IMMUNE COMPLEX MEDIATED VASCULITIS

BOTTOM LINE

Immune complex mediated vasculitis is a group of small vessel vasculitis caused by deposition of immunoglobulin and/or complement on vessel walls. Common features include purpuric skin rash, neuropathy, and renal impairment. Pathology commonly reveals leukocytoclasic vasculitis (LCV) and fibrinoid necrosis with immune complex deposition on immunofluorescence. Specific vasculitis included under immune-complex mediated vasculitis include: anti-glomerular basement membrane disease, IgA vasculitis (Henoch-Schonlein purpura), hypo-complementemic urticarial vasculitis, and Cryoglobulinemic vasculitis (aka: mixed cryoglobulinemia).

ANTI-GLOMERULAR BASEMENT MEMBRANE DISEASE (aka Goodpasture disease)

Epidemiology	Population	• Rare, Incidence: <2/1,000,000 annually (European populations) • Prevalence: 10/1,000,000 hospitalized patients; 10-15% of crescentic GN in large biopsy series • Ethnicity: more commonly reported in Caucasian and Asian populations; rarer in African populations
	Age, sex	• Bimodal age: 30's and 60-70's • Male predominance in younger patients, more pulmonary-renal syndrome • Female predominance in older patients, more renal-only involvement
	Risk factors	• Genetic: HLA-DRB1*1501, -DRB1*0401, -DRB1*01 • Environmental: smoking, possibly prodromal infection, alemtuzumab (used for multiple sclerosis)
Clinical	Systemic	• Weeks of malaise, weight loss, fever
	Renal	• Acute glomerulonephritis 90%, ~ 50% require renal replacement therapy at diagnosis
	Resp	• Diffuse alveolar hemorrhage, DAH (40-60%): dyspnea, cough/hemoptysis, or overt respiratory failure • Small minority may present with DAH without glomerulonephritis.
	Variants	• Overlap Anti-GBM and ANCA-associated vasculitis • Anti-GBM with membranous nephropathy • Anti-GBM without circulating anti-GBM antibodies (but seen on biopsy) • Post-transplant anti-GBM
Investigations	Cr, U/A	• Acute renal failure with red cell casts
	Serology	• Anti-GBM antibody; all should be screened for ANCA as well • Also ANA, rheumatoid factor/cryoglobulins, blood cultures etc. as indicated for differential diagnosis
	Imaging	• X-ray chest, if symptomatic or abnormal X-ray, CT chest • Consider bronchoscopy with serial lavage to diagnose pulmonary hemorrhage and for cultures
	Biopsy	• Light microscopy: crescentic GN • Immunofluorescence: linear deposition IgG along glomerular capillaries
Diagnosis	Suspect anti-GBM in patient presenting with acute GN (AKI, hematuria/proteinuria, casts), particularly if concomitant pulmonary hemorrhage. Confirm with anti-GBM serology and renal biopsy. Screen for infection, other vasculitis.	
Differential	• ANCA-associated vasculitis, IgA-vasculitis, Mixed Cryoglobulinemia, lupus nephritis, phospholipid antibody syndrome (as a mimic, does not cause GN), pulmonary infection with associated AKI	
Treatment	Treat urgently with plasma exchange (PLEX) combined with prednisone and cyclophosphamide • PLEX: daily 4 L exchange for 5% albumin solution until antibodies negative or for 14 days • Methylprednisolone 1g IV x 3 days then prednisone 1mg/kg/d (max 60 mg), taper to 20mg by 6 weeks, taper to discontinuation by month 6-9 • Cyclophosphamide IV or PO (dosing similar to ANCA vasculitis; remember to adjust dose for renal function) • Alternative: Rituximab, mycophenolate mofetil (less evidence than cyclophosphamide) • Transplant: some may be candidates if progress to end stage renal disease	
	Overlap Anti-GBM/ANCA vasculitis: require longer maintenance after PLEX and cyclophosphamide; maintenance is similar to ANCA vasculitis (see ANCA vasculitis chapter)	

IgA VASCULITIS (HENOCH SCHONLEIN PURPURA, IgAV)			
Epidemiology	Population	• Incidence: 3-26/100,000 children, 0.1-1.6/100.000 adults. • All ethnic groups described; lower incidence in African versus Caucasian or Asian children	
	Age, Sex	• Adults: age onset 50 years; Children: age onset 4-7 years; • M>F, 1.5-5.0 : 1.0	
	Risk factor	• Environmental: children typically present fall/winter; adults presentation is less seasonal though may be more common summer and winter	
Clinical	Classic tetrad of pupura, arthritis, abdominal pain, renal disease		
	Skin	• Purpura (lower limb > upper limb > abdomen) 100%. • Skin necrosis (25%), hemorrhagic blisters (8%)	
	MSK	• Arthralgias 100%, arthritis; 15%. Lower > upper extremity migratory oligoarticular	
	GI	• GI symptoms often onset ~7 days after rash. • Pain 100%; bleed 31%, diarrhea 25%, Nausea 20%, perforation. Intussusception rare in adults.	
	Renal	• Prevalence 45-85% of IgAV • Renal failure present in 30% of adult IgAV, onset within 4 months of presentation • Clinically ranges from asymptomatic hematuria/proteinuria ±casts to progressive crescentic glomerulonephritis or nephrotic syndrome • Chronic renal failure in 80% and end stage renal disease in 10-30% of adult patients over follow-up	
	Other	• GU: testicular pain (orchitis) • Neuro: headache, seizures, encephalopathy, deficits, ataxia, peripheral neuropathy (rare) • Resp: Alveolar hemorrhage rare but reported • Ocular: rare uveitis, keratitis, scleritis • Cardiac: rare myocarditis, dysrhythmias	
Investigations	CBC	• Anemia, micro/normocytic, if bleeding. Leukocytosis, thrombocytosis (nonspecific)	
	ESR, CRP	• Elevated (non-specific)	
	Cr, U/A	• Creatinine may be elevated; urinalysis may show varying degrees of hematuria or proteinuria	
	C3, C4	• May be low, particularly if post-infectious (ex: post-streptococcal infection) IgA vasculitis	
	Serum IgA	• Elevated serum IgA 50%, not specific for IgAV	
	Biopsy	• Not always necessary; adults may need biopsy due to lower incidence IgAV and more atypical rash	
		Skin	• Leukocytoclasic vasculitis. IgA and C3 deposition on immunofluorescence. • IgA deposition on skin biopsy: Sensitivity 81%, Specificity 83% PPV 84%, NPV 81% for IgAV
		Renal	• Consider if nephrotic or nephritic syndrome, persistent proteinuria >1g/d at 6 months despite RAAS blockade, or diagnostic uncertainty. • Biopsy findings range from mild mesangial hypercellularity to proliferative glomerulonephritis.
	Imaging	• CT abdomen if abdominal pain to consider alternate diagnoses, may show lymphadenopathy	
	Screen	• Including: ANCA, ANA, RF, serologies (Hep B, C, HIV), cryoglobulins, blood cultures	
Diagnosis	Suspect IgA vasculitis in adult patient (more often pediatric) presenting with compatible purpuric skin rash with joint pain, abdominal pain, and new renal disease with active urine sediment. Consider biopsy of rash; some may require renal biopsy if nephrotic/nephritic syndrome, persistent proteinuria, or diagnostic uncertainty. Differential includes other small-vessel vasculitis, infection and acute renal injury, other systemic rheumatic disease.		
Treatment	• Most cases resolve and only need supportive care or short course of steroids. • Prednisone 0.5-1.0 mg/kg/d (max 40-60mg/d) if severe GI or renal manifestations tapered over 6 months • Refractory: rare, reports of colchicine, dapsone, rituximab, MMF, azathioprine, calcineurin inhibitors, IVIG, cyclo. • Limited data guide treatment discussed below		
	MSK	• Analgesia, avoid NSAID is renal or GI involvement; colchicine 1.2 mg/d if needed	

Treatment (continued)	GI	Benign	• Mild abdominal pain • Symptomatic treatment, or dapsone, colchicine, low-dose prednisone
		Severe	• Ex: massive bleeding, perforation • Surgical evaluation ± surgery, Prednisone 1mg/kg/d ± pulse IV steroids ± cyclophosphamide
	Renal	Mild	• Hematuria, proteinuria <0.5 g/d, normal GFR: observe for 3-6 months. If persistent, add ACEi
		Moderate	• Hematuria, proteinuria >0.5g/d, normal GFR: ACEi .

		Moderate-severe	• Proteinuria >1g/d at 3-6month, acute/rapidly progressive renal failure, crescents on biopsy:
			  • Prednisone 1mg/kg/d ± pulse IV steroids ± Cyclophosphamide similar to AAV
			  • If failure of cyclophosphamide, may consider cyclosporine or rituximab

Prognosis	• Relapses in 20% of adult cases
	• 10-30% develop end-stage renal disease (ESRD), usually within 3 years of disease onset
	• Factors associated with relapse
	  • Disease onset at age > 30, persistent rash, abdominal pain, and hematuria
	• Factors associated with ESRD
	  • Baseline renal function impairment or proteinuria >1 or 1.5 g/day
	  • Macroscopic hematuria
	  • Hypertension
	  • Proteinuria ≥1 g/day during follow-up
	  • On renal biopsy: degree of interstitial fibrosis, sclerotic glomeruli and fibrinoid necrosis		

URTICARIAL VASCULITIS			
Terminology	Urticarial Vasculitis (UV) • Continuum of disease from urticaria with minimal skin vasculitis to life/organ threatening systemic vasculitis (hypocomplementemia associated with worse disease severity)		
	Hypocomplementemic Urticarial Vasculitis (HUV) • UV with hypocomplementemia, but only few or no systemic manifestations		
	Hypocomplementemic Urticarial Vasculitis Syndrome (HUVS) • 6 months urticaria with systemic symptoms, typically: arthritis, mild GN, uveitis/episcleritis, and recurrent abdominal pain. Complement and Cq1 often low and biopsy shows small vessel vasculitis with deposits of immunoglobulins, complement or fibrin		
Epidemiology of HUV	• Unclear epidemiology: changing terminology, rare disease • Age: 40-55 years. Sex: F >> M. • Incidence: 0.7/1,000,000 annually; Prevalence: 9.5/1,000,000		
Clinical	Skin	• Urticaria in UV lasts >24h, more painful/burning/pruritic, resolves leaving purpura or hyperpigmentation. • Common benign urticaria: lasts <24 hours, mostly pruritic, no residual skin changes • Other findings: angioedema (51%), purpura (35%), livedo (14%), target lesions, annular lesions, bullae	
	Systemic	• Fatigue, fever, weight loss (50%)	
	MSK 82%	• Inflammatory arthritis in 50%: migratory transient hand/elbow/feet/ankle/knees. Jaccoud's arthropathy • Inflammatory arthritis more common in HUV rather than NUV • Myositis reported, may resemble idiopathic inflammatory myopathy	
	GI 33%	• Abdominal pain, nausea, vomiting diarrhea • GI bleeding not noted as feature of UV	
	Renal 14%	• Microscopic proteinuria/hematuria • Histology varies: Proliferative necrotizing GN, membranoproliferative GN, tubulointerstitial nephritis	
	Resp	• Most common: COPD or asthma 20-50%. • Also: hemoptysis, pleuritis, pleural effusions, tracheal stenosis • Leading cause of morbidity and mortality	
	Rare	• Cardiac: pericarditis, pericardial effusion, cardiac tamponade, valvulopathy • Ophthalmologic: conjunctivitis, episcleritis, uveitis • Neuro: pseudotumor cerebri, cranial nerve palsies, axonal neuropathy, aseptic meningitis, neuropathy	

Associated conditions	SLE	• Both UV and SLE can cause inflammatory arthritis, GN, low complement, ANA+ • HUV more likely if angioedema, COPD/asthma, uveitis/episcleritis; should have no specific lupus rash • Some patients can present with overlap SLE/UV
	Sjogren	• Sjogren's more likely to be anti-Ro/SSA positive
	Infection	• Prodromal Hep B, Hep C, Lyme, infectious mononucleosis, or after vaccination
	Other	• Complement deficiency, IgM monoclonal gammopathy (Schnitzler's syndrome), IgG/A/D gammopathy • Hematologic malignancy (leukemia, lymphoma), solid malignancy (adenocarcinoma, teratoma) • Drug-induced UV: including diltiazem, fluoxetine, Etanercept, Methotrexate, Cimetidine
Investigations	CBC	• May see anemia, leukocytosis
	Cr, U/A	• Send for baseline in case of renal involvement
	ESR, CRP	• Elevated, nonspecific
	C3, C4	• If HUV, low C3, C4. Low complement is a sensitive marker for systemic disease. • Also low C1, C2 and CH50 (evidence of classical pathway activation)
	C1q	• Low C1q, positive anti-C1q antibodies (these antibodies also seen in SLE, indicate lupus-nephritis risk)
	ANA, ENA	• ANA positive in many UV; may be challenging to differentiate with SLE; but ENA usually negative in UV
	Other	• If systemic disease, for differential consider if indicated: ANCA, cryoglobulins, rheumatoid factor
	Infection	• Screen for hepatitis B or C; consider Borrelia serologies if indicated on history
	Biopsy	• Histology: Leukocytoclastic skin vasculitis (LCV) • I.F.: perivascular and/or basement membrane deposits of immunoglobulin or complement
Diagnosis	Suspect HUVS in patients with painful urticaria lasting >24h and symptoms of systemic disease like angioedema, abdominal pain, renal injury, and arthritis. Low complement suggests systemic disease. ANA is positive in many, though ENA should be negative. Seek supportive skin biopsy showing LCV and perivascular and/or basement membrane deposits of immunoglobulin and complement.	
	Differential	• Benign chronic spontaneous urticaria, bullous pemphigoid, IgA vasculitis, Auto-inflammatory disease (Muckle-Wells Schnitzler's, CAPS), allergic contact dermatitis, cutaneous mastocytosis, acquired angioedema
Treatment	No standardized treatment. Treat according to clinical assessment of disease severity, based on case reports/series	
	Mild	• Symptomatic treatment with antihistamines, NSAIDs
	Moderate	• Prednisone, dapsone, colchicine, hydroxychloroquine
	Severe systemic	• Mycophenolate mofetil, methotrexate, azathioprine, Rituximab, cyclosporine • Anakinra, Canakinumab, omalizumab
ERYTHEMA ELEVATUM DIUTINUM (EED)		
Epidemiology	• Adults 40-60 years, all ethnicities. Presents earlier in those co-infected with HIV	
Clinical	• Eruption of violaceous red-brown/yellow papules, plaques, or nodules on extensor elbows, knees, ankles, hands and fingers. Less common face, trunk, axillae, buttocks, genitalia, palms, soles • Differential diagnosis: Sweet's syndrome, pyoderma gangrenosum, granuloma annulare, Kaposi's sarcoma	
	Associations	• Infection: HIV, streptococcal, hepatitis B/C, tuberculosis • Heme: plasma cell dyscrasias, myelodysplasia, myeloproliferative/lymphoproliferative disease • Autoimmune: IBD, RA, relapsing polychondritis, SLE, GPA, dermatomyositis
Biopsy	• Leukocytoclastic vasculitis; immunofluorescence (not necessary) may show perivascular fibrin, complement, and immunoglobulins	
Treatment	• Steroids and Dapsone 50mg/d titrated usually to 100mg/d (can go up to 300mg/d); get baseline G6PD • Other: Methotrexate, hydroxychloroquine IVIG, surgical excision, treating underlying disease (ex: GPA, Cancer)	

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