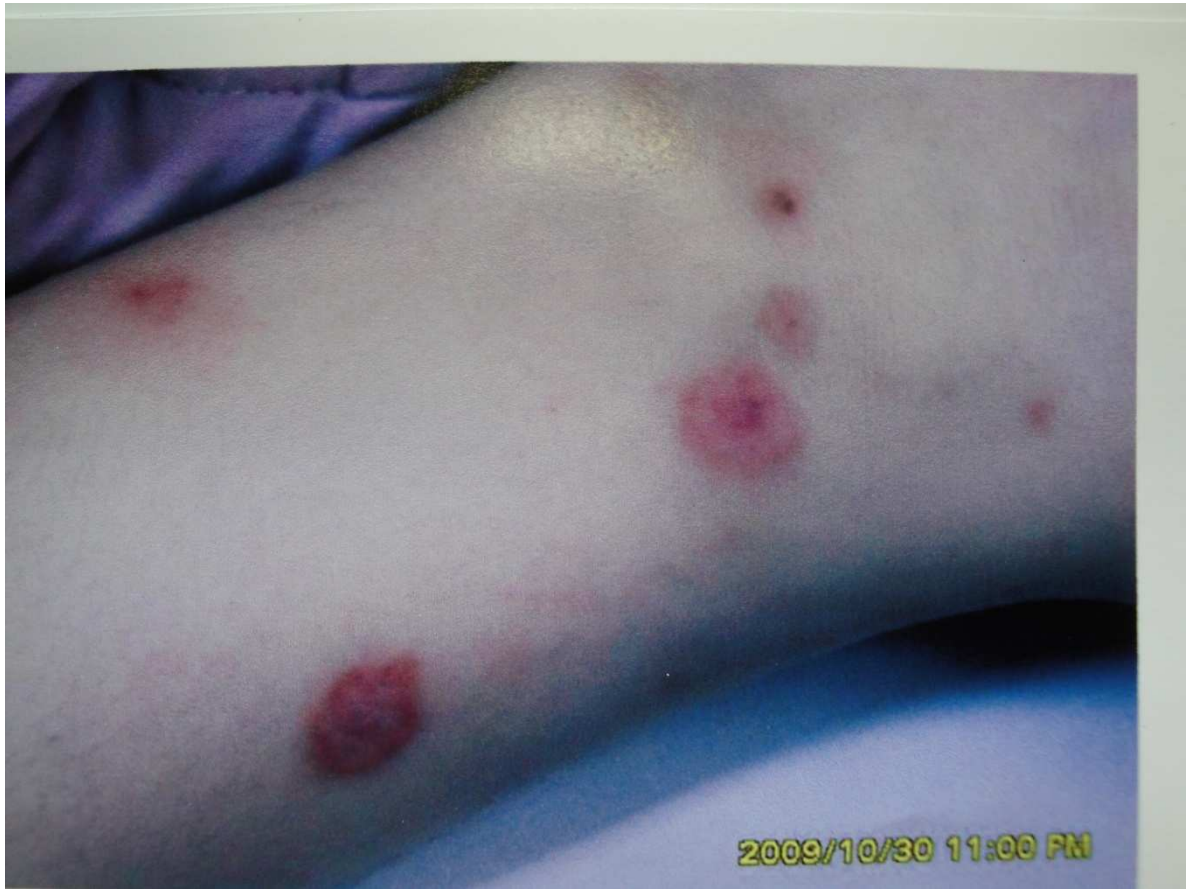
- 11 y/o female
- Admission: 20091103
- 職業:學生
- 種族:Chinese
- 旅遊史:無
- 接觸史:無
- 群聚:無
- 台東家裡種釋迦
- 資料來源: patient and her mother

Chief Complaint

- Skin rash over legs for 5 days



Present Illness-1

- This 11-year-old girl came to OPD due to purpura over legs for several days
- discharged from Hospital 20091005-20091014
- Fresh blood in the sputum 3-4 days prior to last admission
  - Mycoplasma pneumonia
  - Iron deficiency anemia
  - Asthma
  - Suspect pulmonary tuberculosis

Present Illness-2

- Two months ago, she began to have spontaneous epistaxis for several times.
- Her purpura was noted but subsided several days later at that time
- lower leg pain while walking since two months ago
- She couldn't walk on her own due to progressive muscle pain
- Lower leg edema and oral ulcers noted usually
- still mild cough with sputum recently

Past History

- just discharged 20091005 to 20091014
  - Erythromycin
  - Hb electrophoresis: no thalassemia
  - Influenza A Ag: negative
  - Acid fast stain of sputumXIII: negative
  - LGI series due to bloody stool by S/A: normal

Family History

- No family history of TB
- Her older female cousin: SLE

Physical Examination

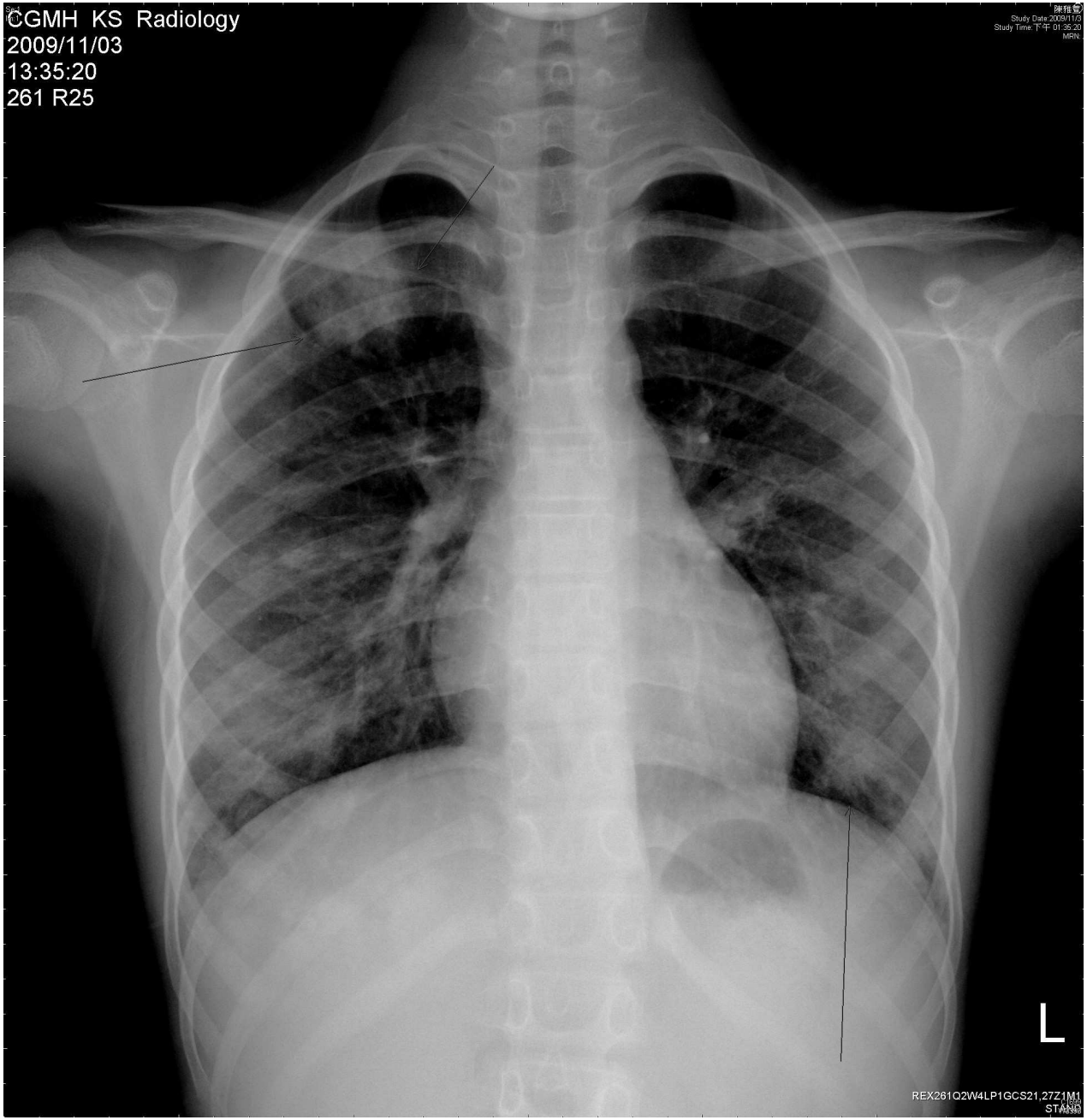
- T:36.4/℃ P:88/min R:18/min BP:129/91/mmHg
- 身高:144CM (20091103) 體重:34KG (20091103)
- consciousness: clear
- respiration: smooth
- Head: no trauma
- Neck: supple LAP: not enlarged
- ENT: np
- Conj:pale
- Sclerae: not icteric
- Throat: mild injected
- Tonsil: not enlarged

- Chest: symmetrical expansion, without chest wall retraction
- BS: bil coarse breathing sounds
- HS: RHB
- Abdomen: soft and flat
- Liver: impalpable
- Spleen: impalpable
- Bowel sound: normoactive
- Ext: lower leg muscle pain, no muscle atrophy,no arthralgia
- Skin: Purpura over lower legs

Laboratory Findings

		20091103 14:13	20091103 14:14
WBC	1000/uL		7.6
RBC	MILON/uL		3.57
HGB	g/dL		8.6
HCT	%		27.8
MCV	FL		77.9
MCH	pg/Cell		24.1
MCHC	g/dl		30.9
RDW-SD	FL		41.0
PLATELET	1000/uL		381
RDW-CV	%		14.3
RETICULCYT	%		1.20
ESR	MM/HR	67	
SEGMENT	%		49.2
LYMPHOCYTE	%		41.7
MONOCYTE	%		3.8
EOSINOPHIL	%		4.9
BASOPHIL	%		0.4

COLOR	Yellow	
TURBIDITY	Clear	
SP.GRAVITY	1.022	
PH	5.5	
LEUKOCYTE	Negative	cell/uL
NITRITE	Negative	mg/dL
PROTEIN	2+ (100)	mg/dL
GLUCOSE	Negative	mg/dL
KETONE	Negative	mg/dL
UBG	0.1	EU/dL
BILIRUBIN	Negative	mg/dL
BLOOD	3+ (200)	cell/uL
RBC	36	/uL
WBC	0	/uL
SQUAMUS	4	/uL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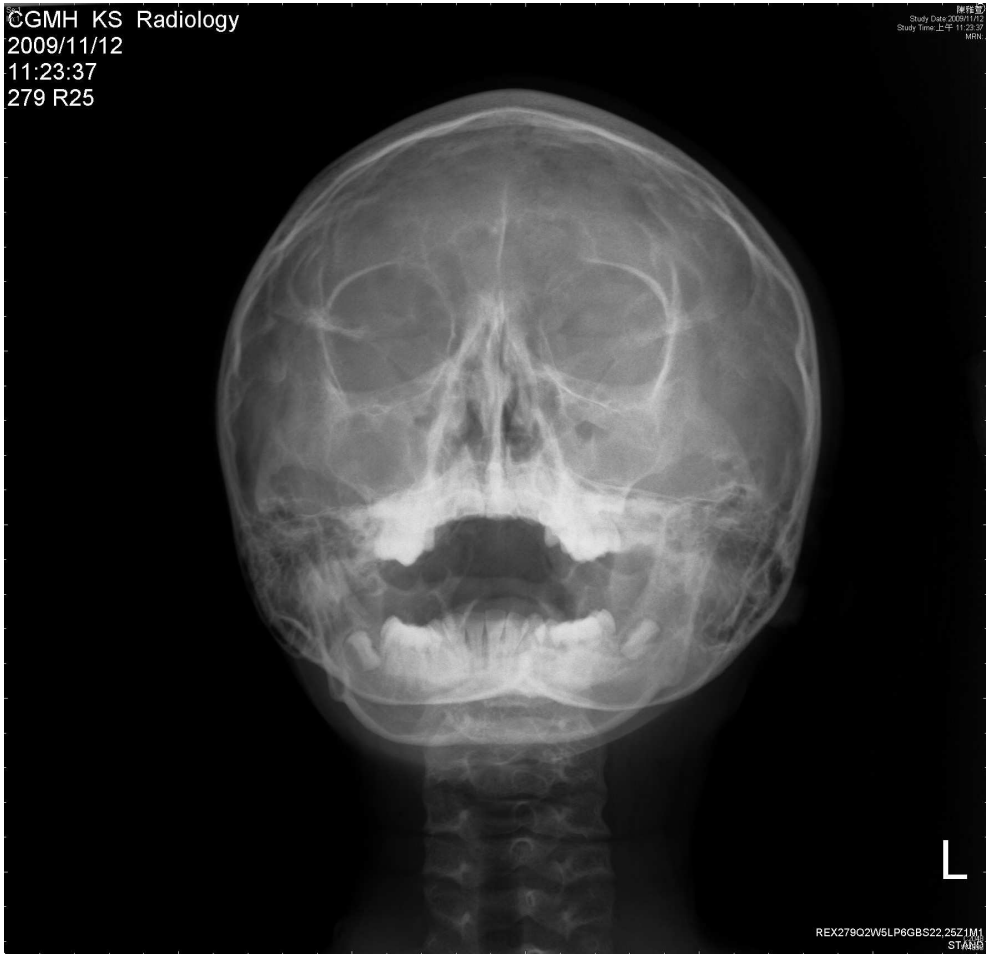
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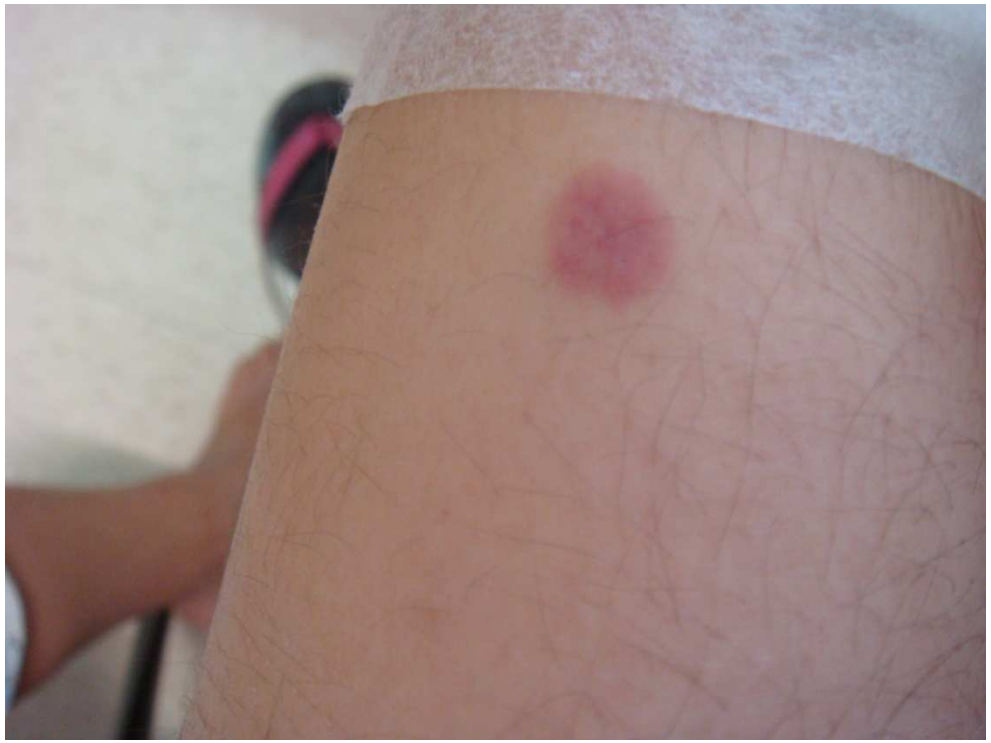
11/19

- Bilateral feet swelling for four days and purpura over legs for two days



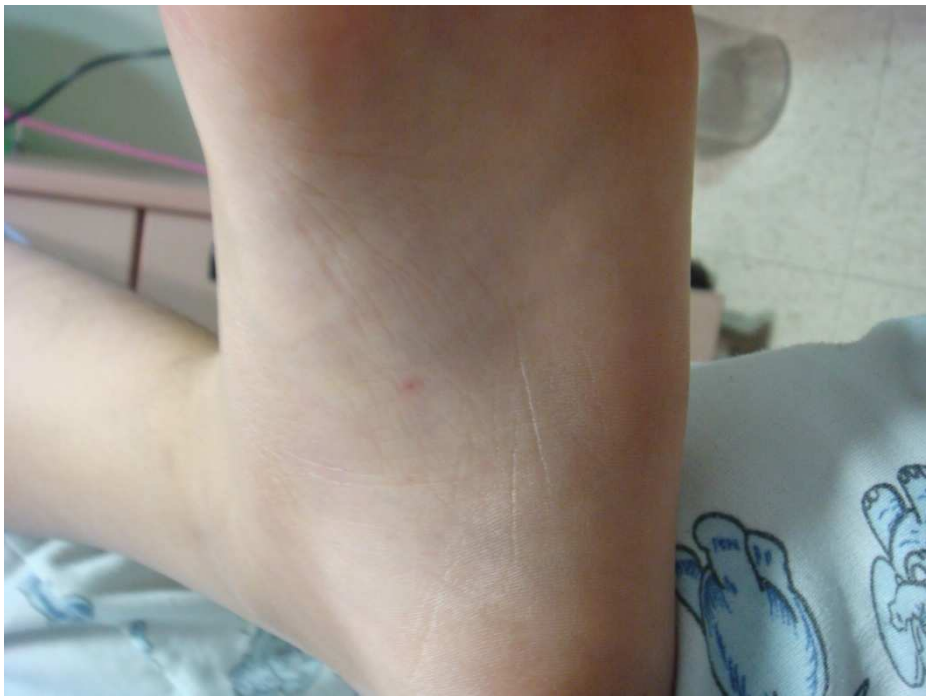


TABLE I. Clinical signs that should raise suspicion for a primary systemic vasculitis

Fever of unknown origin
Unexplained migratory polyarthritis
Mononeuritis multiplex
Rapidly progressive glomerulonephritis
Palpable purpura
Diffuse alveolar hemorrhage
Unexplained infarction in multiple vascular territories
Unexplained multisystem disease

TABLE II. Presentations of vasculitic syndromes to the allergist/immunologist

Vasculitic syndrome	Presentation to allergist/immunologist
GCA	"Sinus" headache
TAK	Headache
WG	Recurrent sinusitis, nosebleed and nasal crusting, otitis media, cough, hoarseness, nonresolving "pneumonia"/pulmonary infiltrates
MPA	cough ± hemoptysis, nonresolving "pneumonia"/pulmonary infiltrates
CSS	Allergic rhinitis, nasal polyposis, asthma, nonresolving "pneumonia"/pulmonary infiltrates, eosinophilia
PAN	Suspected immunologic disease, postprandial abdominal pain with suspected food allergy
KD	Skin rash, soft tissue edema
Cutaneous vasculitis	Skin lesions in which an allergy or drug reaction might be suspected
CV	Skin lesions in which an allergy or drug reaction might be suspected
HSP	Purpura, soft tissue edema, or both in which an allergy might be suspected; food enterocolitis
UV	Chronic or subacute urticaria, angioedema

Lung lesion, skin lesion and hematuria

- Common
  - SLE
  - Henoch-Schoenlein Purpura
  - Atypical infection
    - Mycoplasma infection
- Less common
  - Goodpasture's Syndrome
  - Wegener's Granulomatosis
  - Cryoglobulinemia

SLE

- Criteria for diagnosis of systemic lupus erythematosus
  - Malar rash: negative
  - Discoid rash: over right leg by picture, no discoid rash now
  - Photosensitivity: negative
  - Oral ulcers: painless lip ulcer, subsided now (+)
  - Arthritis: negative
  - Serositis: negative
  - Pericarditis: negative
  - Renal disorder: Persistent proteinuria: 24 hrs protein: 413.6 mg 2+
  - Neurologic disorder: negative
  - Hematologic disorder Hemolytic anemia:
    - IDC:WEAKLY POSITIVE(1104)/D-COOMBS:NEGATIVE(1104)
    - No reticulocytosis: RETICULCYT 1.20% (Auto:0.6~1.9%)
  - Immunologic disorders: negative: Anti-ENA Screening : Negative
  - Anti-DNA: negative: <12.0 IU/mL
  - Antinuclear antibody: 1:40

- C3 123.00 mg/dL 90-180
- C4 21.80 mg/dL 10-40
- 檢查日期：2009/11/03(二)
-

	Normal Range	Boderline
Anti-Beta2 Glycoprotein 1 IgG: 1.2 U/ml	<10	10-15
Anti-Cardiolipin IgG :2.6 GPL/ml	<10	10-15
Anti-cardiolipin IgM :4.1 MPL/ml	<10	10-15

LA . 40.9/32.7

Mixing Tes . 36.3/32.7

Comment S): NEGA LA

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T-CHOL	158	mg/dL	<170 (<18Y)
TG	132	mg/dL	32-148 (>9Y-18Y)
FERRITIN	75.5	ng/mL	F:10-291 M:22-322

Henoch-Schoenlein Purpura

Table 3 Classification criteria for Henoch-Schönlein purpura

Palpable purpura (mandatory criterion) in the presence of at least one of the following four features:

- Diffuse abdominal pain
- Any biopsy showing predominant IgA deposition
- Arthritis* or arthralgia
- Renal involvement (any haematuria and/or proteinuria)

*Acute, any joint.

- ***EULAR/PReS endorsed consensus criteria for the classification of childhood vasculitides***
- *Ann Rheum Dis. 2006 Jul;65(7):936-41*

Henoch-Schoenlein Purpura

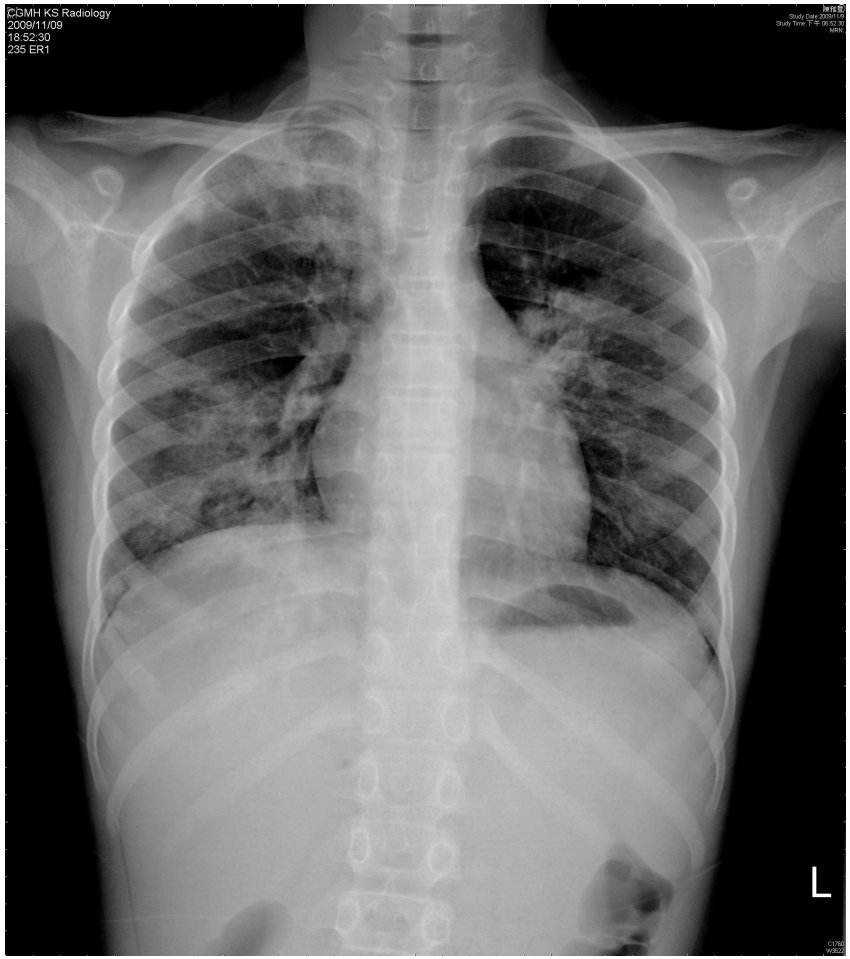
- ESR: 67 MM/HR
- IgA: 273.00 mg/dL (131±60)
- Patients may have a normochromic anemia because of GIB
- Less hemolytic anemia
- In patients with incomplete or unusual presentations, a biopsy of an affected organ (eg, skin or kidney) that demonstrates leukocytoclastic vasculitis with a predominance of IgA deposition confirms the diagnosis
- In children, renal disease is less prevalent/1.8 percent had renal impairment

Atypical infection

Mycoplasma	IgM	IgG
1104	48.4	17.6
1110	47.5	15
1119	57.7	<10

Azithromycin on 11/4,5,6
Doxycyclilne on 11/14-18

11/9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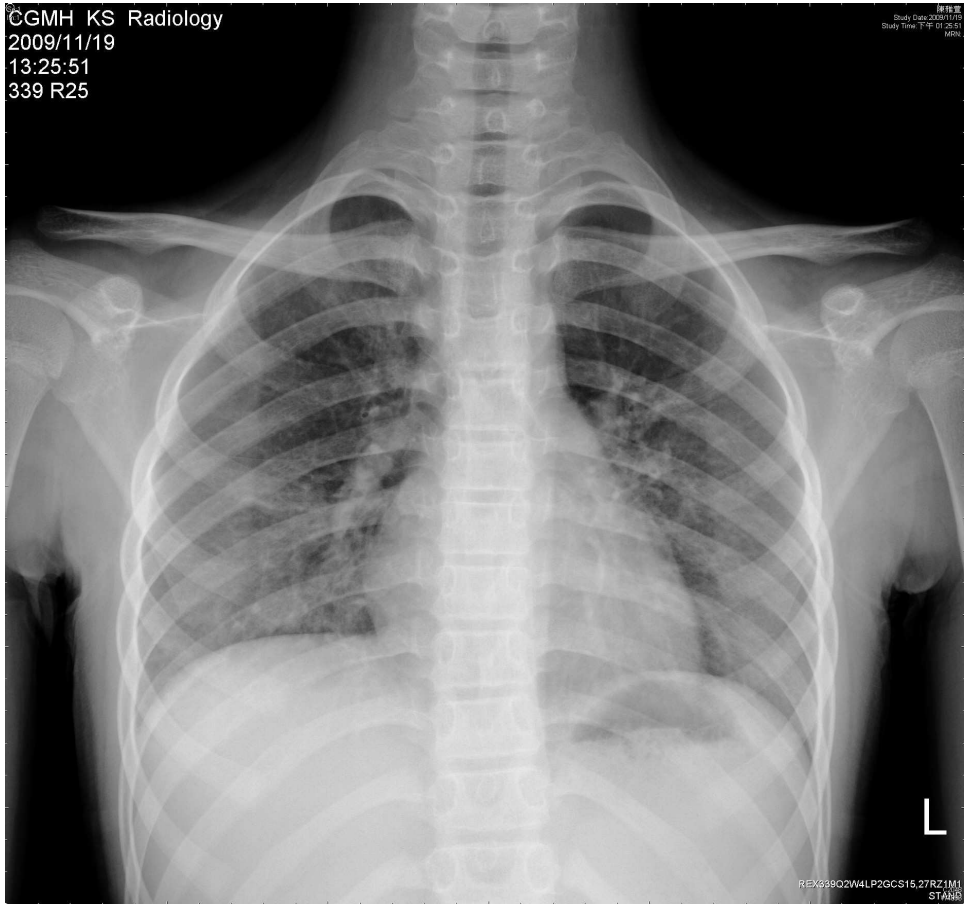
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- A 6-year-old boy presented with an acute infection caused by Mycoplasma pneumoniae associated with respiratory tract and kidney involvement.
- Renal manifestations included acute nephritis with decreased
- The child had an excellent outcome, with rapid normalization of C3 and complete resolution of the acute nephritis.

- Pediatr Infect Dis J. 2003 Dec;22(12):1103-6.
- Acute nephritis and respiratory tract infection caused by Mycoplasma pneumoniae: case report and review of the literature.

Atypical infection

- PPD test: negative
- EB-VCAG EQUIVOCAL 18.1 U/mL
- EB-VCAM NEGATIVE
- CMV IgG NEGATIVE 1.90 AU/mL
- CMV IgM NEGATIVE 0.25 INDEX
- CMV-SV(U) NEGATIVE
- HCV AB NEGATIVE 0.42 S/CO
- ASLO 214.00 IU/mL H (< 200) on 11/6
- ASLO 209.00 IU/mL H (< 200) on 11/19
- Strepto.Ag-U NEGATIVE

Anti-GBM antibody (Goodpasture's) disease

- circulating antibodies are directed against the NC1 domain of the alpha-3 chain of type IV collagen, which is highly expressed in the GBM and alveoli
- usually present with rapidly progressive glomerulonephritis: acute renal failure, nephritic urine sediment, and non-nephrotic proteinuria.
- Pulmonary involvement (alveolar hemorrhage) is present in 60 to 70 percent of patients

Diagnosis of Goodpasture's disease

- demonstration of linear deposits of IgG (which represent binding of anti-GBM antibodies to the GBM) in the kidney biopsy specimen is diagnostic
- Serologic testing for anti-GBM antibodies

- ANCA: almost always anti-myeloperoxidase, or P-ANCA), since up to 40 percent of patients with anti-GBM antibody disease also test positive for ANCA
  - 11/12: P-ANCA(Anti-MPO): 1.2 U/ml
  - 11/19: P-ANCA(Anti-MPO) : 0.6 U/ml

Wegener's granulomatosis

Table 6 Classification criteria for Wegener's granulomatosis

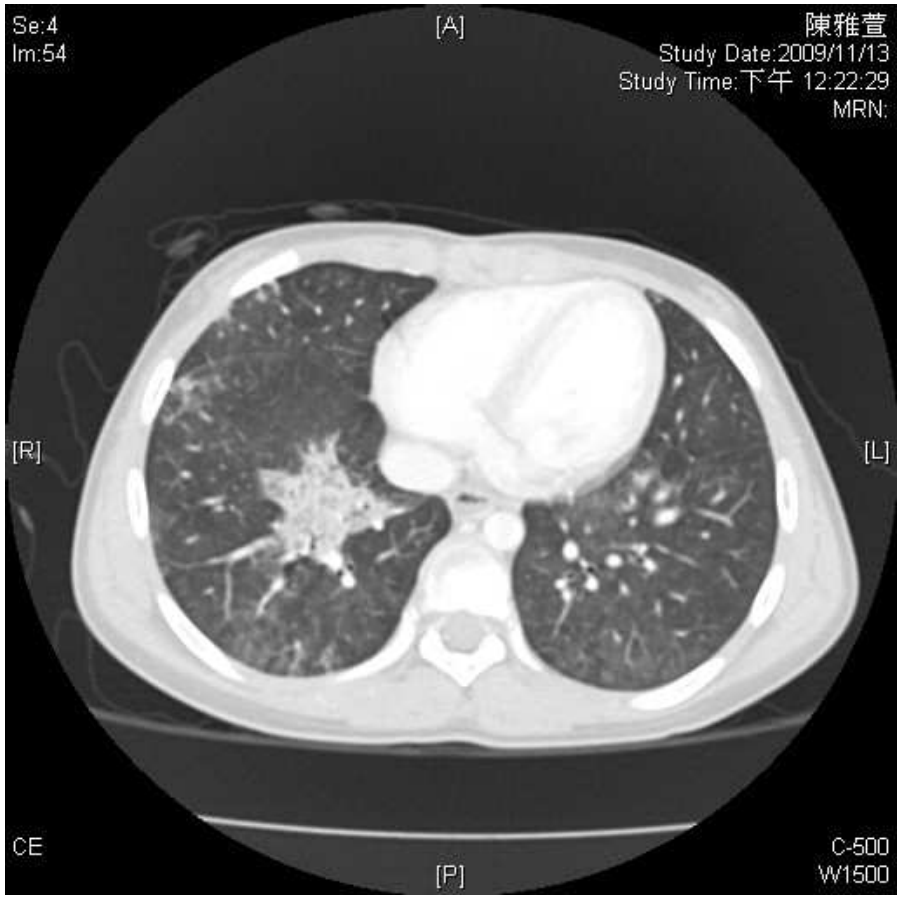
Three of the following six features should be present:

- Abnormal urinalysis*
- Granulomatous inflammation on biopsy†
- Nasal sinus inflammation
- Subglottic, tracheal, or endobronchial stenosis
- Abnormal chest x ray or CT
- PR3 ANCA or C-ANCA staining

*Haematuria and/or significant proteinuria.
†If a kidney biopsy is done it characteristically shows necrotising pauci-immune glomerulonephritis.
ANCA, antineutrophil cytoplasmic antibodies.

11/12: C-ANCA(Anti-PR3): 32.4 U/ml
11/19: 36.4 U/ml

- Wegener's granulomatosis is a rare disease in childhood
  - ***EULAR/PReS endorsed consensus criteria for the classification of childhood vasculitides***
  - *Ann Rheum Dis. 2006 Jul;65(7):936-41*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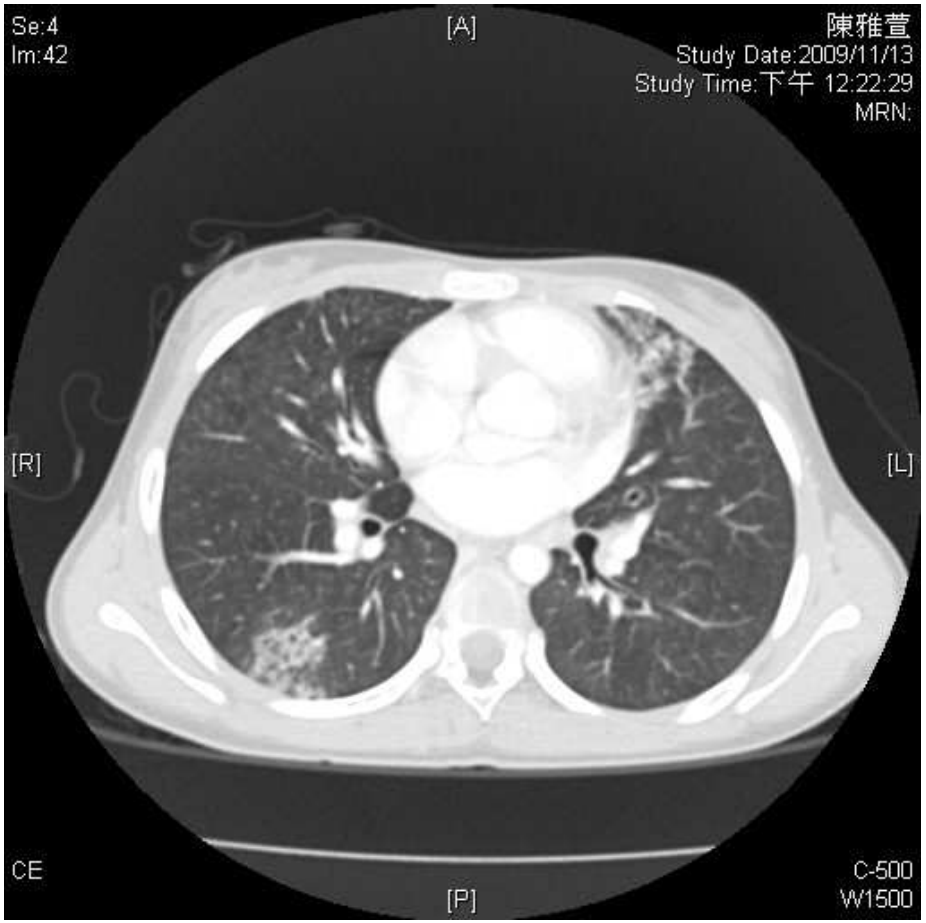
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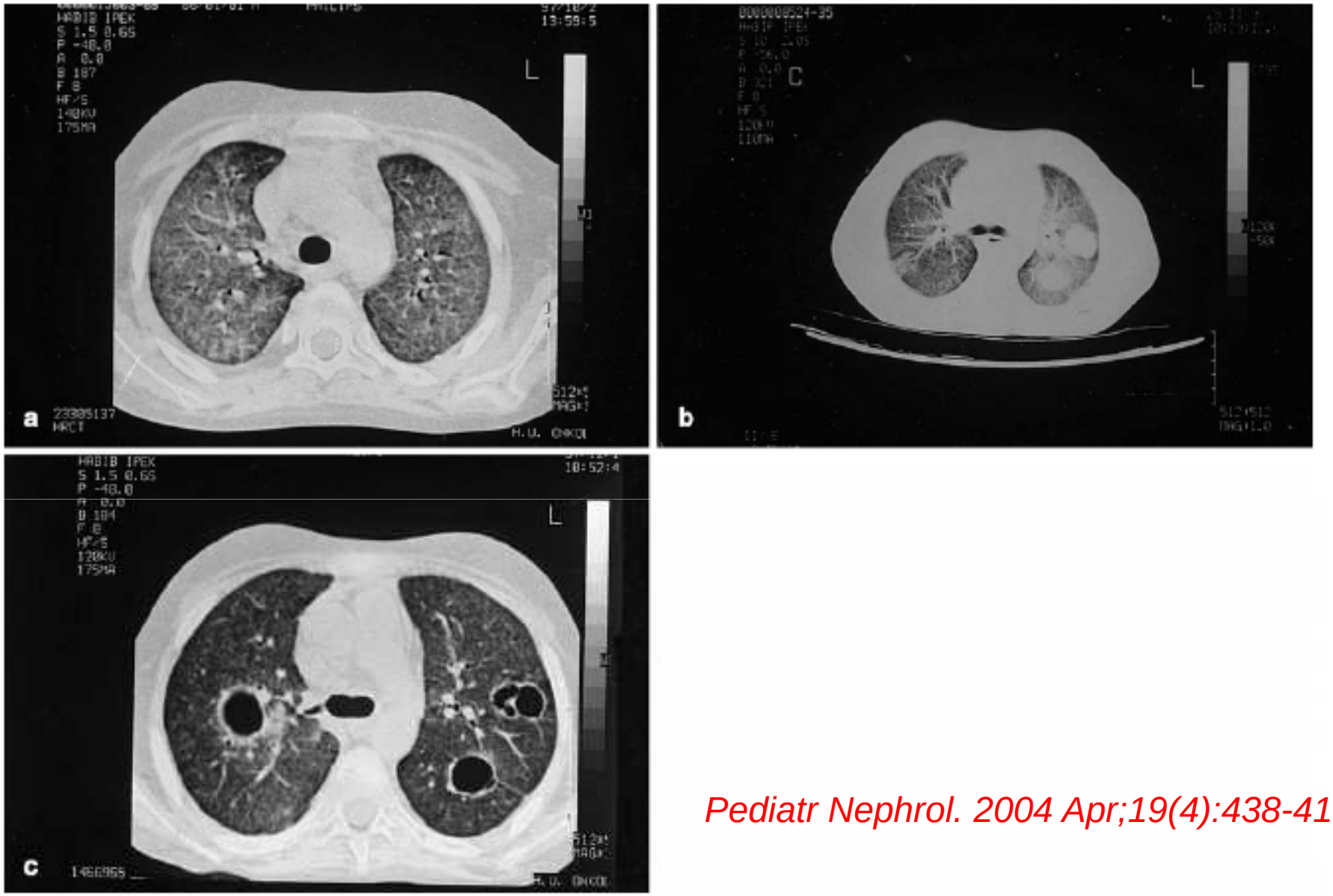
- Subglottic, tracheal, or endobronchial stenosis was added as a new criterion as these features were noted to be frequent in childhood disease.
- CT is almost always a part of investigation, which no longer relies on a plain chest radiography

Computed tomography

- CT scanning has also shown the frequent presence of other findings that may suggest the diagnosis of vasculitis, including:
  - Blood vessels leading to nodules and cavities (feeding vessels).
  - Small peripheral, wedge-shaped densities suggesting pulmonary microinfarction
  - Cuffing of the bronchovascular bundle in a lobar segmental and subsegmental distribution, often associated with narrowing of the bronchial lumen.
  - Enlarged, irregular and stellate-shaped peripheral pulmonary arteries (the "vasculitis" sign)



Pediatr Nephrol. 2004 Apr;19(4):438-41

Fig. 2 a Ground-glass appearance of the lungs on the first computerized tomogram of the thorax. b One month later: pulmonary nodules. c Two months later: cavity formations

C-ANCA

- the sensitivity of cANCA: 28% to 92%, depending on disease expression/specificity: 80% to 100%.
- A positive C-ANCA is usually present and helps distinguish isolated alveolar hemorrhage due to Wegener's granulomatosis from other causes, such as polyarteritis nodosa, idiopathic pulmonary hemosiderosis, systemic lupus erythematosus, and Goodpasture's syndrome

Pathogeneses

- Granulomatous reactions occur, possibly as the result of sensitized T lymphocytes reacting with antigen and releasing various cytokines that recruit macrophages to the site of injury.
- The activated macrophages release lysosomal enzymes and cause local tissue injury
- The most commonly cited hypothesis for the role of ANCA in the pathogenesis of vascular injury is that an undetermined stimulus, perhaps an infection, elicits inflammatory cytokines that induce the expression of ANCA target antigens (proteinase 3 and/or myeloperoxidase) on the neutrophil cell surface.
- The binding of ANCA to these antigens may cause degranulation and respiratory burst of neutrophils, resulting in necrotizing vasculitis

Diagnosis

- The diagnosis of Wegener's granulomatosis should be confirmed by tissue biopsy at a site of active disease.
- Biopsy of a nasopharyngeal lesion (if present) is preferred because it is relatively noninvasive
- However, in the small amount of tissue that can be removed in biopsies from this site, all pathologic features may not be seen
- Biopsy of the skin reveals a leukocytoclastic vasculitis with little or no complement and immunoglobulin on immunofluorescence.

Airway presentation-1

- The most common presenting symptoms and signs of Wegener's granulomatosis related to the upper airway include
  - Nasal crusting
  - Sinus pain
  - Chronic rhinosinusitis
  - Nasal obstruction
  - Smell disturbances
  - Purulent/bloody nasal discharge
  - Excessive tearing (ie, epiphora)
  - Sinus mucocele formation

Airway presentation-2

- Up to 1/3 of patients with pulmonary involvement may have no noticeable symptoms
- However, others present with cough, hemoptysis (due to alveolar hemorrhage and/or tracheobronchial disease), dyspnea, and pleuritic pain

Airway presentation-3

- These symptoms may be accompanied by signs of pulmonary consolidation, pulmonary nodules, and/or pleural effusion.
- Pulmonary symptoms in the absence of upper respiratory tract symptoms or signs are unusual.

CXR

- Nodules that may cavitate
- Alveolar opacities
- Diffuse hazy opacities
- Pleural opacities.

Renal disease

- Renal biopsy reveals a segmental necrotizing glomerulonephritis with few or no immune deposits (pauci-immune) on immunofluorescence and electron microscopy

Other organ systems involved

- Joints (myalgias, arthralgias, arthritis)
- Eyes (conjunctivitis, episcleritis, uveitis)
- Skin (vesicular, purpuric, and hemorrhagic lesions, subcutaneous nodules)
- Nervous system (mononeuritis multiplex, cranial nerve abnormalities, external ophthalmoplegia, tinnitus, hearing loss)
- Heart (pericarditis, myocarditis, conduction system abnormalities)
- Less commonly, the gastrointestinal tract, subglottis or trachea, lower genitourinary tract (including the prostate or ureter), parotid glands, thyroid, liver, or breast

Prognosis-1

- The risk of venous thrombotic events, including deep venous thromboses or pulmonary emboli, also appears to be increased in ANCA-associated vasculitis
- Given that the kidney is a frequent target organ, progressive renal failure is commonly observed in patients with WG.
- End-stage renal disease eventually occurs in approximately 20 to 25 percent of patients

Prognosis-2

- The most serious complications include tracheal or bronchial stenosis that can lead to respiratory failure or postobstructive pneumonia.

Cryoglobulinemia

- RYOGLO: POSITIVE IgG,IgM;WEAKLY POSITIVE IgA
- antibodies that precipitate from serum under conditions of cold and resolubilize on rewarming
- Vasculitis results from the deposition of cryoglobulin-containing immune complexes in blood vessel walls and the activation of complement.

- Approximately 40 percent of normal individuals possess detectable CG, typically in concentrations of less than 80 µg/dL
- Demonstration of a persistently elevated cryocrit, such as greater than 1 percent for three to six months Plus one or more of the following:
  - Clinical indicators of cryoglobulinemic vasculitis or thrombosis, such as lower extremity purpura, particularly with evidence of leukocytoclastic vasculitis on biopsy or diminished serum C4 concentration
  - Direct evidence of cryoglobulins from pathological thrombotic or vasculitic specimens, such as by elution and cryoprecipitation and/or immunofixation. While this direct demonstration of CG may provide the most definitive evidence, it is rarely sought in clinical practice.

- classified into types I, II, and III on the basis of whether monoclonality and rheumatoid factor activity (the ability to bind to the Fc portion of IgG)
  - RF 13.60 IU/mL (< 15)
  - Type I cryoglobulins, which are monoclonal but lack rheumatoid factor activity, are associated with certain hematopoietic malignant neoplasms and often lead to hyperviscosity rather than to vasculitis
  - type II and type III cryoglobulins may be associated with systemic vasculitis involving small (and often medium-sized) blood vessels.
    - Type II CGs are often due to persistent viral infections, particularly hepatitic C and human immunodeficiency virus infections

Approximately 40 to 50 percent of all CG cases are type III, and are often secondary to connective tissue diseases

- Cryoglobulin types II and III are termed mixed cryoglobulins because they consist of both IgG and IgM antibodies
- The IgM components in both type II and type III cryoglobulinemia possess rheumatoid factor activity (i.e., assays for rheumatoid factor are positive)

Autoimmune
Connective tissue diseases
Drug-induced lupus
Polymyositis
Rheumatoid arthritis
Sarcoidosis
Sjögren's syndrome
Systemic lupus erythematosus
Systemic sclerosis
Systemic vasculitis
Behçet's syndrome
Henoch-Schönlein purpura
Kawasaki disease
Polyarteritis nodosa (+/- hepatitis B)

- 90% of patients with vasculitis secondary to mixed cryoglobulins are hypocomplementemic, with C4 levels characteristically more depressed than C3.
- Infection with HCV accounts for at least 80% of the vasculitis cases associated with mixed cryoglobulins

- In a series of 40 patients with mixed cryoglobulinemia and CV, a clinical triad consisting of recurrent palpable purpura (100%), polyarthralgias (73%), and renal disease (55%)
- 22 patients had clinical renal disease manifesting as significant proteinuria, diastolic hypertension (64%), edema (77%), renal failure (46%), and nephritic syndrome (22%)
- Pathology of glomerular disease showed deposition of IgG, IgM, and complement, with coexistent renal arteritis in 15 cases
    - *Khasnis A - J Allergy Clin Immunol - 01-JUN-2009; 123(6): 1226-36*

- Membranoproliferative glomerulonephritis seems to be more common in mixed CG
- Isolated proteinuria or hematuria occur much more frequently than nephrotic or nephritic syndromes or acute renal failure
- Most patients declare a chronic or rapidly progressive disease course within three to five years of diagnosis

- Skin lesions in mixed CG most often reveal leukocytoclastic vasculitis (50 percent), less commonly inflammatory or noninflammatory purpura (10 to 20 percent)
- Direct immunofluorescence microscopy of acute lesions often reveals deposits of IgM, IgG and/or C3 complement

Wegner's granulomatosis and Cryoglobulinemia

- RF and cryoglobulins, suggestive of the presence of circulating IC, were detected respectively in 9 of 39 and 7 of 37 patients
- Haemolytic complement activity and complement components were never decreased, but the C3d breakdown product of C3 was elevated in all the 8 patients studied before treatment

- *Immunopathological studies of polyarteritis nodosa and Wegener's granulomatosis: a report of 43 patients with 51 renal biopsies.*
  - *Q J Med. 1983 Spring;52(206):212-23.*

- renal deposition of CIC is transient, the paucity of Ig deposits being due to rapid clearance of IC by phagocytic cells; or alternatively that vascular and glomerular lesions are not caused by CIC

Table 1—*Immunologic Parameters in Two Patients with Wegener's Granulomatosis*

	Case 1	Case 2
Cryoglobulins	Negative	Negative
Hepatitis B surface antigen	Negative	Negative
Antinuclear antibody	Negative	Negative
Rheumatoid factor	1:1280	Negative
Total hemolytic complement	Normal	Normal
Serum protein electrophoresis	Increased 2 globulin	Increased 2 globulin
Immunoelectrophoresis	Increased IgE	Increased IgE

- *Wegener's granulomatosis. Electron microscopic and immunofluorescent studies.*
  - *Hui AN, Ehresmann GR, Quismorio FP Jr, Boylen CT, Mayberg H, Koss MN.*
    - *Chest. 1981 Dec;80(6):753-6.*

- IgE may be interacting with basophils and mast cells causing the release of vasoactive substances which allow immune complexes to deposit extravascularly.
- Circulating immune complexes fall rapidly with therapy

- The complexes are also capable of activating complement with subsequent chemotaxis and polymorphonuclear leukocytes.
- The leukocytes are able to phagocytose some of the complexes, but in so doing release proteolytic enzymes that can injure surrounding tissue

Final diagnosis

- 1.Wegener’s granulomatosis
- 2.Cryoglobulinemia
- 3.Sinusitis

- Prednisolone 0.6 mg/kg/day
- Cyclophosphamide 1.5 mg/kg/day
- augmentin

CXR before discharge