischemia of the small intestine but rarely the colon or stomach. Small intestine perforation and GI bleeding are the most severe signs.²⁴

Chronic pancreatitis with pseudocysts²⁵ has a particularly poor prognosis. Vasculitis of the

appendix or gallbladder can be the first symptom. The prognoses of those manifestations depend upon whether one or the other is the first overt vasculitis sign or a complication of previously diagnosed and treated PAN.

Cardiac Manifestations

Cardiac involvement results from vasculitis of the coronary arteries and/or their branches, or severe or malignant hypertension. Despite coronary artery vasculitis, angina is rare and coronary angiography is usually normal. Stenosis(es) of the main coronary arteries were found during autopsies of in less than half of the PAN patients.²⁶ Arteriolar involvement and myocardial necrotic foci can be seen.

Left heart failure, the most common cardiac involvement manifestation, occurs early during the course of PAN. Supraventricular rhythm disturbances occur more often than ventricular rhythm disturbances. Pericardium involvement by the vasculitic process is rare. One-third of PAN patients has arterial hypertension but rarely malignant hypertension.

HBV–PAN

When HBV is involved, PAN usually appears during the year following infection. Hepatitis is usually present before PAN onset. We previously observed that some patients developed PAN several years post-contamination and hypothesized that those cases were caused by mutant HBVs. Clinical manifestations are basically the same as those commonly seen in non-HBV–PAN.⁴ Seroconversion usually leads to recovery. Vascular nephropathy can be responsible for sequelae but recovery is possible, even in renal insufficient patients, with little residual impairment of renal function.

Abdominal manifestations and vascular nephropathy are common.

NEUROLOGICAL MANIFESTATIONS

PNS Involvement

Half to three-quarters of PAN patients experience peripheral neuropathy.^{27,28} PNS involvement typically results from focal or multifocal, axonal, ischemic neuropathy caused by arteriolar occlusion of the vasa nervorum, usually of epineurial arteries.^{2,3} For 36.4% (8/22) to 55.6% (15/27) of patients with systemic necrotizing vasculitides,^{29,30} signs of PNS involvement are the initial symptoms. Patients commonly complain of pain or inexplicable sensory symptoms in the days preceding palsy onset. At that time, the physical examination is normal. PAN onset is usually acute, but may be more progressive, particularly in the elderly. Sensory signs are responsible for hypo- or hyperesthesia(s), dysesthesia(s) or frank pain as the prominent and earliest features. Usually, motor deficits start later but are also of sudden onset, sometimes preceding the sensory loss.

The first manifestations often affect the lower limbs, with one particular nerve initially involved. Later, other nerves become affected, with this pattern being referred to as mononeuritis multiplex. In its late stage, so many nerves can be involved that mononeuritis multiplex can be mistaken for a symmetric process. In those cases, only careful history taking will be able to identify the patchy asymmetric pattern of early involvement. Less frequently, distal symmetric sensorimotor polyneuropathy and pure sensory neuropathy may occur. The nerves most frequently affected (in decreasing order), respectively unilaterally and bilaterally, are: the sciatic nerve or its peroneal branch, 62.5–84% of the patients and one-third but asynchronously; the tibial nerve, 27.5–41% and 5%; the ulnar nerve, 25.5–56% and 8%; the median nerve, 21.5% and 3%; the radial nerve 8–29% and 2%; the femoral nerve, 2% unilaterally; and the proximal sciatic nerve or sciatic root unilaterally in another 2%.^{24,31,32} A Guillain–Barré syndrome-like clinical picture has been described, as have radicular syndromes and plexopathies.³³ Exceptionally, some patients with DADA2 have polyneuropathy or mononeuritis multiplex.¹⁵

Some patients with histologically proven peripheral nerve vasculitis seem to have PNS-limited PAN.³⁴ This form has been referred to as non-systemic vasculitis³⁵ and, is called single-organ vasculitis in the 2012 Chapel Hill Nomenclature.¹⁰ This form of PAN is called PAN but, except for the neurological signs, the disease is not systemic. Hence, we wonder if it is the same disease or two entities. Notably, the single-organ form relapses frequently, without systemic inflammation.

In PAN limited to the skin, PNS involvement has also been described. We think that it, too, should be considered a different entity, even though it is referred to as PAN. However, that “an isolated vasculitis is a limited expression of a systemic vasculitis does not imply that the vasculitis will or will not subsequently evolve into systemic disease.”¹⁰ Indeed, Said et al. showed that 37% of the patients with initially isolated peripheral nerve vasculitis subsequently developed systemic vasculitis manifestations, and that 24% of them experienced neuropathy relapses.³² Although some sporadic cases reported had poor outcomes,³⁴ most non-systemic vasculitides, clearly restricted to peripheral nerves, respond favorably to treatment (mainly corticosteroids and immunosuppressants),^{35,36} but improvement may occur very slowly and sometimes only partially. Severe pain and sensory symptoms can sometimes persist for years, or even indefinitely, after the first clinical symptoms, and, evidently, negatively impact the patient’s quality of life.

Because cerebrospinal fluid (CSF) findings are usually normal, lumbar puncture is not done routinely. For the rare patients with such analyses, CSF had moderately increased protein concentrations and rare cellular contents. However, CSF analysis is indicated for patients with plexopathies, clinical manifestations mimicking Guillain–Barré syndrome or to look for a differential diagnosis.

With treatment, mononeuritis multiplex progressively regresses and patients can recover without sequelae. Cranial nerve palsies, most often involving the oculomotor (III), trochlear

(IV), abducent (VI), facial (VII), and acoustic VIII nerves, affects less than 2% of PAN patients. Bladder neuropathy is rarely observed.³⁷

CNS Involvement

PAN affects the CNS in 2–10% of patients.^{6,38} Previously, 20–40% of the patients had CNS involvement but headaches had been included among CNS symptoms and some patients with MPA had probably been included in the series.^{2,28}

CNS involvement usually arises late during the course of the vasculitis; pertinently, a CNS event renders a PAN link questionable. Some authors suggested that hypertension-associated microangiopathy and a prothrombotic state are more frequent components of a CNS event than a vasculitic process.³⁹ Parenchymal biopsy would demonstrate vasculitis but is rarely obtained, given its invasive nature. Only a few cases of biopsy-proven PAN-related CNS vasculitis have been reported.⁴⁰ Most often, clinical and radiological findings and extraneurological signs of disease activity lead the clinician to suspect PAN-related CNS involvement.

Clinical manifestations

Neurological symptoms of PAN-related CNS involvement are highly variable and depend on the territory affected. Their onset can be acute (e.g., stroke or seizures) or more chronic and insidious, like headaches or encephalopathic symptoms (cognitive and vigilance disorders or psychiatric manifestations). Although headaches are common, not all patients have them.³

Motor deficits are common and often explained by small-to-large brain infarction(s). Other potential neurological deficits include speech disorders, sensory deficits or cerebellar ataxia. Although cranial nerve involvement is possible, it has rarely been reported. Encephalopathic manifestations include confusion, cognitive disorders, psychiatric manifestations (mainly depression) and vigilance disorders (ranging from psychomotor retardation to coma). Seizures

are also common.

Frequent visual loss can result from anterior optic neuropathy or posterior (retrobulbar) optic neuropathy.^{3,41,42}

In addition to a neurological work-up, other extraneurological symptoms should be actively sought, as they are frequently present.

Computed-tomography (CT) scan and magnetic resonance imaging (MRI)

Despite its poor sensitivity and specificity, CT scan is often the first imaging examination. MRI is essential for all patients and, when available, should include the following sequences: T1, T2, T2*, fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI)/apparent diffusion coefficient mapping, and gadolinium-enhanced T1. Vascular sequences should be also obtained.

Different lesion patterns can be discerned within a single imaging procedure. Ischemic lesions, isolated or disseminated, are common. Subacute and chronic ischemic lesions are also seen, often associated with acute lesions. Cortical and subcortical regions are frequently involved.³⁸ Multiple ischemic lesions are suggestive of a vasculitic process but can also be seen in atherosclerosis, infections or other vasculopathies. Disseminated lesions of different ages are also suggestive of vasculitis. Multiple patterns of acute ischemic lesions can be seen in grey and white matter (subcortical, peripheral, superficial or deep lesions).

Subcortical and white matter FLAIR hyperintense lesions are frequently seen, but are non-specific, as they are also found in other inflammatory and non-inflammatory conditions. FLAIR lesions in the cortex or posterior areas are rare and more evocative of vasculitis. Gadolinium injection is required in the diagnostic work-up of CNS vasculitis and gadolinium-enhanced lesions are suggestive of an inflammatory process. Meningeal tissues, as well as the parenchyma, can be gadolinium-enhanced. Pachymeningitis is only exceptionally reported in PAN⁴³ and is more often found in granulomatous diseases or primary CNS vasculitis. In our

experience, we never observed pachymeningitis in PAN.

Hemorrhagic lesions can be observed within acute ischemic lesions, indicating hemorrhagic transformation. However, spontaneous parenchymal or subarachnoid hemorrhages, possibly attributable to microaneurysm rupture, have been described.⁴⁴⁻⁴⁶ Some hemorrhagic lesions might also be caused by hypertensive microangiopathy.^{2,39}

The presence of different MRI abnormalities is frequent and suggestive of vasculitis when multiple ischemic lesions are seen concomitantly with small hemorrhages, FLAIR lesions and gadolinium enhancements. Conversely, PAN-related CNS vasculitis is highly improbable in a patient whose MRI is normal.

Cerebral angiography

For patients with imagery-documented ischemic CNS lesions or those suspected of having specific PAN-related CNS vasculitis, angiography is required. Although aneurysm formations are frequent in extraneurological medium-sized vessels, they are more rarely reported in brain vessels.^{38,46,47} Magnetic resonance angiography (MRA), brain CT angiography or digital subtraction angiography are the three main procedures used. The latter technique has the best spatial resolution, enabling analysis of vessels $\geq 500 \mu\text{m}$ but it is an invasive procedure. Although MRA's ability to explore vessels $>700 \mu\text{m}$ is limited, the development of 3-Tesla MRA has increased the procedure's spatial resolution.

In addition to microaneurysms, which occur more frequently in PAN, multiple arterial segmental and focal stenoses ($>80\%$ of lumen narrowings) and occlusions are other typical vasculitis findings.^{38,46,47} It is important to note that those stenoses can also be found in other conditions (e.g., atherosclerosis or reversible cerebral vasoconstriction syndrome). However, in the last two entities, lesions are often diffuse and involve more vessels than vasculitis.

DADA2

In two 2014 reports, patients with DADA2 and early-onset PAN with lacunar strokes,

livedoid rash and intermittent fevers were described.^{16,17} Since then, fewer than 200 patients have been reported. Skin (mainly livedo) and CNS are commonly involved.^{15,18} Observed in more than 50% of those patients, CNS events were predominantly multiple acute or chronic ischemic lacunar infarcts located in the deep-brain nuclei and/or the brain stem, sparing the subcortical white matter. Hemorrhagic events seemed to be a part of the clinical spectrum, even though they occurred more frequently in patients taking aspirin or warfarin.¹⁵ Other rare manifestations included spastic diplegia or paraplegia, peripheral polyneuropathy (with perineuritis), ataxia, neurosensory hearing loss, mononeuritis multiplex, labyrinthitis, encephalopathy and cerebral atrophy.¹⁵

In addition to neurological and skin manifestations, peripheral vascular symptoms, renal and intestinal involvements, and hepatic and splenic involvements leading to portal hypertension have been described. Finally, cytopenias including some bone-marrow failures and hypogammaglobulinemia can be present.^{15-17,48,49}

TREATMENT

Although codified, PAN treatment is essentially based on therapeutics already prescribed for other vasculitides. The newest targeted monoclonal antibodies have been tried anecdotally for PAN patients but were not effective, in sharp contrast to their proven efficacy against ANCA-associated vasculitides. Therefore, PAN treatment remains based on corticosteroids and immunosuppressants for non-HBV-PAN, and antiviral agents combined with plasma exchanges (PEs) for HBV-PAN.

Treatment Stratification According to PAN Form and/or Its Subgroups

To help clinicians choose the most effective therapy and avoid overtreating patients, we revisited the 1996 Five-Factor Score (FFS) in 2011.⁵⁰ The revised FFS, whose items were associated with higher mortality (renal insufficiency (creatininemia >150 μmol/l),

cardiomyopathy, GI manifestations, age >65 years old and absence of ear, nose & throat involvement), has significant prognostic value. When FFS at diagnosis was 0, 1 or ≥ 2 , respective 5-year mortality reached 9%, 21% or 40%. The 1996 FFS version included CNS involvement,⁵¹ but it was no longer a poor-prognosis factor in the revised FFS, mainly because of the small number of PAN patients with CNS manifestations in our vasculitis patient cohort.⁵⁰

Corticosteroids Alone

Corticosteroids alone can effectively treat PAN without poor-prognosis factors, i.e., FFS = 0,⁵² obtaining survival rates similar to those of patients whose induction regimen combined corticosteroids and cyclophosphamide. When PAN fails to respond to corticosteroids alone, adjunction of an immunosuppressant (cyclophosphamide or azathioprine) should be beneficial. One of our recent studies on patients with PAN, EGPA or MPA⁵³ confirmed that adding azathioprine to corticosteroids for patients with FFS = 0 was not more effective than steroids alone and was unable to prevent relapses.

The benefit of adding an immunosuppressant to the induction regimen of patients with CNS involvement has not been proven. However, given that severe clinical manifestations of CNS involvement frequently coexist with other systemic involvements, corticosteroids are rarely prescribed alone.

Corticosteroids and Cyclophosphamide

Combining an immunosuppressant with induction corticosteroids has transformed the prognosis of severe non-HBV-PAN. When cyclophosphamide is indicated for PAN patients, 1–3 intravenous pulse(s) should be preferred to oral intake, as systemic administration achieves a more rapid clinical response. In combination with corticosteroids, 6 intravenous cyclophosphamide pulses usually suffice to induce remission. An azathioprine or methotrexate maintenance-therapy regimen is then prescribed for 12–18 months.

Treatment of HBV– and Other Virus-Related–PAN

Virus-associated vasculitides require specific therapeutics. In the context of chronic HBV infections, the PAN can be successfully treated with corticosteroids and immunosuppressants, obtaining short-term outcomes comparable to those obtained with PEs and antiviral agents.⁴

However, in the virus-infection setting, immunosuppressants can be deleterious, enhancing virus replication, and, over the long term, perpetuating chronic HBV infection and facilitating progression towards cirrhosis, which may subsequently evolve to hepatocellular carcinoma.

Because antiviral drug efficacies against chronic hepatitis and PEs for PAN have been demonstrated, we devised an etiological therapeutic regimen for HBV–PAN. Initial corticosteroids, to rapidly control the most severe life-threatening PAN manifestations common during the first weeks of overt vasculitis, were stopped abruptly to enhance immunological clearance of HBV-infected hepatocytes and favor HBe-antigen-to-anti-HBe-antibody seroconversion; then, PEs were added on to control the course of PAN.

An induction regimen combining an antiviral (vidarabine, interferon-alpha-2b or, more recently, lamivudine, entecavir etc..) and PEs to treat HBV–PAN was able to achieve excellent overall therapeutic outcomes in several weeks. That antiviral–PE strategy amplified the seroconversion rate from 14.7% with conventional treatment to 49.4%.⁴

Plasma Exchanges

At present, no trial-documented proof supports the systematic prescription of PEs at the time of non-HBV–PAN diagnosis, even for patients with poor-prognosis factors.^{52,54}

In contrast, for HBV–PAN, because corticosteroids and immunosuppressants cannot be recommended, PEs are essential to clear immune complexes and immediately control serious disease symptoms, while buying time for the antiviral's effect to take hold.

Specific Considerations on Peripheral Neuropathy

A long-term analyses of patients included in our prospective studies confirmed our initial results in terms of survival and relapse rates, and showed that those with peripheral neuropathy at PAN onset more frequently required an immunosuppressant combined with corticosteroids to manage their relapses than patients without that symptom initially.^{55,56} That observation over the long-term leads us to hypothesize that induction with corticosteroids and an immunosuppressant—independently of disease severity—could prevent late relapses. However, that hypothesis should be tested in a prospective trial.

DADA2

The first DADA2 patients with severe symptoms received corticosteroids and immunosuppressants, which yielded various outcomes, including several flares at corticosteroid tapering.¹⁵ To date, treatment of DADA2 symptoms mainly relies on anti-tumor necrosis factor agents, which limits stroke recurrences. Rituximab has been used to treat DADA2-associated cytopenias and hypogammaglobulinemia can be managed with gammaglobulin substitution.¹⁵ Bone-marrow failure and severe immune deficiency might require hematopoietic stem-cell transplantation.^{48,49} Because plasma ADA2 levels can be measured, infusions of fresh-frozen plasma were considered to replace insufficient ADA2. However, the ADA2 half-life and the large plasma volumes required to be effective render this approach impractical.¹⁵

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