The Storm and
A Decathlete
28-5-2010
Inter-hospital Geriatric Meeting

Dr TC Chan
Dr KH Luk
Queen Mary Hospital
MSF 74/M

- Live alone
- ADL-I
- Walk unaided
- Non smoker non drinker
• Past medical history
  – Primary biliary cirrhosis with positive anti-mitochondria antibodies follow up C hospital
  – Not on any regular medication
- Admitted C hospital for
  - General malaise
  - Weight loss of ~5kg in 1 month
- Physical examination unremarkable, haemodynamically stable
- Ix result
  - WBC increase
  - CXR right lower zone haziness
  - albumin 26 g/L
  - ALP 187 U/L
- Treated as sepsis with Augmentin and discharge the 2nd day
• After discharge, malaise persist
• His son was not satisfied with C hospital and bring the patient to Queen Mary Hospital
• History
  – Malaise and weight loss of 5kg over 1 month
  – Appetite decrease
  – Decrease self care ability
  – No other localizing symptom
    • Cough, shortness of breath, sputum production, nausea, vomiting, alternation of bowel habit, haematuria, arthralgia, myalgia, neck stiffness, blurring of vision
  – No other systemic symptom
    • Fever, night sweating, chills, rigor
• Physical examination
  – Afebrile
  – BP 120/80 P 72 regular
  – SaO2 99% RA
  – Cachexic
  – Other P/E → generally unremarkable
    • Chest NAD
    • CVS
      – heart sound normal and NO murmur
    • Abdomen
      – soft, NO organomegaly, PR NO mass
    • CNS
      – Cranial nerve intact, power 5-/5 generally, NO neck stiffness, NO sensory loss
• **CBP**
  - WBC 14.4 (x10^9/L)
    - Neutrophil 11.7
    - Lymphocyte 0.8
    - Monocyte 0.8
    - Eosinophil 0.3
  - Hb 10.6 g/dL
    - MCV 87.2 fL
    - MCH 29.3 pg
  - Plt 527 x 10^9/L

• **L/RFT**
  - Na 134 mmol/L, K 3.9 mmol/L
  - Urea 4.3 mmol/L
  - Creatinine 58 umol/L
    - Albumin 22 g/L
    - Globulin 46 g/L
    - Bili 10 umol/L
    - ALP 187 U/L
    - AST 10 U/L, ALT 20 U/L

• **Clotting**
  - PT 11.4 second
  - INR 1.0
  - APTT 31.3 second
• **CXR**
  – Clear

• **Urinalysis**
  – **Protein** 30 mg/dL
  – Nitrites and Leucocytes esterases –ve
  – Occult blood small, cast -ve
• Imp: Sepsis for investigation
• General Team Consulted Geriatrics
  – deconditioning
  – rehabilitation plan
What will be your decision?

- Send to rehabilitation hospital for rehabilitation?
- Further investigation?

Takeover the patient and further investigate and manage before transfer
• Multi disciplinary assessment
  – Physiotherapist
    • Premorbid walk unaided
    • Walk with frame + supervision
  – Occupational therapist
    • Premorbid ADL independent and live alone
    • MMSE 26/30
    • BADL still independent but feel tired easily
    • Self care ability limited

  – MORE THAN SIMPLE DECONDITIONING
- ESR >140 mm/hr
- CRP 16.90 mg/dl
- Iron profile
  - Iron 4.7 umol/L
  - Serum TIBC 27 umol/L
  - Ferritin 1482 pmol/L
  - TRF Saturation 17%
- LDH 201 U/L
- Stool for OB
  - negative
• Major abnormal finding
  – Increase WBC
  – NcNc anemia
  – Markedly increase inflammatory marker
  – Hypoalbuminemia
  – Significant weight loss
  – Markly decrease exercise tolerance
  – AFEBRILE
• Hypoalbuminemia
  – Related to underlying primary biliary cirrhosis?
  – Unlikely
    • No stigmata of chronic liver disease
    • Albumin 3/12 ago normal
    • Normal spleen size
    • Normal clotting profile
• 3 major categories of DDx
  – Malignancy
  – Infective
  – Autoimmune

• For the hypoalbuminemia
  – Decrease uptake
  – Increase loss
  – Increase use (catabolism)
  – Decrease production
• Malignancy and Infection
  – Tumor marker
    • Ca 19.9, CEA, AFP negative
  – MT2
    • Not reactive
  – Bld culture, urine culture
    • no growth
  – Echocardiogram
    • no vegetation
  – Sputum, early morning urine, gastric aspirate x AFB smear
    • All negative
  – Serum and Urine electrophoresis
    – -ve
  – Weli Felix, Typhoid, Brucellosis antigen, Legionella antigen
    • All unremarkable
  – PET/CT
    • No evidence of focal occult infection or FDG-avid malignancy
• Autoimmune
  – Anti-ds DNA
    • 5 IU/ml
  – C3
    • 133 mg/dl
  – C4
    • 36 mg/dl
  – Anti-mitochondria
    • positive

– RF
  • 270 IU/ml

– Anti CCP
  • <16 units

– Anti ENA
  • Negative
• Autoimmune
  – ANA
    • Cytoplasmic staining, titre cannot be interpreted
  – ANCA
    • Perinuclear ANCA by immunofluorescence
    • MPO ANCA titre 196 RU/ml
• Active finding
  – Increase WBC
  – Anemia
  – Marked hypo albumin
  – Increase inflammatory marker
  – Positive p-ANCA / MPO-ANCA
  – Conclusion: Active ANCA +ve vasculitis
ANCA +ve Vasculitis

Do you agree?
• ANCA +ve vasculitis
  – Small vessel vasculitis
    • WG (Wegener’s granulomatosis)
    • MPA (Microscopic polyangiitis)
    • Churg strauss syndrome
    • Drug related vasculitis
• NO TCM, OTC intake
• Chest
  – CXR unremarkable
  – PET CT show old TB scar
• Renal
  – 24 hour urine for protein: 0.3g
• Nerve
  – NCV: no vasculitic change
• Detail clinical examination of skin
  – unremarkable
• Other occult infection / occult malignancy which cannot be detected by PET/CT
• Active ANCA +ve vasculitis without major organ involvement but with significant catabolism
  – Direction
  – Empirical immunosuppressant?
• DDx 1
• PET/CT limitation
  – Major Malignancy / infection that may not be able to be detected...

Tell you later...
• DDx 2
• ANCA: high sensitivity and specificity
• All international guideline suggest
  – histological proof is essential before starting immunosuppressant
  – Should not dependent solely on autoimmune marker for guiding subsequent diagnosis
• Luckily, one more important information!
• For the hypoalbuminemia
  – Decrease uptake
    • Malnutrition
  – Increase loss
    • Renal loss 0.3g protein / 24 hours
  – Increase use (catabolism)
    • Active inflammation
  – Decrease production
    • PBC (should not be significant)
• **Additional information**
  - Stool for alpha-1-antitrypsin for calculation of alpha-1-antitrypsin clearance
    - Increased
    - A sensitive test for PLE
  - Chromium-labeled albumin scan
    - Protein losing enteropathy over ascending colon or level proximal to ascending colon
    - A specific test for PLE
      - Protein losing enteropathy
• **Active ANCA +ve vasculitis + isolated protein losing enteropathy (no other major organ involvement)**
  - NO case report in pubmed

• **Infective/malignant cause of protein losing enteropathy which cannot be detected in PET/CT**
  - TB ileitis (especially in this locality and evidence of old TB scar)
  - Stromal tumor
    - Colonoscopy arranged
• Investigation, investigation and investigation...
  – Patient was weaker and weaker...
    progressive weight loss, extreme poor appetite
  – Functional status: walk with frame ➔
    chairbound ➔ nearly bedbound...
  – Any definitive plan?

Interhospital Geriatrics Meeting
• Patient become more and more miserable…
• Daily multi disciplinary support
  – PT, OT, MSW, clinical psychologist
  – Geriatrician
• “多謝哂你啲!”
• **Rheumatologist**
  – Send the patient to rehabilitation hospital for rehabilitation
  – The possibility of vasculitis is LOW

• **Geriatrician**
  – Save the patient who have an excellent premorbid...
Final plan

• Nutrition issue
  – Enteral feeding

• Disease issue
  – Dependent on colonoscopy result
    • positive result for TB ileitis or stromal tumor
      – Treat according
    • negative result and/or vasculitic change and/or non-specific inflammation
      – Treat as ANCA +ve vasculitis
God works in mysterious ways
• 12 hours before scheduled colonoscopy
  – Massive lower gastrointestinal bleeding
• Urgent colonoscopy
  – Whole colon full of fresh blood and blood clots
  – Blood throughout colon despite suction of >2L blood
  – Detailed inspection of colonic mucosa impossible
• CT angiogram
  – No definite bleeding site can be located
• SMA and Coeliac angiogram
  (intervention angiogram)
• SMA and Coeliac angiogram (intervention angiogram)
  – No definite bleeding site can be located
  – Vasculitic change over liver parenchyma (Very unusual)
• Bleeding cannot stopped
  – Urgent consult SRG
    • No single bleeding site identified
    • General status poor
      – Unlikely to benefit from a GA surgical procedure for identification of site of bleeding
      – In case of bleeding from multiple sites or if diffuse bleeding → resection is probably not likely
  – Continue supportive management
• **Supportive transfusion**
  – Total 8 unit of fresh blood transfused
• **Start steroid**
  – Methylprednisolone
• **Amount of bleeding decrease but persist**
• Day 2 of steroid
  – Sudden deterioration
    • Desaturation
    • Shock
  – CXR
    • New right middle zone consolidation + frothy change over other part of chest
  – Big gun antibiotics, inotropes, ICU
• Day 3 of steroid
  – Severe pulmonary edema
  – Multiple organ failure
  – Normal cardiac function
  – Succumbed
What is the underlying diagnosis?
• Post mortem
• Answer?
• Polyarteritis Nodosa involving Liver, kidney, GI tract, adrenal...
• PAN is really a kind of vasculitis
• Then...
  – Why PAN is not considered?
Final outcome

- We failed to save our patient
- But his son highly appreciated our multi-disciplinary care, who cared his father as a whole
- They invited us to join their patient’s funeral
Review

- Clinical use of (PET/CT) and its limitation
- Clinical significance of ANCA
- ANCA associated Vasculitis in Older Patients
- Polyarteritis Nodosa
- Why PAN is not considered in our patient initially?
- Meaning of Decathlon
• Clinical use of PET/CT
  – Detection of malignancy
  – Staging and follow-up patients with malignancy
  – Identifying underlying cause for pyrexia of unknown origin or prolonged inflammatory syndrome
• Basic knowledge about PET
  – A type of radioisotope scan using FDG
  – FDG
    • Glucose analogue
    • Follow a metabolic pathway partially similar to glucose
    • When being uptake by cell, only partially metabolized
    • Manifested as “hot spots” in FDG imaging
    • Some malignancy, infectious process
  – Difficulties in interpretation in area with increased normal glucose metabolism
    • Brain, bone marrow
• **Basic knowledge about PET**
  - Some tumor may have only insignificant FDG uptake
    • Highly differentiated tumor
    • Tumor with modest glucose activity e.g. prostate cancer, mucinous carcinoma
  - Some location may have high distribution and interfere its interpretation
    • Urinary system (due to accumulation of FDG activity in urine)
• Major malignancy detected by PET
  – Head and neck
  – Breast
  – Lung (small and non-small)
  – Colorectal
  – Malignant lymphoma (HL and NHL)
  – Malignant melanoma
  – Gynaecologic tumor
  – Iodine-negative thyroid carcinoma
  – Malignant bone tumors
  – Testicular cancer
  – sarcoma
• Major malignancy NOT detected by PET
  – Malignancy in urinary system
  – Malignancy in brain
  – Early stage of Ca Lung
  – Neuroendocrine tumor (Ga-DOTATOC)
  – Prostate tumor (\(^{11}\text{C}-^{18}\text{F}\)-choline)
<table>
<thead>
<tr>
<th>Site</th>
<th>Number</th>
<th>PET positive cases</th>
<th>PET negative cases</th>
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<tr>
<td>Colon</td>
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<td>14</td>
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<tr>
<td>Thyroid</td>
<td>11†§</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Lung</td>
<td>10</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Stomach</td>
<td>9‡</td>
<td>7</td>
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<tr>
<td>Liver</td>
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<td>3</td>
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<tr>
<td>Bladder</td>
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<tr>
<td>Kidney</td>
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<tr>
<td>Breast</td>
<td>3‖</td>
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<td>Gallbladder</td>
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<td>Prostate</td>
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<td>Esophagus</td>
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<tr>
<td>Pancreas</td>
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<tr>
<td>UP*</td>
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<td>1</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>65</strong></td>
<td><strong>46</strong></td>
<td><strong>19</strong></td>
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</table>
Major cause of pyrexia of unknown origin or prolonged inflammatory syndrome that cannot detected by PET

- Infection in urinary system
- Infection in brain
- Vasculitis of small and medium vessel
- Other rheumatological disease e.g. PMR

<table>
<thead>
<tr>
<th>Category</th>
<th>No. of cases</th>
<th>True positive</th>
<th>True negative</th>
<th>False positive</th>
<th>False negative</th>
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<td>Infection</td>
<td>12 (17%)</td>
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<td>Bronchiectasia/pneumonia</td>
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<tr>
<td>Diverticulitis</td>
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<tr>
<td>Pyelonephritis</td>
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<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Abdominal abscesses</td>
<td>1</td>
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<td>Osteomyelitis</td>
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<td>Tonsillitis</td>
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<td>1</td>
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<tr>
<td>Chronic persistent yersiniosis</td>
<td>4</td>
<td>4</td>
<td>-</td>
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<td>-</td>
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<tr>
<td>Neoplasm</td>
<td>5 (7%)</td>
<td>5</td>
<td>-</td>
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<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>3</td>
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<tr>
<td>Metastatic breast cancer</td>
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<td>Adenocarcinoma with unknown</td>
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<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>5 (7%)</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Non-infectious inflammatory disease</td>
<td>16 (23%)</td>
<td>6</td>
<td>7</td>
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<td>Large-vessel vasculitis</td>
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<td>Polyarthritis rheumatica</td>
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<td>Henoch-Schölein purpura</td>
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<td>1</td>
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<tr>
<td>Microscopic polyangiitis</td>
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<td>-</td>
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<tr>
<td>Psoriatic arthritis</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Adult-onset Still’s disease</td>
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<td>Systemic lupus erythematosus</td>
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<tr>
<td>Cryoglobulinaemia</td>
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<tr>
<td>Miscellaneous</td>
<td>2 (3%)</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Drug fever</td>
<td>1</td>
<td>1</td>
<td>-</td>
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<tr>
<td>Hypertriglyceridaemia</td>
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<td>-</td>
<td>1</td>
<td>-</td>
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<tr>
<td>No diagnosis</td>
<td>35 (50%)</td>
<td>-</td>
<td>26</td>
<td>9</td>
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</table>
Anti-Neutrophil Cytoplasmic Antibodies (ANCA)
• **1st introduced in 1982**
  - A kind of antibody directed against neutrophil cytoplasmic antigens in patient with pauci-immune glomerulonephritis

• **2 ways of identifying**
  - Indirect immunofluorescence assay (IF)
  - Enzyme-linked immunosorbent assay (ELISA)
• By IF
  – Perinuclear-ANCA or p-ANCA
  – Cytoplasmic-ANCA or c-ANCA
  – More sensitive
• By ELISA
  – Antibodies towards proteinase 3 antigen or PR3-ANCA
  – Antibodies towards myeloperoxidase antigen or MPO-ANCA
  – More specific
• Clinical practice
  – +ve IF → screening with ELISA
  – c-ANCA → PR3-ANCA
  – p-ANCA → MPO-ANCA
5 major principles for ANCA
• Significance of positive finding
  – Principle 1
  – +ve IF alone is inadequate
    • Common false +ve finding
      – Especially p-ANCA
      – False +ve in nearly all immune mediated conditions e.g. connective tissue disorders, inflammatory disease, autoimmune hepatitis etc
      – Atypical patterns are commonly seen
    • Subjective component to the interpretation of IF assays
      – Visual interpretation
  – Must followed with ELISA assay
• Significance of positive finding
  – Principle 2
  – According to Chapel Hill Definition 1994
    • The Landmark conference which incorporate ANCA into its diagnostic purpose for different vasculitis
  – Major vasculitis with ANCA +ve
    • Wegener’s granulomatosis
    • Microscopic polyangiitis
    • Churg-Strauss Syndrome
    • Pauci-immune GN
    • Drug related vasculitis

A positive ANCA, particularly if confirmed to be due to antibody with a specificity for PR3 or MPO argues against PAN and in favor of one of the ANCA-associated vasculitides


Diagnostic value of standardized assay for ANCA in idiopathic systemic vasculitis.

Kidney Int 1998; 53:743
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>New patients</th>
<th>Historical patients</th>
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<tbody>
<tr>
<td></td>
<td>No therapy</td>
<td>All</td>
</tr>
<tr>
<td>All diagnoses</td>
<td>126</td>
<td>169</td>
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<tr>
<td>Wegener's granulomatosis (all)</td>
<td>73</td>
<td>97</td>
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<tr>
<td>a WG, granulomas in biopsy</td>
<td>21</td>
<td>31</td>
</tr>
<tr>
<td>b WG, glomerulonephritis in biopsy</td>
<td>37</td>
<td>44</td>
</tr>
<tr>
<td>c WG, vasculitis in biopsy, no GN</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>d WG, no histology support</td>
<td>8</td>
<td>13</td>
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<tr>
<td>Microscopic polyangiitis</td>
<td>34</td>
<td>44</td>
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<tr>
<td>Idiopathic RPGN</td>
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<td>12</td>
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<tr>
<td>Classical polyarteritis nodosa</td>
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<td>10</td>
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<tr>
<td>Churg-Strauss syndrome</td>
<td>4</td>
<td>6</td>
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Abbreviations are: WG, Wegener’s granulomatous; RPGN, rapidly progressive glomerulonephritis.

### Table 2. Disease control patients

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N</th>
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<tr>
<td>Temporal arteritis</td>
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<tr>
<td>Takayasu arteritis</td>
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<tr>
<td>Rheumatoid arthritis with vasculitis</td>
<td>7</td>
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<td>Systemic lupus erythematosus</td>
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<td>Mixed essential cryoglobulinemia</td>
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<tr>
<td>Henoch-Schönlein purpura</td>
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<tr>
<td>Other glomerulonephritis (GN)</td>
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<td>Membranous nephropathy</td>
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<tr>
<td>IgA nephropathy</td>
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<tr>
<td>MPGN</td>
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<tr>
<td>Minimal lesions</td>
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<tr>
<td>FSGS</td>
<td>2</td>
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<tr>
<td>Crescentic GN (not pauci-immune)</td>
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<tr>
<td>Chronic sclerosing GN</td>
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<td>Immune-complex GN</td>
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<td>Post-streptococcal GN</td>
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<tr>
<td>Anti-GBM disease</td>
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<tr>
<td>Tuberculosis</td>
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<tr>
<td>Sarcoidosis</td>
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<td>Ulcerative colitis</td>
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<td>Crohn's disease</td>
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<td>Other vasculitides</td>
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<td>Serum sickness</td>
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<td>Infective endocarditis</td>
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<td>Visceral sepsis</td>
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<td>Behçet's disease</td>
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<tr>
<td>Scleroderma/MCTD with vasculitis</td>
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<tr>
<td>Total</td>
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Table 5. Sensitivity and specificity of the combination of IIF-test and ELISA results in patients with systemic vasculitis

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<tr>
<th></th>
<th>Sensitivity %</th>
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<th></th>
<th></th>
<th></th>
<th>pANCA + anti-MPO</th>
<th>cANCA/PR3a or pANCA/MPO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>cANCA + anti-PR3</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Copenhagen</td>
<td>Raisdorf</td>
<td>Leiden</td>
<td></td>
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<tr>
<td>New patients</td>
<td></td>
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<td></td>
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<tr>
<td>Wegener's granulomatosis</td>
<td>97</td>
<td>55 (57)</td>
<td>56 (58)</td>
<td>54 (56)</td>
<td>16 (16)</td>
<td>71 (73)</td>
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<tr>
<td>Microscopic polyangiitis</td>
<td>44</td>
<td>7 (16)</td>
<td>5 (12)</td>
<td>7 (15)</td>
<td>22 (49)</td>
<td>30 (67)</td>
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<tr>
<td>Idiopathic RPGN</td>
<td>12</td>
<td>4 (36)</td>
<td>4 (36)</td>
<td>4 (36)</td>
<td>6 (46)</td>
<td>10 (82)</td>
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<tr>
<td>Classical polyarteritis nodosa</td>
<td>10</td>
<td>1 (10)</td>
<td>1 (10)</td>
<td>1 (10)</td>
<td>1 (10)</td>
<td>2 (20)</td>
<td></td>
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<tr>
<td>Churg-Strauss syndrome</td>
<td>6</td>
<td>2 (33)</td>
<td>2 (33)</td>
<td>0 (0)</td>
<td>2 (33)</td>
<td>3 (56)</td>
<td></td>
</tr>
<tr>
<td>Historical patients</td>
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<tr>
<td>Wegener's granulomatosis</td>
<td>75</td>
<td>32 (43)</td>
<td>31 (41)</td>
<td>36 (48)</td>
<td>15 (19)</td>
<td>46 (62)</td>
<td></td>
</tr>
<tr>
<td>Microscopic polyangiitis</td>
<td>19</td>
<td>1 (5)</td>
<td>1 (6)</td>
<td>1 (6)</td>
<td>7 (36)</td>
<td>8 (42)</td>
<td></td>
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<tr>
<td>Idiopathic RPGN</td>
<td>6</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>4 (60)</td>
<td>4 (60)</td>
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</tr>
<tr>
<td>Classical polyarteritis nodosa</td>
<td>3</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Churg-Strauss syndrome</td>
<td>3</td>
<td>1 (33)</td>
<td>0 (0)</td>
<td>1 (33)</td>
<td>0 (0)</td>
<td>1 (33)</td>
<td></td>
</tr>
<tr>
<td>Control patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease controls</td>
<td>184</td>
<td>1 (99)</td>
<td>1 (99)</td>
<td>1 (99)</td>
<td>2 (99)</td>
<td>3 (98)</td>
<td></td>
</tr>
<tr>
<td>Healthy controls</td>
<td>740</td>
<td>1 (100)</td>
<td>1 (100)</td>
<td>1 (100)</td>
<td>0 (100)</td>
<td>1 (100)</td>
<td></td>
</tr>
</tbody>
</table>

RPGN is rapidly progressive glomerulonephritis. New patients were newly diagnosed after the start of the study, old patients were analyzed retrospectively.

a Anti-PR3 result is average of the sensitivity of the 3 anti-PR3 ELISAs

Sensitivity 70%, specificity 99% for small vessel vasculitis

• **Significance of positive finding**
  
  – Principle 3
  
  – **Should not rely on +ve ANCA for definitive diagnosis of small vessel vasculitis**
    
    • I. Histological proof is essential
    • II. Exclude other differentiate diagnosis
• 4 major organs commonly involved
  - Renal
    • Rapidly deteriorating renal function
    • Significant proteinuria
    • Haematuria with cast
  - Skin
    • Palpable purpura
  - Nerve
    • Mononeuritis multiplex
  - Lung
    • haemoptysis
• Significance of positive finding
  – Principle 4
    • Can it be false positive?
    • Positive predictive value of ANCA
      – Very much dependent on the clinical presentation
    • Proper ordering of ANCA
      – Decrease false positive
Using Antineutrophil Cytoplasmic Antibody Testing to Diagnose Vasculitis: Can Test-Ordering Guidelines improve Diagnostic Accuracy?

Arch Intern Med. 2002; 162: 1509-1514
• Retrospective study for all ordered ANCA from 1997 to 1998

• To analyze
  – sensitivity, specificity, positive predictive value and negative predictive value
  – towards ANCA associated vasculitis
  – before and after imposing guideline criterion for ordering an ANCA test
<table>
<thead>
<tr>
<th>Guideline</th>
<th>Clinical Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Glomerulonephritis, especially rapidly progressive</td>
<td>(A) Creatinine level &gt;2.0 mg/dL (&gt;176.8 μmol/L) (normal range, 0.7-1.3 mg/dL [61.9-114.9 μmol/L]) immediately prior to ANCA testing or (B) urinary red blood cell casts or hematuria with &gt;5 red blood cells per high-powered microscopic field</td>
</tr>
<tr>
<td>2. Pulmonary hemorrhage, especially pulmonary renal syndrome</td>
<td>Hemoptysis or pulmonary hemorrhage</td>
</tr>
<tr>
<td>3. Cutaneous vasculitis with systemic features myalgias, arthralgias, or arthritis</td>
<td>Purpura, rash or livedo with concurrent fever, weight loss, myalgias, arthralgias, or arthritis</td>
</tr>
<tr>
<td>4. Multiple lung nodules</td>
<td>At least 1 nodule seen on any imaging study‡</td>
</tr>
<tr>
<td>5. Chronic destructive disease of the upper airways</td>
<td>Epistaxis or erosive changes seen on clinical examination or imaging studies not due to previous surgery</td>
</tr>
<tr>
<td>6. Long-standing sinusitis or otitis</td>
<td>(A) Hearing loss, blocked ears, or ear pain or (B) sinusitis or otitis specified as the reason for ANCA test ordering by the physician</td>
</tr>
<tr>
<td>7. Subglottic, tracheal stenosis</td>
<td>(A) Visualized on imaging studies or (B) tracheal stenosis specified as the reason for ANCA test ordering by the physician</td>
</tr>
<tr>
<td>8. Mononeuritis multiplex or other peripheral neuropathy</td>
<td>Sensory or motor changes, including cranial nerve palsies</td>
</tr>
<tr>
<td>9. Retro-orbital mass</td>
<td>Radiographic visualization of a mass lesion</td>
</tr>
</tbody>
</table>

*ANCA indicates antineutrophil cytoplasmic antibody.
†Based on the article by Hagen et al.†
‡Not all patients had specialized imaging studies to detect multiple lesions, so a single nodule was accepted.
### Before imposing guideline

<table>
<thead>
<tr>
<th>ANCA Test Result</th>
<th>AVV Present</th>
<th>AVV Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Negative</td>
<td>3</td>
<td>470</td>
</tr>
</tbody>
</table>

Sensitivity: 81%  Specificity: 98%

PPV: 54%  NPV: 99%

### After imposing guideline

<table>
<thead>
<tr>
<th>ANCA Test Result</th>
<th>AVV Present</th>
<th>AVV Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Negative</td>
<td>3</td>
<td>357</td>
</tr>
</tbody>
</table>

Sensitivity: 81%  Specificity: 98%

PPV: 62%  NPV: 99%
• Significance of positive finding
  – Principle 5
    • Arteriography
      – Useful in large and medium sized vasculitis
      – Not useful in small sized vasculitis
        » Affected vessels are below the resolution of usual angiograms
Clinically suspected case

- Exclude other DDx
  - Biopsy of affected organ

Small vessel vasculitis

Further confirmed with ELISA

- ve ANCA IF

Clinically suspected case

- Digital Subtraction Arteriogram
- Exclude other DDx
  - Biopsy of affected organ

Medium and large vessel vasculitis

Further confirmed with ELISA

+ ve ANCA IF

Clinically suspected case
ANCA associated vasculitis in older patients

Medicine 2008; 87: 203-209
• Are there any difference in initial clinical presentation or laboratory data?
<table>
<thead>
<tr>
<th></th>
<th>Older Patients</th>
<th></th>
<th>Younger Patients</th>
<th></th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(≥65 yr) No. (%)</td>
<td>(≤65 yr) No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male/female</td>
<td>49/50</td>
<td>58/77</td>
<td></td>
<td></td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>72.1 ± 5.6</td>
<td>49.3 ± 13.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPO-ANCA/PR3-ANCA</td>
<td>94/5</td>
<td>108/26</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fever</td>
<td>63/99 (63.6)</td>
<td>84/135 (62.2)</td>
<td></td>
<td></td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Fatigue</td>
<td>57/99 (57.6)</td>
<td>79/135 (58.5)</td>
<td></td>
<td></td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Weight loss</td>
<td>45/99 (45.5)</td>
<td>64/135 (47.4)</td>
<td></td>
<td></td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Muscle pain</td>
<td>28/99 (28.3)</td>
<td>43/135 (31.9)</td>
<td></td>
<td></td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>35/99 (35.4)</td>
<td>61/135 (45.2)</td>
<td></td>
<td></td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Skin rash</td>
<td>17/99 (17.2)</td>
<td>28/135 (20.7)</td>
<td></td>
<td></td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Pulmonary involvement</td>
<td>75/99 (75.8)</td>
<td>66/135 (48.9)</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>33/99 (33.3)</td>
<td>41/135 (30.4)</td>
<td></td>
<td></td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Nodules or cavities</td>
<td>8/99 (8.1)</td>
<td>17/135 (12.6)</td>
<td></td>
<td></td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Alveolar or interstitial infiltration</td>
<td>47/99 (47.5)</td>
<td>43/135 (31.9)</td>
<td></td>
<td></td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Pulmonary interstitial fibrosis</td>
<td>37/99 (37.4)</td>
<td>25/135 (18.5)</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>9/99 (9.1)</td>
<td>2/135 (1.5)</td>
<td></td>
<td></td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Urinary protein (g/24 h)</td>
<td>1.67 ± 1.79</td>
<td>2.45 ± 2.29</td>
<td></td>
<td></td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Initial Scr (μmol/L)</td>
<td>399.7 ± 255.7</td>
<td>446.7 ± 371.5</td>
<td></td>
<td></td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>eGFR (mL/min per 1.73 m$^2$) (median and range)*</td>
<td>12.5 (2.70–153.7)</td>
<td>13.3 (1.87–156.8)</td>
<td></td>
<td></td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Ophthalmic</td>
<td>18/99 (18.2)</td>
<td>38/135 (28.1)</td>
<td></td>
<td></td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Otic</td>
<td>35/99 (35.4)</td>
<td>46/135 (34.1)</td>
<td></td>
<td></td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Upper respiratory tract</td>
<td>15/99 (15.2)</td>
<td>37/135 (27.4)</td>
<td></td>
<td></td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>5/99 (5.1)</td>
<td>11/135 (8.1)</td>
<td></td>
<td></td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Nervous system</td>
<td>21/99 (21.2)</td>
<td>24/135 (17.8)</td>
<td></td>
<td></td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Anemia</td>
<td>87/99 (87.9)</td>
<td>105/135 (77.8)</td>
<td></td>
<td></td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>56/99 (56.6)</td>
<td>57/135 (42.2)</td>
<td></td>
<td></td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Thrombocytosis</td>
<td>31/99 (31.3)</td>
<td>47/135 (34.8)</td>
<td></td>
<td></td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Elevated ESR</td>
<td>91/99 (91.9)</td>
<td>109/135 (80.7)</td>
<td></td>
<td></td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Elevated CRP</td>
<td>61/99 (61.6)</td>
<td>60/135 (44.4)</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BVAS</td>
<td>21.3 ± 6.7</td>
<td>20.4 ± 5.3</td>
<td></td>
<td></td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Abbreviations: Scr = serum creatinine, eGFR = estimated glomerular filtration rate, BVAS = Birmingham vasculitis activity score.

*eGFR (mL/min per 1.73 m$^2$) = 175 × (plasma creatinine)$^{-1.234}$ × age$^{-0.019}$ × 0.79 (if female) (from reference 11).
• Elderly patient (>65)
  – More significant
    • Pulmonary involvement
    • Increase ESR
    • Increase CRP
    • Leucocytosis
  – Less significant
    • Upper respiratory tract involvement
    • 24 hour urinary protein
• Are there any difference in treatment outcome?
• Remission rate at 6 months
  – Significantly lower in elderly patient
    • 78% vs 90%
• Mortality rate
  – Significantly worse in elderly patient
• Are there any difference in treatment related complication rate?
• More significant secondary pulmonary infection rate in elderly
  – 29% vs 7%
• Are there any difference in relapse rate for those respond patient?
• Relapse rate
  – No significant difference between young and old for those who respond
Major message

• Although elderly patient may be associated with increased complication from conventional treatment, if successfully treated, the relapse rate is NOT higher
Polyarteritis Nodosa
Polyarteritis Nodosa

• Systemic necrotizing vasculitis typically affects medium sized muscular arteries
• **Epidemiology**
  – Prevalence: 2-33 per million

• **Etiology**
  – Idiopathic
  – Hepatitis B virus (Oriental)
    • Up to 33%
  – Hairy cell leukaemia

_Hepatitis B virus-associated polyarteritis nodosa: clinical characteristics, outcome, and impact of treatment in 115 patients._ Medicine 2005; 84: 313
• Pathogenesis
  – Immune complexes mediated disease
    • Medium sized arterial inflammation
  – Inflammation of vessel wall
    → weakening of vessel wall
    → aneurysm formation
    → rupture and life threatening bleeding
• Clinical feature
  – Constitutional
    • Fatigue, weakness, fever, arthralgia
  – Skin
    • Livedo reticularis, skin ulcer, tender erythematous
    • Palpable purpuric lesion
  – Renal disease
    • Renal impairment, hypertension
    • Urinalysis: sub-nephrotic proteinuria, modest haematuria, absent red blood cell casts
  – Neurologic disease
    • Mononeuritis multiplex
    • Stroke (rare)
  – Lung
    • Rarely involved
  – Gastrointestinal disease
TABLE 1. Demographics, Gastrointestinal Manifestations and Radiologic Findings in 62 Patients With Small and Medium-Sized Vessel Vasculitides*

<table>
<thead>
<tr>
<th></th>
<th>All (n = 62)</th>
<th>PAN (n = 38)</th>
<th>CSS (n = 11)</th>
<th>WG (n = 6)</th>
<th>MPA (n = 4)</th>
<th>RAAV (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr, mean ± SD</td>
<td>48 ± 18</td>
<td>47 ± 18</td>
<td>37 ± 15</td>
<td>49 ± 7</td>
<td>48 ± 27</td>
<td>70 ± 9</td>
</tr>
<tr>
<td>M:F ratio, n</td>
<td>46/16</td>
<td>27/11</td>
<td>37/1</td>
<td>49/7</td>
<td>1/3</td>
<td>2/1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>60 (97)</td>
<td>37</td>
<td>10</td>
<td>6</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>21 (34)</td>
<td>12</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17 (27)</td>
<td>6</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Hematochezia or melena</td>
<td>10 (16)</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hematemesis</td>
<td>4 (6)</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Esophageal ulcerations</td>
<td>7 (11)</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Gastroduodenal ulcers</td>
<td>17 (27)</td>
<td>12</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Colorectal ulcerations</td>
<td>6 (10)</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gastritis</td>
<td>4 (6)</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Surgical abdomen †</td>
<td>21 (34)</td>
<td>12</td>
<td>4</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>11 (18)</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Bowel perforations</td>
<td>9 (15)</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Intestinal occlusion</td>
<td>4 (6)</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>GI ischemia/infarction</td>
<td>10 (16)</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Appendicitis</td>
<td>6 (10)</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cholecystitis</td>
<td>5 (8)</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td>3 (5)</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal angiography (n = 39)</td>
<td>26/39 (67)</td>
<td>23/31</td>
<td>3/5</td>
<td>0/2</td>
<td>0</td>
<td>0/1</td>
</tr>
<tr>
<td>Abnormal abdominal CT (n = 24)</td>
<td>18/24 (75)</td>
<td>11/16</td>
<td>1/1</td>
<td>3/3</td>
<td>2/3</td>
<td>1/1</td>
</tr>
</tbody>
</table>

*Values are numbers (with percentages in parentheses when meaningful) of patients per group, unless indicated otherwise.
†A single patient may have 2 or more surgical complications, for example, pancreatitis and perforations and peritonitis.
• Investigation (Chapel Hill definition)
  – ANCA -ve
  – Digital subtraction Arteriogram
    • Show characteristic multiple aneurysm
  – Tissue biopsy
    • Definitive but with higher risk of bleeding due to presence of aneurysm
  – Hepatitis B serology

Why PAN is not considered in our patient initially?
Clinically suspected case

+ve ANCA IF

Further confirmed with ELISA

Small vessel vasculitis

- Exclude other DDx
- Biopsy of affected organ

Medium and large vessel vasculitis

- Exclude other DDx
- Biopsy of affected organ
- Digital Subtraction Arteriogram
• Are there any report of polyarteritis nodosa with +ve MPO-ANCA+p-ANCA OR c-ANCA+PR3-ANCA?
• PUBMED search
  – 2 case reports only
  – Both initially diagnosed as microscopic polyangiitis but subsequent confirm PAN by autopsy or arteriogram
  – Initially with classical multi-organ involvement


Two cases of classical PAN associated with MPO-ANCA. Nippon Jinzo Gakkai Shi. 2006; 48(4): 371-376
• Are there any polyarteritis nodosa presented with protein losing enteropathy?
- PUBMED search
  - NO
• In our case, are there any investigation that may allow earlier identification of the disease?
• Digital subtraction arteriogram
Why PAN is not considered?

- Atypical presentation
  - Protein losing enteropathy
  - Without other major organ involvement

- Atypical investigation result
  - +ve p-ANCA / MPO-ANCA
• Major message from our patient
  – patient with high tire ANCA +ve but
    • without major organ involvement
    • +/- with protein losing enteropathy or other gastrointestinal involvement
    • + negative result from PET/CT
      – In those situation
        » Digital Subtraction Arteriogram may provide additional clue
Thank you very much