Remembering GPA

Not To Be Missed…

Jan D. Zieren, DO, MPH, FACOFP*dist*

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VALUES | EDUCATION | SERVICE

DISCLOSURES

Speaker has no disclosures.

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Granulomatosis with Polyangiitis

GPA (Formerly known as Wegener's Granulomatosis)

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OBJECTIVES

- **Describe** – History and Classification of GPA
- **Distinguish** – Etiology & Pathophysiology
- **Classify** – Impact of GPA disease
- **Interpret** – presenting signs and laboratory tests for diagnosing GPA
- **Integrate** – awareness of treatments and referrals required for GPA patients
- **Evaluate** – efficacy of treatments and monitoring of GPA patients

HISTORY

1897 – McBride - first description of patient

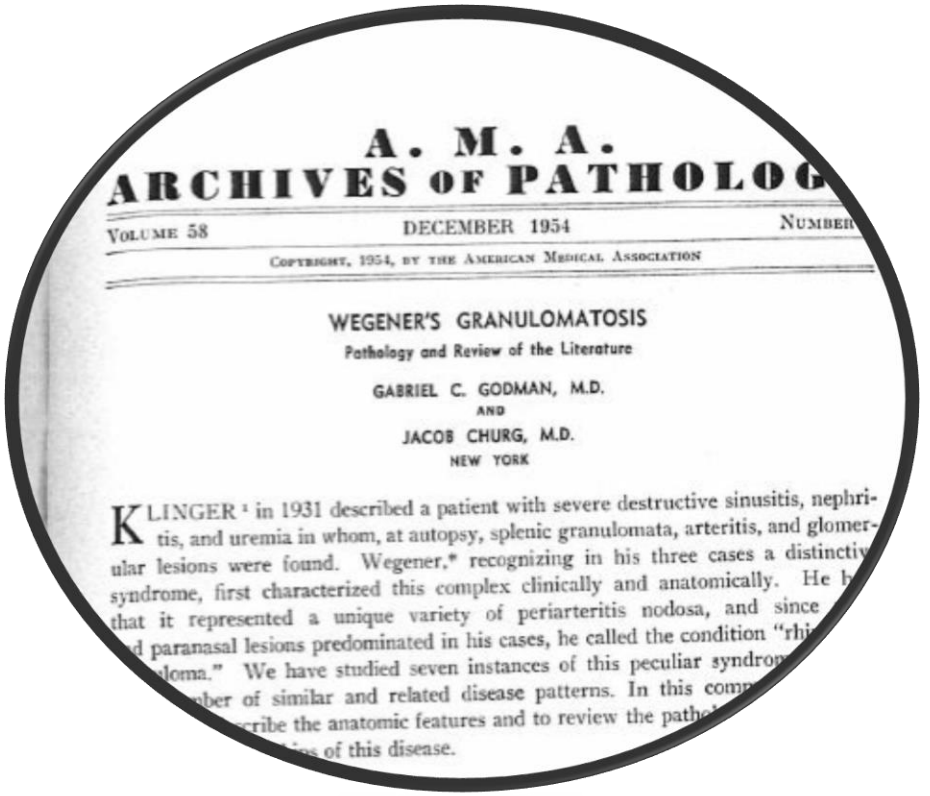
1931 - Klinger - described symptoms and presentation sequence of a patient

1936 - Wegener – published three patients with similar findings as a syndrome

1954 - Godman and Churg – identified three characteristic pathologic features

referred to as Wegener's Granulomatosis

2011 - Name officially changed to GPA or **granulomatosis with polyangiitis** (Wegener's)



A. M. A.
ARCHIVES OF PATHOLOG

VOLUME 58 DECEMBER 1954 NUMBER

WEGENER'S GRANULOMATOSIS

Pathology and Review of the Literature

GABRIEL C. GODMAN, M.D.
AND
JACOB CHURG, M.D.
NEW YORK

KLINGER [1] in 1931 described a patient with severe destructive sinusitis, nephritis, and uremia in whom, at autopsy, splenic granulomata, arteritis, and glomerular lesions were found. Wegener,* recognizing in his three cases a distinctiv syndrome, first characterized this complex clinically and anatomically. He h that it represented a unique variety of periarteritis nodosa, and since d paranasal lesions predominated in his cases, he called the condition "rhi loma." We have studied seven instances of this peculiar syndro ber of similar and related disease patterns. In this comp cribe the anatomic features and to review the pathe ies of this disease.

CLASSIFICATION of GPA

- Autoimmune
- **Vasculitis/Polyangiitis** (small vessels) –
- **Necrotizing** Granulomatous inflammation
- **Systemic** vasculitis

GRANULOMATOSIS WITH POLYANGIITIS

AMERICAN COLLEGE of RHEUMATOLOGY

ACR classification criteria for Granulomatosis with Polyangiitis
(formerly, Wegener's Granulomatosis)

Classification Criteria

1. **Nasal /Sinus or Oral inflammation**

   Painful or painless oral ulcers or purulent or bloody nasal discharge.

2. **Abnormal chest radiograph**

   Pulmonary **nodules**, fixed pulmonary infiltrates or pulmonary cavities.

3. **Abnormal urinary sediment**

   Microscopic **hematuria** with or without red cell casts.

4. **Granulomatous inflammation**

   Biopsy of an artery or perivascular area showing **granulomatous** inflammation.

The presence of two or more of these four criteria yields a sensitivity of 88 percent and a specificity of 92 percent.

CHAPEL HILL Criteria

- Necrotizing **granulomatous inflammation of the upper and lower respiratory tracts**
- Necrotizing glomerulonephritis - common – not essential for the classification
- Necrotizing **vasculitis of small *(and medium-size)* vessels**

SYSTEMIC VASCULITIS

- Primary Vasculitis Syndrome
  - Non-Infectious
- Secondary Vasculitis Syndrome
  - Associated with Underlying Conditions
    (Connective Tissue Disorders; Tumors; Infection; Drug Induced)

Primary VASCULITIDES

- LARGE vessel disease –
  - Giant Cell Arteritis
  - Takayasu's Arteritis
- MEDIUM vessel disease –
  - Polyarteritis Nodosa (PAN)
  - Kawasaki's Disease
- SMALL vessel disease –
  - Immune Complex Vasculitides
  - ANCA-Associated Vasculitides (AAV)

IMMUNE COMPLEX VASCULITIDES
(SMALL VESSEL DISEASE)

- IgA Vasculitis (Henoch-Schönlein Purpura)
- Cryoglobulinemic Vasculitis
- Hypocomplementemic urticarial vasculitis (Anti-C1q vasculitis)
- Anti-glomerular basement membrane disease (Goodpasture Syndrome)

ANCA-ASSOCIATED VASCULITIDES - AAV
(SMALL VESSEL DISEASE)

- Microscopic polyangiitis - **MPA**
- Eosinophilic granulomatosis with polyangiitis - **EGPA**
  (Churg-Strauss syndrome)
- Granulomatosis with polyangiitis - **GPA**
  (Wegener's granulomatosis)

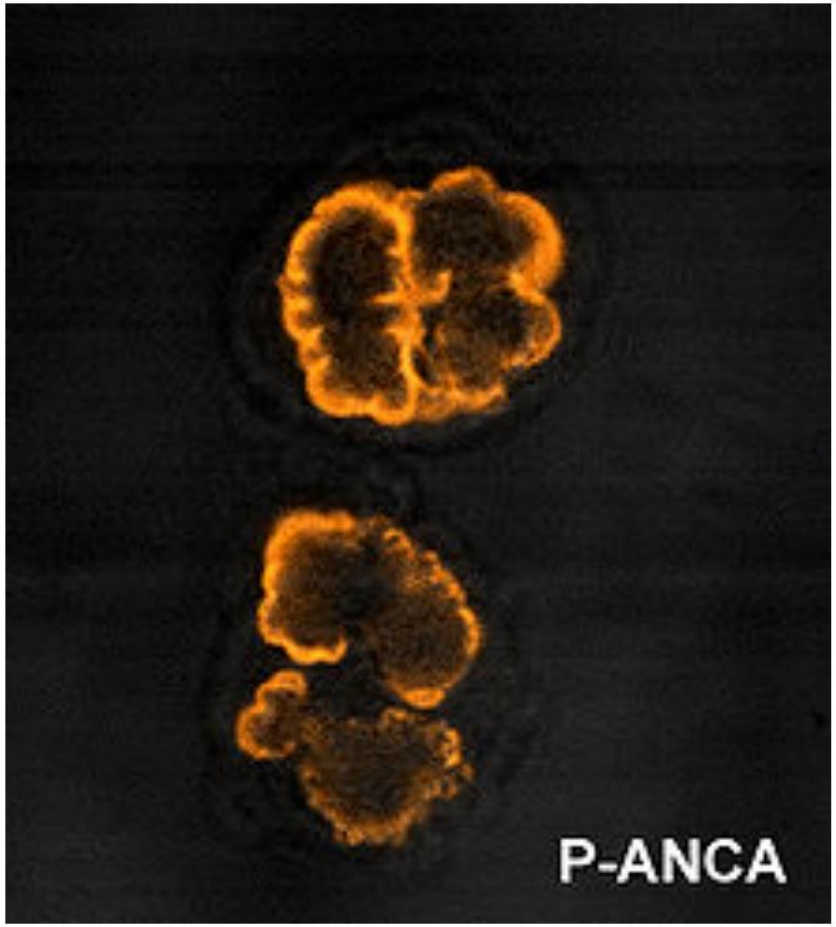
anti-neutrophil cytoplasmic antibodies

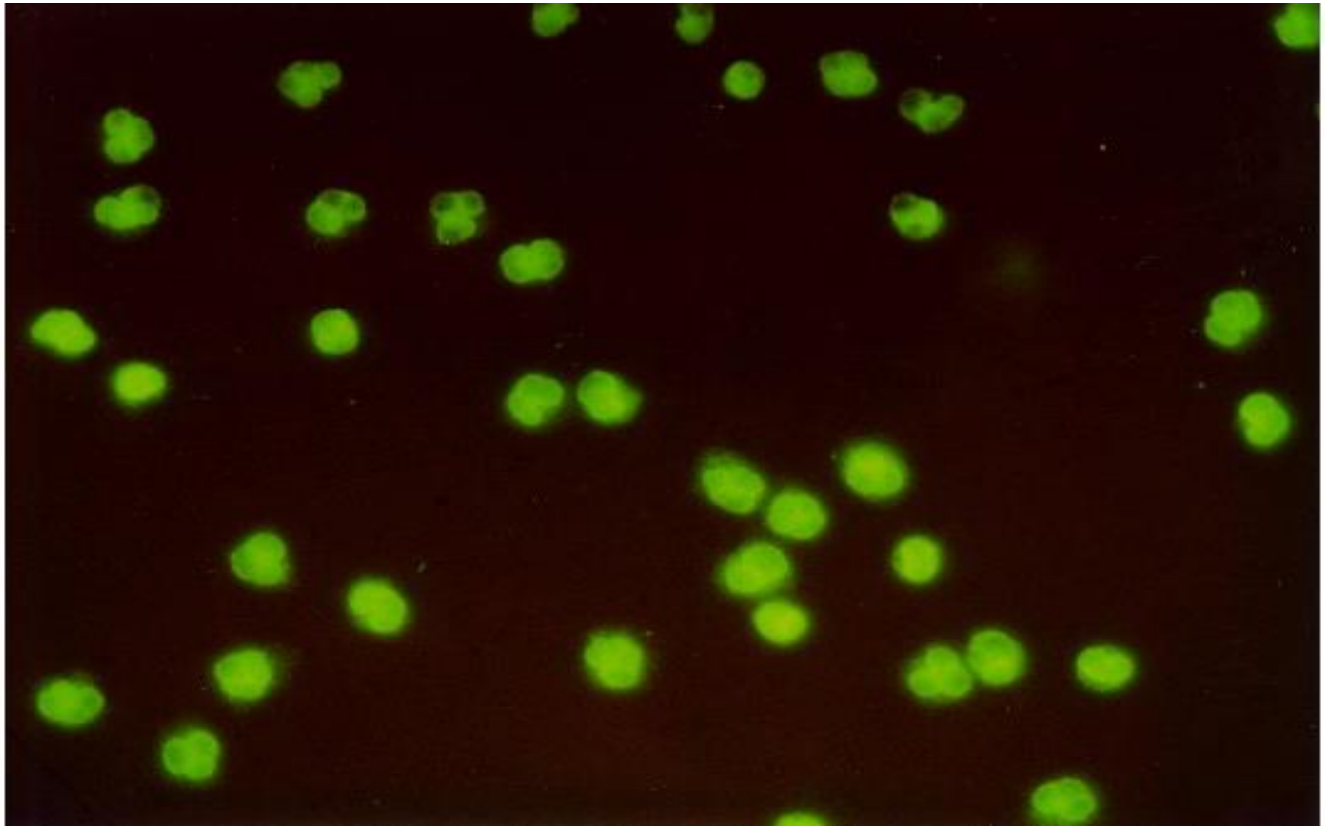
ANCA

Autoantibodies directed against antigens found in cytoplasmic granules of neutrophils

p-ANCA pattern = MPO-ANCA

(myeloperoxidase)

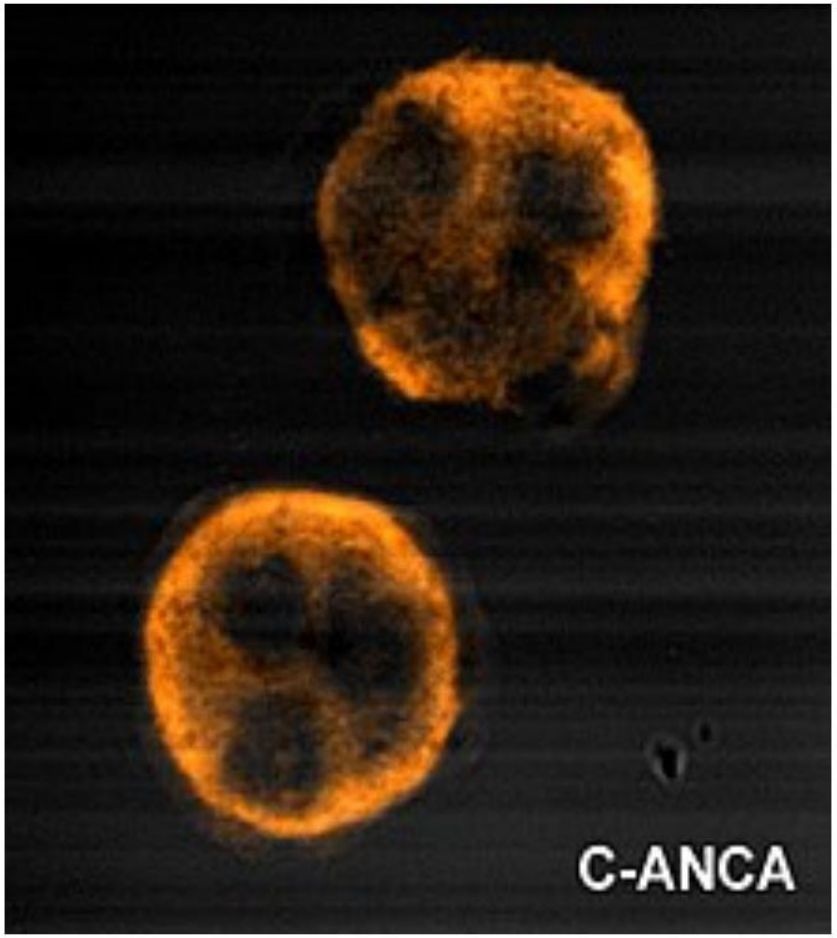


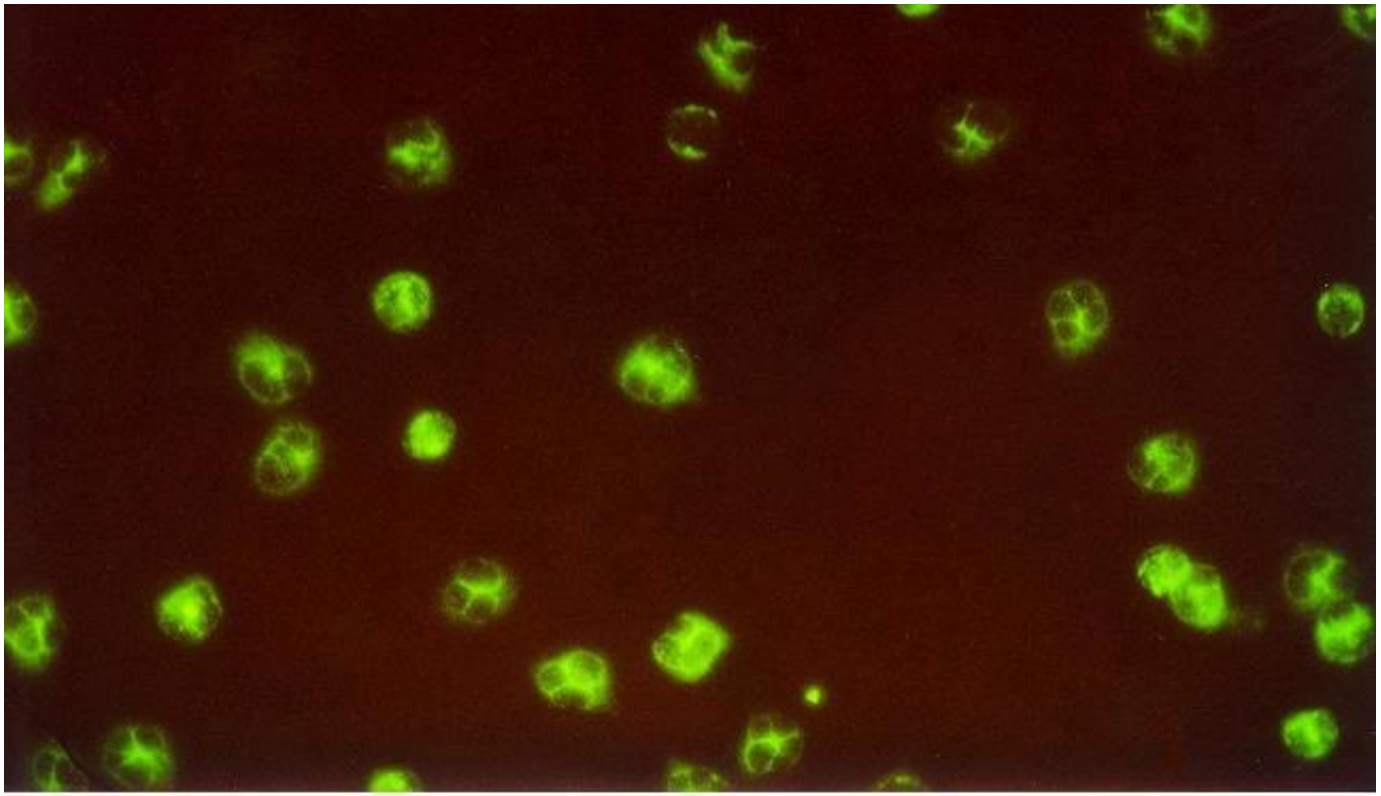


P-ANCA immunofluorescence pattern. Perinuclear antineutrophil cytoplasmic antibody staining pattern by indirect immunofluorescence shows perinuclear staining, whereas cytoplasm is nonreactive. Image courtesy of K. Orr, MD.

c-ANCA pattern = PR3-ANCA

(proteinase 3)





C-ANCA immunofluorescence pattern. Staining for antineutrophil cytoplasmic antibody by indirect immunofluorescence shows heavy cytoplasmic staining, whereas nuclei are nonreactive. Image courtesy of K. Orr, MD.

Role of ANCA in GPA

- PR3-ANCA – specificity 90% for GPA
- ANCA – suggestive of humoral autoimmunity?
- ANCA - serum concentrations do not always correlate with disease activity or relapses
- ANCA – pathogenic role?

PATHOPHYSIOLOGY

- Granulomatous inflammation
- Vasculitis targets small arteries and arterioles
- Renal = necrotizing glomerulonephritis
- ANCA marker - ? Direct pathogenic role
- Autoreactive PR3-specific T cells
- B cells may play a key role in disease pathogenesis

ETIOLOGY

- Poorly understood - Unknown etiology
- Categorized as noninfectious
- Lack of evidence for a causative infectious agent
- Autoimmune inflammatory process
- Responds to immunosuppressive therapy
- Characteristic granulomatous inflammation -

ETIOLOGY – Risk Factors

- Genetics – predisposed, then triggered?
- Infections (?) – bacterial/mycobacterial/fungal/viral
- Chemicals – pollution, smoking
- Toxins – solvents, inhaled toxins
- Environmental – silica, heavy metals – farming –
- Pharmacologic (?) – secondary form =
  drug induced ANCA-associated vasculitis

EPIDEMIOLOGY

Incidence

- 5-10 cases / million in U.S.
- Equal frequency males and females
- Peak incidence – adults
- Rare in childhood/young adults

Prevalence

- US – 3/100,000 individuals
- Northern European descent
- France – 22 per million inhabitants in 2000
- Exceedingly rare in Africa and Japan

Disease Course

90% of patients into remission with treatment

One-quarter relapse within 2 years and over half relapse within 5 years.

All forms of GPA can relapse

ANCA titers do not appear to be predictive of relapse

Two Phenotypes of GPA??

- LOCALIZED – primarily ENT involvement / naturally limited to upper respiratory tract / recurrent and refractory

- DIFFUSE – manifest through additional renal involvement – more serious initially, relapse less common

Morbidity

- Relapses
- Refractory cases
- Side-effects of therapy
- Disease related co-morbidities
- Infections

Mortality

- *Initial mean survival rate = 5 months*
- Current (since the 1970s) 5 year survival > 80%

Main causes of mortality in first year

infection (32%) and kidney failure (18%)

- Non-renal (limited disease) – mortality rate up to 40%

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GARY GILES, BS

CASE - PERSONAL INTERVIEW

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DIAGNOSIS of GPA

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Clinical Presentation

Systemic signs/symptoms

Localized or visceral signs/symptoms

Constitutional Symptoms

- Fever
- Night sweats
- Malaise
- Arthralgia and/or Myalgia
- Weight loss

Upper Respiratory Symptoms

- Sinusitis
- Constant runny nose
- Bloody noses
- Ulcers or sores around nares
- Ear pain / muffled feeling with hearing loss
- Hoarseness

Lower Respiratory symptoms

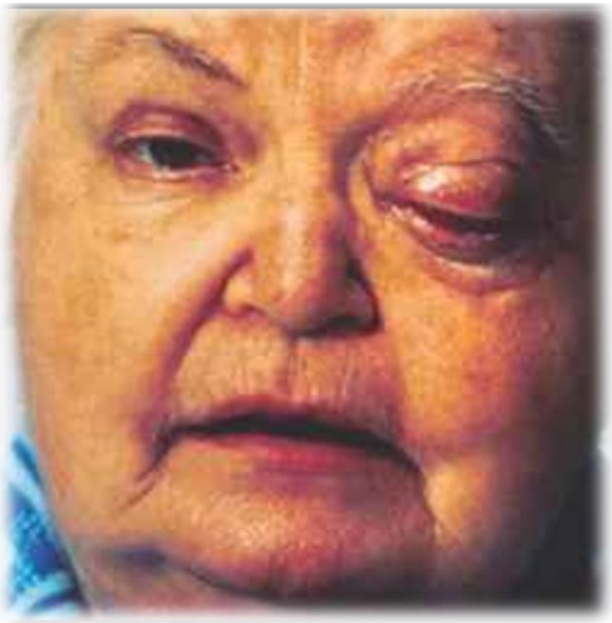
- Cough
- Shortness of breath
- Chest pain
- Hemoptysis

Additional possible presenting symptoms

- Ocular – redness; tearing; pain; visual change
- Cutaneous – purpuric/hemorrhagic skin lesions; ulcerative lesions; nodular lesions
- Musculoskeletal – arthralgias; myalgias; joint swelling; muscle weakness
- Neurologic – headache; numbness or dysesthesias; focal weakness;

ATYPICAL & UNCOMMON
Presentations

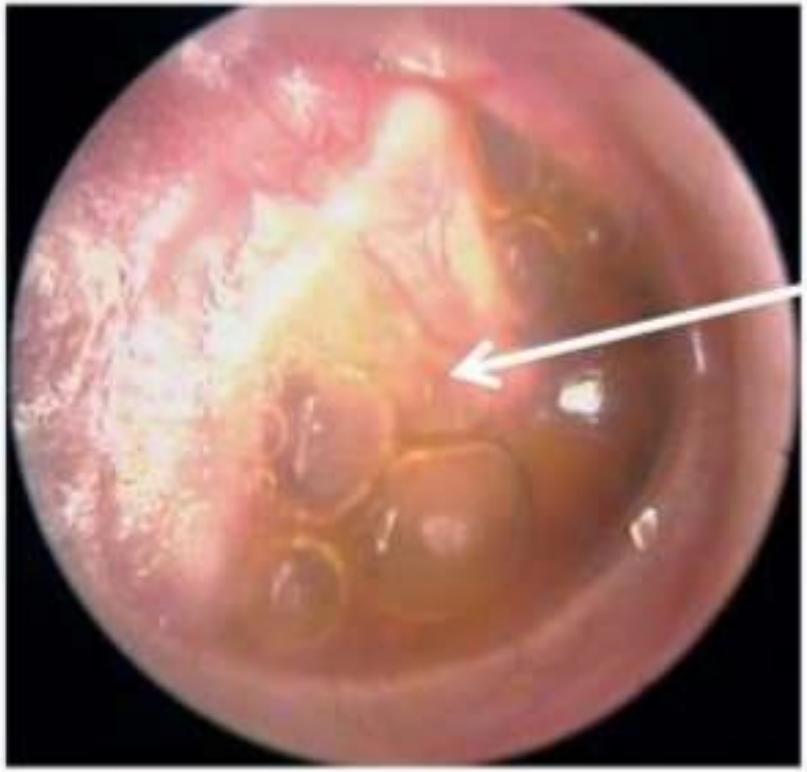
- Massive lower GI bleed – isolated necrotizing granulomatous vasculitis
- Tumefactive subcutaneous mass in the thigh
- Prostatomegaly with obstructive uropathy and advanced renal failure
- GI vasculitis with thrombocytopenia and coagulopathy
- Septic shock from pancolonic, superficial micro-ulceration of mucosa (mimicking ulcerative colitis)



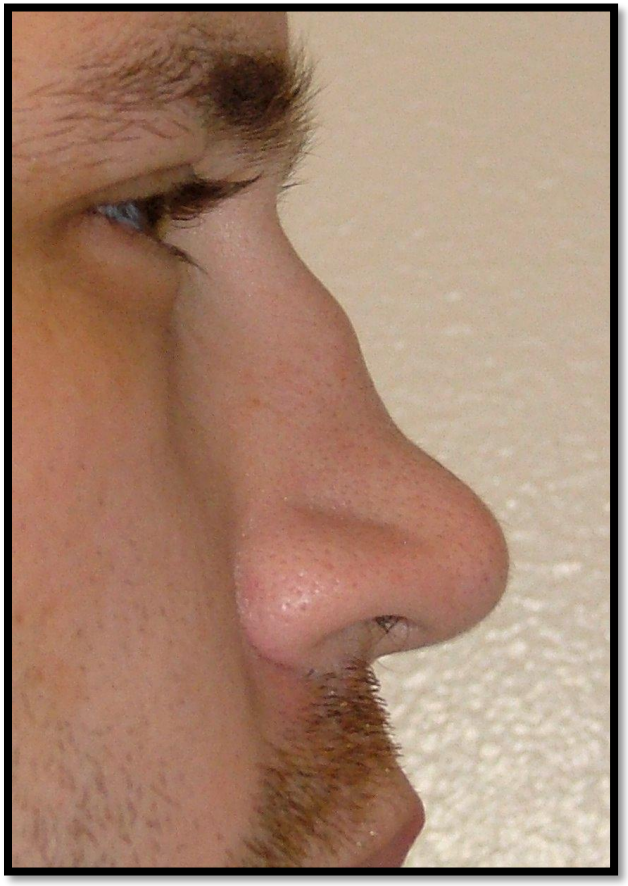
Scleritis in a patient with granulomatosis with polyangiitis (1)
https://upload.wikimedia.org/wikipedia/commons/6/63/Recurrent_scleritis.jpg

Ocular

Serous Otitis Media



Note effusion on otoscopy by fluid line and air bubbles



Saddle-nose appearance

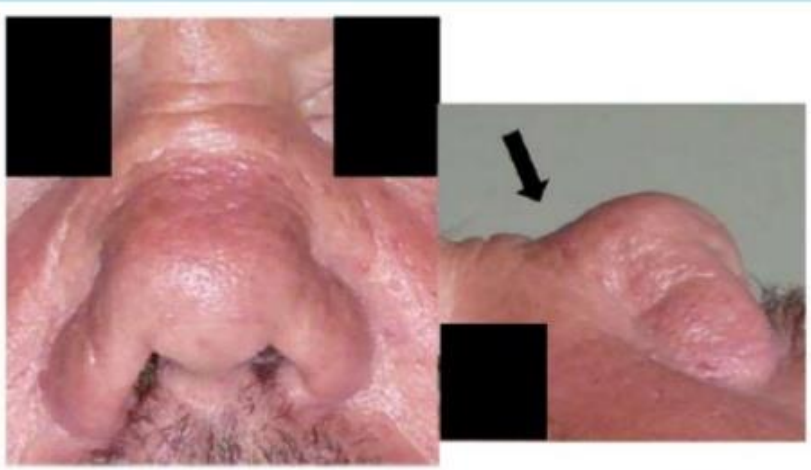
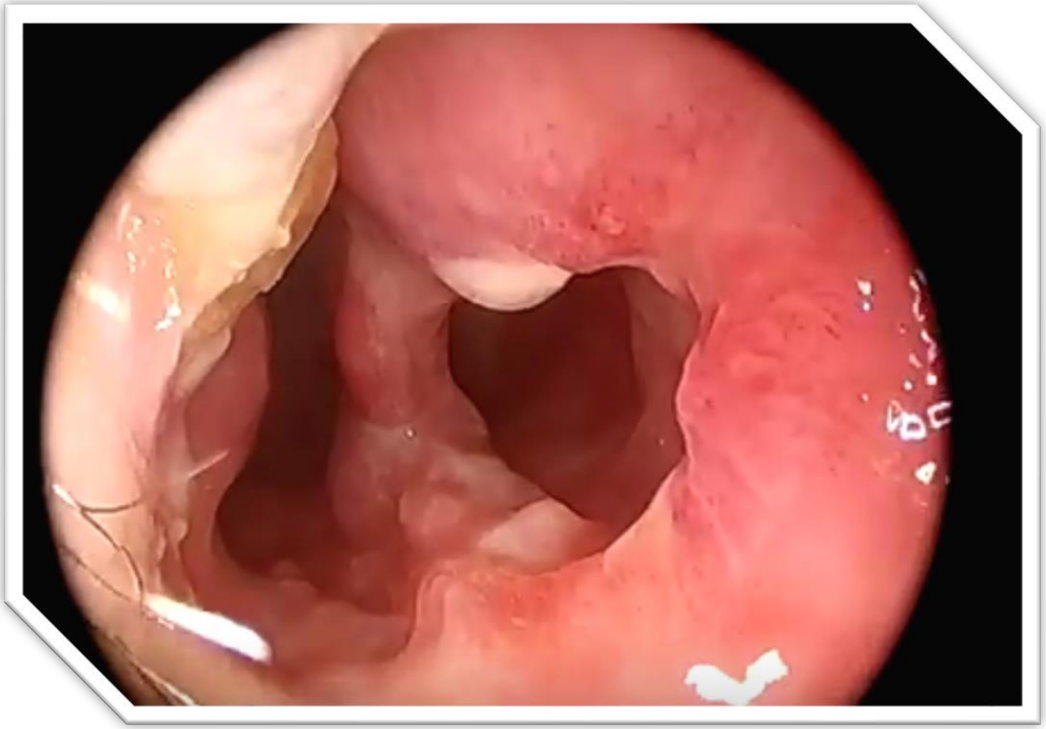


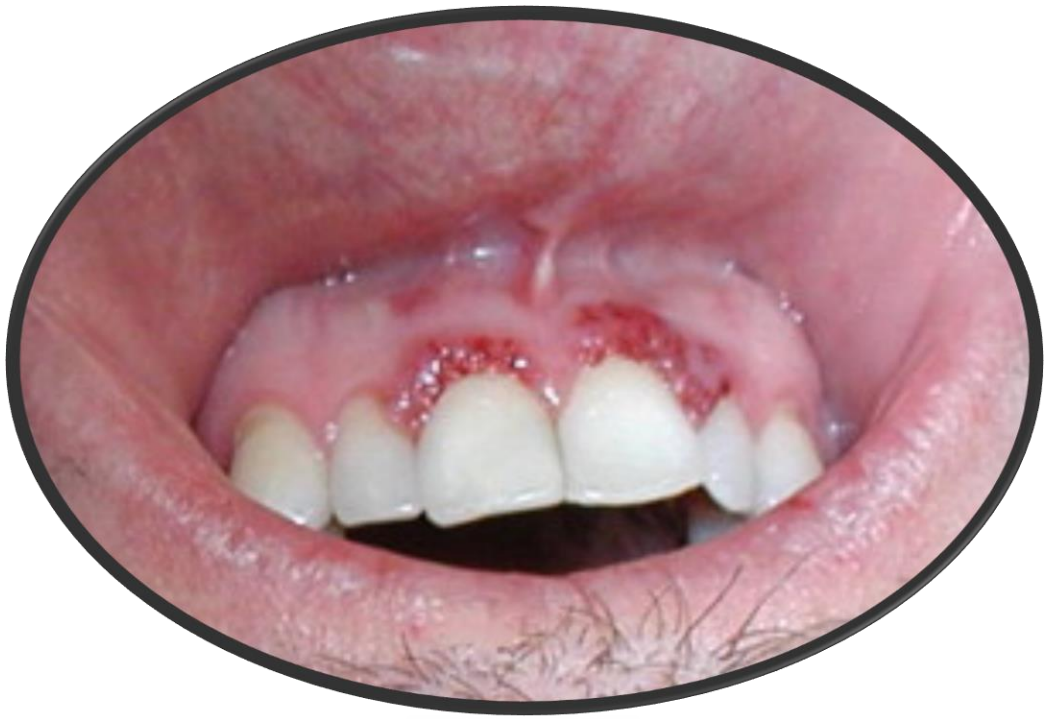
Fig. 1. Nasal deformity with a saddle-nose appearance (black arrow) in GPA.

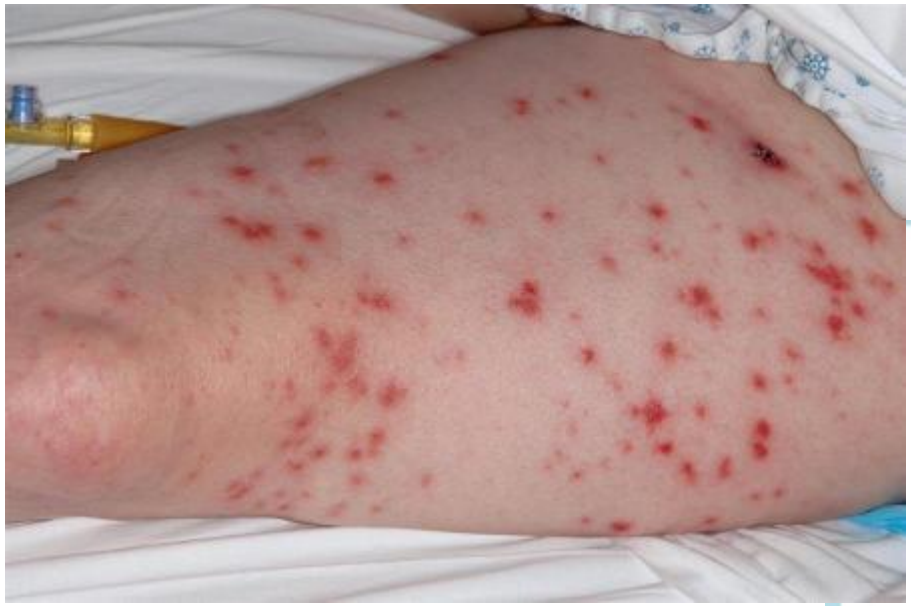
Comarmond C, Cacoub P. Granulomatosis with polyangiitis (Wegener): clinical aspects and treatment. Autoimmunity reviews. 2014;13(11):1121-5.

NASAL SEPTAL PERFORATION



Strawberry gingivitis





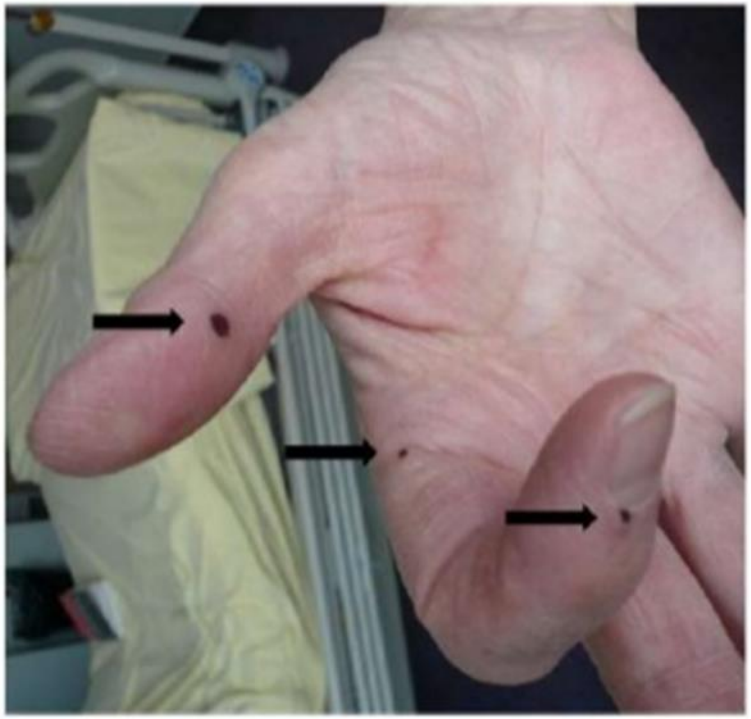


Fig. 2. Necrotic vascular purpura (black arrows) of the upper limbs in GPA.

Cutaneous

Musculoskeletal Findings

Large or medium joint arthritis

Polyarticular arthralgia - symmetrical small joints

Neurologic Findings

Mononeuritis multiplex

Hypo- or hyperesthesia

Cranial nerve paralysis

LABORATORY TESTING

- CMP
- CBC
- ESR/CRP
- Urinalysis
- Urine microscopy
- Rheumatoid Factor
- ANCA

BIOPSY

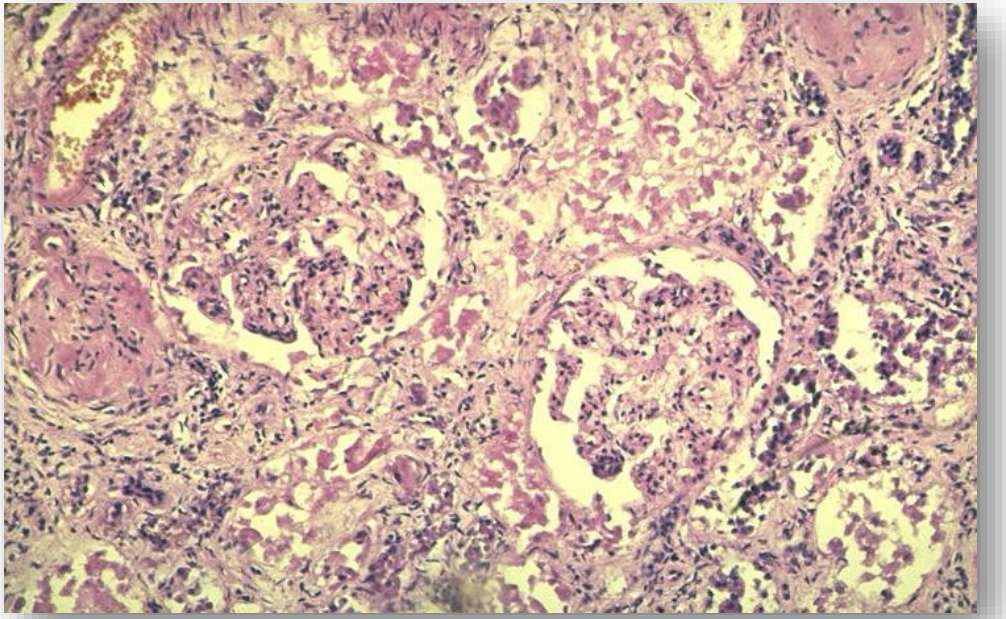
RENAL

LUNG

PERIPHERAL NERVE

MUSCLE

SKIN



INTERPRETING LABS

- Positive ANCA test in setting of triad (otorhinolaryngeal, lung and renal) involvement is generally sufficient to diagnose.

10-20% with renal involvement and up to 50% of those without renal involvement may have a negative ANCA test.

- Additionally might need to test for proteinase 3 antibody (anti-PR3) and myeloperoxidase antibody (anti-MPO)

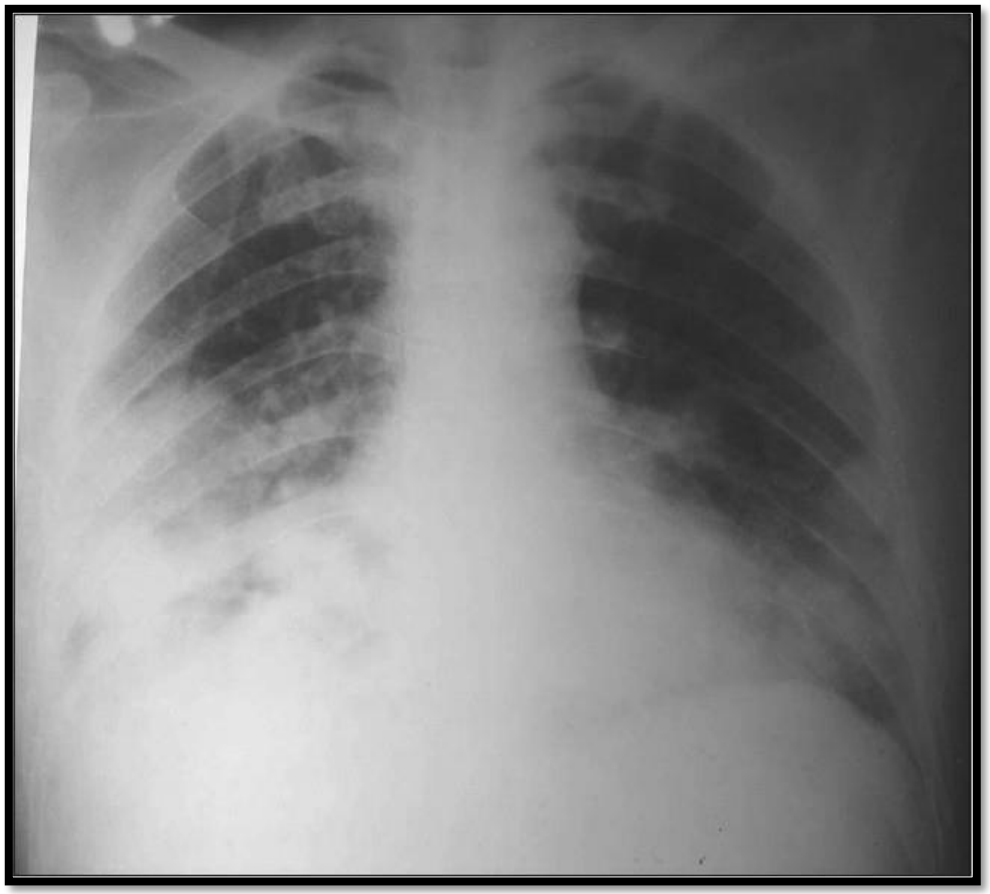
IMAGING STUDIES

Chest x-ray

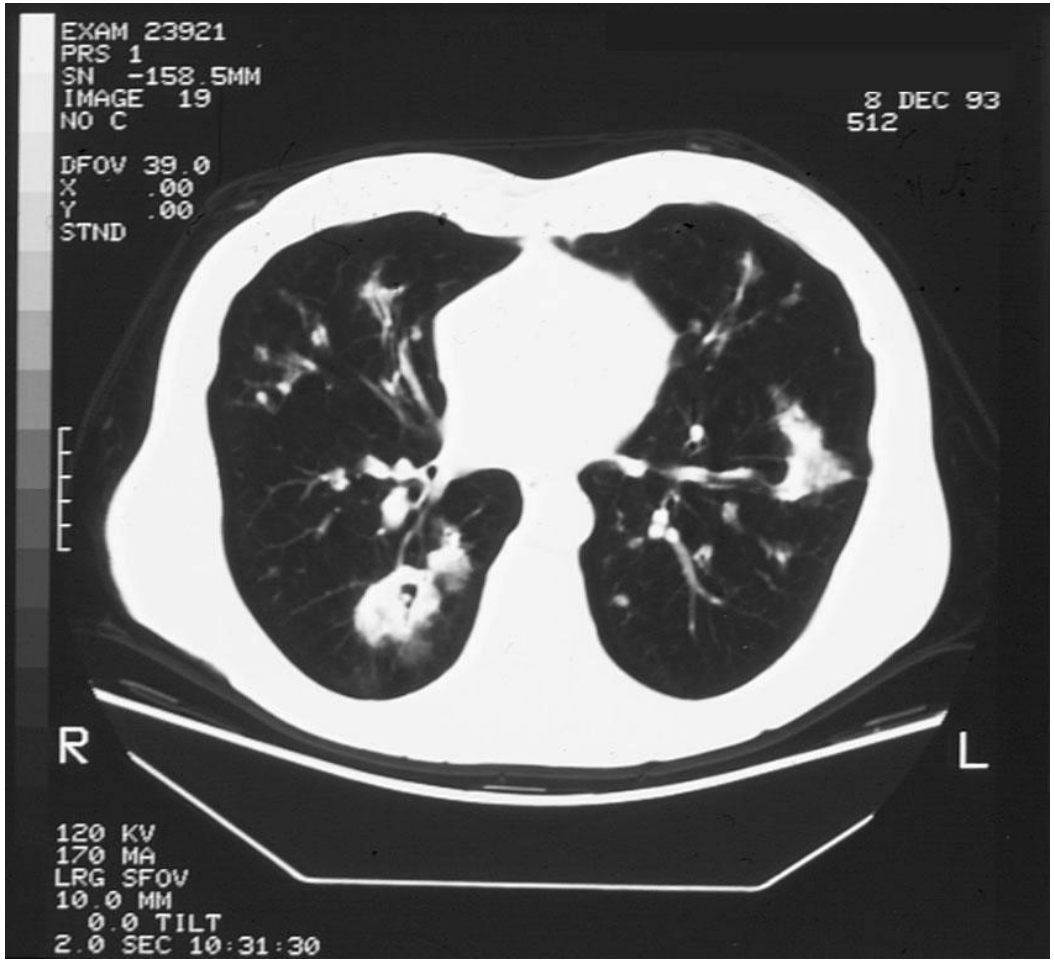
Chest CT

Sinus CT

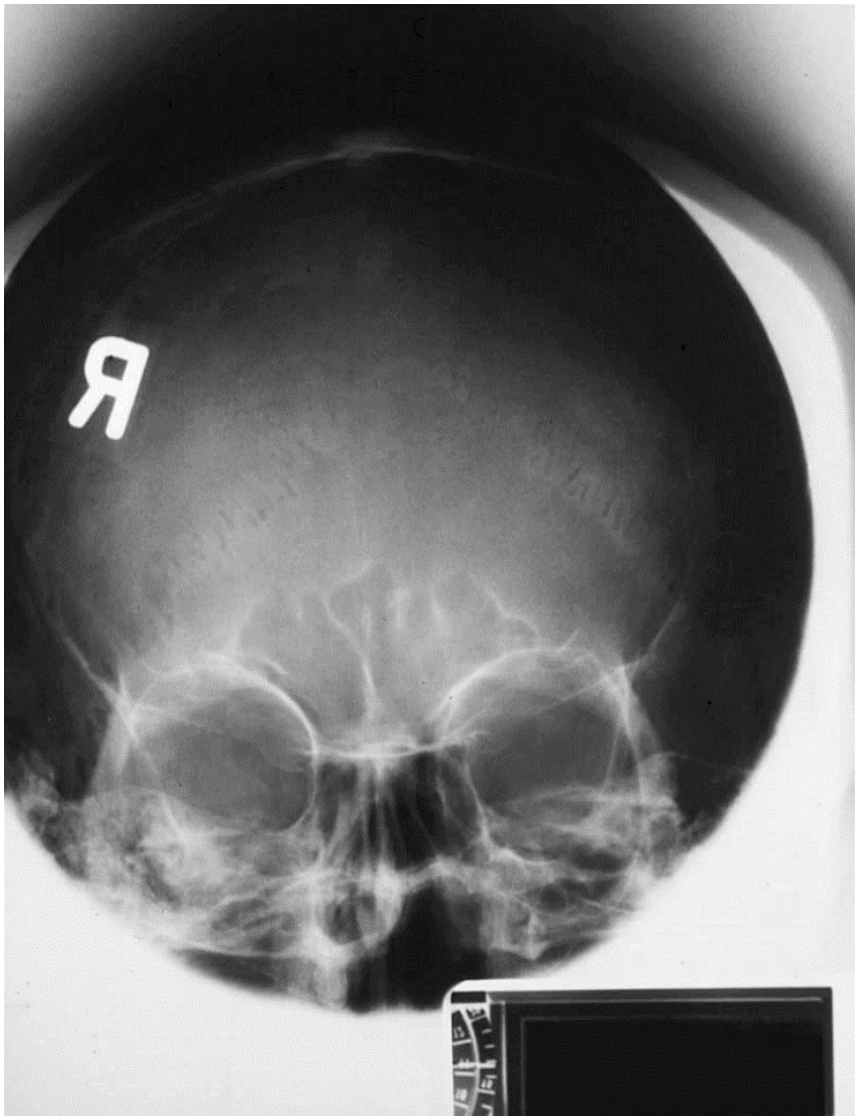
Chest x-ray



CT scan chest



Sinus CT



DIFFERENTIAL CONSIDERATIONS

- Churg-Strauss syndrome
- Microscopic polyangiitis
- Classic polyarteritis nodosa
- Cryoglobulinemic vasculitis
- Henoch-Schönlein purpura
- SLE (and other connective tissue diseases)
- Sarcoidosis
- Systemic Infections
- Goodpasture syndrome
- Cocaine abuse
- Medication – induced vasculitis
- Pulmonary malignancy
- Non-Hodgkin Lymphoma

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TREATMENT of GPA

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TREATMENT

- Inducing remission
- Maintaining remission

- Disease Relapse
- Refractory Disease

INDUCING REMISSION

ACTIVE / ACUTE DISEASE

- LIFE-THREATENING DISEASE
- NON-LIFE-THREATENING
- ISOLATED

INDUCING REMISSION

ACTIVE / ACUTE DISEASE
CORTICOSTEROIDS & CYTOTOXIC AGENTS

- Glucocorticoids
- Cyclophosphamide
- Rituximab

MAINTAINING REMISSION

- **MEDICATIONS**
- ASSESSMENT for disease activity or disease manifestations/relapse
- MONITORING for treatment related toxicity
- MONITORING for immunosuppressive sequelae
- PROPHYLAXIS therapy for *Pneumocystis jiroveci*
- MONITORING for and TREATMENT of corticosteroid-induced osteoporosis

REMISSION MEDICATIONS

- Azathioprine
- Methotrexate
- Rituximab
- Leflunomide
- Tapering glucocorticoid dose
- Prophylactic medications

PROPHYLAXIS CONSIDERATIONS

- Pneumocystis pneumonia
- Hemorrhagic cystitis
- Osteoporosis

MONITORING GPA PATIENTS

- Early detection of relapse
- Early intervention to minimize tissue damage related to active GPA
- Support for chronic damage from prior disease activity
- Monitor for infection, malignancy or further disease/treatment related complications

COMPLICATIONS – of GPA

Disease Related

- Infection
- Chronic Renal Failure
- Saddle nose deformity
- Deafness
- Venous Thromboembolism
- Accelerated Atherosclerosis
- Peripheral Nerve Damage
- Pulmonary Fibrosis
- Blindness

Treatment Related

- Diabetes Mellitus
- Osteoporosis
- Bone Marrow Toxicity
- Gonadal Failure
- Malignancy

DISEASE RELAPSE

- Choice of therapies for remission induction influenced by efficacy and tolerability of previously used agents
- Cyclophosphamide exposure should not exceed 25 g cumulative lifetime
- Treat with alternative – rituximab
- Use immunosuppressive therapy judiciously

REFRACTORY DISEASE

Progressive disease that is unresponsive to glucocorticoids and cyclophosphamide for an adequate period

Treatment-Resistant from toxicity

Progressive decline in renal function

Persistence of/or new appearance of extrarenal manifestations of active vasculitis

FUTURE PROSPECTS

- Intravenous Immunoglobulin
- Mycophenolate mofetil
- 15-Deoxyspergualin
- Antithymocyte globulins
- Alemtuzumab
- Abatacept
- Stem cell transplantation

SUMMARY

- Describe – history and classification of GPA
- Distinguish – etiology and pathophysiology
- Classify – impact of GPA
- Interpret – presenting signs and laboratory tests for diagnosing GPA
- Integrate – awareness of treatments & referrals required
- Evaluate – efficacy of treatments and monitoring of GPA patients

CONCLUSION

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