

REVIEW

Gastrointestinal Involvement in Polyarteritis Nodosa

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Polyarteritis nodosa (PAN) is a necrotizing, focal segmental vasculitis that affects predominantly medium-sized arteries in many different organ systems. It is associated with hepatitis B virus (HBV) in about 7% of cases, a decline from about 30% before the mandatory testing of blood products and the widespread vaccination programs. HBV PAN is an early postinfectious process. The hepatitis is silent in most cases, with mild transaminase level increases in 50% of patients. Gastrointestinal involvement occurs in 14% to 65% of patients with PAN. Postprandial abdominal pain from ischemia is the most common symptom. When transmural ischemia develops, there may be necrosis of the bowel wall with perforation, associated with a poor prognosis. Liver involvement occurs in 16% to 56% of patients, although clinical manifestations related to liver disease are quite rare. Acalculous gangrenous cholecystitis may develop owing to arteritis involving the wall of the gallbladder. Microaneurysms on arteriography or computed tomography angiography are characteristic of PAN, but are seen in other conditions. Tissue biopsy may confirm the diagnosis, although involvement is segmental. Corticosteroids are used for non-HBV PAN with cyclophosphamide added for severe disease. For PAN related to HBV, a 2-week course of corticosteroids is begun, with plasma exchanges and an antiviral agent. Corticosteroids and cyclophosphamide have improved patient outcome so that the 1-year survival rate is now about 85%.

This review is based on selected articles from the 3085 articles found in the English literature identified by a Medline search of "polyarteritis." Additional relevant publications were taken from the reference lists of the retrieved articles. Because the definition of polyarteritis nodosa (PAN) has changed over the years, early studies included patients with microscopic polyangiitis (MPA) and probably other diseases as well.

PAN is a necrotizing, focal segmental vasculitis that affects medium-sized muscular arteries in many different organ systems. It spares the aorta and its major branches as well as capillaries and arterioles that lack muscular coats. Deposition of antigen-antibody complexes in the vessel walls leads to inflammation, edema, and eventually necrosis of the tunica intima and media. The transmural necrotizing inflammation is characterized by fibrinoid necrosis and infiltration predominantly by polymorphonuclear leukocytes (Figure 1). This process weakens the arterial wall, resulting in stenosis, thrombosis, aneurysmal dilatation, and rupture. The organs supplied by

these vessels may have impaired perfusion, resulting in ulcerations, infarcts, or ischemic atrophy.

The American College of Rheumatology criteria for the classification of PAN are not very helpful for the clinician because they do not take into account the fact that for the diagnosis to be made clinically, evidence of vascular involvement must be shown by either biopsy or angiography. For classification purposes, a patient with vasculitis shall be said to have PAN if at least 3 of the following 10 criteria established in 1990 for the classification of PAN¹ are present: (1) weight loss greater than 4 kg or more, (2) livedo reticularis, (3) testicular pain or tenderness, (4) myalgias or weakness, (5) mononeuropathy or polyneuropathy, (6) diastolic blood pressure greater than 90 mm Hg, (7) increased blood urea nitrogen or serum creatinine levels, (8) presence of hepatitis B reactants in serum, (9) arteriographic abnormality, and (10) biopsy of small- or medium-sized artery revealing granulocyte or mixed leukocyte infiltrate in an arterial wall. The presence of 3 or more criteria yields a sensitivity of 82.2% and a specificity of 86.6%.

The variable clinical presentation and the rarity of the disease often results in a delayed diagnosis. The onset of PAN usually is gradual, lasting weeks to months. Initial symptoms often are nonspecific. Constitutional symptoms, such as malaise, weight loss, and fever, are common. Myopathy and myalgias occur, particularly of the calf muscles, along with arthritis or arthralgia of the large joints. Renal involvement occurs in 6% to 66% of patients as a result of ischemia from stenosis of renal arteries, sparing the glomeruli.²⁻⁴ Orchitis frequently is found. The clinical presentation of testicular PAN may include pain, swelling, or local mass, thus leading to a preoperative diagnosis of acute orchitis, torsion, or tumor. Peripheral neuropathy is a manifestation in 38% to 72% of patients, with mononeuritis multiplex involving the longest nerves first. Mononeuritis multiplex is one of the most specific clues that a patient has vasculitis. Involvement of the central nervous system presents with a wide range of symptoms such as psychiatric disturbances, convulsions, or meningitis.³⁻⁷ Skin lesions, in 11% to 58% of patients, include livedo reticularis, splinter hemorrhages, and palpable purpura.^{4,7} Ocular disease presents as neuroreti-

Abbreviations used in this paper: GI, gastrointestinal; HBV, hepatitis B virus; MC, mixed cryoglobulinemic vasculitis; MPA, microscopic polyangiitis; PAN, polyarteritis nodosa.

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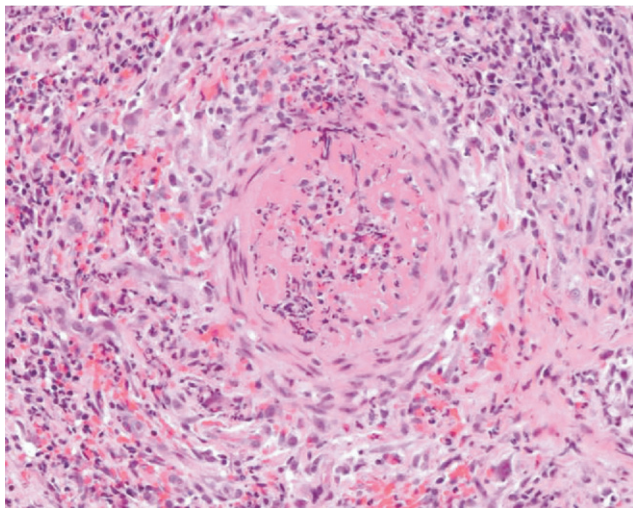


Figure 1. PAN, acute lesion. Acute inflammation of the arterial wall with extension of the inflammatory infiltrate into the surrounding soft tissue. Segmental fibrinoid necrosis of lumen and wall.

nitis or paralysis of extraocular muscles. Involvement of coronary arteries results in myocardial infarction and sudden death.

The mean age for PAN ranges from 42 to 54 years old.^{2,5} The annual incidence of PAN ranges from 2.4 to 77 per 1,000,000 in England and the hepatitis B virus (HBV) hyperendemic Alaskan Eskimo populations, respectively.^{8,9} Its overall prevalence is 2 times higher in those with European ancestry than in non-Europeans.¹⁰

Differential Diagnosis of Polyarteritis Nodosa

The differential diagnosis includes MPA and mixed cryoglobulinemic vasculitis (MC). MPA, in contrast to PAN, is more common, involves small vessels, and is associated with alveolar hemorrhage and rapidly progressive necrotizing glomerulonephritis. MPA is more likely than PAN to be antineutrophil cytoplasmic antibody positive and have systemic symptoms.¹¹ Overlap forms occur with involvement of medium-sized vessels in MPA and small-sized vessels in PAN. Another closely related condition, MC, shares certain clinical manifestations with PAN, such as peripheral neuropathy, arthralgia, myalgias, and purpuric skin lesions. PAN is characterized by severe acute polyvisceral failure, often life-threatening. This contrasts with MC, which manifests as subacute skin and neurologic symptoms. PAN generally has less severe liver disease than MC as well as the presence of microaneurysms. Necrotizing glomerulonephritis is associated with MC but usually not with PAN.

Secondary Causes of Polyarteritis Nodosa

Infections

In the past, the frequency of HBV in PAN was more than 30%.¹² However, it has declined with the commencement of immunization programs and the mandatory testing of blood transfusions so that the frequency is now about 7%.¹³ Most cases now are related to intravenous drug use and sexual transmission.¹⁴ Conversely, less than 1% of patients with HBV de-

velop PAN. HBV PAN is characterized by hepatitis B (HB) antigens and high HBV replication with circulating immune complexes containing hepatitis B surface (HBs) antigen and anti-HBs, supporting the concept that lesions could result from the deposition of viral Ag/Ab complexes.^{12,15}

HBV PAN is an early postinfectious disease with HBV infection occurring within 12 months preceding PAN.¹⁴ Hepatitis is silent in most cases,¹⁶ with a mild transaminase level increase in 50% of patients.¹⁷ HBV PAN has a higher incidence of gastrointestinal (GI) involvement than PAN without HBV.¹⁸ Lethal GI complications, such as bleeding and perforation, cause the survival rate at 1 year to be poorer in PAN related to HBV than in PAN without HBV.¹⁹ Furthermore, there is more malignant hypertension, renal infarction, and orchiepididymitis in PAN related to HBV than in the remainder of PAN patients.¹⁶ Relapses are rarer in HBV-related PAN than in non-HBV disease.²⁰

Rarely, PAN is associated with parvovirus B19²¹ or cytomegalovirus.²² PAN associated with chronic parvovirus infection may benefit from intravenous immunoglobulin therapy.

Other Secondary Causes of Polyarteritis Nodosa

PAN is found in 1% of patients with familial Mediterranean fever; these patients have PAN at a young age with a good prognosis.^{23,24}

PAN-like vasculitides may be associated with bone marrow-related tumors, particularly leukemia. Rarely, it is associated with solid tumors such as bronchogenic carcinoma and adenocarcinoma of the stomach and colon.²⁵⁻²⁷ Colonic adenocarcinoma was found with localized necrotizing vasculitis, suggesting that local factors may be pathogenic. A temporal relationship between the two has been shown with spontaneous resolution of vasculitis after tumor removal.

There are case reports showing the association of a PAN-like vasculitis with Dieulafoy's ulcer,²⁸ ulcerative colitis,²⁹ α 1-antitrypsin deficiency,³⁰ *Yersinia* enterocolitis,³¹ and amebic colitis.³² It can cause a colitis resembling Crohn's disease, with the distinction made on pathology.³³

Clinical Picture of Gastrointestinal Involvement

GI involvement occurs in 14% to 65% of patients with PAN and is a major cause of morbidity and mortality.^{7,12,34-37} Most patients have systemic symptoms, such as hypertension, myalgias, and cutaneous disease. If localized to the GI tract, the small bowel or gallbladder most commonly are affected.³⁸ Abdominal complaints develop over weeks or months, with pain being the most common symptom.³⁴ It is worse after meals if it is caused by mesenteric arteritis and resulting ischemia. The pain is characteristically intermittent with maintenance of appetite during pain-free intervals. There may be nausea, vomiting, melena, hematochezia, diarrhea,³⁹ or constipation. Ischemic colitis presents with abdominal pain and diarrhea, sometimes bloody, often requiring surgery.⁴⁰ If ischemia is limited to the mucosa or submucosa, ulceration and bleeding may occur. When transmural ischemia develops, there is necrosis of the bowel wall,⁴¹ perforation,⁴² and infarction, associated with a poor prognosis.⁴³ Perforations may occur with colonoscopy³⁴ so care should be taken with minimal insufflation and with termination of the procedure once ischemic areas are identified.



Figure 2. Hepatic arteriogram of a 56-year-old woman with PAN shows multiple saccular and fusiform aneurysms of medium and small hepatic arteries. Additional findings are smooth tapering of vessels, dilatations, and occlusions of intrahepatic branches.

The most common causes of an acute abdomen in PAN are bowel infarction, perforation,⁴⁴ cholecystitis, and gallbladder infarctions.³⁴ Patients should be referred to a surgeon for persistent tenderness, especially with rebound or guarding, and/or with a high lactate level. Early treatment of perforations is essential to reduce the significant mortality that is associated with an acute abdomen in this disease. This mortality rate, higher than that of other PAN patients, has been improving over the years.^{34,45} This improvement probably is owing to earlier diagnosis, aggressive immunosuppressive treatment, and better perioperative management than available in the past. Healing after an intestinal resection may be delayed owing to ischemia in the tissues.

Multiple hemorrhagic refractory gastric, duodenal, and jejunal ulcers have been described.^{46,47} Although not as common as small-bowel disease, colonic involvement may include ulcerations⁴⁸ with penetration or perforation⁴⁹⁻⁵¹ or ischemic pseudomembranous colitis.⁵² The transverse colon rarely is involved.²⁸ Systemic vasculitis involving the appendix most often is caused by PAN.⁵³

Liver involvement occurs in 16% to 56% of patients.^{36,54,55} Clinical manifestations related to liver disease, however, are quite rare. Necrotizing vasculitis may be found in the liver biopsy specimen,^{56,57} whereas hepatic arteriograms may show caliber changes with corkscrew vessels and distal microaneurysms (Figure 2).⁵⁸ If involving the portal vein and hepatic arteries, the vasculitis can lead to atrophy of a liver lobe,⁵⁹ liver infarction,⁶⁰ acute liver failure,⁶¹ or nodular regenerative hyperplasia.⁶² Rarely, aneurysmal rupture occurs in the liver, resulting in hemobilia⁶³ or subcapsular or intrahepatic hemorrhage, particularly of the right hepatic lobe.⁶⁴⁻⁶⁶ Ascites has been described in case reports, perhaps owing to serositis rather than to liver disease.^{58,67}

Vasculitis of small- and medium-sized arteries supplying the small bile ducts leads to intrahepatic sclerosing cholangitis characterized by a fibrous collar around the ducts, periductal inflammation, and ductal proliferation.⁶² Acalculous gangre-

nous cholecystitis may develop owing to arteritis involving the wall of the gallbladder.⁶⁸ Unusual complications are biliary strictures⁶⁹ and intracholecystic hemorrhage, presumably from rupture of an aneurysm of the cystic arteries into the gallbladder lumen.⁷⁰

Pancreatic involvement occurs in 35% to 37% of autopsy cases,⁷¹⁻⁷⁸ with acute pancreatitis, pancreatic infarcts, pseudocysts, pancreatic masses, or the abrupt onset of pancreatic insufficiency.⁷⁵ Vascular changes in the pancreas may resemble those seen in classic PAN, with medium-sized arteries compromised by fibrinoid necrosis and inflammation. Hepatitis B surface antigen and HBV DNA have been found in the cytoplasm of acinar cells, together with the picture of necrotizing pancreatitis.⁷⁸ Involvement can even be localized to the pancreas without evident systemic disease.

Diagnosis of Polyarteritis Nodosa

Arteriography is a primary modality used to diagnose PAN, being positive in more than 60% of patients (Figures 2 and 3).^{34,37} Saccular aneurysms form in the weakened portion of the vessel wall. Vascular lesions tend to occur at branching points⁷⁹⁻⁸¹; they are focal and segmental in different stages of development.⁷⁹ In the chronic stage, fibroblast proliferation results in wall thickening, producing stenosis or occlusion.⁸¹ Renal and hepatic arteries are involved most commonly. Aneurysms have been described in the mesenteric vasculature,⁸² typically the superior mesenteric artery.³⁴ Aneurysms, up to 1 cm in diameter, tend to be multiple and intraparenchymal.⁸⁰ They rarely affect single vessels.⁸³ These aneurysms can rupture,⁸⁴ especially in the presence of hypertension. Rupture, although infrequent, occurs mainly in renal or mesenteric vessels and can lead to intraluminal, retroperitoneal, or, less commonly, intraperitoneal hemorrhage.⁸⁵ Bleeding may be controlled by radiologic embolization.⁸⁶

Microaneurysms in PAN are not pathognomonic because they have been reported in other diseases such as systemic lupus erythematosus⁸⁷ and Wegener's granulomatosis.⁸⁸ Nor does a normal abdominal angiogram exclude vascular involvement by PAN because it may just be present histologically. Aneurysms may disappear with healing or thrombosis or appear in a new location with continued arteritis. Therefore, the angiographic



Figure 3. Abdominal aortogram of a 52-year-old man with PAN shows multiple aneurysms of the intrarenal arterial branches ranging in size from 2 to 5 mm.

findings need to be interpreted in conjunction with clinical and histologic examinations. It is not possible to predict on clinical grounds what the angiographic appearance will be,³⁷ although clinical recovery tends to parallel angiographic normalization.¹⁴

Computed tomography scan shows bowel wall thickening with the target sign. The small intestine is the most commonly affected part of the GI tract, followed by the mesentery and colon.⁸⁰ Three-dimensional computed tomography angiography has the sensitivity to detect aneurysms in medium-sized arteries with a diameter as small as 3 mm^{57,81,89} and has the benefit of being noninvasive. Doppler ultrasound also can show aneurysms.⁹⁰ The role of angiographic imaging in detecting microaneurysms remains to be shown.

Tissue biopsy may confirm the diagnosis although involvement is segmental. Common biopsy sites include the sural nerve, muscle, and skin lesions if present. Although deep intestinal biopsies are optimal to make the diagnosis, they pose a danger in a condition predisposed to infarction and perforation. Classic PAN involves medium-sized vessels with inflammation consisting of monocytes, lymphocytes, and polymorphonuclear neutrophils with a necrotizing angitis. The elastic lamina is destroyed and the media undergoes fibrinoid necrosis.

Treatment

Corticosteroids along with a potent immunosuppressive agent, particularly cyclophosphamide, are the mainstay of treatment for hepatitis B- and C-negative PAN. Cyclophosphamide, added particularly in the presence of severe GI involvement, reduces the incidence of relapse but does not change the 10-year survival rate.^{45,91} Its side effects, such as hemorrhagic cystitis, bladder fibrosis, and bone marrow suppression, limit its use. Plasma exchanges can be prescribed for severe life-threatening classic PAN as a combined rescue therapy although trials have not proven its benefits when being prescribed systematically for all patients with PAN.^{92,93}

The protocol for HBV PAN by a French group starts with corticosteroids, which are given for only 2 weeks to contain the inflammatory process that can rapidly lead to organ damage.^{94,95} Long-term use stimulates viral reproduction and chronic liver disease, reducing survival.¹⁷ Instead, rapid discontinuation of steroids triggers a rebound of immunologic clearance of HBV-infected hepatocytes and favors seroconversion from hepatitis B e antigen to anti-HBe antibody.¹⁶ Plasma exchanges can be started initially to remove the immune complexes, which are the major determinants of vessel inflammation,⁹² although their role has yet to be established in controlled studies. They are continued until seroconversion of hepatitis B e antigen to anti-HBe antibody or until 2 to 3 months of sustained clinical recovery. An antiviral agent, such as interferon- α is added to facilitate immune-complex clearance by diminishing the viral load.¹⁴ The addition of lamivudine resulted in 66% seroconversion of hepatitis B e antigen to anti-HBe antibody,⁹⁵ the same rate that was obtained with interferon,⁹⁵⁻⁹⁸ with fewer side effects and oral rather than subcutaneous administration. Because lamivudine is only used for 6 months, the appearance of mutants, which occurs with prolonged therapies, is not of major concern. Hepatitis B surface antigen becomes undetectable in 33% to 50% of patients.^{95,99} The combination of interferon and lamivudine may be useful in certain cases.^{100,101} There are no reports involving adefovir or entecavir.

Prognosis

If left untreated, patients with PAN have a dismal prognosis.⁷ Corticosteroids and cyclophosphamide have decreased mortality dramatically.^{2,6,7,12} The 1-year survival rate is 85%, which is significantly greater than the 70% survival rate in patients with HBV-PAN.¹⁹ Prognostic factors are proteinuria, renal insufficiency, cardiomyopathy, severe GI manifestations, and central nervous system involvement.⁵¹ A poor outcome was associated with bleeding, perforation, infarction, and/or pancreatitis, but not with abdominal pain or cholecystitis. Multivariate analysis showed that proteinuria and GI tract involvement were the major factors of poor prognosis. Patients die from bowel infarction, peritonitis, or serious GI bleeding.^{2,12,18} In contrast, another analysis indicated that renal and cardiac disease, not GI involvement, were the major predictors of poor prognosis.³⁶

Conclusions

PAN is a systemic necrotizing vasculitis with protean manifestations in the GI tract. Although rare, it is important to diagnose because the prognosis is dismal without proper treatment.

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