***** no patient handout***

Vasculitis

Synopsis

Vasculitis is a nonspecific term that encompasses a large and heterogeneous group of disorders that are characterized by inflammation of blood vessels. No uniform classification system for vasculitis exists, although subtypes are often categorized by the size of the vessels involved, the type of circulating immune complexes, and other histopathologic and clinical features. In many cases, damage to the blood vessels results in leakage of red blood cells and the development of palpable purpura on the skin. Other common cutaneous signs of vasculitis include skin ulcerations, **Raynaud phenomenon**, and **livedo reticularis**.

It is important to distinguish a primary systemic vasculitis from one associated with medications, infection, malignancy, or a connective tissue disorder, as the best course of treatment may differ. Drug-induced vasculitis should be quickly recognized and managed by removing the causative medication. Ongoing drug-induced vasculitis can lead to glomerulonephritis, pulmonary hemorrhage, mononeuritis multiplex, and other complications of end-organ involvement.

Several types of vasculitis are more likely than others to be mistaken for **cellulitis**. Among these are **polyarteritis nodosa** and variants of **leukocytoclastic (hypersensitivity) vasculitis** such as **erythema elevatum diutinum** and **urticarial vasculitis**. **Kawasaki disease** and **Henoch-Schönlein purpura** may present with some lesions that mimic cellulitis, but these diseases occur predominantly in children. On rarer occasions, other vasculidities such as **granulomatosis with polyangiitis**, **Behçet syndrome**, **cryoglobulinemia**, and **livedoid vasculopathy** may present similarly to cellulitis. Other primary vasculitic syndromes include eosinophilic granulomatosis with polyangiitis, **microscopic polyangiitis**, **Takayasu arteritis**, and **giant cell (temporal) arteritis**. Vasculitis may occur in association with such diseases as rheumatoid arthritis, systemic lupus erythematosus, and dermatomyositis.

Polyarteritis nodosa (PAN) refers to a necrotizing vasculitis of small- and medium-sized arterioles. It is the least distinctive of the vasculidities. The exact etiology is unknown, but it likely involves immune complex deposition, autoantibodies, inflammatory mediators, and adhesion molecules. Any organ may be affected, but PAN most commonly involves the skin, peripheral nerves, kidneys, joints, and gastrointestinal (GI) tract. Symptoms may include malaise, fever (in 50% of cases), weakness, myalgias, arthralgias, abdominal pain, cutaneous ulcers, livedo reticularis, testicular pain, and weight loss. Polyarteritis nodosa has been associated with infection with hepatitis B, hepatitis C, human immunodeficiency virus (HIV), cytomegalovirus (CMV), parvovirus B19, human T-cell lymphotropic virus (HTLV), and streptococci. There appears to be an association with inflammatory bowel disease. Polyarteritis nodosa usually affects individuals in mid- to late adulthood. It is slightly more common in men, and there is no apparent racial predilection.

"Leukocytoclastic vasculitis" (LCV) is a pathologic term that refers to inflammation of small blood vessels, usually with an inflammatory infiltrate and necrosis of the vessel wall. This form

of vasculitis may be localized to the skin where it is most commonly seen as palpable purpura, or it may also involve the other organs such as the kidneys, the joints, or the GI tract. The exact pathogenesis remains elusive, but LCV appears to involve circulating immune complexes, autoantibodies, and inflammatory mediators.

Erythema elevatum diutinum refers to a rare subtype of LCV. It is associated with upper respiratory infections (especially streptococcal), HIV, hematologic disease, and rheumatologic disorders. It presents with arthralgias and erythematous to violaceous papules, plaques, and nodules with a predilection for extensor surfaces.

Urticarial vasculitis is also considered to be a variant of LCV. This presentation may be idiopathic, or it can occur in association with serum sickness, connective tissue disorders, infections, and after the administration of potassium iodide or nonsteroidal anti-inflammatory agents (NSAIDs). Urticarial vasculitis affects mainly women. The skin lesions last 3-5 days. Episodic arthralgias are a major clinical manifestation and affect the wrists, fingers, knees, ankles, and toes. General features include fever, malaise, myalgias, lymphadenopathy, and hepatosplenomegaly.

Patients with antineutrophil cytoplasmic antibody (ANCA)-positive drug-induced vasculitis commonly have antibodies to multiple granule proteins, such as myeloperoxidase (MPO), cathepsin G, lactoferrin, and human leukocyte elastase (HLE).

Drug-induced vasculitis frequently presents with skin involvement and, if progressive, can include any of the following symptoms of systemic involvement: myalgias, arthralgias, dyspnea, hoarseness, vision impairment from retinal vessel involvement, and abdominal pain. Onset of the vasculitis is variable, ranging from weeks to years after starting therapy. The following medications are among the most frequent causes of drug-induced vasculitis: anti-thyroid agents such as propylthiouracil and methimazole, minocycline, hydralazine, phenytoin, granulocyte colony-stimulating factor (G-CSF), allopurinol, D-penicillamine, cefaclor, and methotrexate.

Methyldopa can cause life-threatening cardiac complications including cardiac myocyte necrosis and cardiomyopathy. Isotretinoin has been reported to induce vasculitis, sometimes with renal involvement. Levamisole, a veterinary medication banned for human use, has been shown to cause vasculitis. Cocaine contaminated with levamisole is a near-epidemic occurrence in cocaine users, leading to **cocaine levamisole toxicity**.

Unlike cellulitis, the lesions of vasculitis are often multifocal and/or bilateral. Ulceration, palpable purpura, and livedo reticularis may be present. Be sure to ask the patient about the presence of specific symptoms such as myalgias, arthralgias, hematuria, or neuropathy.

Codes

ICD10CM:
L95.9 – Vasculitis limited to the skin, unspecified

SNOMEDCT:
31996006 – Vasculitis

Look For

Polyarteritis nodosa:
The lower extremities are typically involved with painful cutaneous and subcutaneous nodules. Lesions can ulcerate, bullae can form, and, rarely, there can be purpura or gangrene. Livedo reticularis is a common associated finding, as are nailfold infarcts.

Subcutaneous nodules are 5-10 mm in diameter, are often found in groups, and are located along the blood vessels.

Leukocytoclastic vasculitis:
Palpable purpura is the most common finding, consisting of nonblanching 1-3 mm violaceous, round papules, characteristically involving the lower extremities. These may coalesce into plaques and occasionally may ulcerate. Older lesions may have a brownish-red color. Nodules and livedo reticularis are also seen infrequently. In severe cases, vesicles, bulla, and ulcers on the ankles and legs can appear.

Erythema elevatum diutinum presents as multiple infiltrated, pink or red to violaceous nodules or papules. They may or may not be painful. The lesions may coalesce to form gyrate lesions similar to granuloma annulare on the dorsum of the hands or extensor surfaces.

In the urticarial form, wheals may appear prior to the purpura, or the wheals may contain foci of purpura. These lesions tend to last longer than those of classic urticaria and may leave behind some hyperpigmentation as they resolve.

Diagnostic Pearls

Polyarteritis nodosa is distinct from leukocytoclastic vasculitis, which usually presents as smaller areas (a few millimeters) of purpura.

The American College of Rheumatology criteria for the classification of PAN includes 3 out of 10 of the following:

1. Unintentional weight loss exceeding 4 kg since the onset of illness
2. Testicular pain not attributable to other causes
3. Livedo reticularis
4. Presence of hepatitis B surface antigen or antibody
5. Development of hypertension
6. Presence of a blood urea nitrogen >40 mg/dL or creatinine >1.5 mg/dL that cannot be explained by dehydration or obstruction
7. Diffuse myalgias or muscular weakness

8. Development of one or more neuropathies

9. Biopsy of a small- or medium-sized artery with polymorphonuclear leukocytes (PMNs) in the artery wall

10. Arteriogram showing aneurysms or occlusions of visceral arteries not explained by other causes

Diascopy is a simple and useful maneuver. It consists of pressing a glass slide over a purpuric papule and demonstrating the presence of red blood cells within the skin (nonvasculitic papules will blanch).

Be sure to take a careful history of medications and other ingestants. Patients with drug-induced vasculitis tend to produce antibodies to multiple ANCA antigens, whereas patients with idiopathic vasculitis tend to produce antibodies to a single ANCA antigen.

Differential Diagnosis & Pitfalls

In the immunosuppressed patient or the patient with low PMNs, the distribution of the lesions may be similar to that in the normal host, but the degree of induration and the purpura may be less.

There is overlap between drug-related vasculitis syndromes, including **drug-induced lupus**, **serum sickness**, **serum sickness-like syndrome**, and other entities. Vasculitis can occur in autoimmune disease, and the situation may be complex because patients may also be taking medications that cause vasculitis. Discerning causes can be difficult, as medication-related vasculitis can present months or years after the medication was initiated.

- Microscopic polyarteritis
- **Thromboangiitis obliterans**
- **Drug-induced lupus**
- **Systemic lupus erythematosus**
- **Polyarteritis nodosa**
- **Leukocytoclastic vasculitis**
- **Henoch-Schönlein purpura**
- **Cryoglobulinemia**
- **Cryofibrinogenemia**
- **Granulomatosis with polyangiitis**

- **Eosinophilic granulomatosis with polyangiitis**
- **Erythema elevatum diutinum**
- Infection (eg, **Rocky Mountain spotted fever**, **gonococcemia**, **subacute bacterial endocarditis**, viral infections)
- Hypersensitivity reactions (eg, **drug-induced hypersensitivity syndrome**)

Other causes of large- and medium-sized vessel vasculitis:

- **Giant cell arteritis** (see **polymyalgia rheumatica**)
- **Takayasu arteritis**
- **Polyarteritis nodosa**

Nonvasculitic purpura on the lower extremities may be palpable in:

- Over-anticoagulation with Coumadin (warfarin) or heparin
- Early **disseminated intravascular coagulation**
- **Arthropod bite** (pruritic)
- **Capillaritis**
- **Livedoid vasculopathy**
- **Erythema multiforme**
- **Cellulitis**
- **Thrombotic thrombocytopenic purpura**
- **Sepsis**
- Endocarditis
- **Cholesterol emboli**
- **Scurvy**
- **Lymphomatoid granulomatosis**

Best Tests

Confirmation of cutaneous vasculitis is achieved by skin biopsy.

In drug-induced vasculitis, the ANA is often positive. MPO-ANCA, antihistone, and IgM anticardiolipin antibodies may be present as well. The C4 level may be low. Patients with idiopathic vasculitis, on the other hand, tend to have low ANA titers, low anticardiolipin antibody titers, low antihistone antibody titers, and normal C4 levels.

Testing to elucidate systemic involvement often includes a CBC with differential, ESR, C-reactive protein (CRP), urinalysis, chest x-ray, creatine phosphokinase, renal and liver function tests, fecal occult blood testing, and an electrolyte panel.

Be sure to take a careful history of medications and other ingestants.

Further workup to rule out infectious or rheumatologic etiologies is indicated once vasculitis is confirmed. This is often accomplished with the following tests:

- Antinuclear antibodies (ANA)
- ANCA
- Rheumatoid factor
- Anti-Ro and anti-La
- Complement levels
- Cryoglobulins
- Anti-phospholipid antibodies
- HIV and hepatitis B and C serologies
- Rapid plasma reagin (RPR) or venereal disease research laboratory (VDRL)

Some patients may require further investigations to better characterize the vasculitis and the nature of its systemic involvement. These tests include but are not limited to echocardiography, angiography, direct immunofluorescence tests of skin biopsy samples, electrocardiogram, pulmonary function testing, nerve conduction tests, electromyography, or screening for malignancy (serum protein electrophoresis, bone marrow biopsy, etc).

Management Pearls

Therapy is directed at any underlying trigger, such as infection or a medication, if such an inciting factor can be identified. Any causative medication should be discontinued.

For patients with vasculitic lesions primarily in the lower extremities, encourage rest with elevation of the legs. NSAIDs may be used for myalgias and arthralgias in patients whose renal

function is not compromised.

Antihistamines can be prescribed for pruritus, especially in urticarial forms:

- Diphenhydramine hydrochloride (25, 50 mg tablets or capsules): 25-50 mg every 24 hours at bedtime or every 6 hours as needed, or
- Hydroxyzine (10, 25 mg tablets): 12.5-25 mg every 6 hours as needed, or
- Cetirizine hydrochloride (5,10 mg tablets): 5-10 mg every 24 hours, or
- Loratadine (10 mg tablets and RediTabs): 10 mg tablet or RediTab every 24 hours.

Depending on the clinical scenario, the following consultations may be needed or helpful:

- Dermatology
- Gastroenterology
- Rheumatology, allergy, or immunology
- Nephrology
- Neurology
- Cardiology
- Pulmonology

Provide local wound care to any skin ulcerations. Surgical consultation may be needed for the debridement of necrotic tissue or in the context of any acute abdominal symptoms.

In addition to treating the primary disease, excellent supportive care for the various involved organ systems is necessary. A number of individuals can be treated as outpatients, but others may require hospitalization. This judgment needs to be tailored to the unique clinical scenario.

Cannabis has been associated with vascular disease, but that finding may be confounded by the frequent presence of a smoking history. Patients with potential cannabis-related vascular disease who are cigarette smokers should be on a rigorous anti-cigarette smoking program.

Therapy

For polyarteritis nodosa:
The following 5 prognostic indicators may help guide treatment. Patients without these factors may be treated with corticosteroids alone, whereas patients in whom one or more factors are

present often warrant additional and more aggressive therapies:

- Cardiomyopathy
- Gastrointestinal manifestations
- Central nervous system involvement
- Renal insufficiency (creatinine greater than 1.6 mg/dL)
- Proteinuria greater than 1 g/day

Systemic corticosteroids (prednisone 1 mg/kg every 24 hours). Patients will often need at least 6 months of systemic corticosteroids before a long taper (3-6 months) can be started. For severe systemic disease, begin with pulse doses of methylprednisolone (15-30 mg/kg intravenously daily administered over 60 minutes for 1-3 days).

Immunosuppressives, including cyclophosphamide (1-2 mg/kg by mouth every 24 hours) are indicated for patients with poor prognostic factors and/or who have not responded appropriately to more conservative regimens. Cyclophosphamide and corticosteroid therapy is often combined. Azathioprine (1-2.5 mg/kg by mouth every 24 hours) has also been used.

Intravenous immunoglobulin (IVIg), infliximab, pentoxifylline, and tamoxifen have demonstrated success in isolated case reports, as has removal of the tonsils (thus eliminating a source of chronic streptococcal disease).

Patients with concomitant hepatitis B infection should receive antiviral drugs (interferon alpha-2b or vidarabine) in addition to corticosteroids. Plasma exchange may also be used.

For forms of leukocytoclastic vasculitis:
Patients without systemic involvement may be safely observed or managed with conservative, symptomatic measures as above.

Colchicine (0.6 mg by mouth every 8-12 hours) or dapsone (100-150 mg by mouth every 24 hours) may be tried for patients in whom the disease is limited to the skin and/or joints. The two may also be used in combination.

Patients with visceral involvement will often need systemic corticosteroids (prednisone 0.5-2 mg/kg by mouth every 24 hours) with or without another immunomodulatory drug:

- Azathioprine: 2-3 mg/kg by mouth every 24 hours.
- Cyclophosphamide: 1-2 mg/kg every 24 hours.
- Methotrexate*: 10-25 mg by mouth weekly.

- Mycophenolate mofetil: 1-2 g by mouth every 24 hours.

Exclude infectious causes of LCV prior to instituting any of these therapies.

*Careful monitoring is required for methotrexate therapy. If toxicity from methotrexate is encountered or anticipated (eg, in patients with renal dysfunction or overdose), leucovorin or glucarpidase rescue may be needed.

Other therapies such as rituximab†, plasmapheresis, interferon-alpha, and IVIg have also been used.

†An FDA boxed warning recommends that all patients be screened for hepatitis B virus (HBV) before starting rituximab treatment, due to a risk for reactivation of HBV in patients with prior infection. Screening should include both hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc). If screening indicates prior HBV infection, consult a hepatitis expert and closely monitor the patient during and several months after rituximab therapy.

Treat any secondarily infected lesions with an appropriate topical or systemic antibiotic.

Drug Reaction Data

Below is a list of drugs with literature evidence indicating an adverse association with this diagnosis. The list is continually updated through ongoing research and new medication approvals. Click on Citations to sort by number of citations or click on Medication to sort the medications alphabetically.

Medication	Citations
5-aminosalicylic acid derivative	1
abatacept	1
ACE inhibitor	7
acebutolol	1
acetaminophen	3

Medication	Citations
adalimumab	5
all-trans-retinoic acid (ATRA)	2
allopurinol	7
Alpha-adrenergic agonist	2
amiodarone	2
amlodipine	2
amoxicillin	1
amoxicillin + clavulanic acid	1
amphotericin B	1
Anthelmintic	6
Antiarrhythmic	4
Anticoagulant	7
Anticonvulsant	7

Medication	Citations
Antidiabetic	3
Antifungal	1
Antigout	7
Antimalarials	4
Antimetabolite	6
Antimycobacterial	5
Antineoplastic antibiotic	1
Antineoplastic antimicrotubular	1
Antiviral	3
Aromatase inhibitor	1
atenolol	1
atorvastatin	1
Atypical antipsychotic	2

Medication	Citations
azathioprine	2
azithromycin	1
belinostat	1
benzodiazepine	1
Beta adrenergic agonist	2
Beta blockers	4
Beta-lactam antibiotic	1
bexarotene	1
bisphosphonate	1
bortezomib	1
BRAF kinase inhibitor	2
Calcineurin inhibitor	1
Calcium channel blocker	4

Medication	Citations
captopril	2
carbamazepine	2
carvedilol	1
cefoperazone	1
cefoxitin	1
cefprozil	1
celecoxib	6
cephalosporin	2
Chelating agents	3
chlormezanone	1
chlorzoxazone	1
cimetidine	1
ciprofloxacin	7

Medication	Citations
clarithromycin	1
clindamycin	1
clopidogrel	1
clozapine	1
cocaine	6
Coumadin	7
cromolyn	1
cyclosporine	1
cytarabine	1
daclizumab	1
deferiprone	1
diazepam	1
diflunisal	1

Medication	Citations
diltiazem	2
Diuretic	6
dronedarone	1
efavirenz	1
enalapril	3
etanercept	5
etodolac	2
etoposide	1
exemestane	1
famciclovir	2
fenbufen	1
fluoroquinolone	11
furosemide	2

Medication	Citations
gabapentin	1
gefitinib	2
gemcitabine	2
glatiramer acetate	1
glimepiride	1
glyburide	2
Glycopeptides	4
golimumab	1
Gonadotropin releasing hormone agonist	2
Granulocyte colony-stimulating factor	4
guanethidine	1
Histamine H2 antagonist	2
hydralazine	7

Medication	Citations
hydrochlorothiazide	2
hydroxyurea	1
ibuprofen	1
icodextrin	1
imipenem	1
indinavir	1
indomethacin	1
infliximab	4
interferon	1
isoniazid	4
Isotretinoin	2
itraconazole	1
iv immune globulin	4

Medication	Citations
leflunomide	3
leuprolide	2
levamisole	8
levofloxacin	1
Lincosamides	1
lisinopril	1
macrolide	2
maprotiline	1
marijuana	1
mefloquine	2
meprobamate	1
mesalamine	1
metformin	2

Medication	Citations
methimazole	6
methotrexate	3
methyldopa	1
methylphenidate	1
metolazone	1
minocycline	10
mirabegron	1
Monoclonal antibody	2
Muscle relaxant	2
nabumetone	1
naproxen	1
natalizumab	1
nicotine	1

Medication	Citations
nimesulide	1
nivolumab	1
nizatidine	1
non-NRTI antiretroviral	1
NRTI antiretroviral	1
NSAID	16
ofloxacin	3
olanzapine	1
olaparib	1
omalizumab	1
omeprazole	1
orlistat	2
oxacillin	1

Medication	Citations
pantoprazole	1
paroxetine	1
penicillamine	4
penicillin antibiotic class	2
pergolide	1
phenylbutazone	2
phenylpropanolamine	2
phenytoin	3
potassium iodide	1
pramipexole	1
pristinamycin	1
procainamide	1
propylthiouracil	13

Medication	Citations
protease inhibitors	1
Proton pump inhibitor	2
pyrazinamide	1
quinidine	1
quinine	2
ramipril	1
Retinoid	5
ribavirin	1
rifampin	1
risedronate	1
ritodrine	1
rituximab	4
rofecoxib	3

Medication	Citations
Selective serotonin reuptake inhibitor	1
simvastatin	1
sitagliptin	1
sodium benzoate	1
sorafenib	1
sotalol	1
statin	2
streptokinase	2
sulfamethoxazole + trimethoprim	1
sulfonamide	2
sulfonylurea	3
tadalafil	1
tamoxifen	2

Medication	Citations
terbutaline	1
tetracycline antibiotic class	10
thalidomide	1
Therapeutic gold & gold compounds exposure	1
thioridazine	1
ticlopidine	1
torsemide	1
trastuzumab	1
trazodone	1
Tricyclic antidepressant	1
trimethadione	1
trimethoprim	2
Typical antipsychotic	1

Medication	Citations
Tyrosine kinase inhibitor	3
valproate	1
vancomycin	4
vemurafenib	2
vinorelbine	1
zafirlukast	3
zidovudine	1