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## Dermatologic Manifestations of Rheumatic Disease: Cutaneous Manifestations of Vasculitides

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# Cutaneous Manifestations of Vasculitides

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## Disclaimer:

This module uses terminology related to race and ethnicity in order to describe fictional patients and discuss medical conditions. We recognize that “race” (i.e. an individual’s socially-constructed phenotype, which is often viewed as biologic) and “ethnicity” (i.e. an individual’s geographic birthplace or cultural/national heritage) are imperfect terms that do not fully encapsulate the breadth of human diversity.

Additionally, we recognize that race, ethnicity, sex, and gender have traditionally been attributed as risk factors for certain health condition, when in reality, many of these risks may be more accurately explained by underlying socioeconomic and sociocultural factors.

In efforts to emphasize patient-centered care and autonomy, this module assumes that all racial-, ethnic-, sex-, and gender-related terms utilized are those specifically preferred by the patient. We are also committed to dissecting potentially biased risk factors in order to promote more equal, just, and comprehensive healthcare for all persons, regardless of their identity, beliefs, or background.

# Goals and Objectives

After this module, participants should be able to:

- Recognize dermatologic lesions / conditions associated with systemic vasculitis
- Understand the vascular processes, vessel of involvement, and histologic changes related to the cutaneous findings
- Construct a differential diagnosis regarding various dermatologic lesions
- Utilize skin findings and other clinical parameters, as well as histologic and laboratory results to make the correct diagnosis

# Introduction

Skin findings are common in patients with systemic diseases, including diseases associated with vasculitis. In fact, cutaneous lesions are often the presenting sign. As such, clinicians need to be aware of various dermatologic conditions associated with systemic vasculitis as their presence will frequently trigger, and may aid in, a more focused investigation. This module will begin with the definition of terms and findings often found in vasculitis, followed by a review of several systemic vasculitides, highlighting how characteristic cutaneous lesions may be predictive of the vessel of involvement as well as the associated histologic changes. Moreover, significant clinical and laboratory findings utilized to make the correct diagnosis will be emphasized. This module is not meant to be an exhaustive review of vasculitis, but to serve as an introduction to understanding disease processes and how systemic vasculitis and skin findings interrelate.

Of note, only vasculitides will be entertained in the various differential diagnoses and discussions within this module. Lesions commonly seen in vasculitis include various types of nodules and purpura. Diseases other than vasculitis can cause identical skin lesions, but these other diseases will not be included in this module.

## Cutaneous Lesions Associated with Systemic Vasculitis

This section will delineate and define the skin lesions commonly seen in cases of systemic vasculitis. Vessels of involvement (small / medium / large) often determine the cutaneous lesion that develops, making skin lesions very helpful in constructing a more focused differential diagnosis.

# Petechiae

Description: Non-blanching and non-palpable, pinpoint (1-2 mm), round red spots that appear on the skin due to any type of microvascular hemorrhage of blood into the skin.

Vascular significance: Hemorrhage from small vessels, such as capillaries, which can be due to a variety of causes, including clotting abnormalities and trauma, but is often associated with small-vessel vasculitis.

Image unavailable

[Petechiae](#). Visual Dx. Updated March 27, 2023. Accessed February 5, 2022.



# Macular purpura

Description: Flat, non-blanching and non-palpable, red to purple spots (3-10 mm) that appear on the skin due to extravasation of blood into the skin. The only difference between petechiae and purpura is lesional size.

Vascular significance: Vascular hemorrhage due to a variety of causes including clotting abnormalities and trauma, but may also be caused by small vessel vasculitis.

Image unavailable

[Macular purpura](#). Visual Dx.  
Updated March 27, 2023.  
Accessed February 5, 2022.

# Palpable purpura

Description: Slightly elevated (palpable), non-blanching, purple-red spots (3-10 mm). The cause of the elevation (palpability) is inflammation around the small blood vessels in the dermis.

Vascular significance: Usually signifies the presence of a cutaneous vasculitis, most commonly leukocytoclastic, small-vessel vasculitis.

Image unavailable

[Palpable purpura](#). American College of Rheumatology. Updated March 27, 2023. Accessed February 5, 2022.

# Retiform/stellate purpura

Description: Painful, non-blanchable, dark red-to-purple patches or plaques (ranging in size from 1 cm to greater than 10 cm) with peripheral branching - often described as star-shaped or “stellate”. May be purpuric, necrotic, or ulcerated.

Vascular significance: Diagnostic for vascular thrombosis and cutaneous ischemia, which could be due to several causes, including small-to-medium vessel vasculitis.

Image unavailable

[Retiform purpura](#). Visual Dx.  
Updated March 27, 2023.  
Accessed February 5, 2022.

# Livedo reticularis

Description: Net-like, mottled or lacy, pattern of pinkish to violaceous discoloration.

Significance: Marker for inadequate arterial flow into the capillary bed due to a variety of different reasons. The color change is due to venous dilatation which lowers the pressure gradient across the capillary bed in a physiologic attempt to augment flow.

Image unavailable

[Livedo reticularis](#). Visual Dx.  
Updated March 27, 2023.  
Accessed February 5, 2022.

# Subcutaneous nodules

Description: Tender red raised nodules (greater than 5mm, usually 1-2cm). Lesions are often solitary, but when numerous they may be in a linear pattern along the path of the blood vessels.

Vascular significance: Marked inflammation of medium-to-large vessels; associated with medium-to-large vessel vasculitis.

Image unavailable

[Subcutaneous nodule](#). Visual Dx.  
Updated March 27, 2023.  
Accessed February 5, 2022.

# Ulcers

Description: Cutaneous defect due to loss of epidermis down into dermis (through the basement membrane zone) and sometimes deeper into subcutis or fascia. Wound bed contains a mixture of necrotic and granulation tissue with marked vascularity and surrounding erythema.

Vascular significance: A variety of disorders cause ulcers, but can be due to small-to-medium-to-large-vessel vasculitis.

Image unavailable

[Ulcer](#). Visual Dx. Updated March 27, 2023. Accessed February 5, 2022.

# Digital necrosis

Description: When acute, one sees edematous digits (fingers or toes) that may be erythematous or pale blue; untreated it can progress to necrosis with eschar.

Vascular significance: Vascular ischemia and/or thrombosis resulting in tissue ischemia; can be due to a variety of causes, including medium-vessel vasculitis.

Image unavailable

[Digital necrosis](#). American College of Rheumatology. Updated March 27, 2023. Accessed February 5, 2022.

## Histologic Findings Associated with Systemic Vasculitis

This section will delineate and define the histologic findings associated with different types of systemic vasculitis. The histologic findings are very helpful in constructing a more focused differential diagnosis.



# Leukocytoclasia

Description: The presence of intact neutrophils and neutrophilic debris within vessel walls.

Significance: Process where neutrophils infiltrate the vessels and degranulate, causing vascular destruction, and self-destruction.

# Leukocytoclastic vasculitis (LCV)

Description: Disruption of small blood vessels by neutrophils infiltrating the vessel wall and degranulating resulting in leukocytoclasia and subsequent deposition of fibrin within the lumen and/or vessel wall.

Significance: Inflammatory vascular damage of small blood vessels, classically presents as palpable purpura.

Image unavailable

[Leukocytoclastic vasculitis.](#)

DermNet. Updated March 27, 2023. Accessed February 5, 2022.

# Interface dermatitis

Description: Refers to inflammation along the basement membrane zone, the “interface” between the epidermis and the dermis. It is often classified by the cell type dominating the inflammation; it may also be cell-poor. In the cell-poor variant, cellular cytotoxicity may be due to antibody-mediated damage.

Significance: Cell-poor types of interface dermatitis are common in connective tissue diseases such as lupus and dermatomyositis.

Image unavailable

[Interface dermatitis](#). Indian Journal of Dermatology. Updated March 27, 2023. Accessed February 5, 2022.

# Fibrinoid necrosis

Description: The formation, or deposition, of a homogeneous acidophilic refractile material, that somewhat resembles fibrin, within the walls of blood vessels and dermis.

Significance: Caused by a pattern of cell death that is characterized by vascular endothelial damage and exudation of plasma proteins.

Image unavailable

[Fibrinoid necrosis](#). American College of Rheumatology. Updated March 27, 2023. Accessed February 5, 2022.

# Necrotizing granulomatous vasculitis

Description: Fibrinoid necrosis of the vascular media with endothelial hyperplasia associated with an intravascular, and perivascular, infiltrate of predominantly neutrophils with irregular contour and necrosis of the neutrophils, and nuclear debris. In addition one often sees palisading histiocytes and multinucleated giant cells with scattered, hyperchromatic nuclei.

Significance: Histologically distinct form of small-to-medium-vessel vasculitis (i.e., granulomatosis with polyangiitis).

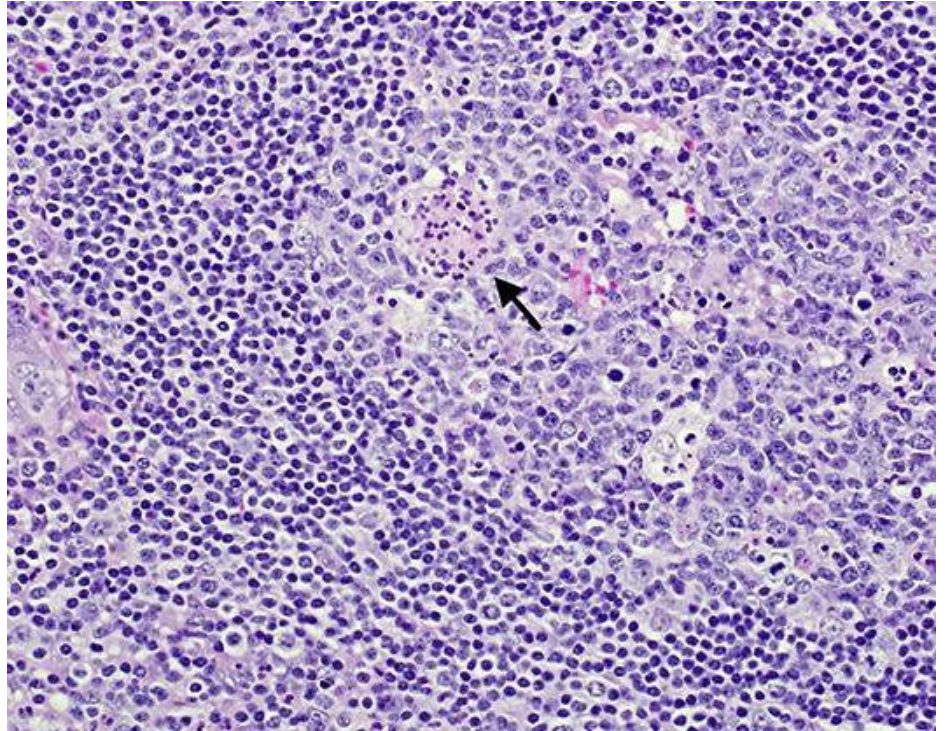
Image unavailable

[Necrotizing granulomatous vasculitis.](#)  
American College of Rheumatology.  
Updated March 27, 2023. Accessed  
February 5, 2022.

# Neutrophilic microabscesses

Description: A small collection of neutrophils.

Significance: Histologic finding that is seen in various diseases including small-and medium vessel vasculitis (i.e., granulomatosis with polyangiitis).



Germinal center with neutrophil microabscess. (Fig 3) from [Typhoid Fever and Acute Appendicitis: A Rare Association Not Yet Fully Formed](#) by Daniel J. Sartori, et al. is licensed using a Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC) license.

## Special Laboratory and Histologic Studies Used to Diagnosis Vasculitic Disorders

This section will define special studies used in diagnosing cases of vasculitis.

## Direct immunofluorescence (DIF)

Description: Histological staining procedure for identifying specific antigens present in tissue samples using antibodies labeled with fluorophore.

Significance: Particular staining patterns will identify specific antigens which can narrow the differential diagnosis, and often indicate the correct diagnosis.

## Antineutrophil Cytoplasmic Antibodies (ANCA) test

Description: Blood test that detects the presence of antineutrophil cytoplasmic autoantibody proteins (ANCA). Different types are more common in different diseases. The 2 most common ANCAs are:

p-ANCA, predominantly targets myeloperoxidase (MPO).

The 'p' refers to the predominant perinuclear staining pattern.

c-ANCA, predominantly targets proteinase 3 (PR3).

The 'c' refers to the predominant cytoplasmic staining pattern.

Significance: A (+) ANCA test strongly suggests the possibility of an autoimmune vasculitis.

# ANCA-associated Vasculitides

- ANCA-associated vasculitides are a group of disorders characterized by necrotizing inflammation of small and medium sized blood vessels. Though any organ system may be affected, the most commonly affected include the upper and lower respiratory tracts and the kidneys. The various diseases have characteristic presentations. Cutaneous involvement occurs in about 20% of cases.
- The 3 major diseases that are partially defined by the presence of ANCA are:
  - Granulomatosis with polyangiitis (GPA)
    - Formerly named Wegener's granulomatosis
  - Microscopic polyangiitis (MPA)
  - Eosinophilic granulomatosis with polyangiitis (EGPA)
    - Also referred to as Churg-Strauss syndrome
  - Drug-induced ANCA-associated vasculitides (DIAV)
- c-ANCA (anti PR3) is present in:
  - 80% of cases of GPA
  - 20-40% of MPA
  - 35% EGPA
- p-ANCA (anti-MPO) is present in:
  - 50% MPA
  - 35% EGPA
  - May also be seen in other systemic diseases



# Other Abbreviations Used in this Module

- CBC - complete blood count, includes white blood cells, red blood cells, and platelets
- CMP - complete metabolic panel; includes tests for electrolytes, renal and hepatic function
- WBC - white blood cell
- RBC - red blood cell
- ESR - erythrocyte sedimentation rate. Elevated levels are found in states of inflammation.
- CRP - C-reactive protein. Elevated levels are found in states of inflammation.
- IgA - Immunoglobulin A
- BUN - blood urea nitrogen, a marker of kidney function
- HBV - hepatitis B virus
- HCV - hepatitis C virus
- ANA - antinuclear antibody
- H&E - tissue staining with a combination of two stains: hematoxylin and eosin. Hematoxylin stains cell nuclei purplish, and eosin stains the cytoplasm and extracellular matrix pink; other structures will take on different shades, hues, due to combinations of these colors.

# Case #1

Image unavailable

[Palpable purpura](#). Visual Dx.  
Updated March 27, 2023.  
Accessed February 5, 2022.

A 12-year-old previously healthy male (he/him/his) presented with an erythematous rash on both lower extremities which had developed about a week earlier. Over the prior 2 weeks he had also developed joint pains and blood in his urine. Most recently he complained of abdominal pain.

Palpable, non-blanching, red, round lesions, ranging in size from 3-5 mm in diameter, were present on bilateral lower legs

Differential diagnosis based on skin findings of palpable purpura, which suggest a small-vessel vasculitis in a previously healthy 12-year-old includes the following:

Hypersensitivity vasculitis

Granulomatosis with polyangiitis

Systemic lupus erythematosus

Henoch-Schonlein purpura

Mixed cryoglobulinemia

# Labs

Urinalysis: microscopic hematuria  
Elevated serum IgA  
Negative ANA (antinuclear antibody)  
Negative ANCA  
Normal complete blood count, including platelets  
Normal complete metabolic panel  
Normal coagulation studies

# Biopsies

Histologic findings from a skin biopsy stained with H&E demonstrated leukocytoclastic vasculitis (LCV) without fibrinoid necrosis of the blood vessels.  
DIF identified vascular deposition of IgA immune complexes.

Image unavailable

[Leukocytoclastic vasculitis pathology](#). DermNet. Updated March 27, 2023. Accessed February 5, 2022.

Case #1 Diagnosis:

Immunoglobulin A vasculitis (IgAV), also known as Henoch Schonlein purpura (HSP)

# Pathophysiology of IgAV

- Immune-mediated **small**-vessel vasculitis associated with IgA deposition
- Underlying cause of IgAV/HSP is unknown, but multiple infectious and chemical triggers have been recognized.
  - Immunologic, genetic, and environmental factors all seem to play a role
  - The disease often follows an nonspecific upper respiratory infection.

# Significant clinical findings in IgAV

Palpable purpura, most commonly in dependent areas

Abdominal pain

Usually young individuals, though may occur in adults

# Significant laboratory findings in IgAV

No laboratory test is diagnostic for IgAV/HSP

LCV accompanied by deposition of IgA immune complexes within affected organs, including skin and kidneys

Hematuria is common, but not required for diagnosis

An elevated serum IgA is common, but is not required for diagnosis, nor is an elevated IgA specific for the diagnosis of IgAV/HSP



# Diagnostic criteria for IgAV

American College of Rheumatology criteria for diagnosis of IgAV/HSP:

- Palpable purpura
- Age of onset  $\leq 20$  years
- Acute abdominal pain
- Biopsy demonstrating granulocytes (neutrophils) within the walls of small arterioles and/or venules

# Epidemiology

- Primarily childhood disease between ages 3 and 15 years
- Annual incidence 10-20 per 100,000 in children under 17 years of age
- Peak incidence between 4 and 6 years of age
- Approximately 10% of IgAV/HSP cases occur in adults

# Prognosis

- Spontaneous resolution is usual (94% in children, 89% in adults)
- Complete resolution of symptoms commonly occurs within 8 weeks
- Progressive renal disease is rare in children, but may more common in adults
- Rarely, patients may develop intestinal intussusception
- Primary management includes supportive and symptomatic treatment
- More aggressive disease may be treated systemic corticosteroids

# Distinguishing IgAV from other causes of LCV

The other diseases listed in the differential diagnosis may also present with the clinical picture of palpable purpura and LCV, but they are distinguished based on other clinical and laboratory findings, including histologic studies:

- Hypersensitivity vasculitis
  - This condition may be idiopathic, but may also be a consequence of entities such as infection or medications. The vasculitis is immune-complex mediated, but DIF would not be specific for IgA. Serum IgA would be normal.
- Granulomatosis with polyangiitis
  - Discussed in depth below
- Systemic lupus erythematosus (SLE)
  - LCV with palpable purpura can be seen in SLE. However, other signs and symptoms would be different. SLE is more likely to present with symptoms such as photosensitivity and joint pains. Although SLE often affects the kidneys, rarely will patients have abdominal pain. Serologic tests for SLE would be present, such as an ANA. IgA would be normal. Histologic changes might show vasculitis, but one would also see a cell-poor interface dermatitis. DIF would demonstrate deposition of numerous immunoglobulins, not only IgA.
- Mixed cryoglobulinemia
  - Cryoglobulinemia encompasses a few different entities, due to the cause of the cryoglobulins. Often, cryoglobulin deposits can be seen inside of the affected vessels. DIF would not show IgA deposition.

# Case #2

Image unavailable

[Palpable purpura](#). American College of Rheumatology. Updated March 27, 2023. Accessed February 5, 2022.

A 70-year-old male (he/him/his) with osteoarthritis presented with a painful rash on both legs, general malaise, and fevers that began about 2 months ago. Over this same time frame he reported developing a dry cough, chest pain, and sinus pain with nasal discharge.

Skin: Palpable purpura were present on both legs, as were several small necrotic ulcers, and a rare stellate purpuric lesion. Lesions ranged in size from 4-15 mm in diameter; some were associated with hemorrhagic blisters.

Facial examination revealed nasal perforation.

Differential diagnosis of types of vasculitis that have skin findings of palpable purpura, small ulcers and small nodules include:

Polyarteritis nodosa (PAN)

Granulomatosis with polyangiitis (GPA)

Microscopic polyangiitis (MPA)

Drug-induced vasculitis (DIAV)

# Labs

Positive c-ANCA (PR3)

ESR: 30 (nl: 0-15 mm/h)

BUN 58 mg/dl (nl: 10-20 mg/dl)

Serum creatinine 3.4 mg/dl (nl: 0.8-1.1 mg/dl)

Urinalysis showed mild proteinuria; microscopic hematuria and RBC casts

Chest x-ray: nodular cavitary lesions and lung infiltrates

# Biopsies

Histologic findings from a skin biopsy stained with H&E demonstrated LCV with fibrinoid necrosis of the vessel walls without granulomatous inflammation. DIF was negative.

Image unavailable

[Fibrinoid necrosis](#). American College of Rheumatology. Updated March 27, 2023. Accessed February 5, 2022.

Renal biopsy showed segmental necrotizing glomerulonephritis without deposition of immune complexes (pauci-immune).

Image unavailable

[Segmental necrotizing glomerulonephritis](#). American College of Rheumatology. Updated March 27, 2023. Accessed February 5, 2022.

Case #2 Diagnosis:  
Granulomatosis with Polyangiitis (GPA)

# Pathophysiology of GPA

GPA is a rare multisystem disease characterized by granuloma formation and necrotizing vasculitis of **small-medium** sized vessels. It most commonly affects the upper respiratory system and the kidneys. Only 30-50% of patients have skin manifestations.

The pathogenesis of GPA is not fully understood, but there may be a pathologic role for the cANCA target, PR3, or PR3 antibodies.

PR3 is expressed on the cell surface of neutrophils which may inhibit their destruction by macrophages, prolonging antibody development. ANCA binding to PR3 on neutrophils results in vessel damage.

Since vessel damage is a result of ANCA binding to PR3 and is not due to immune complex deposition, GPA is referred to as “pauci-immune” or “non immune complex-mediated” vasculitis.

PR3 may also trigger cytokine activation, resulting in granuloma formation.



# Significant clinical findings in GPA

Classic generalized GPA is a triad of necrotizing granulomas of the upper and lower respiratory tract, systemic vasculitis, and necrotizing glomerulonephritis.

Renal involvement may occur in up to 90% of patients and untreated may result in end stage renal disease. Severe renal involvement is associated with a poorer prognosis.

Cutaneous manifestations occur less than 50% of cases and include palpable purpura, nodules, small ulcers and digital necrosis. Mucosal ulcers may also be present.

The classic facial finding is a “saddle-nose” deformity due to tissue destruction from the vasculitis.

# Significant laboratory findings in GPA

- (+) ANCA
  - ANCA is recognized as both sensitive and specific for GPA
  - Present in 80–90% of patients with GPA
  - 80–95% of GPA cases are associated with c-ANCA
    - Rare cases are associated with p-ANCA
    - Rare cases are ANCA negative
- When renal involvement is present, the urinalysis will demonstrate changes consistent with glomerulonephritis:
  - Variable amounts of proteinuria
  - Microscopic hematuria
  - RBC casts
- Chest X-ray and/or CT usually reveal various abnormalities including nodules.
- Biopsies of other affected organs typically demonstrate vasculitis or necrotizing and/or granulomatous inflammation.
  - Granulomas are rarely seen in skin biopsies.
  - Immune complex deposition is not seen in GPA (AKA “pauci-immune” type of vasculitis).

# Diagnostic criteria for GCA

The ACR criteria include:

- Urinary sediment showing RBC casts, or more than five red blood cells per high power field
- Abnormal findings on chest radiograph
- Oral ulcer or nasal discharge
- Granulomatous inflammation on biopsy
- The presence of two or more out of the above four criteria was associated with a 92% specificity and 88% sensitivity

Another diagnostic system referred to as ELK was proposed by DeRemee:

- In ELK, E stands for ears, nose, and throat or upper respiratory tract, L for lung, and K for kidney.
- Per these criteria, any typical manifestation involving the ELK, along with positive c-ANCA or typical histopathological finding, qualifies for a diagnosis of GPA.

# Epidemiology

- In the USA the estimated rate is 3 cases per 1 million people
- Peak incidence 64-75 years of age
- Northern European heritage increases the risk
  - 80%-90% of cases occur in those of Northern European heritage

# Prognosis

- If untreated or severe, 90% of GPA patients die within 2 years
  - Most common cause of death is respiratory or renal failure.
  - In cases of non-renal GPA the mortality is 40%.
- Treatment is based on immune modulation
  - Historically, cyclophosphamide was the gold standard therapy with a 90% response and 75% complete remission rates. Between 30-50% relapsed at least once.
  - Other options include glucocorticoids, methotrexate, and more recently rituximab.

# Distinguishing GPA from the other conditions in the differential diagnosis:

The other diseases listed among the differential diagnoses may also present with the clinical picture of palpable purpura, nodules and or ulcers. Although 3 of the conditions are ANCA-associated, they are differentiated based on other clinical and laboratory findings, including histologic studies:

- Polyarteritis nodosa (PAN)
  - Discussed in detail below, but it is not associated with ANCA
- Microscopic polyangiitis (MPA)
  - Although some feel that GPA and MPA may be part of a clinical spectrum the lack of upper respiratory involvement and the lack of granulomas on histology differentiate MPA from GPA.
- Drug-induced ANCA-associated vasculitis (DIAV)
  - The pathogenesis of DIAV is likely multifactorial, and poorly understood.
  - The clinical and laboratory findings are similar to the non-drug induced, ANCA-associated diseases; only concomitant use of a potential drug helps to differentiate the processes.
  - Numerous medications, from a wide variety of pharmacologic classes, have been implicated.
  - The more commonly implicated medications include anti-thyroid medications, tumor-necrosis factor (TNF) inhibitors and cocaine, especially when adulterated with levamisole.

# Case #3

Image unavailable

[Subcutaneous nodule](#). Visual Dx.  
Updated March 27, 2023.  
Accessed March 27, 2023.

A 50-year-old man (he/him/his) with controlled hypertension complained of a painful rash on both lower legs that began 2 months ago and was worsening. Review of systems was significant for weight loss, fatigue, intermittent fevers, numbness and tingling in his toes and fingers, as well as muscle and joint pain for the past 4-6 months.

His blood pressure was 145/95

Tender, red, palpable subcutaneous nodules were present on bilateral lower legs ranging from 1 cm to 2 cm in diameter.

# Differential diagnosis:

Cutaneous polyarteritis nodosa

Classic polyarteritis nodosa

Granulomatosis with polyangiitis

Microscopic polyangiitis

# Labs

Serum creatinine 2 mg/dL (nl: 0.8-1.1 mg/dl)

Serum BUN 48 mg/ dl (nl: 10-20 mg/dl)

Urinalysis showed mild proteinuria as well as few RBCs and WBCs

Negative HBV, HCV, HIV serologies

ESR 60 mm/hr (nl: 0-15 mm/hr)

CRP 9 mg/L (nl: < 3 mg/L)

Negative ANCA

# Biopsies

Biopsy of the skin nodule revealed inflammation and destruction of medium-sized arteries in the deep dermis. Hyalinization of the vessel wall was present with fibrinoid necrosis and narrowing of the vascular lumen. A perivascular infiltrate consisted primarily of neutrophils and lymphocytes. DIF was negative.

# Imaging

Arteriogram demonstrated numerous aneurysms along the renal arteries and microaneurysms of smaller arterioles within the kidneys.



Case #3 Diagnosis:  
Classic Polyarteritis Nodosa (PAN)

# Pathophysiology of PAN

- PAN is a systemic necrotizing vasculitis that most commonly affects arterial vessels of the skin, joints, peripheral nerves, gastrointestinal tract, heart, eyes, and kidneys. Lungs are relatively spared.
- The pathogenesis of PAN is unknown.
  - Some cases are related to hepatitis B infection.
  - It has also been associated with various other viral and bacterial infections.
    - Cases associated with hepatitis C infection are mostly likely to have skin only disease (cutaneous PAN), without systemic involvement.
  - Some genetic mutations have been associated.
  - May be associated with the presence of other connective tissue diseases.
- It classically affects **medium**-sized and small muscular arteries, preferentially at vessel bifurcations. The result is microaneurysm formation, sometimes with aneurysmal rupture resulting in hemorrhage, thrombosis, organ ischemia and/or infarction.
- It spares the aorta and smaller vessels (capillaries and arterioles) as well as the venous system.
- Inflammation may start in the vessel intima and progress to include the entire arterial wall resulting in destruction of the internal and external elastic lamina and fibrinoid necrosis.
  - May result in weakening of vessel walls and the development of aneurysms.
  - May result in thrombus formation
  - May result in tissue ischemia/infarction/tissue necrosis and hemorrhage
- Presenting symptoms will vary, depending upon the organ most affected.
  - In this case, the major organs of involvement were the kidneys. Other cases would have slightly different laboratory abnormalities and angiography results.

# Significant clinical findings in PAN

Cutaneous lesions are present in only 20-50% of patients and may include livedo reticularis, cutaneous nodules, ulcers, and digital ischemia.

# Significant laboratory findings in PAN

- Elevated serum creatinine and BUN (suggestive of renal involvement)
- Elevated hepatic enzymes most commonly seen in association with HBV-associated PAN
- Other laboratory abnormalities would suggest involvement of other organ systems
- Negative ANCA
- Elevated ESR
- Elevated CRP
- Arteriography: Aneurysms associated with classic PAN are most commonly found in the kidney, liver, and mesenteric arteries. Their presence is associated with more severe and extensive disease.

# Biopsy findings in PAN

- Diagnostic biopsies must include medium sized arterioles.
- Classic changes include necrotizing panarteritis with predominately polymorphonuclear infiltration of arteries and arterioles of the affected organs.
- Skin biopsies must be deep enough to reach affected vessels in the deep dermis and subcutis; more superficial biopsies will be non specific.
- There is no DIF pattern consistent with the diagnosis of PAN
- Nerve biopsies may reveal axonal degeneration and fiber loss.
- If renal involvement is present, renal biopsy is contraindicated due to risk of arteriolar rupture and hemorrhage.

# Diagnostic criteria for PAN

- In 1990 the American College of Rheumatology established a group of 10 criteria for the classification of classic PAN. The presence of 3 or more of the listed criteria was associated with a sensitivity of ~ 82% and specificity of close to 87%.
  - Otherwise unexplained weight loss > 4 kg
  - Livedo reticularis
  - Testicular pain or tenderness
  - Myalgias (excluding that of the shoulder and hip girdle), weakness of muscles, tenderness of leg muscles, or polyneuropathy
  - Mononeuropathy or polyneuropathy
  - Diastolic blood pressure > 90 mmHg
  - Elevated levels of serum blood urea nitrogen
  - Evidence of hepatitis B virus infection in serum
  - Characteristic arteriographic abnormalities not resulting from noninflammatory disease processes (image 1)
  - A biopsy demonstrating neutrophilic, or a mixed leukocytic infiltrate in an arterial wall

# Epidemiology

- In USA: 3-4.5 cases/100,000
- Males > females with a ratio of 1.6-2:1
- More common in those 45-65 years of age

# Prognosis

- Early diagnosis and treatment are critical
- Untreated PAN has a poor prognosis
- 10-20% of patients die within 5 years, 50% of those patients dying within 3 months
- Poorer prognosis associated with the following:
- Gastrointestinal involvement, due to risk of perforation
- Significant renal involvement, as measured by proteinuria > 1g/day and/or a decrease in glomerular filtration rate (GFR)
- Cardiac involvement with resultant cardiomyopathy
- Central nervous system involvement
- Treatment significantly improves outcome
- 50-60% 5-year survival rate
- But there is a high relapse rate
- Overall, the major causes of death are renal failure, mesenteric/cardiac/cerebral infarctions, and complications of immunosuppressive therapy.
- Other complications include gangrene of the extremities, skin ulcers, encephalopathy, and peripheral neuropathy
- Best prognosis in patients with only cutaneous involvement
- Cutaneous PAN lasts months-years with exacerbations and remissions (spontaneous or due to treatment)
- Low risk of relapse in patients with HBV-associated PAN if they seroconvert to negative.

# Case #4

A 70-year-old male (he/him/his) with controlled hypertension presented with recurring headaches and jaw pain, triggered by chewing, as well as intermittent fevers. These symptoms have been worsening over the past 2-3 months. Six months earlier he reported an episode of transient vision loss in his right eye.

There were no specific skin lesions, but moderate tenderness to palpation was noted on bilateral temporal areas.

His neurologic exam was within normal limits.

Ophthalmologic exam revealed pallor and edema of the optic disc.



# Differential diagnosis

Giant cell arteritis

Takayasu arteritis

Granulomatosis with polyangiitis

Polyarteritis nodosa

# Labs

- ESR 80 mm/hr (normal 2-20 mm/hr)
- CRP 3.2 mg/dL (normal 0.8-1.1 mg/dL)
- Negative ANCA
- CBC
  - Hgb 11 g/dL (normal 12.5-15 g/dL)
  - MCV 90 fL (normal 80-100 fL)
  - Platelet 550,000/uL (normal 140,000-450,000/uL)

# Biopsies

Typically a skin biopsy is not performed when skin lesions are not present. If it is performed in this condition it is rarely helpful because the vessel of involvement is of large caliber which is typically difficult, and dangerous, to reach with a routine punch biopsy.

Case #4 Diagnosis:  
Giant Cell Arteritis (GCA); otherwise known  
as temporal arteritis

# Pathophysiology of GCA

Giant cell arteritis (GCA) is a systemic inflammatory vasculitis of unknown cause; it is the most common form of systemic vasculitis in adults. Although classified as a **large** vessel vasculitis, medium and small arteries may also be affected. Histopathologically it is characterized by transmural granulomatous inflammation. Signs and symptoms of GCA usually reflect involvement of the temporal artery and include headache, scalp tenderness, visual changes, and claudication of the tongue and jaw. Constitutional symptoms of fever, malaise and weight loss are not uncommon. Tenderness and increased thickness of temporal arteries are the most recognizable signs of GCA on physical examination. An ophthalmologic exam may show changes of anterior ischemic optic neuropathy including pallor and edema of the optic disc, with or without splinter hemorrhages. Skin manifestations are uncommon in GCA. Necrosis of the scalp and tongue, due to ischemia, are the most common mucocutaneous manifestations, but are very rare. Laboratory tests usually show elevated acute phase reactants (ESR, CRP), markers of systemic inflammation. A normochromic, normocytic anemia and a mild thrombocytosis are also commonly present.

GCA is a complex disorder of cell-mediated immunity triggered by unknown antigens. Ultimately, CD4 cells infiltrate the arterial walls, fragment the internal lamina, interact with histiocytes (activated macrophages) and produce multinucleated giant cells causing granulomatous lesions. This inflammatory process results in luminal occlusion → lack of blood flow → tissue ischemia leading to the various signs and symptoms of GCA.

# Significant laboratory findings in GCA

- ESR > 50 mm/hr (normal 10-20 mm/hr)
- Elevated CRP
- Elevated LFTs
- Biopsy histology
  - Panarteritis composed of CD4+ lymphocytes and macrophages
  - Giant cells (common but not required for diagnosis)
  - Fragmented internal elastic lamina (common)
  - Transmural inflammation, or inflammation confined to adventitia or to the small vessels surrounding the temporal artery

# Diagnostic criteria (3 or more must be present for diagnosis)

- Age of more than 50 years
- New-onset headache
- Temporal artery abnormality (i.e., tenderness to palpation, decreased pulsation)
- ESR greater than or equal to 50 mm/h
- Classic temporal artery biopsy
- A positive biopsy is the gold standard diagnostic test for GCA (100% specificity). Unfortunately the reported sensitivity has a wide range, from a low of 15% to a high as 87%.
- Some imaging studies may be used instead of, or in combination with, the biopsy

# Epidemiology

- Incidence in USA
- 0-5-27/100,000 adults > 50 years of age
- Female:Male ratio of 3.2:1
- Smoking raises the risk in females
- Almost never occurs before age 50 years
- Incidence peaks between age 70-79 years
- 80% of patients older than 70 years
- Highest incidence among Caucasian Americans of Scandinavian descent
- GCA is less common in Latinos, Asians, Arabs, and African Americans, though formal data on these populations are scant

# Prognosis

- Variable duration
- Visual loss is a significant risk, if untreated
- 1-2 years → chronic
- Does not affect overall life expectancy, unless there is aortic involvement and dissection
- Relapses are most common when prednisone doses are below 20mg/day

# Other cutaneous manifestations of GCA

Image unavailable

[Scalp necrosis](#). Dargham, Bassel & Kang, Julianna & Gavin, Joshua & Nandan, Abhishek. (2022). Drug-Associated Giant Cell Arteritis with Scalp Necrosis After Treatment with Pembrolizumab: a Case Report. SN Comprehensive Clinical Medicine. 4. 10.1007/s42399-022-01120-5.

Image unavailable

[Tongue necrosis](#). Truffaut L, Lefebvre P. Tongue Necrosis in Giant-Cell Arteritis. N Engl J Med. 2018 Jun 28;378(26):2517. doi: 10.1056/NEJMicm1709412. PMID: 29949496.



# Distinguishing GCA from the other conditions in the differential diagnosis:

The diseases listed in the differential diagnosis for GCA may present with more typical cutaneous stigmata as discussed in sections above. Nodules and/or ulcers may be present in several conditions which can be distinguished based on other clinical and laboratory findings, including histologic studies:

- Takayasu arteritis
  - Takayasu arteritis is a rare granulomatous vasculitis affecting large and medium sized arteries, most characteristically the aorta and its branches. As in GCA, fever and malaise may be common constitutional symptoms; however, unlike GCA, signs and symptoms of cardiac disease or renal predominate. Additionally, women of childbearing age, especially those of Asian descent are more commonly affected.
- Granulomatosis with polyangiitis (see previous section)
- Polyarteritis nodosa (see previous section)

# Module Summary

- Vasculitis encompasses a variety of disorders affecting the vascular system
- The vessel of involvement impacts the different characteristic patterns of clinical involvement
- The pathophysiologic vascular changes also impact the clinical presentations
- Cutaneous findings are a direct result the vascular changes
  - Cutaneous lesions can reflect the size of the affected vessel
  - Cutaneous lesions can also reflect the histologic/physiologic vascular changes
- Clinical findings, laboratory studies and histologic evaluation are best used in combination to make the correct diagnoses