POLYARTERITIS NODOSA

BOTTOM LINE

Polyarteritis nodosa (PAN) is a rare necrotizing vasculitis affecting medium-sized muscular arteries and occasionally small muscular arteries most commonly supplying kidneys, skin, joints, muscles, nerves, and GI tract; lungs are usually spared. PAN variants include single-organ disease—cutaneous PAN. PAN is not associated with antibody positivity. Treatment of mild disease includes steroids often combined with Azathioprine, methotrexate, or mycophelolate mofetil. Severe disease causing significant organ dysfunction is treated with cyclophosphamide. Patients with mild PAN associated with Hepatitis B/C infection may be treated with antivirals initially, with steroids and plasma exchange reserved for severe cases.

EPIDEMIOLOGY

- True idiopathic systemic PAN is rare; diseases previously called PAN have more recently been identified and classified as other forms of vasculitis (ex: ANCA-associated vasculitis, DADA2, vasculitis associated with drug exposure or infection)

- Prevalence and Incidence in European countries
  - Prevalence: ~30/1,000,000
  - Incidence ~0-9/1,000,000 annually

Sex	• Slight male predominance 1.5:1.0
Age	• Peak age 40-60 years-old; young patients presenting with PAN-like features and stroke should be screened for adenosine deaminase 2 deficiency (ADA2)
Hepatitis B	• Hepatitis B association: historically as high as 10-30%, depending on series. • Association with PAN is declining alongside declining Hepatitis B prevalence, now associated in <5% of PAN

CLINICAL MANIFESTATIONS

CLINICAL VARIANTS

- "Classic" PAN: idiopathic systemic generalized medium/small vessel necrotizing arteritis affecting multiple organs
- HBV-associated PAN: medium-vessel necrotizing systemic arteritis associated with hepatitis B infection
- Cutaneous PAN: skin-limited medium vessel vasculitis, typically presenting in lower limbs

SYSTEMIC FEATURES

Systemic 93%	Fatigue, weight loss, fever
Neuro 75%	Mononeuritis multiplex (70%), polyneuropathy (75%), CNS (5%)
MSK ~50%	Arthralgias 49%, myalgias 58%
Skin 50%	Livedo reticularis, purpura, cutaneous nodules, ulcers mainly in lower extremities
Renal 50%	Renovascular hypertension (35%, severe 7%), infarct, AKI, minimal proteinuria and hematuria,
GI 38%	Abdominal pain (35%), bleeding and perforation (3%), cholecystitis, appendicitis, pancreatitis, splenic infarct
GU 17%	Orchitis: testicular pain, swelling, infarction; more common with hepatitis B
Cardiovasc. 22%	Cardiomyopathy (7.5%), coronary arteritis/MI, pericarditis, limb claudication, digital ischemia ±necrosis, VTE/DVT
Ocular 10%	Retinal vasculitis (4.3%), optic ischemia, conjunctivitis, episcleritis, keratitis, uveitis
ENT	Hearing loss, temporal arteritis
Resp	PAN does not typically affect the lungs; lung involvement may suggest an alternate diagnosis
Other history	Drug history (?drug induced), exposure history (?hepatitis B, bacterial endocarditis), family history early strokes (?DADA2). Screen for other vasculitis (especially ANCA-associated), other rheumatic diseases (ex: RA, SLE, ANCA).

INVESTIGATIONS

No diagnostic bloodwork, but needed to screen the extent of systemic involvement and evaluate alternate diagnoses	
CBC	May show anemia of chronic inflammation or iron deficiency if GI bleeding/ischemia
ALT	Usually normal
Cr, U/A	↑Cr if renal artery involved. U/A may show mild proteinuria/hematuria, no casts (i.e.: no glomerulonephritis)

INVESTIGATIONS, continued		
ESR, CRP	Usually elevated	
C3, C4	Should be normal	
Antibodies	No antibody association; negative ANA, RF, ANCA (unless positive by chance)	
Infectious	Hepatitis B and C serology. Blood cultures (?septic emboli differential) HIV: If mononeuritis multiplex and co-infected Hep B/C Lyme serology: if mononeuritis multiplex and Lyme exposure on history	
Other rheum in indicated	• Cryoglobulins, phospholipid antibodies • Plasma ADA2 activity assay and genetic testing for CECR1 mutation on chromosome 22q11.1 • Test if pediatric PAN, family history of early-onset strokes, atypical immunodeficiency with autoimmunity and/or lymphoproliferation	
Imaging	X-ray	• Screening X-ray chest: parenchymal lung involvement may suggest alternate diagnosis
	Conventional arteriography	• Medium vessel saccular/fusiform microaneurysms (15mm in diameter) with co-existent stenoses. • Predominantly mesenteric, renal and hepatic arteries • Sensitivity and Specificity 90% invasive with risk of bleeding, embolization, and pseudoaneurysm
	CT or MR Angiography	• Similar findings to Conventional Arteriography, though may not detect smaller microaneurysms • Benefit of imaging for ischemic parenchymal changes (ex: bowel, renal infarcts)
Histology	Common Targets	• Skin (including subcutaneous fat with medium-sized arteries), nerve (sural, superficial peroneal, superficial radial) and muscle (muscle less sensitive).
	Findings	• Focal, segmental, panmural necrotizing inflammation of medium muscular arteries (small vessels may be involved *in addition*) • Infiltrate of lymphocytes, macrophages, variable number of neutrophils and eosinophils • Predilection for bifurcations and branch points. Granuloma and giant cells should be absent.

DIAGNOSIS

PAN is rare but should be suspected in a patient, more often middle-aged, presenting with marked systemic symptoms and organ dysfunction reasonably explained by medium-sized vascular lesions (ex: livedo, necrotic skin ulcers, peripheral neuropathy, ischemic colitis, hypertension with hematuria/proteinuria without casts). PAN involving a single organ, such as cutaneous PAN, may also occur. Demonstration of micro-aneurysms on vascular imaging is the hallmark of PAN; consider abdominal vascular imaging in patients with suspected PAN. Diagnosis is ideally confirmed with biopsy revealing focal and segmental transmural necrotizing vasculitis of medium-sized muscular arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules. Common biopsy targets of a symptomatic organ are deep skin, nerve, or combined nerve/muscle biopsy.

DIFFERENTIAL DIAGNOSIS: any disease that can cause aneurysms and embolism/thrombosis/vasospasm	
Infectious	• Viral: HBV, CMV, HTLV1, HIV, EBV, HCV • Bacterial: endocarditis with distal emboli • Fungal: mycotic aneurysm with distal emboli
Cardiovasc.	• Atherosclerosis • Embolic diseases: atrial myxoma, cholesterol crystals
Rheum	• Vasculitis: ANCA-associated, IgA vasculitis, cryoglobulinemic vasculitis, Cogan's, FMF-associated, DAD2, SAVI • Systemic rheumatic disease: SLE, RA, idiopathic inflammatory myopathy,
Drug-related	• Including allopurinol, minocycline, propylthiouracil, amphetamines, ergotism
Heme	• Anti-phospholipid antibody syndrome • Malignancy hair cell leukemia
Other	• Segmental arterial mediolysis (SAM): noninflammatory arterial disease looks like PAN on angiogram. Patients present with life-threatening hemorrhages for aneurysmal rupture. • Ehlors-Danlos, fibromuscular dysplasia (cause of aneurysms) • Immunodeficiency: Including deficiency in RAG1, RAG2, or TAP

CLASSIFICATION CRITERIA

PAN is a ***clinical diagnosis***. Classification criteria are not meant as diagnostic criteria to diagnose disease in a single specific patient. Classification criteria are a standardized way of recruiting a well-defined homogenous population of patients in research studies in order to ensure comparability across studies of a heterogenous disease.

ACR CLASSIFICATION CRITERIA 1990

- Unexplained weight loss ≥4 kg
- Livedo reticularis
- Testicular pain/tenderness
- Myalgias (excluding shoulder and hip girdle), or weakness of muscles, or tenderness of leg muscles
- Mononeuropathy or multiple mononeuropathy or polyneuropathy
- New diastolic blood pressure >90 mmHg
- Elevated BUN (>14.3 mmol/L) or creatinine (>132 umol/L)
- Hepatitis B virus infection
- Angiographic evidence of aneurysms/occlusions of visceral arteries not due to atherosclerosis, fibromuscular dysplasia, or other noninflammatory cause
- A biopsy of small- or medium-sized artery containing polymorphonuclear cells

Patient is classified as PAN if ≥3 of 10 criteria present. Sensitivity 82%, Specificity 86%

TREATMENT

Severe PAN: Vasculitis with life- or organ-threatening manifestations (e.g., renal disease, mononeuritis multiplex, muscle disease, mesenteric ischemia, coronary involvement, limb/digit ischemia, five-factor score ≥1)

Induction	• Methylprednisolone 0.5-1.0g IV daily x 3 (if organ/life-threatening disease), *or/then*
	• Prednisone 1mg/kg/day (max 60-80mg/d) for 4 weeks with taper over 6-8 months, *and*
	• Cyclophosphamide (CYC), various options for induction:
	  • CYC 15mg/kg IV week 0, 2, 4 then every 3 weeks for 3-6 months (until 3 months post-remission, max 1.2g)
	  • CYC 1.5-2mg/kg/day PO for 3 months (until remission), then 1.5mg/kg/day x 3 months (max 200mg)
	  • Remember to dose-reduce CYC for renal function and age
	• If unable to tolerate Cyclophosphamide
	  • Methotrexate 20-25mg/week, *or*
	  • Azathioprine 2mg/kg/d, *or*
	  • Mycophenolate mofetil 1.0-1.5g BID (MMF is less well studied in PAN)

Maintenance	• Azathioprine 2mg/kg/d, *or* • Methotrexate 20-25mg/week, *or* • Mycophenolate mofetil 1000-1500mg BID • Duration: at least 18 months

Non-severe PAN: Vasculitis without life- or organ-threatening manifestations (e.g., mild systemic symptoms, uncomplicated cutaneous disease, mild inflammatory arthritis)

Induction and maintenance	• Prednisone 0.5-1.0mg/kg/day for 2-4 weeks with taper over 6 months, *and* • Methotrexate 20-25mg/week, *or* • Azathioprine 2mg/kg/d, *or* • Duration: at least 18 months

Specific cases

Cutaneous PAN	Mild	• Nodules, livedo: NSAIDs, colchicine
	Moderate	• Pain, ulceration, necrosis: Prednisone ≤30mg/day with taper plus NSAIDs, colchicine, hydroxychloroquine dapsone, methotrexate, or azathioprine
DADA2	• Prednisone 1mg/kg/day (max 60-80mg/d) with taper over 6-8 months, *and* • TNF inhibition (ex: infliximab, adalimumab)	

Hepatitis B/C related	• Targeted anti-viral therapy
	• If necessary for severe disease:
	  • Prednisone 1mg/kg/day x 2 weeks only (can worsen viral infection)
	  • Plasma exchange	

TREATMENT (continued)	
Adjunctive	• Physiotherapy: if nerve, muscle involvement • PCP prophylaxis: Sulfamethoxazole/trimethoprim if on cyclophosphamide and steroids • Gastric ulcer prophylaxis: PPI if on steroids • Osteoporosis prophylaxis: bisphosphonate if indicated
PROGNOSIS	
Five-year relapse-free survival	• 59% for non-HBV-related PAN • 67.0% for HBV-related PAN • Higher relapses seen in non-HBV related PAN and cutaneous PAN
Risk factors for morality	• Age >65 years, • Hypertension • Gastrointestinal manifestations requiring surgery or at least consultation
Five-year mortality	• 12% for patients with FFS = 0 • 26% for patients with FFS = 1 • 46% for patients with FFS ≥ 2

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