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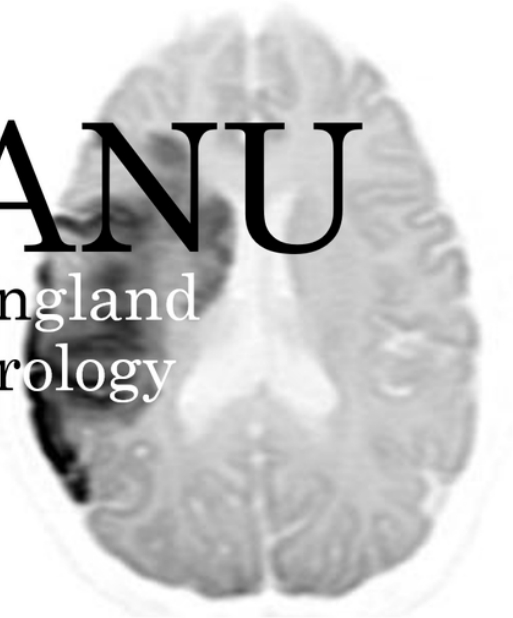
North of England
Acute Neurology
Update



Neurology of acute medicine: tricky cases

Dr Christopher Kobylecki FRCP PhD
Consultant Neurologist

MANCHESTER 1824
The University of Manchester

Manchester Centre for Clinical Neurosciences

Salford Royal NHS
NHS Foundation Trust

Objectives

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- Neurological crossover with general medicine
- Illustrative cases
- Diagnoses (and treatments) not to miss

- 61 year old male
- PMH asthma
- TIA October 2018
  - Weakness R arm/leg for 4 hours
  - Diagnosed atrial flutter, started apixaban + digoxin

- Admitted with confusion Jan 2018
  - Progressively reduced mobility, drowsy
  - Neurological examination grossly normal
  - Transient skin rash

- No useful history from patient
  - Disorientated to time and place
  - No insight into problems
  - Inattentive, drowsy but easily rousable
- Fundoscopy normal, PERLA
- Eye movements full
- Cranial nerves otherwise normal
- Mild 4+/5 pyramidal weakness L side
- Reflexes brisk L side, L plantar extensor

- What is the clinical syndrome?

- Encephalopathy
  - Previous stroke
  - Possible new stroke

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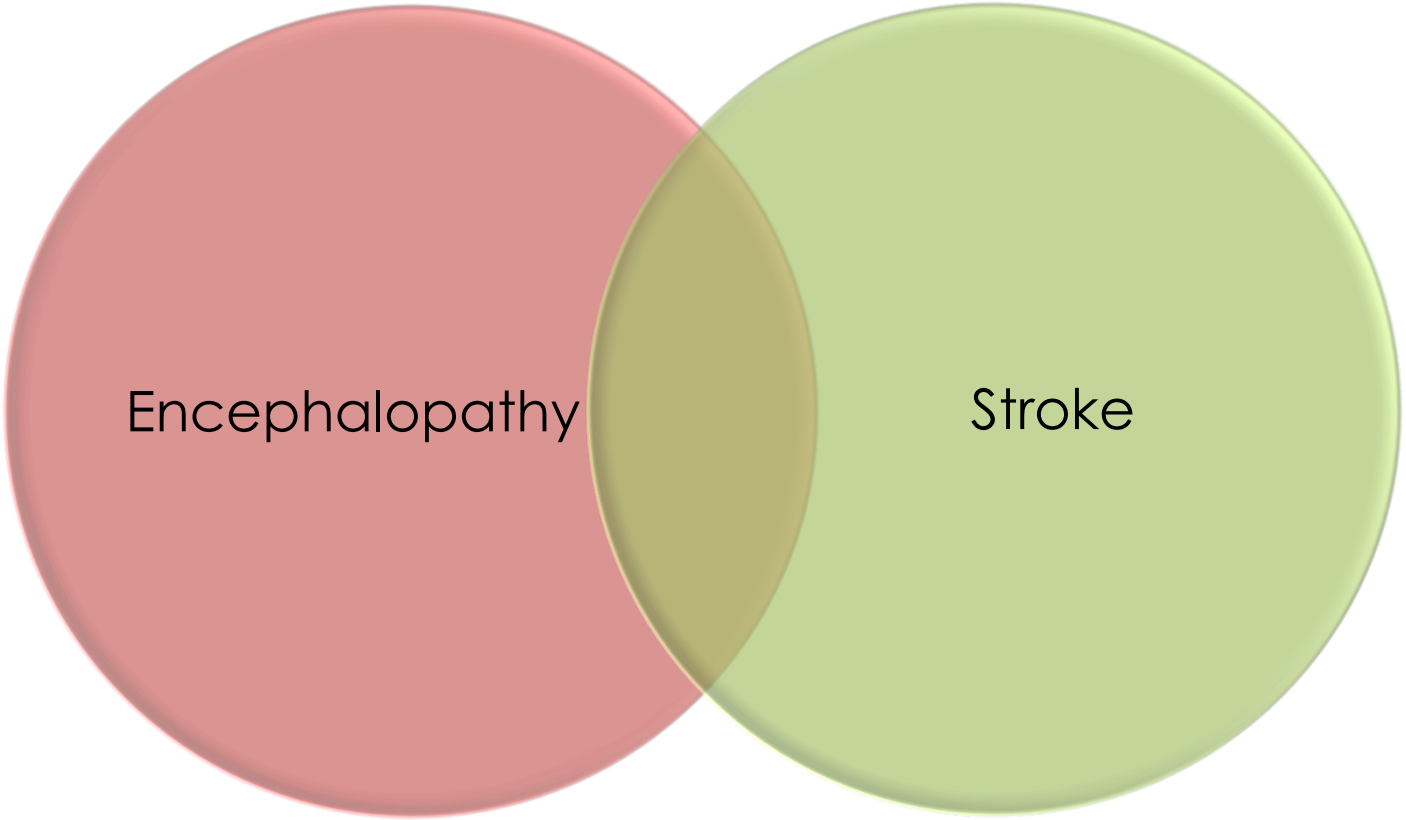
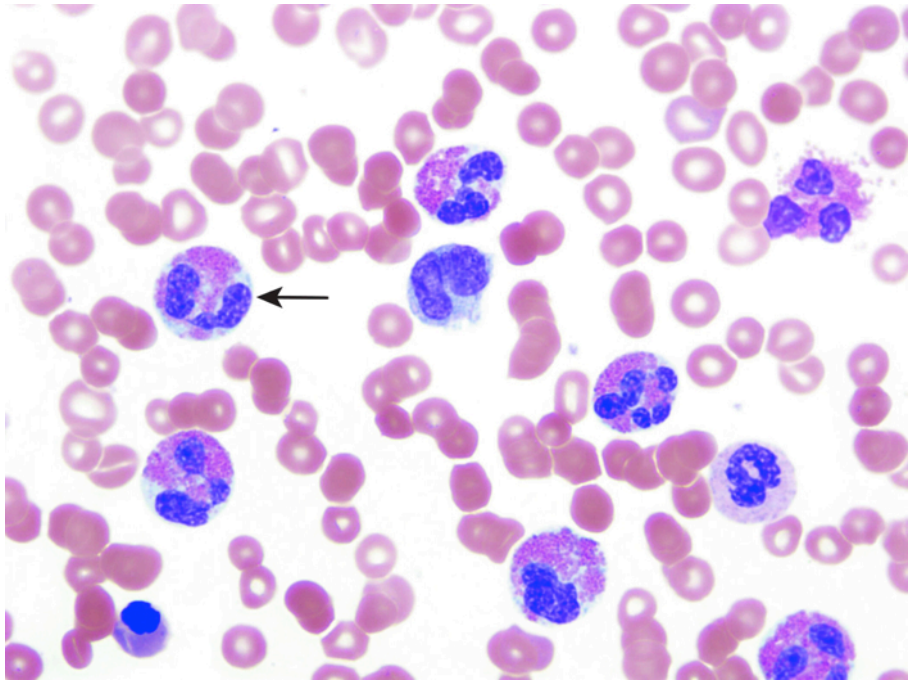


Stroke alone does not typically cause encephalopathy
Exceptions e.g. thalamic strokes

- Hb 122
- WBC **41.8**
  - Neutrophils 9.1
  - Eosinophils **29.6 (71%)**
  - normal range 0-0.4
- Platelets 299

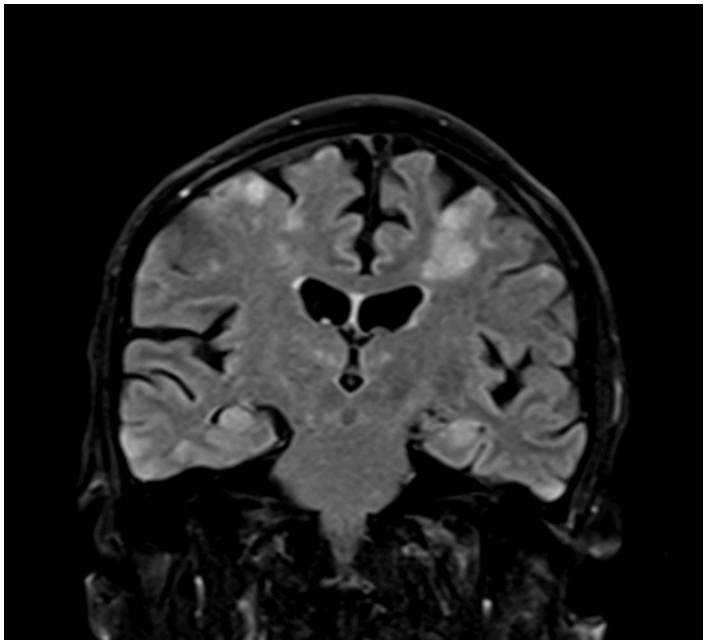
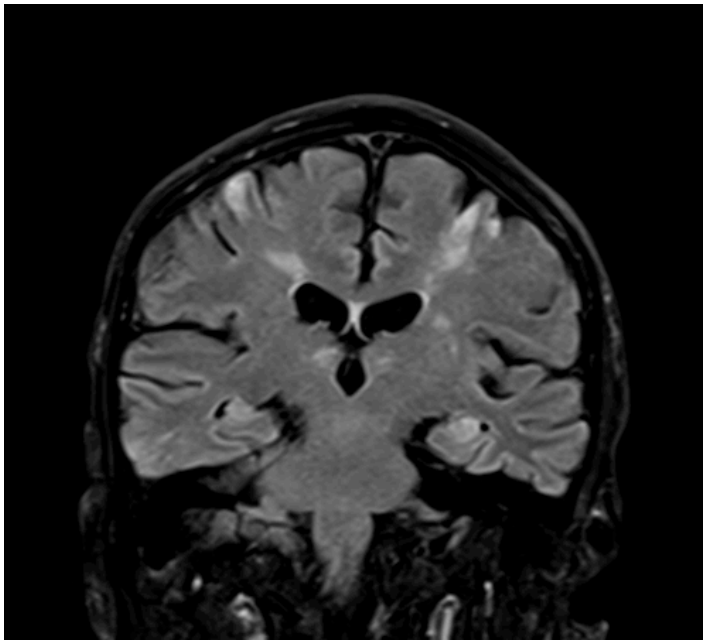
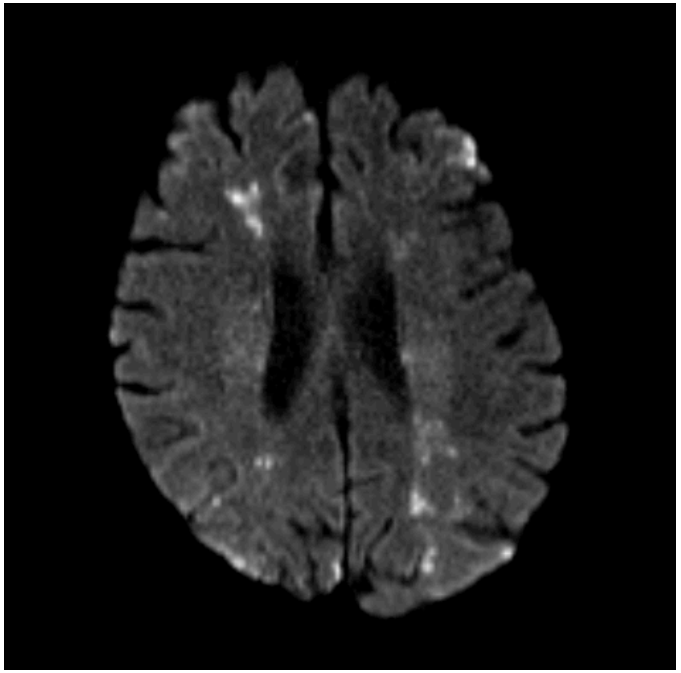
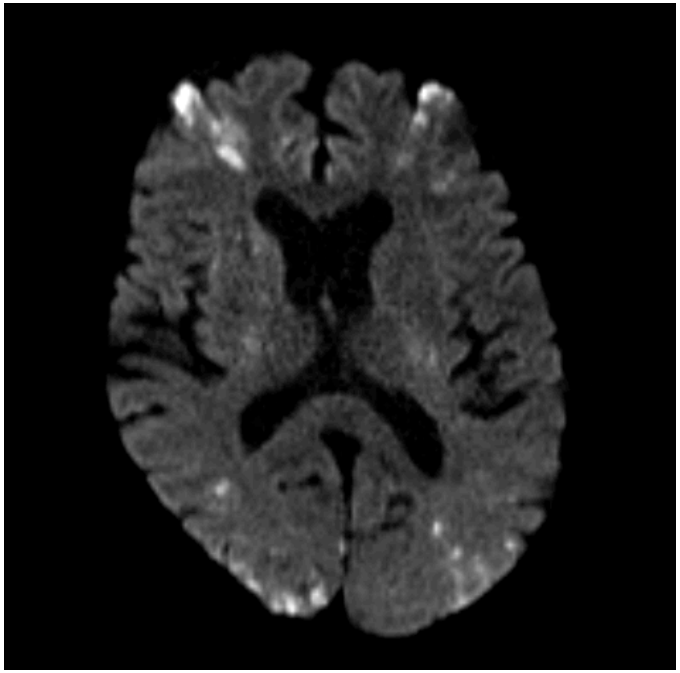


- What is the differential diagnosis?
- What additional tests would help?
- How could this be causing his neurological presentation?

- B_{12} 390 ng/l
- Folate >23.4 μ g/l
- Ferritin 1054 μ g/l (20-300)
- U&E, Ca^{2+} normal
- Alk Phos 194 u/l, albumin 30 g/l, ALT normal
- IgG raised at 22.7 g/l, no paraprotein

- IgE 1659 kU/l(<113)
- Hepatitis B serology negative
- Hepatitis C serology negative
- HIV 1&2 antibody negative
- VDRL negative

- ANA **positive**
  - SS-A, SS-B, Jo-1 negative
  - C3, C4 levels normal
  - Anti-dsDNA **38** iu/ml (<9.9)
- ANCA **positive** (atypical)
  - MPO Ab **57.9** (<0.9)
  - PR-3 Ab <0.2 (<0.9)
- Lupus anticoagulant negative
- Cardiolipin antibodies negative
- β 2 glycoprotein antibodies negative

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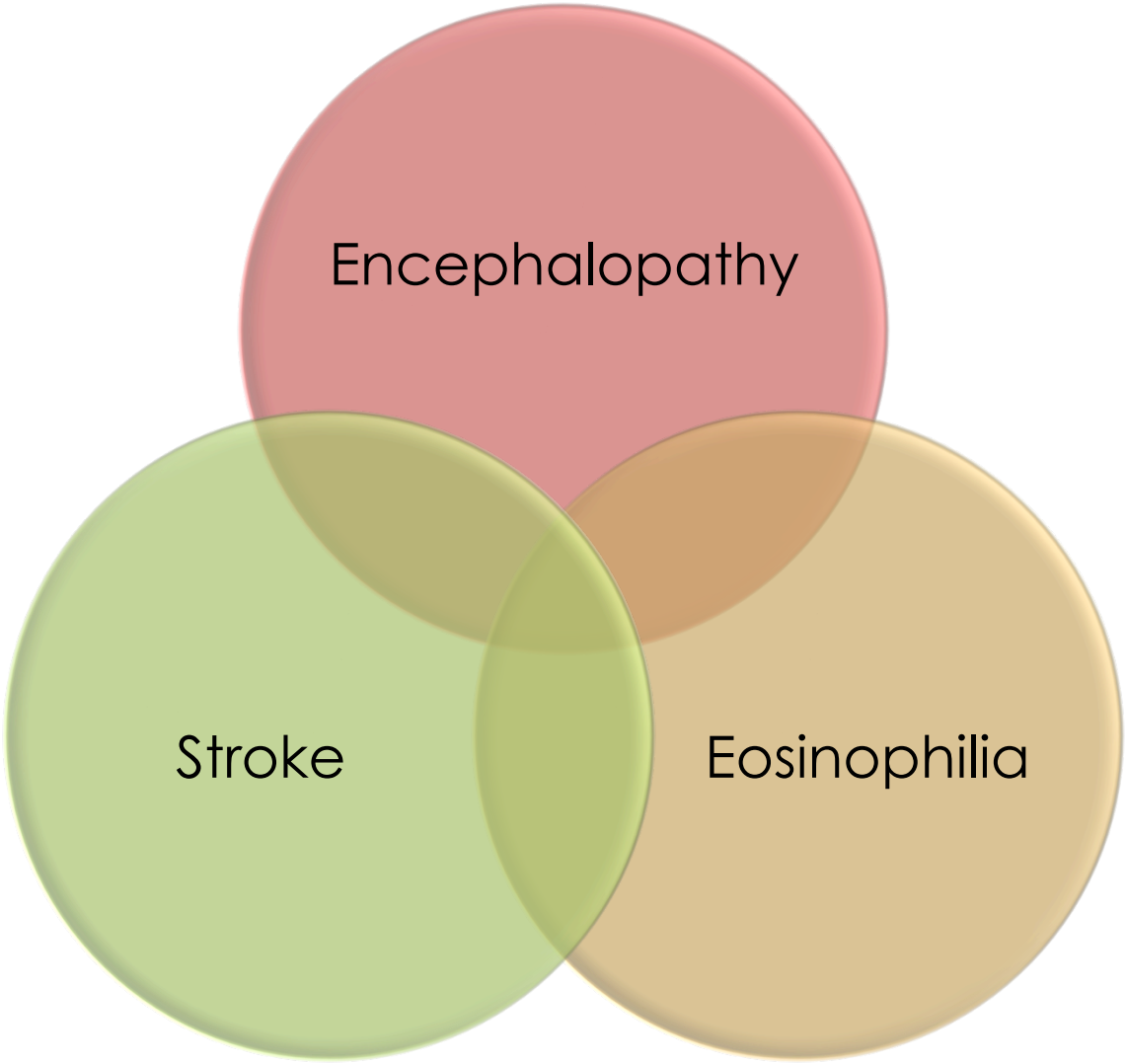


Infection

Parasitic

Inflammatory

Hypersensitivity

Drug reaction

GPA/EGPA

Pulmonary eosinophilia

Metabolic

Adrenal insufficiency

Malignancy

T cell lymphoma

Hodgkin disease

ALL

Familial

Hyper-IgE syndrome

Episodic angioedema and eosinophilia

Eosinophilia-myalgia

Primary (clonal)

Evaluation of eosinophilia

Tests	Other evaluations
Toxocariasis, HIV serology	Detailed family history
Aspergillus IgE, IgG	Drug history and database evaluation
Tryptase Vitamin B_{12} (malignancy)	Full travel history
Evaluation of clonal markers	
Peripheral blood smear	
CT thorax	
Strongyloides screening HTLV-1 serology	If appropriate residence/ travel history
Evaluation for solid malignancy	

Features suggestive of clonal HE

Hepatosplenomegaly

Splenomegaly

Anaemia

Thrombocytopenia

Lack of steroid response

Groh M *et al. Eur J Int Med* 2015;26:545-553.

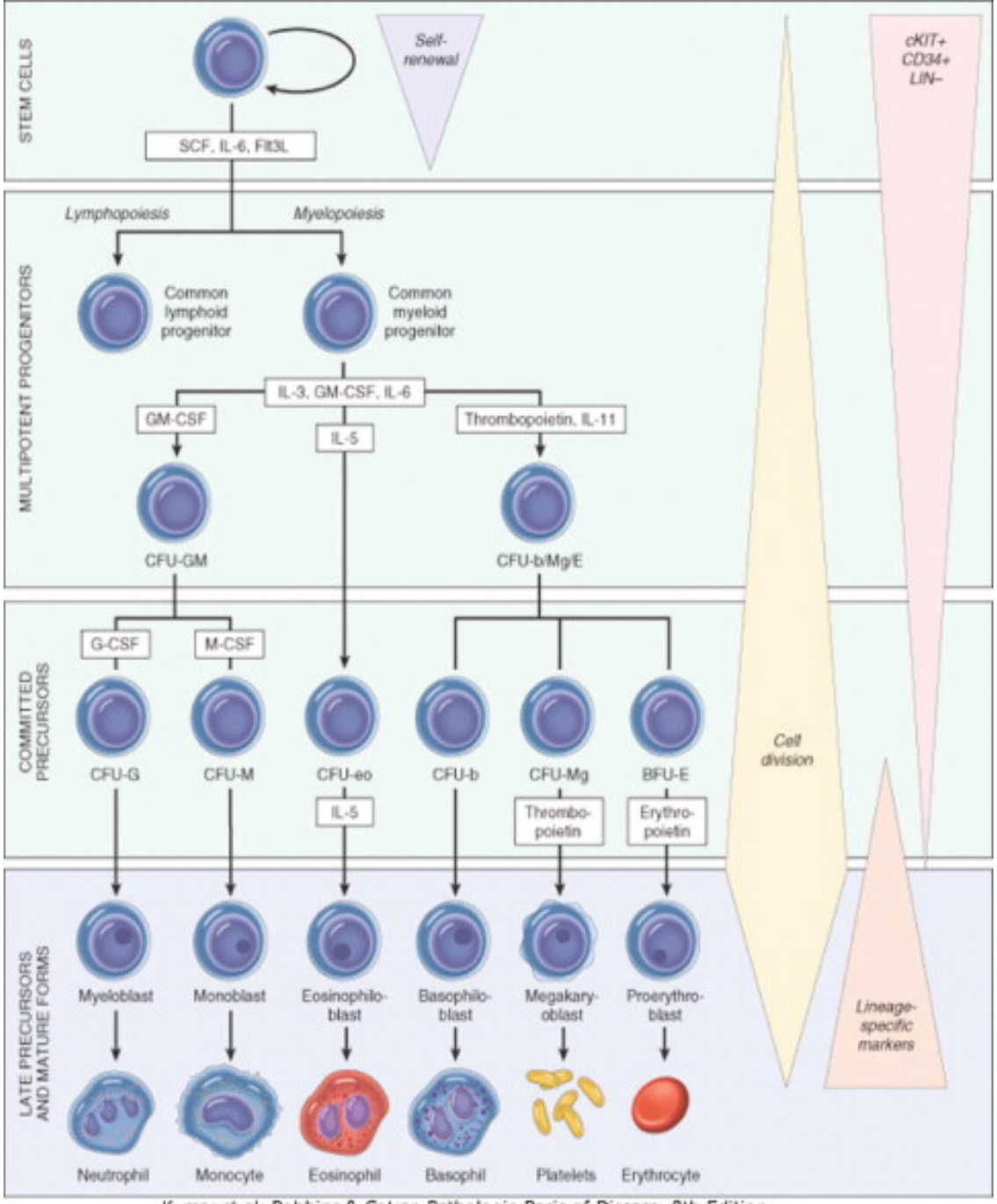


TABLE 1 Revised 2016 World Health Organization (WHO) classification of myeloid neoplasms

1. Acute myeloid leukemia and related neoplasms

2. Myeloproliferative neoplasms (MPN)
   - Chronic myeloid leukemia, *BCR-ABL1* positive
   - Chronic neutrophilic leukemia
   - Polycythemia vera
   - Primary myelofibrosis (PMF)
     - i PMF, prefibrotic/early stage
     - ii PMF, overt fibrotic stage
   - Essential thrombocythemia
   - Chronic eosinophilic leukemia, not otherwise specified
   - Myeloproliferative neoplasms, unclassifiable

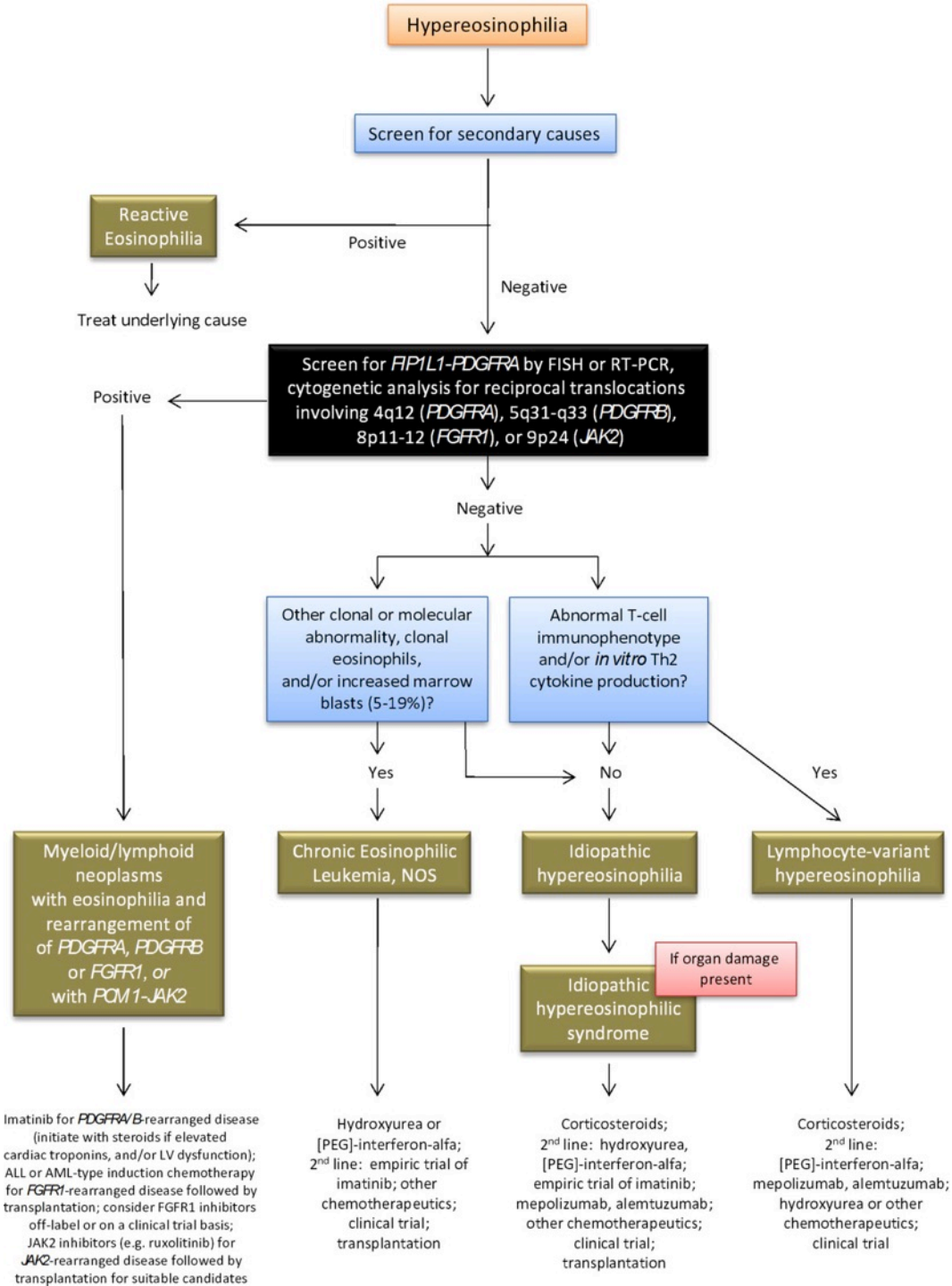
3. Myelodysplastic syndromes (MDS)
   - MDS with single lineage dysplasia
   - MDS with ring sideroblasts (MDS-RS)
     - MDS-RS with single lineage dysplasia
     - MDS-RS with multilineage dysplasia
   - MDS with multilineage dysplasia
   - MDS with excess blasts
   - MDS with isolated del(5q)
   - MDS, unclassifiable
     - i Provisional entity: Refractory cytopenia of childhood
   - Myeloid neoplasms with germ line predisposition

4. MDS/MPN
   - Chronic myelomonocytic leukemia
   - Atypical chronic myeloid leukemia, *BCR-ABL1* negative
   - Juvenile myelomonocytic leukemia
   - MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
   - MDS/MPN, unclassifiable

5. Mastocytosis

6. Myeloid/lymphoid neoplasms associated with eosinophilia and rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1*, or with *PCM1-JAK2*
   - Myeloid/lymphoid neoplasms with *PDGFRA* rearrangement
   - Myeloid neoplasms with *PDGFRB* rearrangement
   - Myeloid/lymphoid neoplasms with *FGFR1* abnormalities
   - Provisional entity: Myeloid/lymphoid neoplasms with *PCM1-JAK2*

Gotlib J. *Am J Hematol* 2017;92:1243-1259.


Hypereosinophilia
Screen for secondary causes
Reactive Eosinophilia
Positive
Negative
Treat underlying cause
Screen for FIP1L1-PDGFRA by FISH or RT-PCR, cytogenetic analysis for reciprocal translocations involving 4q12 (PDGFRA), 5q31-q33 (PDGFRB), 8p11-12 (FGFR1), or 9p24 (JAK2)
Positive
Negative
Other clonal or molecular abnormality, clonal eosinophils, and/or increased marrow blasts (5-19%)?
Abnormal T-cell immunophenotype and/or in vitro Th2 cytokine production?
Yes
No
Yes
Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of of PDGFRA, PDGFRB or FGFR1, or with PCM1-JAK2
Chronic Eosinophilic Leukemia, NOS
Idiopathic hypereosinophilia
Lymphocyte-variant hypereosinophilia
If organ damage present
Idiopathic hypereosinophilic syndrome
Imatinib for PDGFRA/B-rearranged disease (initiate with steroids if elevated cardiac troponins, and/or LV dysfunction); ALL or AML-type induction chemotherapy for FGFR1-rearranged disease followed by transplantation; consider FGFR1 inhibitors off-label or on a clinical trial basis; JAK2 inhibitors (e.g. ruxolitinib) for JAK2-rearranged disease followed by transplantation for suitable candidates
Hydroxyurea or [PEG]-interferon-alfa; 2nd line: empiric trial of imatinib; other chemotherapeutics; clinical trial; transplantation
Corticosteroids; 2nd line: hydroxyurea, [PEG]-interferon-alfa; empiric trial of imatinib; mepolizumab, alemtuzumab; other chemotherapeutics; clinical trial; transplantation
Corticosteroids; 2nd line: [PEG]-interferon-alfa; mepolizumab, alemtuzumab; hydroxyurea or other chemotherapeutics; clinical trial

Summary so far

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- What is the clinical syndrome?
- What are the possible mechanisms for this?
- What further investigations will be useful?

Summary so far

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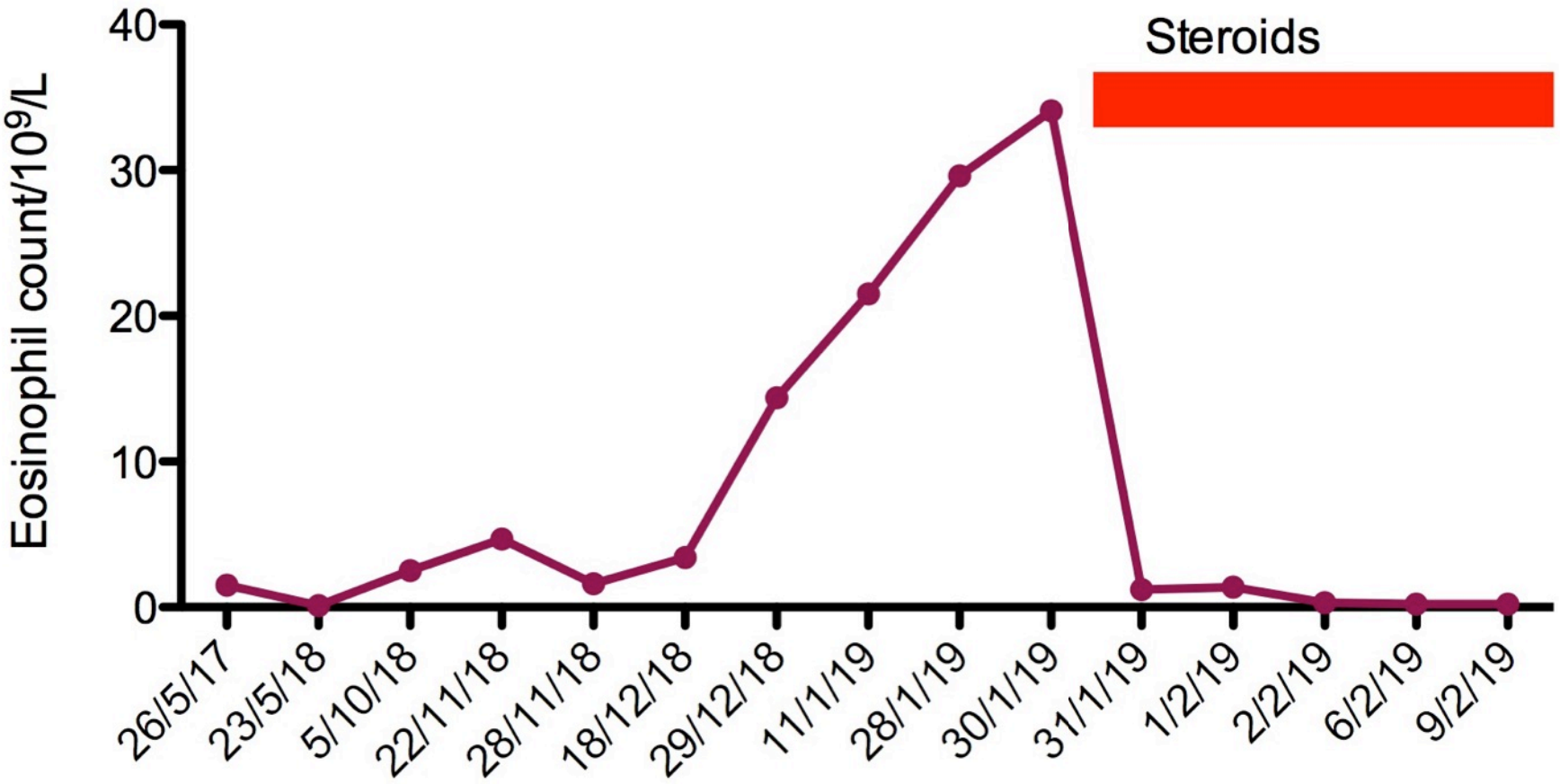
- What is the clinical syndrome?
  - Encephalopathy with multiple infarcts
  - Both embolic and small vessel perforator involvement
- What are the possible mechanisms for this?
  - ANCA-associated vasculitis (EGPA)
  - Hypereosinophilic syndrome
  - Cardiac involvement
- What further investigations will be useful?


Steroids
Eosinophil count/10⁹/L
40
30
20
10
0
26/5/17
23/5/18
5/10/18
22/11/18
28/11/18
18/12/18
29/12/18
11/1/19
28/1/19
30/1/19
31/1/19
1/2/19
2/2/19
6/2/19
9/2/19

- Speckled myocardium
- Mild-moderate AR, mild MR
- Pericardial effusion
- Aortic and mitral valve vegetations

- Troponin I **845** (pre steroids)

- Does this change your thoughts?
- Can we explain all this with existing data?
- What is the next step?

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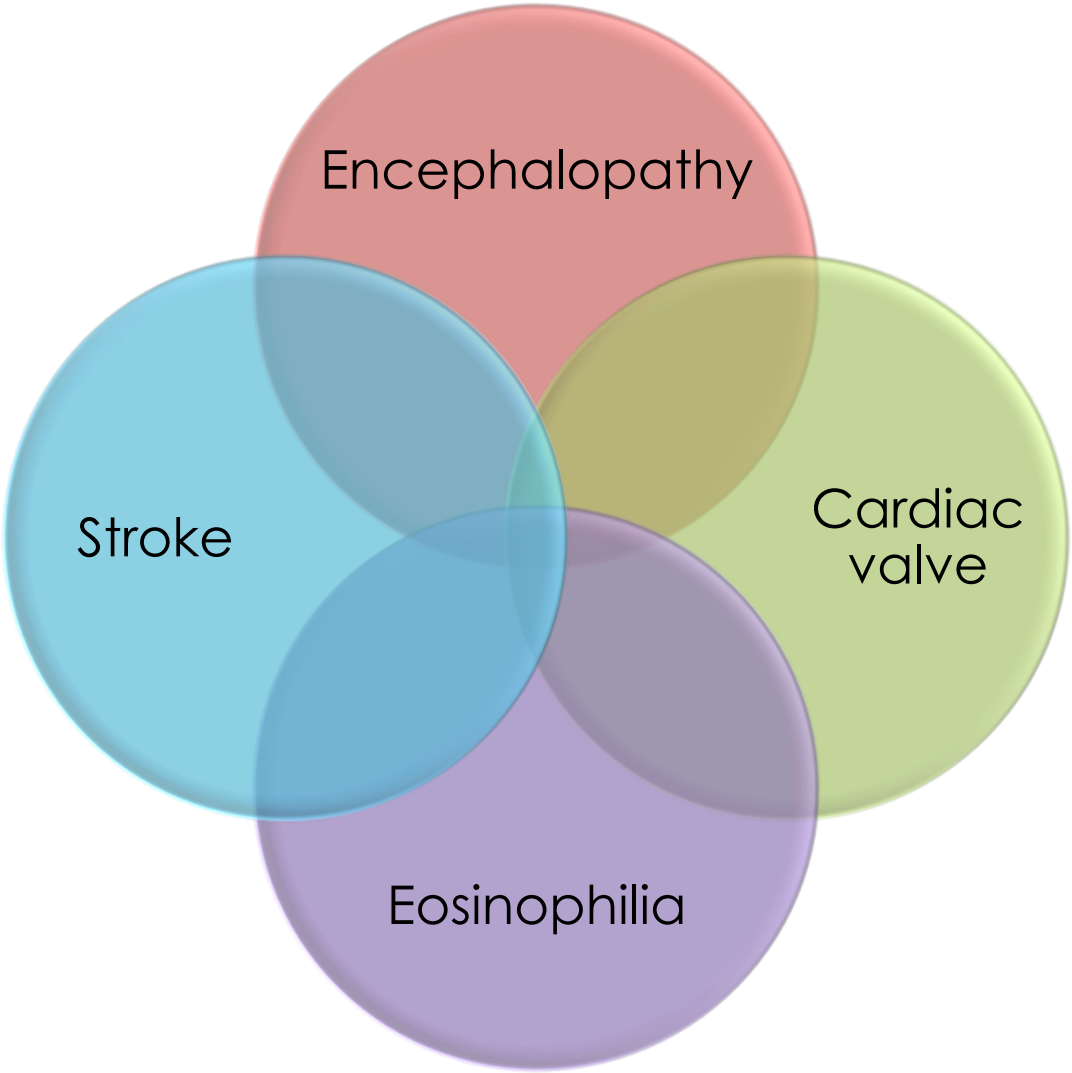

- Bone marrow biopsy
  - Marrow replaced by 70% eosinophils
  - No blasts or malignancy
  - BCR-ABL and PDGFR-A mutations negative
- Multiple blood cultures sent

Endocarditis

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- 30% infective endocarditis patients have neurological manifestations
  - Presenting feature in half of these
- Younger patients
  - More likely underlying congenital heart disease
  - Staph/Strep infections
- Older patients
  - MVP, AS, prosthetic valves, invasive procedures
  - Indwelling devices, IVDA
  - Staph/Strep
  - May be culture negative (HACEK/fungal/*C. burnetii*)

Neurology of IE

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Stroke

- Ischaemic stroke (multiple emboli)
- ICH/SAH
- Mycotic aneurysm rupture

Risk factors

- *S. aureus*
- Fungi
- Larger vegetations
- Increasing size despite antibiotics

Infections

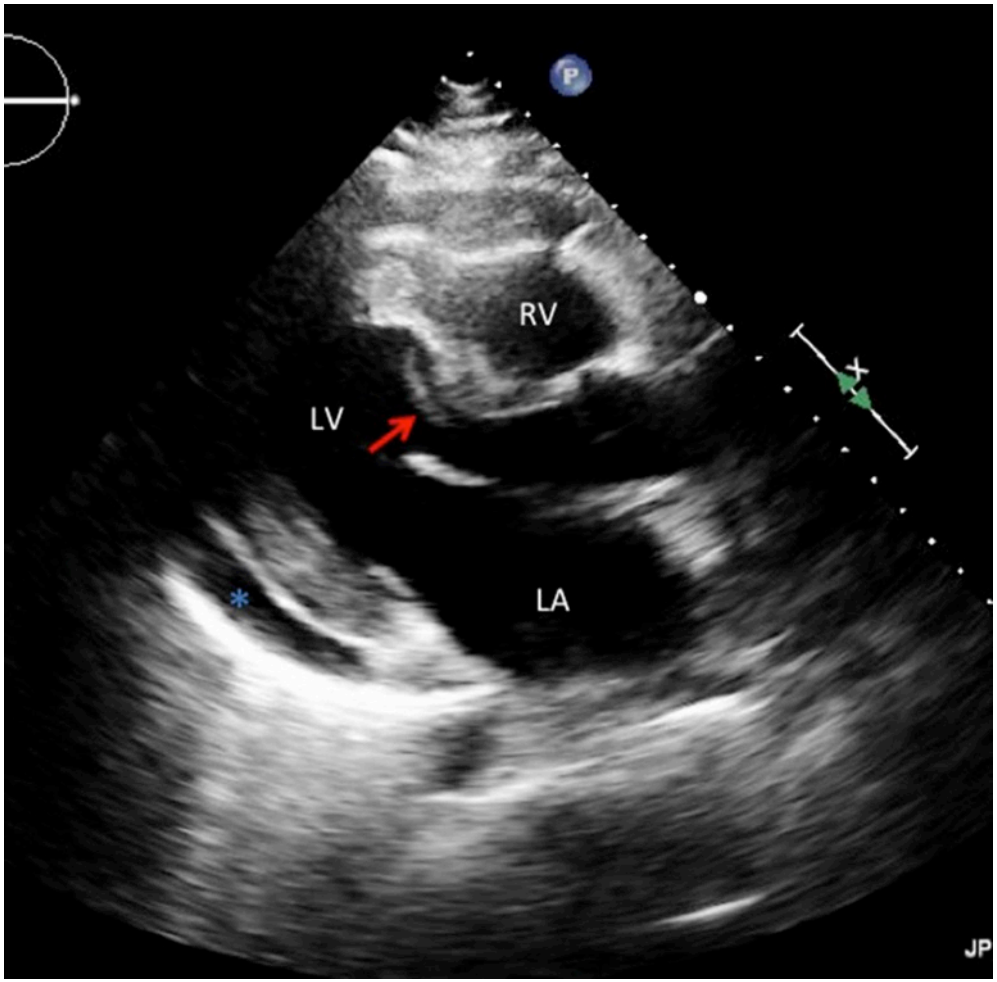
- Meningitis
- Meningo-encephalitis
- Abscess
- Ventriculitis
- Ependymitis

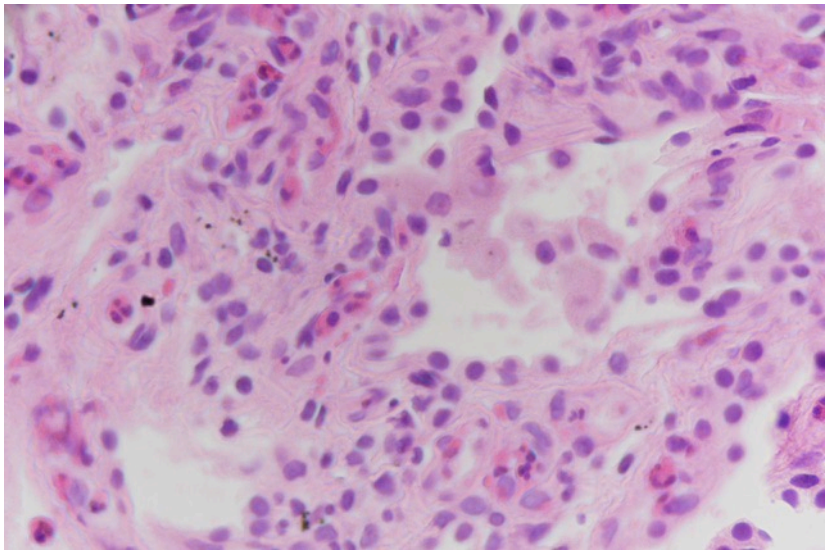
High risk of haemorrhage from septic emboli
Continue anticoagulation only in mechanical heart valves

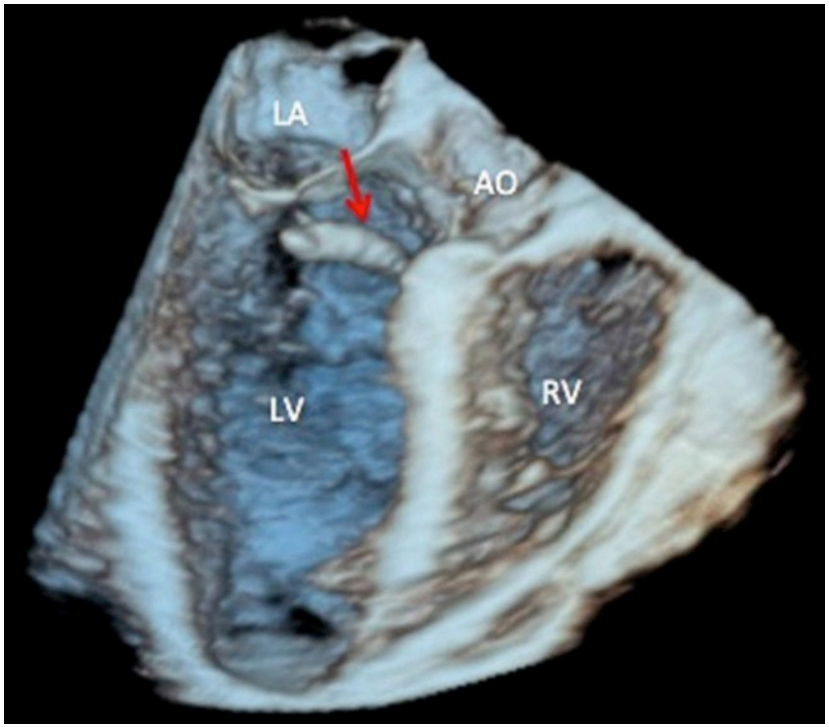
CASE REPORT

Churg-Strauss vasculitis presenting with steroid-responsive left ventricular cardiac mass

Sumaiah Jamal Alarfaj,[1] Rabah Al-Mehisen,[2] Imad Elhag,[3] Nayef Mohammed Kazzaz[4]







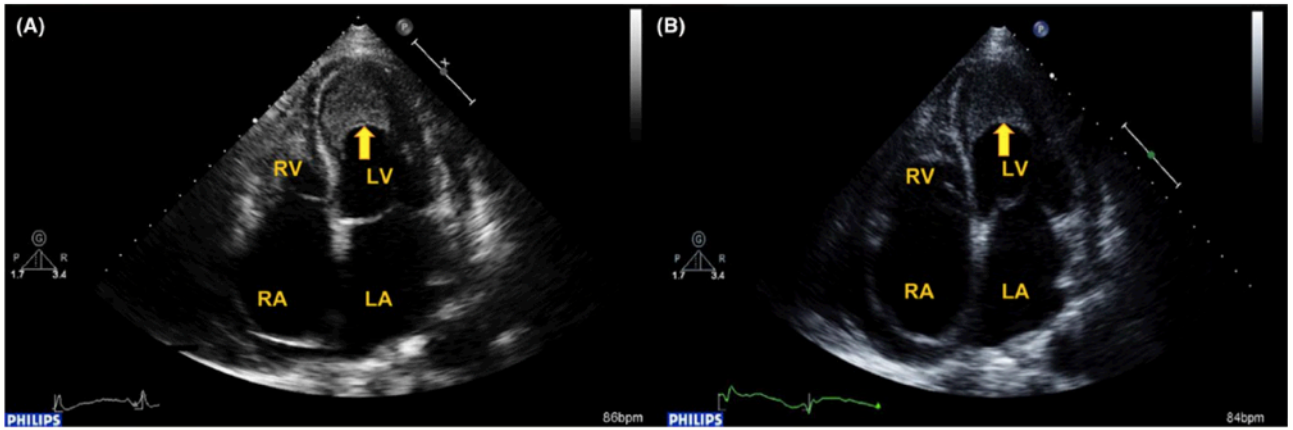
Alarfaj SJ *et al. BMJ Case Rep* 2018;epub

CASE REPORTS Section Editor - Brian D. Hoit, MD

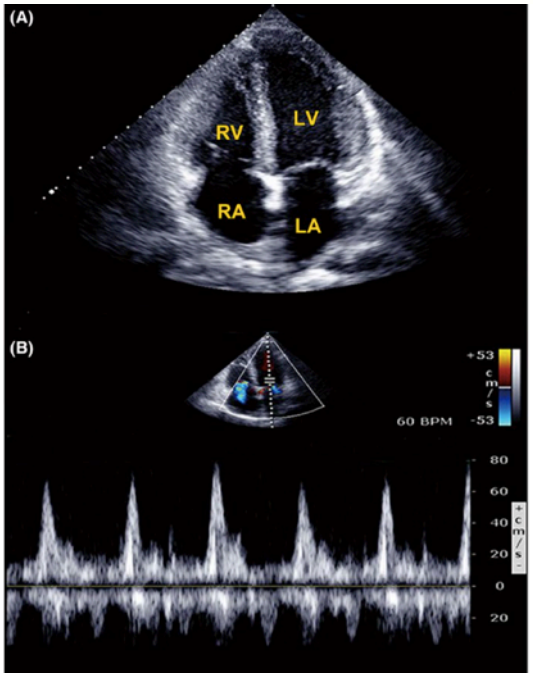
WILEY Echocardiography

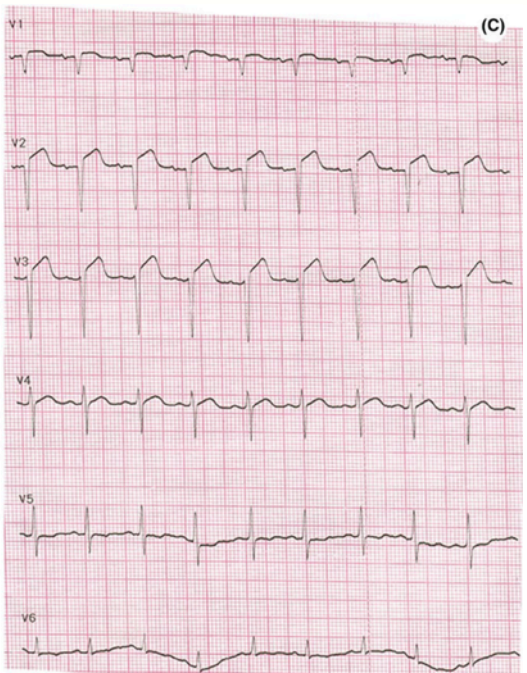
Cardiac involvements in hypereosinophilia-associated syndrome: Case reports and a little review of the literature

Xuanyi Jin MD | Chunyan Ma MD, PhD | Shuang Liu MD, PhD | Zhengyu Guan MD | Yonghuai Wang MD | Jun Yang MD, PhD



HES due to PDGFR mutation
Pre and post imatinib





EGPA

Transferred SRFT

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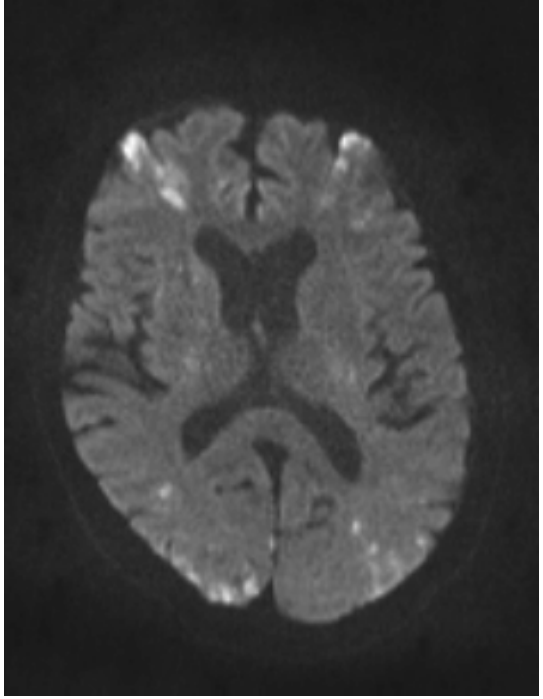
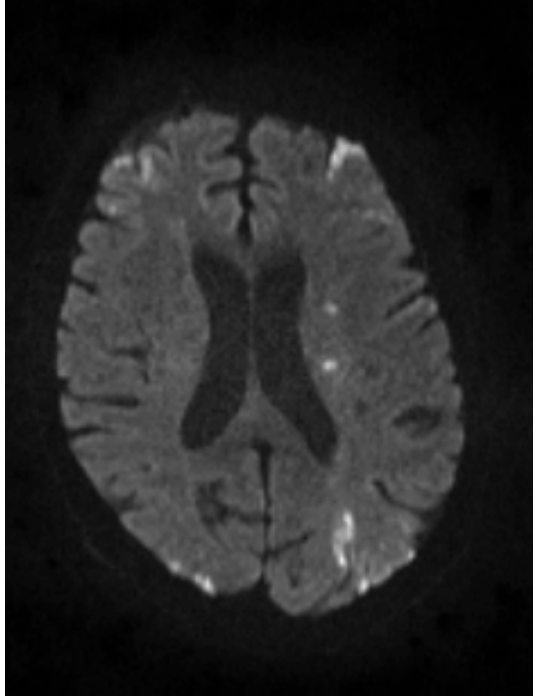
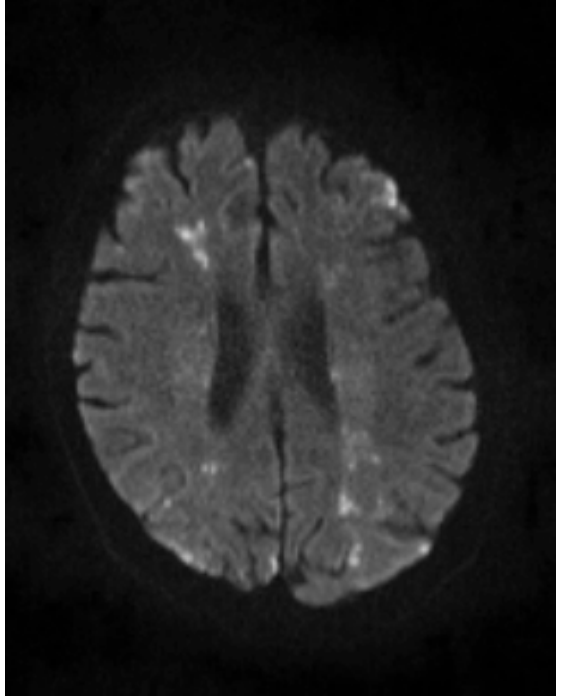
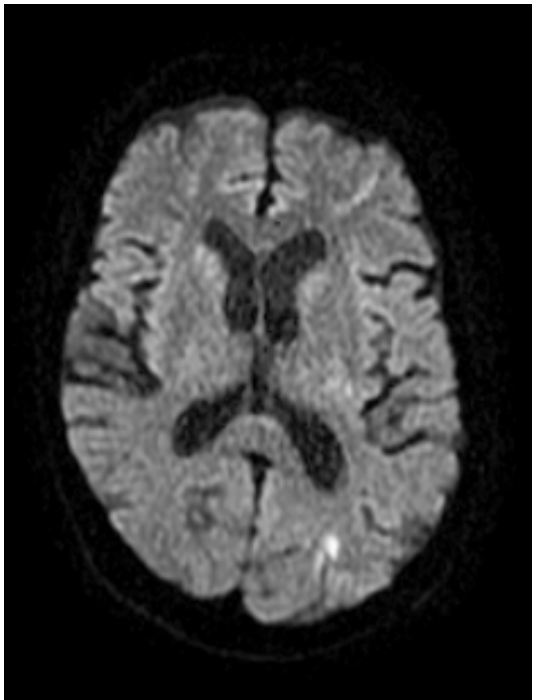
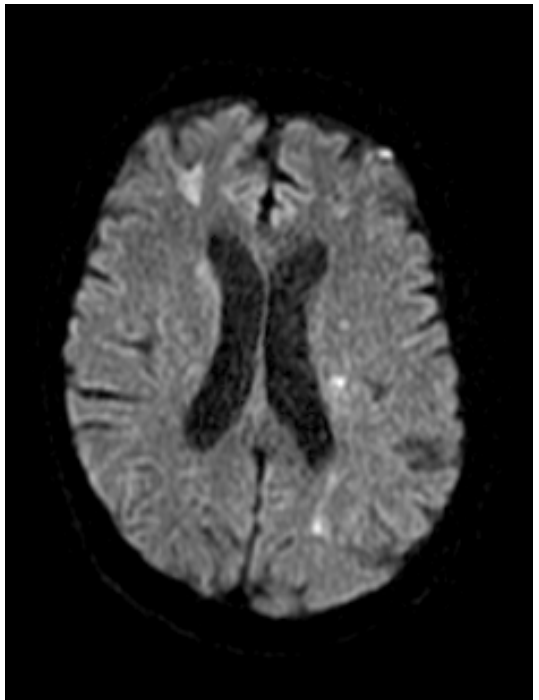
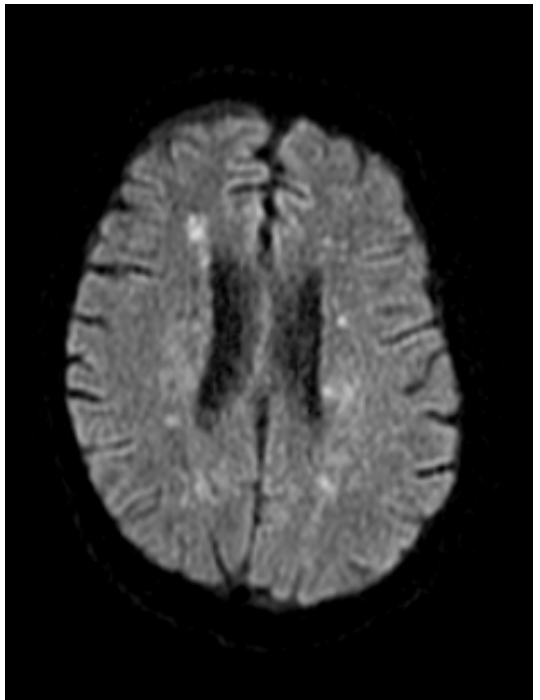
- Remained encephalopathic
  - Disorientated, inattentive
- Systolic murmur heard on examination
- No limb weakness, power 5/5
- Started gentamicin+vancomycin, serial blood cultures
- Continued prednisolone 60 mg
- TOE
  - Moderate MR, moderate AR
  - Mitral valve lesion not suggestive of vegetation
  - Aortic – endocarditis/valvulitis
  - Appearances overall seem more consistent with vasculitis

- Started cyclophosphamide
- Repeat TTE 22/2/19
  - No change in aortic valve
  - Troponin I normalised post steroids
- Cognitively improved
- Repeat MR brain – no new infarcts
- 2 cycles cyclophosphamide to date

Diagnosis

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- Eosinophilic granulomatosis with polyangiitis
  - CNS vasculitis
  - Cardiac involvement with valvulitis and thromboembolism

ALLERGIC GRANULOMATOSIS, ALLERGIC ANGIITIS, AND PERIARTERITIS NODOSA *

JACOB CHURG, M.D., and LOTTE STRAUSS, M.D.

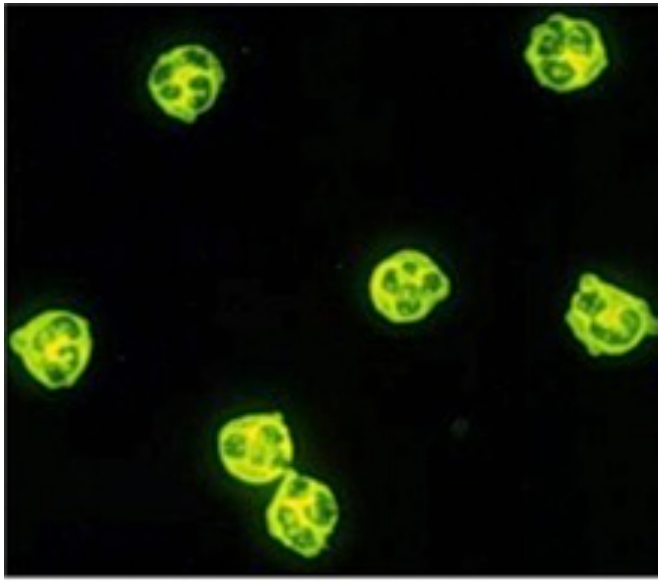
(From the Laboratories, Division of Pathology, the Mount Sinai Hospital, New York 29, N.Y.)

Lotte Strauss

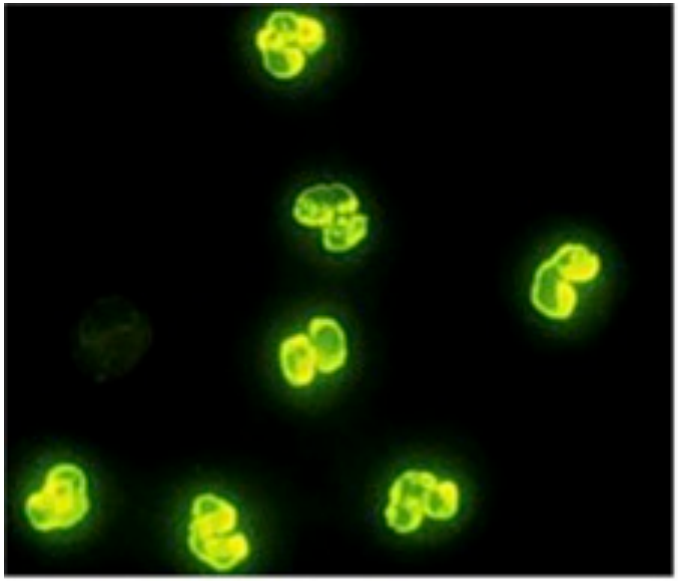
Jacob Churg

https://slideplayer.es/slide/141063/

- ANCA positive in 30-70% eGPA[1]
  - Most common MPO positive (P-ANCA)
- ANCA status relates to eGPA phenotype[2]
  - ANCA positive associated with "vasculitic" phenotype
  - Poorer prognosis if ANCA-negative (cardiomyopathy)



C-ANCA Pattern



P-ANCA Pattern

1. Groh M *et al. Eur J Int Med* 2015;26:545-553.
2. Sinico RA *et al. Arth Rheum* 2005;143:632-8.

Multisystem involvement in EGPA

- Respiratory
  - Asthma usually present at onset
  - Full pulmonary evaluation recommended
- Cardiac
  - Leading cause of EGPA mortality
  - Chest imaging, echocardiogram, ECG, trop I
  - Cardiac MRI and PET may be more sensitive
- Renal
  - Renal function and urinalysis at onset and regular monitoring
- Gastrointestinal
  - Predictive of poor outcome
  - Imaging and endoscopy
- ENT involvement associated with better outcome

Groh *M et al. Eur J Int Med* 2015;26:545-553.

Secondary vasculitis

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Infection
HBV
HIV, VZV
Syphilis

Malignancy

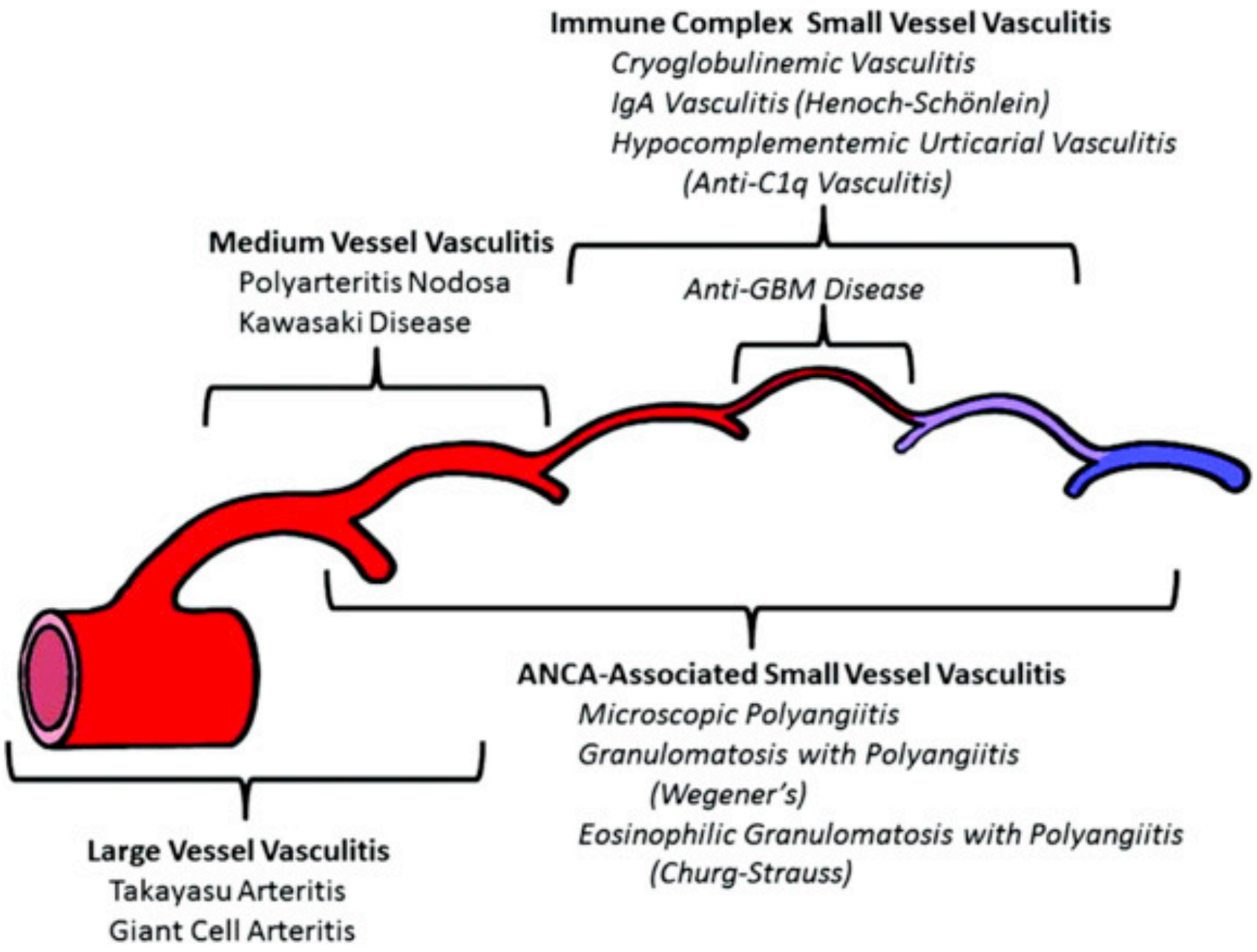
Connective tissue disease
RA, SLE, Behçet's
MCTD, Sjögren

Organ transplant

Drugs
Penicillin
Sulfonamide
Amphetamine, cocaine

Cryoglobuinaemia
Reduced complement

Jennette JC *et al. Arthritis Rheum* 1994;37:187-92.



Wu EY *et al. J Allergy Clin Immunol* 2018;6:1496-1504.

Investigation of vasculitis

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Blood	Imaging	Other	Pathology
FBC, ESR	CXR	EEG	Nerve biopsy
U&E, LFT, CK	CT thorax, abdo, pelvis	NCS/ EMG	Muscle biopsy
Serum electrophoresis	MRI brain with contrast	Lumbar puncture	Temporal artery biopsy
Immunoglobulins	MR angiogram		Meningeal/ brain biopsy
ANA, RF, Complement Cryoglobulins ENA, anti-Sm	SPECT/PET		Skin biopsy
c-ANCA, p-ANCA MPO, PR-3	Systemic/cerebral angiogram		Lymph nodes
HBV, HCV serology HIV, Lyme	Echocardiogram		

CNS vasculitis

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- Headache
- Encephalopathy
- Stroke (ischaemic/haemorrhagic)
- Visual symptoms
- Cranial nerve palsies

- 76 year old female
- Background – asthma, hypertension
- 5 week history R>L leg weakness
  - Pain, burning, numbness both feet
  - Catching feet when walking
- 2 week history pain and weakness of grip L hand
- No new weight loss/fever

- Cranial nerves normal
- Weak finger abduction L hand
- Bilateral foot drop
  - Weakness plantar flexion, inversion L foot
- UL reflexes and knee jerks present
  - Ankle jerks absent
  - Plantar responses flexor
  - Reduced pin prick sensation below knees

- WBC **27.4**
  - Neutrophils 8.4
  - Eosinophils **16.7** (gradually rising over 5 months)
- CRP 175
- ESR 52 mm/h
- Lumbar puncture – WBC <1, protein normal
- ANA, anti dsDNA negative
- **MPO antibody 8.0** (<0.9)
- PR-3 antibody <0.2 (<0.9)

- Clinical syndrome
  - Mononeuritis multiplex
- Aetiology
  - Granulomatous polyangiitis with eosinophilia (MPO positive)
- Received steroids and cyclophosphamide
  - Eosinophils dropped to 1.0 following treatment
  - Good eventual neurological recovery

PNS involvement

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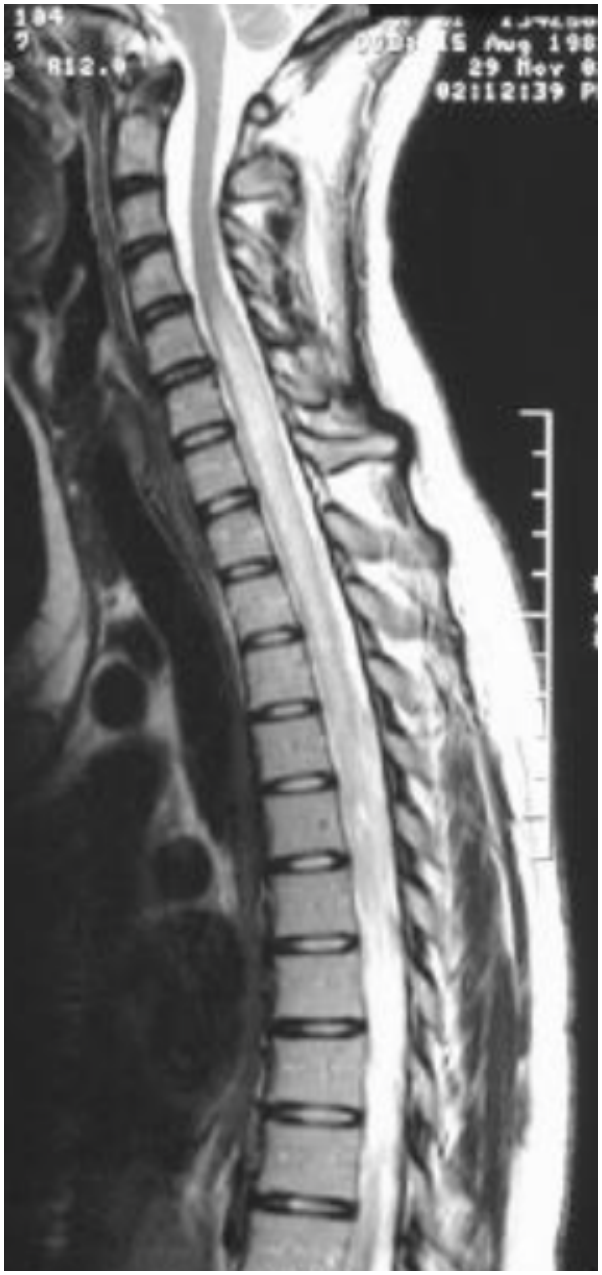
- Mononeuritis multiplex
  - Painful sequential individual peripheral nerve involvement
- Evaluate for vasculitis
- Look for systemic signs e.g. rash, pulmonary features, weight loss



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- 21 year old female
- 5 year history SLE
- LL weakness over 10 days
  - Bladder/bowel involvement

- Transverse myelitis secondary to SLE

Krishnan AV *et al*. Neurology 2004;62:2087.

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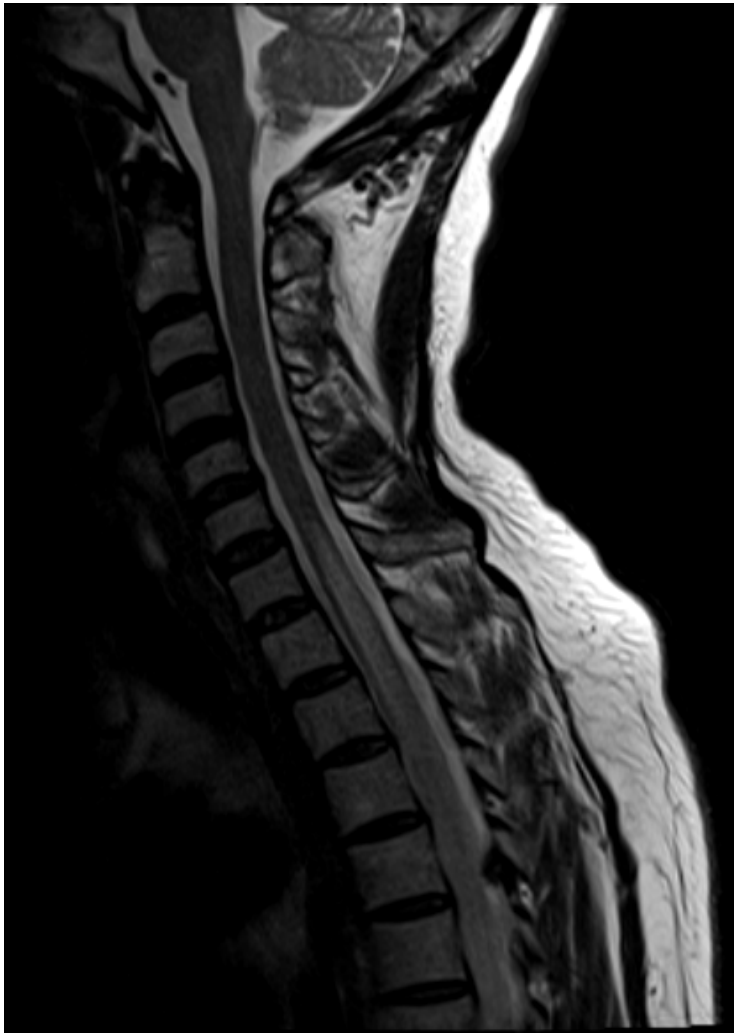
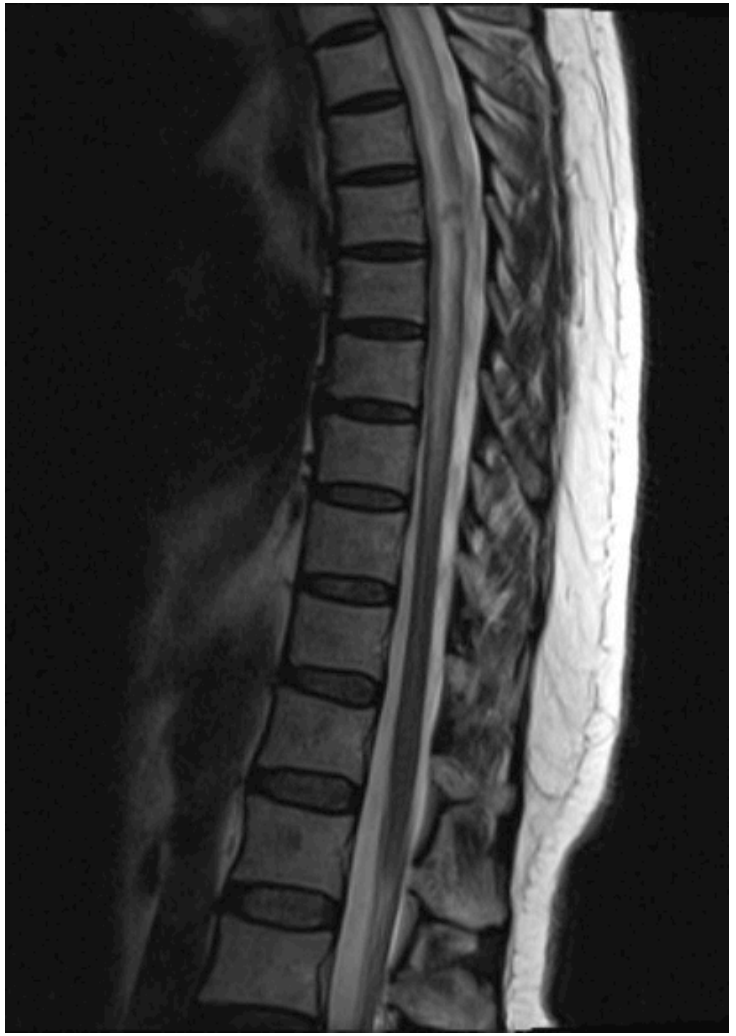
- 59 year old female
- 10 day history weakness/sensory disturbance
  - now unable to mobilise
  - No UL symptoms
  - Urinary retention, faecal incontinence
  - No craniobulbar/visual symptoms

- Examination
  - Alert and orientated, catheterised
  - Cranial nerves normal including fundi
  - Tone normal in UL, increased in LL
  - UL power normal
  - Grade 2-3/5 pyramidal LL weakness
  - LL reflexes brisk, plantars extensor
  - Vibration sensation absent to costal margin
  - Pin prick diminished to T4 bilaterally





Anticardiolipin antibodies positive

Aquaporin-4 antibodies positive

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- Diagnosis: neuromyelitis optica
- Transferred to Salford ANU
- 5 days of IV methylprednisolone and oral steroid taper
- Plasma exchange x 5
- Transferred to regional spinal rehab
- Slow recovery but after 1 year able to mobilise with stick

Antibodies suggestive of rheumatological conditions e.g. cardiolipin/ANA may be positive!

Treatment of NMO

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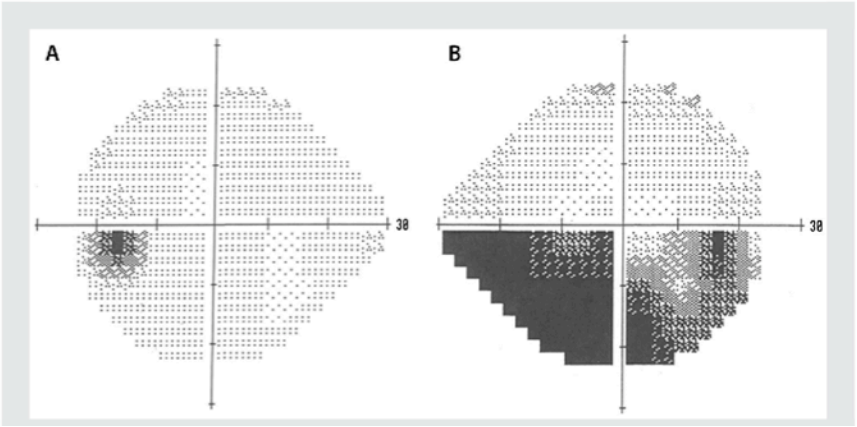
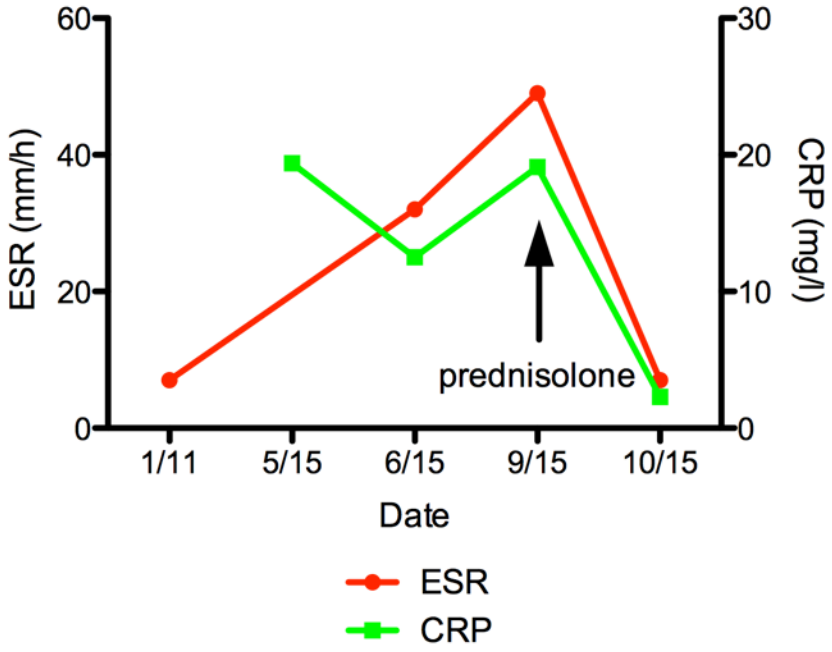
- High dose steroids + oral taper
- Early plasma exchange if fails to respond
  - Associated with better outcomes
- Long term immunosuppression





- 68 year old male
- PMH AF, T2DM, IHD, hypertension
- Woke up with loss of vision R eye
  - Painless
  - No headache or systemic features
- Visual acuity finger counting on R
  - Optic disc swelling

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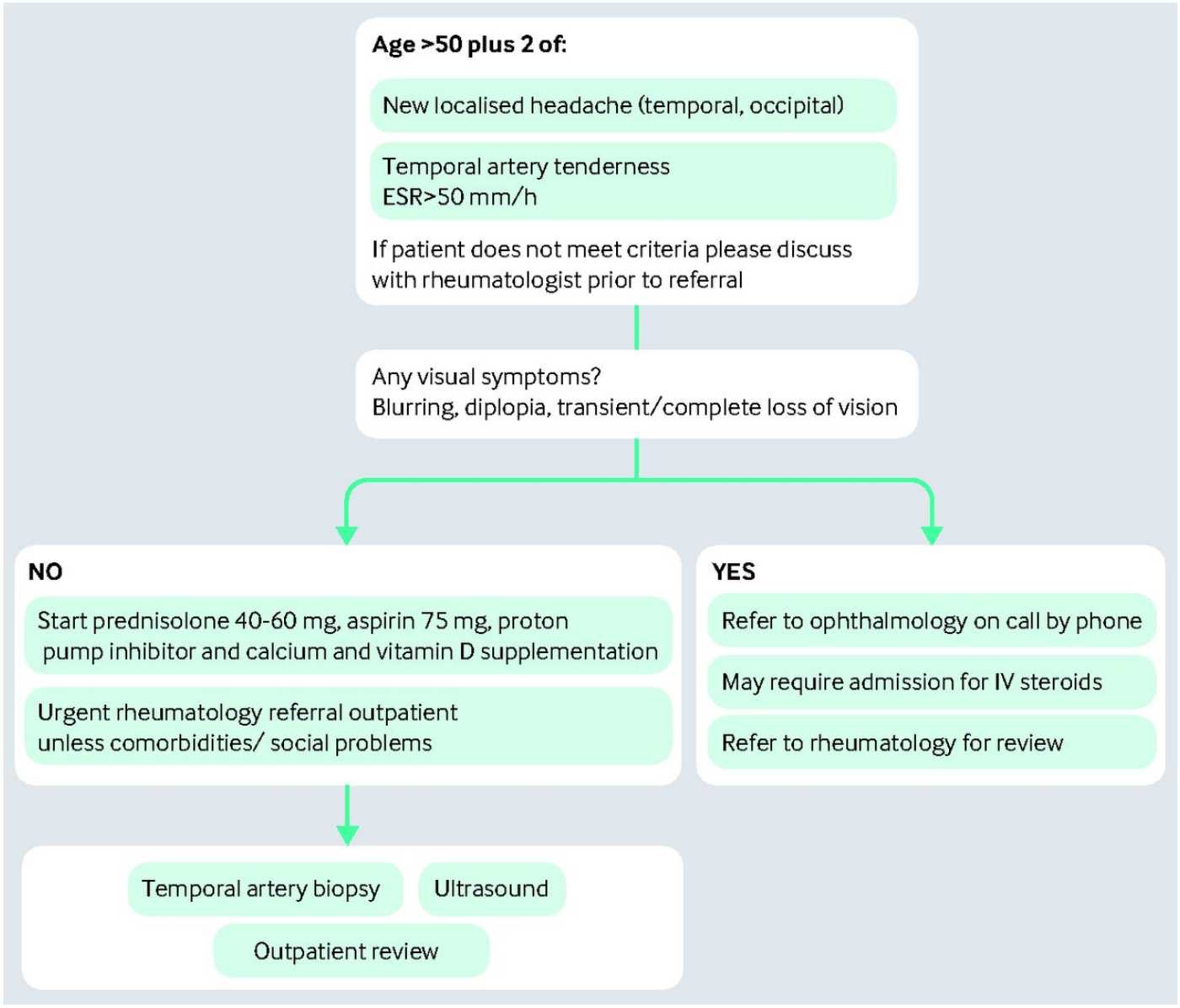

Lazarewicz K, Watson P. *BMJ* 2019;365:i1964.

- 34 year old female
- Admitted with fever, headaches, reduced conscious level, left sided weakness
- CSF 180 lymphocytes
  - Protein 1.2 g/l
  - Glucose 2.4 mmol/l (plasma glucose 6)
- Abnormalities in brainstem on MR

- Working diagnosis: *Listeria* meningitis/ rhombencephalitis

- Readmitted 3 months later
- Unsteady, double vision, headaches
- Left oculomotor palsy, right sided weakness
  - Brisk reflexes R side
  - R plantar extensor

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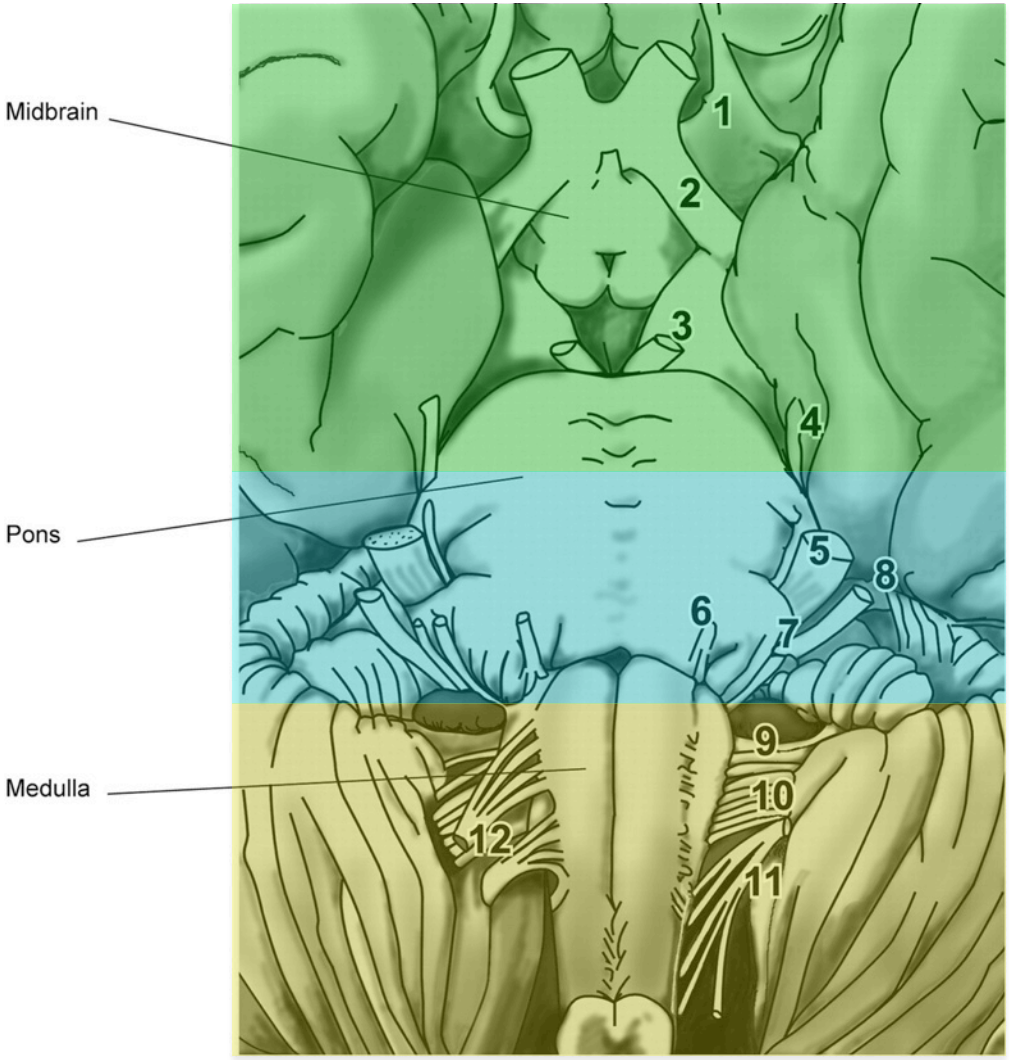
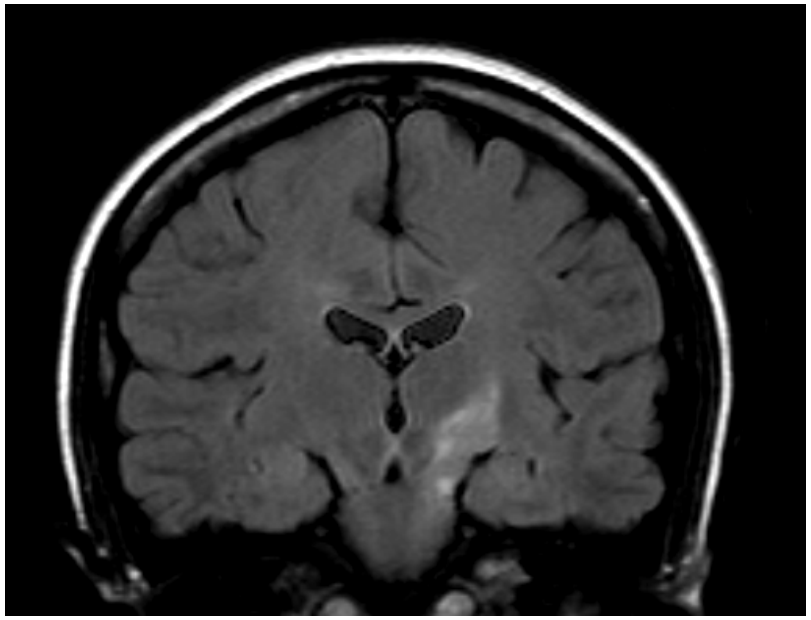


- What is the clinical syndrome?
- Left midbrain syndrome
- Previous meningitis

Gates P. *Pract Neurol* 2011;11:167-172.



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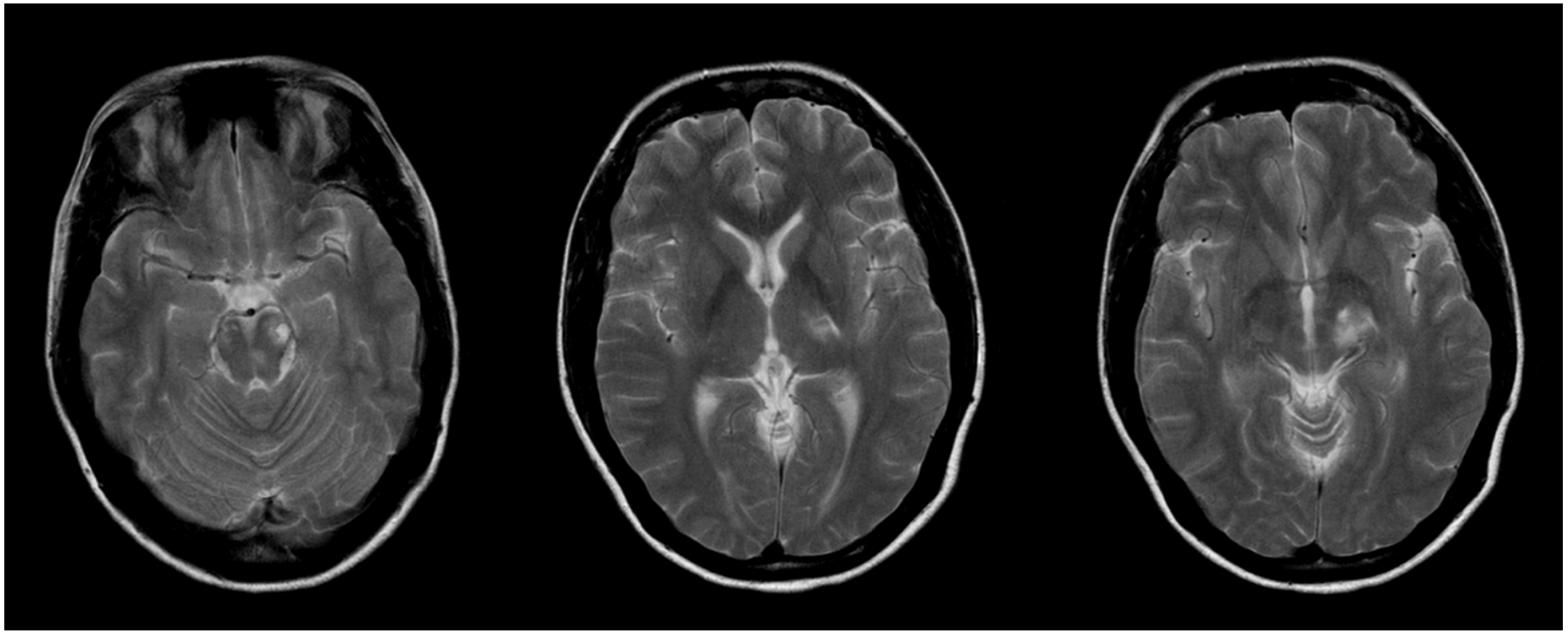
Recurrent oral and genital ulceration over last 6 months

Diagnosis: Behçet's disease



Behçet's disease

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- Neurological involvement
- Intra-axial
  - Parenchymal inflammation
  - Recurrent sterile meningitis
- Extra-axial
  - Venous sinus thrombosis
  - Intracranial aneurysm formation
- Oral or genital ulcers usually present at presentation

- 78 year old female
- Rheumatoid arthritis, well controlled
  - Prednisolone + leflunomide/ methotrexate
- 4 week history headache + transient L sided weakness/numbness
- ESR **83** mm/h, CRP normal
- CSF
  - WBC **23**
  - Protein **0.75**

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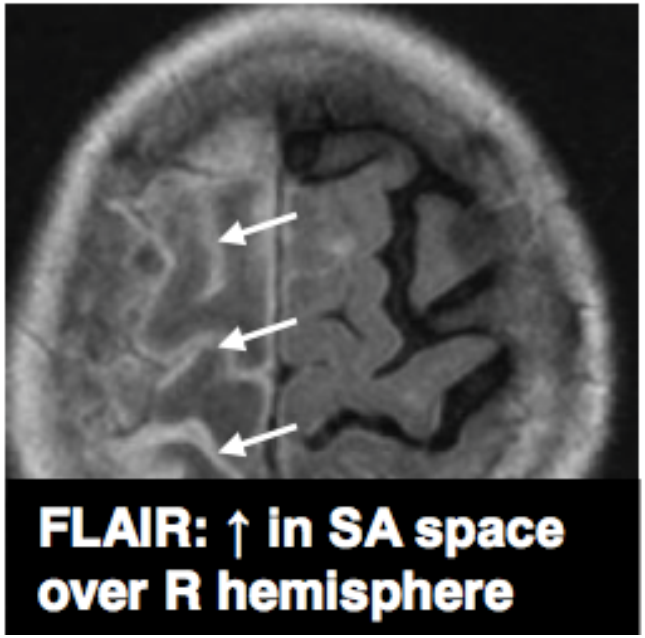

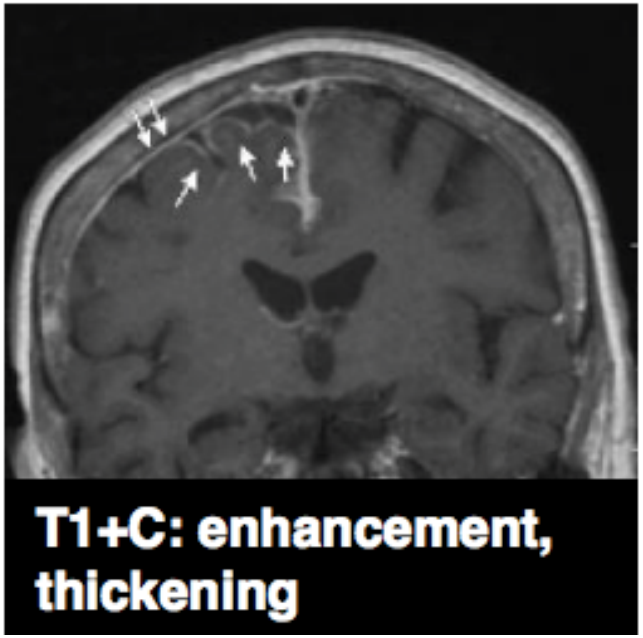

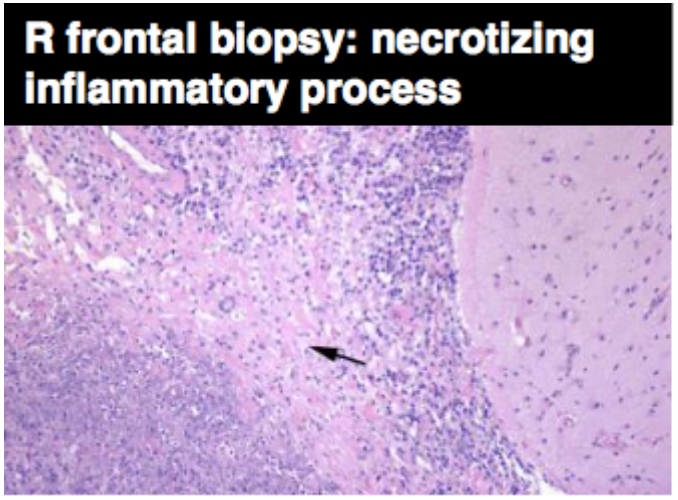

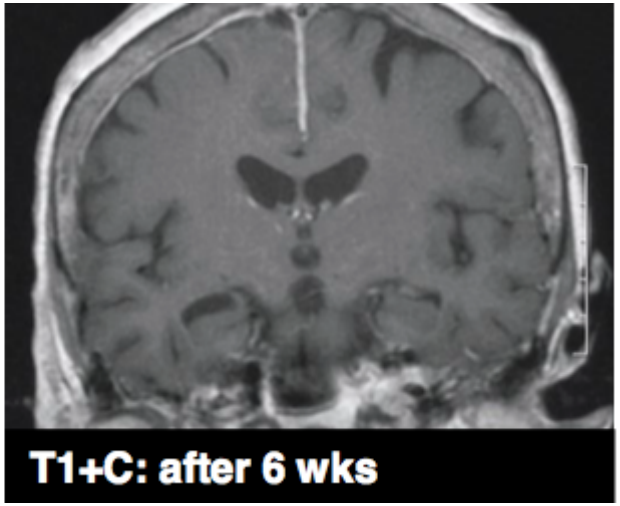

- Rheumatoid meningitis
- Can occur in otherwise stable disease
- Treatment: increased steroids, symptoms and imaging improved

Chowdry V *et al. J Neuroimaging* 2005;15:286-8.

Meningeal involvement

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- GPA and EGPA
- Rheumatoid arthritis
- IgG4 disease

- Don't forget malignant meningitis
  - Older people, systemic disturbance, history of cancer
  - CSF abnormalities often non-specific (slightly raised protein/cells or low glucose)
  - May need multiple large volume CSF samples

Conclusions

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- Connective tissue disease may affect all parts of nervous system
- Systemic features are crucial
  - Diagnostic
  - Monitoring for complications
- May mimic other medical conditions