Long case

Cross Canada Rounds June 2019
Julie Duncan

Voting at:
poIlEv.com/julieduncan351

Background history

- 16 year old female
- Presented with a 1 month history of pain in small joints of the hands, associated with initial fever for 4 days
- Progressed to larger joints, worse in the morning
- 3 weeks prolonged menses and syncopal episode had prompted emergency attendance
- Joint pain had started to affect activity

Background history

- Rheumatology consulted
- No change to voice, swallow or ‘breathing’
- Asked about rashes: had developed a dry rash over knuckles, margins of fingers, thighs, left elbow, treated as eczema and improved
- Bruising over her eye-lids and periorbital swelling
- Fever 1 week before consultation

Past medical history

- Term delivery, normal scans
- Caesarian section for breech presentation
- No RDS, but NICU for jaundice (phototherapy)
- Normal developmental milestones
- No previous admissions or surgeries
- No recent travel / sick contacts

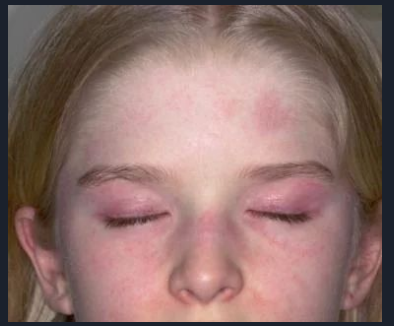
Family / social history

- Port Coquitlam, plans to go to college
- 19 year old sister, problems with vision one year previous, resolved with topical therapy (unclear diagnosis), also has eczema
- Mother (50y) eczema, photosensitive rash, allergies
- Father (55y) hypertension, dyslipidaemia, gout
- Parents Taiwanese, non consanguineous
- Grandmother hepatitis B
- No autoimmune disease in the family

Examination

- Normal blood pressure, HR and RR
- Febrile to 40.3 degrees
- Uncomfortable and unwell on general exam
- Head and neck exam: normal pupillary response and normal nasopharynx, no ulcers
- Oropharynx: telangiectasias of her gums, no ulcers
- No lymphadenopathy
- Cardiovascular and respiratory exam normal
- Abdomen soft, no hepatosplenomegaly

Examination



- Skin: erythematous papules over the left third MCP and a faint, flaking rash over left elbow
- Marked erythema of her eyelids with associated edema
- Effusions and limited movement of small and large joints (upper and lower limbs)
- Strength assessment graded at 3/5 for shoulder flexion, 3/5 for hip flexion; 4/5 for neck flexion, grip strength fair

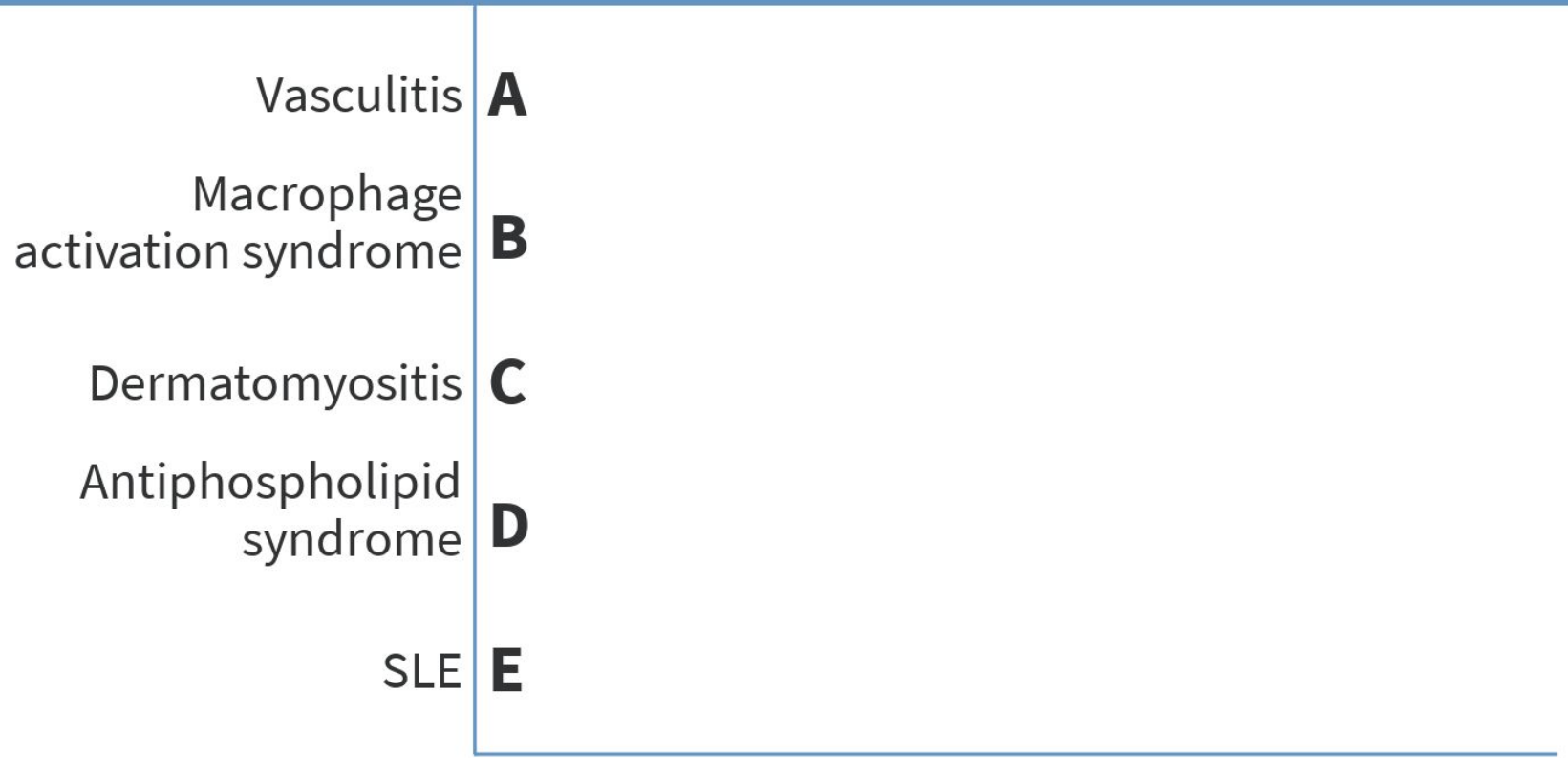
Investigations

- CBC: WCC 3.8, Hb 81, Pl 211, retics 48
- CRP 0.16, ESR 14, CK 1545
- Coagulation: INR 1, APTT 46, vWF elevated, vWF antigen high, mixing studies suggested inhibitor
- Low C3 (0.66), normal C4 (0.21)
- ANA, dsDNA, ANCAs, cardiolipin, RhF, SSB, Smith, SCL-70, Jo-1 all negative
- Haptoglobin normal, ferritin 4165
- Igs normal
- Normal pelvic ultrasound
- Raised AST/ALT (195/362)

Differential diagnosis

A. Vasculitis
B. Macrophage activation syndrome
C. Dermatomyositis
D. Antiphospholipid syndrome
E. SLE

Differential diagnosis

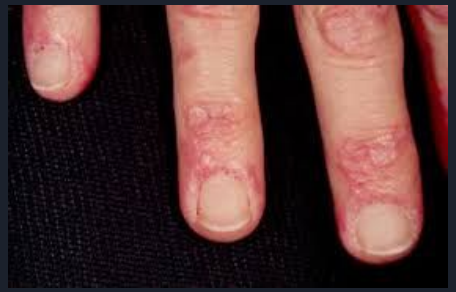


Diagnosis: Juvenile dermatomyositis

- Rare autoimmune inflammatory myositis

  Diagnosis:
- Typical skin findings (heliotrope rash and/or Gottron sign/papules)

  Additional criteria: (probable +2, definite +3)
- Symmetrical proximal muscle weakness +/- myalgia
- Elevated muscle enzymes
- Muscle histopathology
- Typical findings on MRI



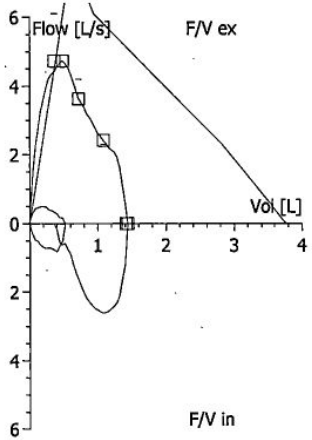
Initial progress

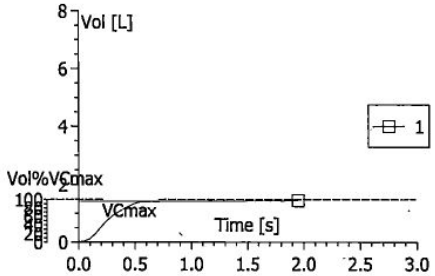
- MRI lower limbs: diffuse myositis - extensive muscle, fascial and subcutaneous edema
- Pulsed steroids and methotrexate
- Strength improved, increased mobility
- CK trending down
- Baseline echo, lung function tests and DEXA scan organised as outpatient
- 2 week follow up: voice changes of concern, swallow study arranged
- Seen by GI for persistent transaminitis - Wilson’s suspected (low caeruloplasmin)

3 weeks after diagnosis

- Swallow study - poor oral control, sluggish swallow, no aspiration
- Worsening ulcerative rash
- Little change to weakness
- Escalation of therapy:
  - Further pulse steroids
  - IV cyclophosphamide
- Mitogen myositis antibody study is positive for anti-MDA5

		Pred	PRE	%Pred	POST	%Pred	%Chng
FVC	[L]	3.76	1.44	38			
FEV1	[L]	3.41	1.41	41			
FEV1/FVC	[%]		98				
PEF	[L/s]	7.80	4.72	61			
FEF25/75	[L/s]	4.21	3.50	83			
PIF	[L/s]		2.62				
DLCOc SB	[ml/min/mmHg]	25.22	8.22	33			
DLCO SB	[ml/min/mmHg]	25.22	7.87	31			
VA	[L]		3.13				
DLCOc/VA	[ml/min/mmHg/L]		2.62				
ERV(SB)	[L]		0.55				
FRC(SB)	[L]	2.96	2.07	70			
RV-SB	[L]	1.50	1.52	101			
TLC-(SB)	[L]	5.40	3.26	60			
SpO2(ox.)	[%]		99				
H.R.	[bpm]		117.00				
Nitric	[ppb]						





'Variable patient effort with no reproducible results on FVC and DLCO. End of test criteria not met in spirometry'

How would you interpret her PFTs?

		Pred	PRE	%Pred	POST	%Pred	%Chng
FVC	[L]	3.76	1.44	38			
FEV1	[L]	3.41	1.41	41			
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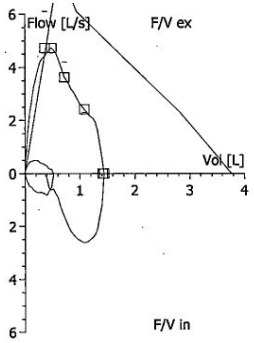
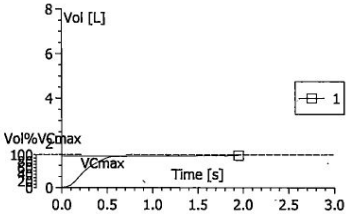




- Uninterpretable due to suboptimal effort
- Concerning for restrictive disease and poor diffusing capacity
- Restrictive disease but likely normal diffusing capacity
- Classical for myopathic weakness

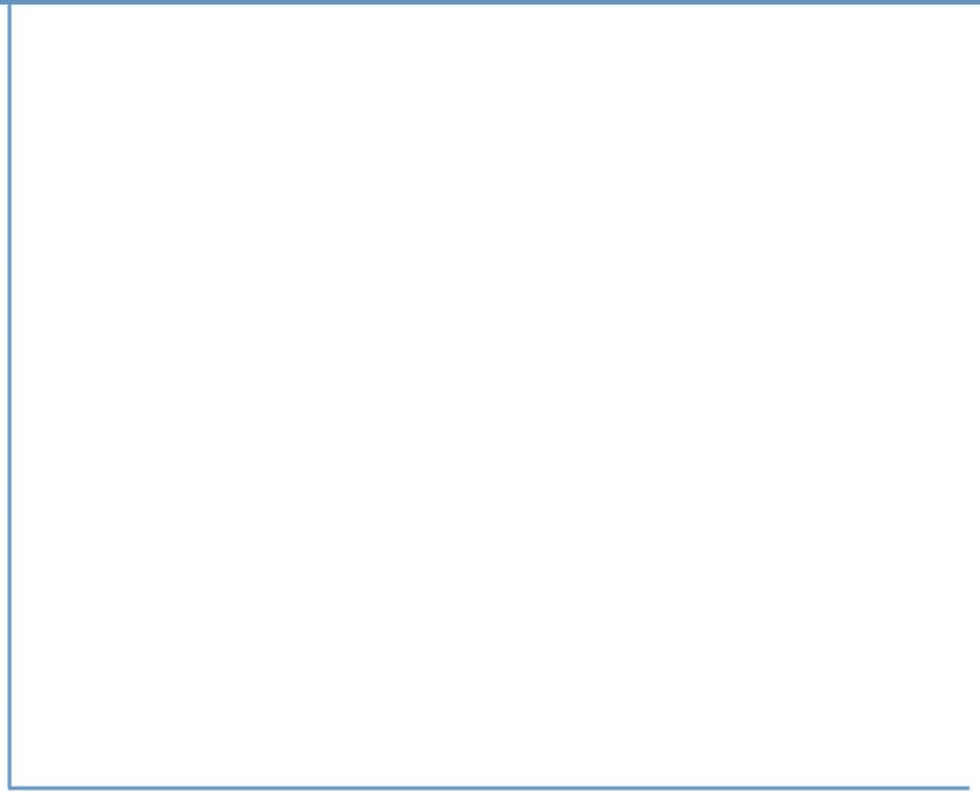
How would you interpret her lung function tests?

Uninterpretable due to poor technical manouver

Concerning for restrictive disease and poor diffusing capacity

Restrictive disease and normal diffusing capacity

Classical for myopathic weakness



British trivia break

You're about to go on holiday, it's 7am, and you're sat in the departure lounge. What do you drink?

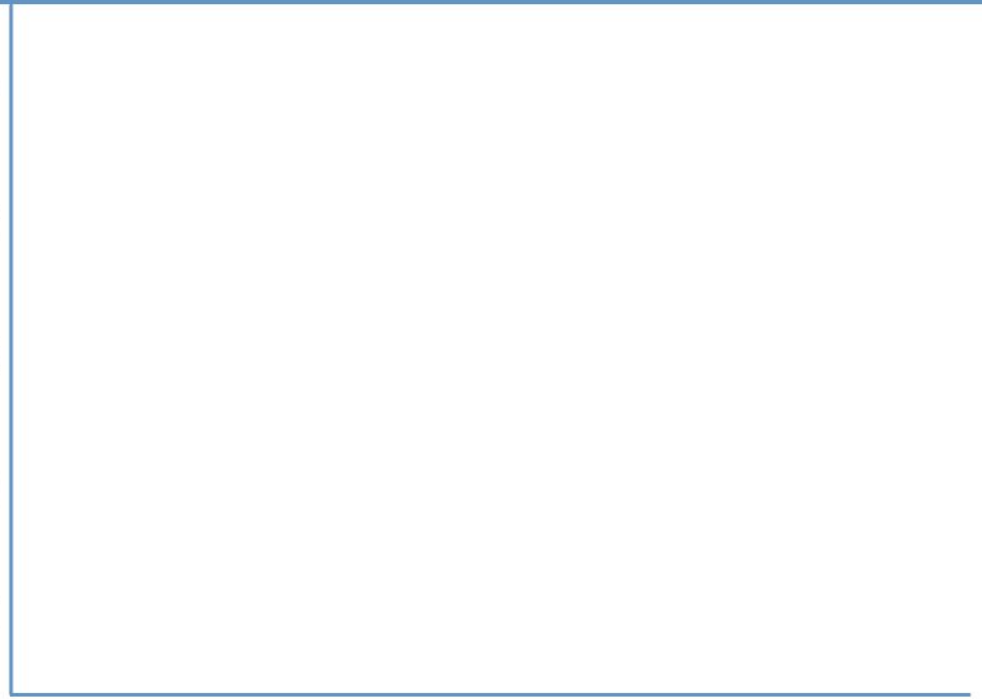
A cup of Earl Grey

A cup of builders breakfast

A coffee

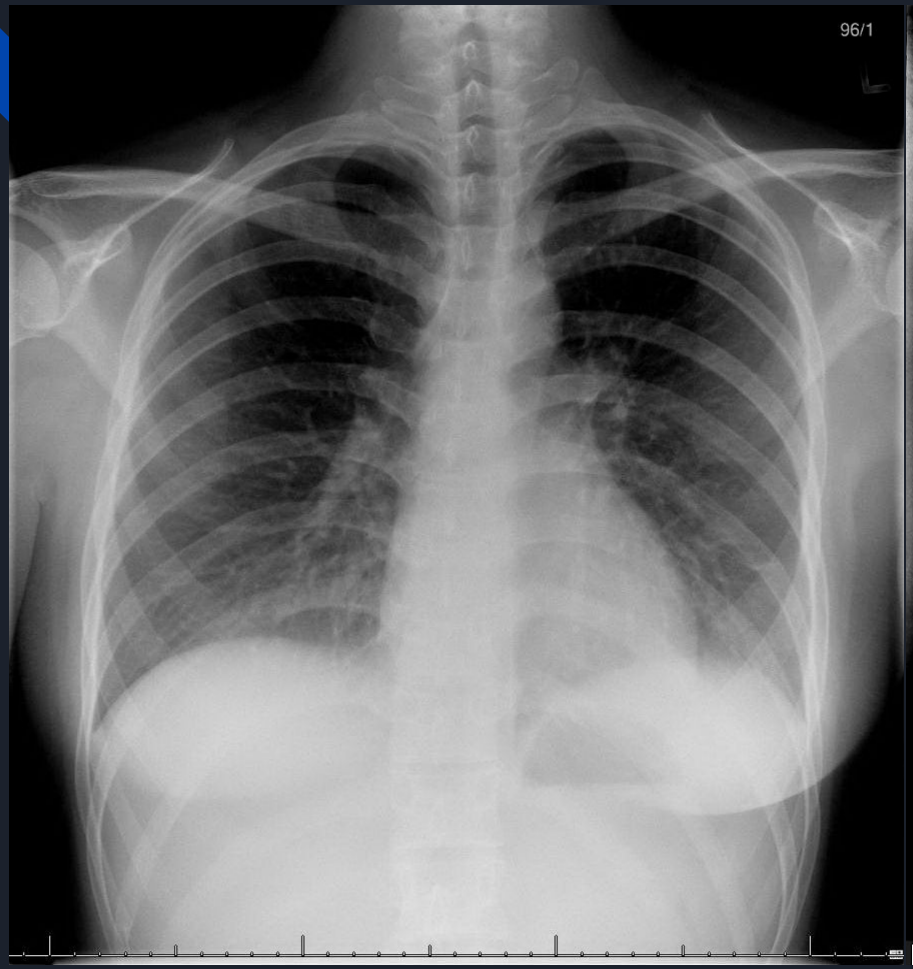
A pint (you're on holiday after all)

An OJ



6 weeks after diagnosis

- Presented with fever and rhinitis
- In context of immunosuppression, admitted for intravenous antibiotics pending blood cultures
- Blood cultures MSSA, meropenem
- 2 days into admission, developed cough and oxygen requirement
- Sudden increase to 5L overnight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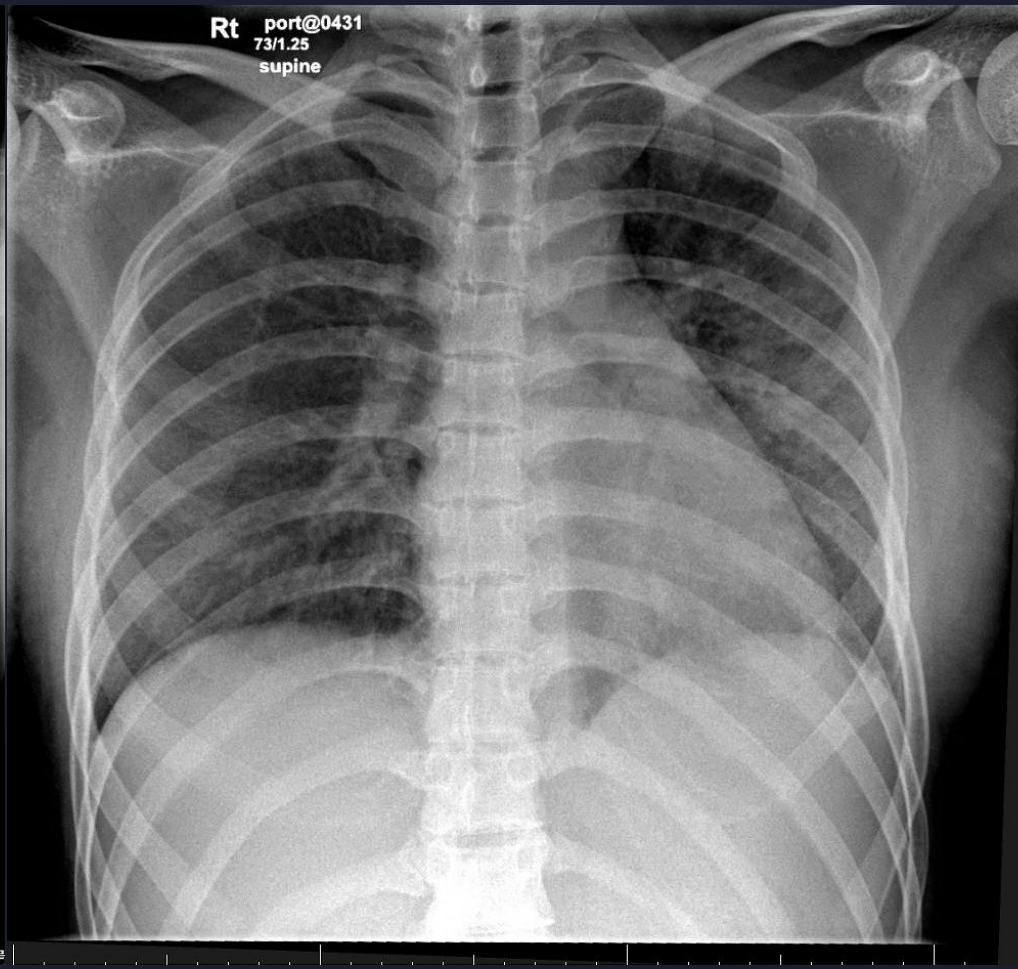
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port@0431
73/1.25
supine

Differential diagnosis

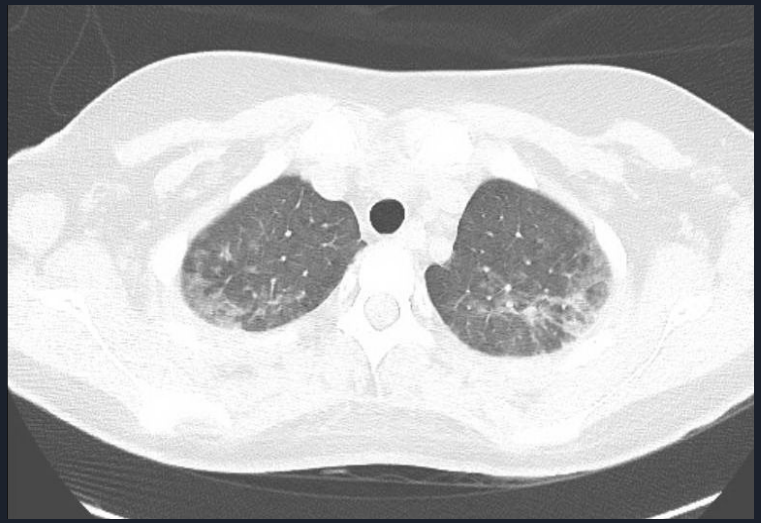
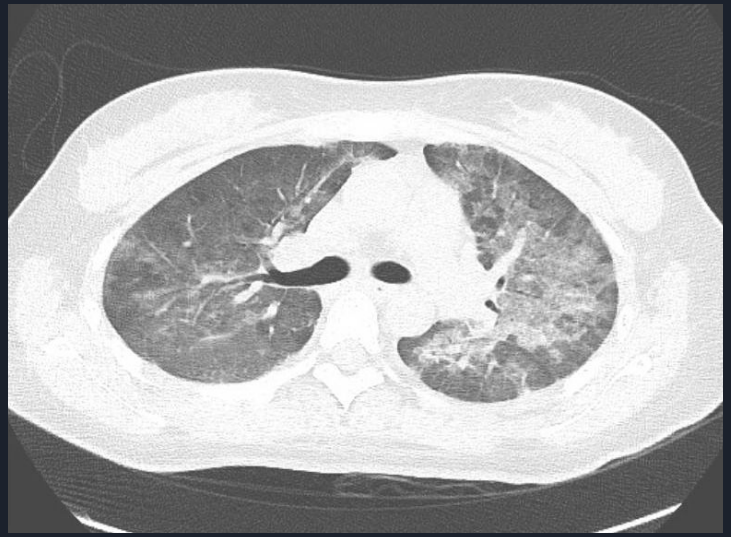
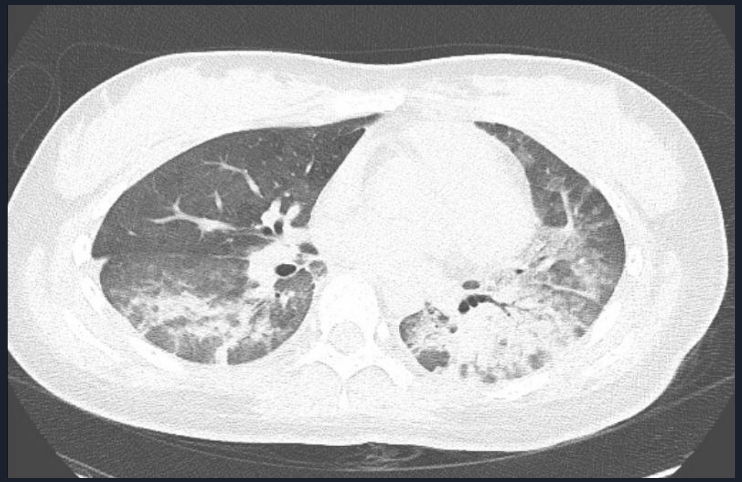
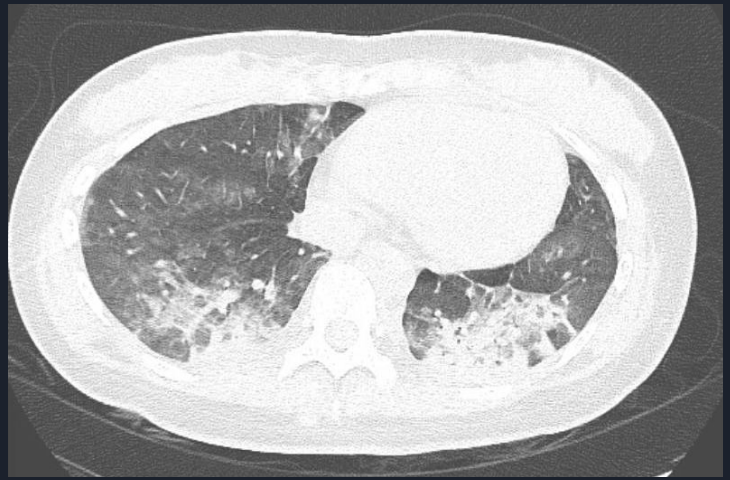
- Infectious process:
  - Bacterial agents including Staph aureus (given her MSSA sepsis)
  - Other community-acquired pneumonia
  - Viral: CMW considering immunosuppression
  - Fungal: aspergillus, opportunistic pathogens including PJP
- Underlying pneumonitis secondary to cyclophosphamide (less likely given her acute presentation)

What is your next step?

1. CT chest
2. Bronchoscopy/BAL
3. CT chest and bronchoscopy/BAL
4. Continue antibiotics and cover for fungal infection including PJP pneumonia
5. ID consult

What is your next step?

CT chest	**A**
Bronchoscopy and BAL	**B**
CT chest and bronchoscopy/BAL	**C**
Continue antibiotics, cover for fungal infection including PJP pneumonia	**D**
ID consult	**E**

CT chest

‘Extensive opacification - combination of systemic inflammatory response and volume overload. ARDS and acute infectious change also in the differential, no specific features of opportunistic infection’

Bronchoscopy

- Neutrophils 3%, lymphocytes 53%, no eosinophils
- No evidence of alveolar haemorrhage
- Bacterial culture and AFBs negative
- Viral panel negative
- PJP staining positive

- Intubated post bronchoscopy, admission to PICU

PICU course

- PJP treatment with septra
- Continued on steroids, hyperglycaemia requiring insulin
- Persistent oxygen requirement, FiO2 > 0.7
- Repeat CT suggestive of fungal infection, but also ILD
- Course anti-fungal antibiotics
- Fever and pancytopenia 1 month after diagnosis
- Bone marrow aspirate showed MAS, further pulse steroids, ciclosporin, antibiotics
- Failed extubation attempts and FiO2 still 0.5

Progress

- Tracheostomy 6 weeks after admission
- Respirology asked to re-consult to investigate reason for prolonged intubation

Differential diagnosis:

- Slow recovery of ARDS
- JDM-related ILD
- Further infection (possibly fungal)

British trivia break

The hairdresser holds up their mirror, you hate your new haircut. What do you do?

Politely ask them if they could maybe make it more like what you had in mind

Call in sick at work for a few days to ensure minimum embarrassment

Tell them it's "great", then go and get it fixed at a place round the corner

Tell them exactly what you think, and refuse to pay

Smile and nod, before tipping them

Respiratory complications of JDM

- JDM 2-3 cases per million children per year
- Lung involvement much rare than adult DM
- Largest case series[1] only 1 of 105 patients developed symptomatic ILD
- Other case series[2-4] report higher rates of ILD detected by PFTs / HRCT scanning, but most not histologically confirmed
- Important to recognise ILD can be rapidly progressive and fatal
- PFT monitoring recommended

[1]Rheum Dis Clin North Am 28(4): 833-857 (2002); [2]Pediatric Pulmonology 48:1016-1025 (2013); [3]Rheumatology 53: 644-649 (2014); [4]Rheumatology 54: 784-791 (2015)

Symptoms and investigation in ILD

- Cough and dyspnoea, can occur without symptoms
- PFTs: restrictive defect, decreased lung volumes and reduced DLCO
- Decreased DLCO not specific for ILD, may also occur with PH
- HRCT initial procedure for suspected ILD - linear opacities, areas of consolidation and ground glass attenuation
- Differential aspiration, infection, drug induced lung disease
- BAL to rule out infection
- Lung biopsy may be required for diagnosis (fibrosis, interstitial pneumonitis and BOOP all reported)

Respiratory muscle weakness

- Also gives a restrictive defect
- Distinguish from ILD
- Mild and non-progressive
- Reduced MIPs MEPs
- Normal DLCO
- Increased RV without decreased FEV1/FVC ratio

Treatment

- High dose corticosteroids, weaned over 1-2 years
- Pulse methylprednisolone for more severe weakness
- Observational studies only for other treatments
- Most common is methotrexate (weekly)
- Reduces duration and cumulative steroid dose, often added at initiation of treatment
- Alternative cyclosporin
- Others: IVIg (adult data), cyclophosphamide with severe or life threatening disease (including ILD)
- Small case series: clinical improvement with rituximab

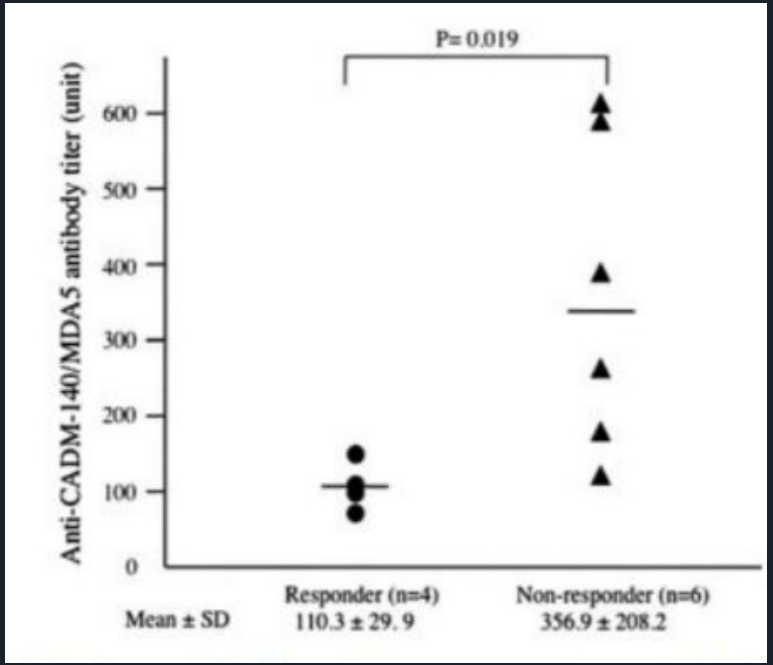
anti-MDA5 antibodies

- MDA5 (melanoma differentiation-associated gene 5)
- Recognises intracellular viral dsDNA
- Triggers interferon response, suppresses viral replication
- Regulates cellular growth suppression and apoptosis
- Hypothesised pathogenesis:
- Infection of lung or skin may upregulate expression of MDA5
- Leads to cell apoptosis and release of MDA5
- Triggers an autoimmune response

Arthritis and Rheumatism 2009 60:7 p2193-2200

anti-MDA5 antibodies

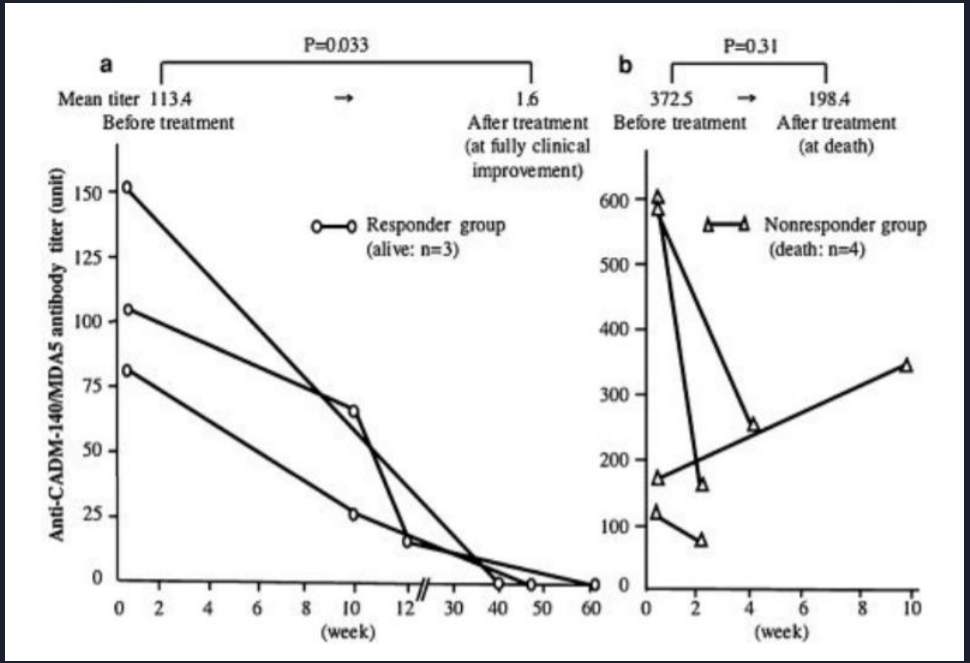
- Associated with poor prognosis
- Titres can predict response to typical DM treatment



Mod Rheum 23: 496-502 (2013)

anti-MDA5 antibodies

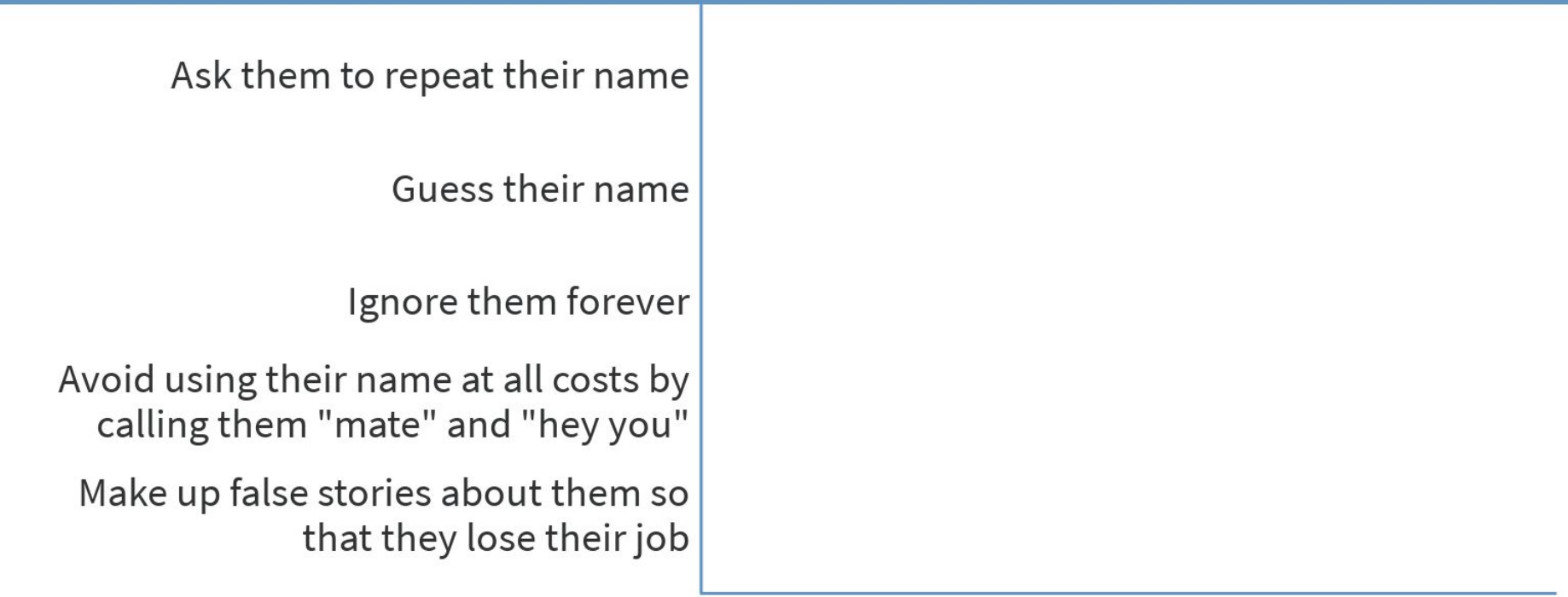
- Predicts disease outcome in patients with DM and rapidly progressive ILD
- Anti-MDA5 reported in 6-38% JDM in Japanese/ Korean/ Chinese cohorts of JDM associated with rapidly progressive ILD



Mod Rheum 23: 496-502 (2013)
Best Pr Res Clin Rheum 31: 535-557 (2017)

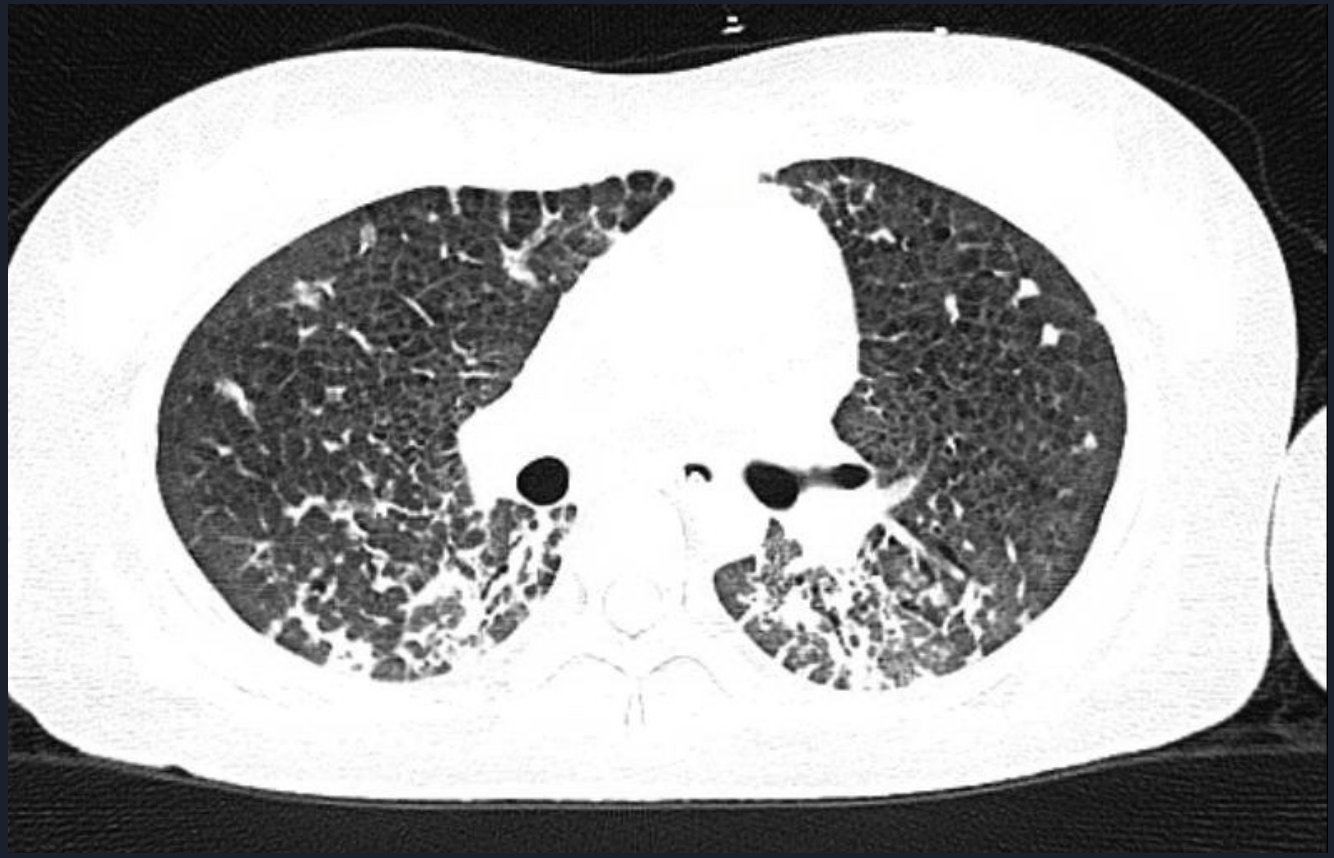
British trivia break

You're introduced to a new colleague but don't quite catch their name. How do you react?



Differential diagnosis

- Slow recovery of ARDS
- JDM-related ILD
- Further infection (possibly fungal)
- Repeat CT



Reticular interstitial thickening with an apicobasal gradient, minimal traction bronchiectatic changes
Background of diffuse ground-glass airspace opacification and interlobular septal thickening
Suggestive of progressive interstitial lung disease in a patient with juvenile dermatomyositis

2.5 months after admission

- IVIg
- Tracheal tube aspirate for fungal culture
- Galactomannan normal
- Unlikely to tolerate bronchoscopy and biopsy
- Course of amphotericin, AKI, switched to posaconazole
- Little change in clinical status, ongoing ventilation and oxygen requirement

What next?

- Continue current treatment, wait for recovery

- Refer for lung transplant

What next?

Continue current treatment, wait for recovery

Refer for lung transplant

Transplant assessment

- MRI lower extremities: muscle signal abnormality
- Fatty infiltration - dissuse immobilisation / corticosteroid use / disease progression
- Muscle biopsy - mild disease activity
- Transferred to adult services
- Rehabilitation, VV ECMO
- Lung transplant 4 months after diagnosis

June 2019

- No longer using a wheelchair
- Exercise rehabilitation
- High school graduation May
- Normal x-ray
- FEV1 and FVC continue to climb (50% predicted)
- Monthly follow up

Questions?