TB or Not TB
Brian Chong
Mr ID

• 57 year old truck driver from Gunnedah
• Premorbidly independent and reasonably active
• Background: hypertension, gout, dyslipidaemia
• Seeing cardiologist due to progressive dyspnoea on exertion
Go to hospital now!

- Referred from cardiologist’s rooms with findings of severe aortic regurgitation + possible vegetation on echocardiogram
- Commenced on empirical antibiotic treatment for endocarditis:
  - Benzylpenicillin
  - Flucloxacillin
  - Gentamicin
- Transferred to JHH for urgent aortic valve replacement
ID involved – is there endocarditis?

- 4 sets of negative blood cultures
- Afebrile throughout admission
- ESR 5, CRP 4
- ‘I think I had Q fever 20 years ago’
  - Q fever phase I IgG 1:50 (cutoff <25)
- Observed off antibiotics for a week prior to surgery
- O/E: BP 115/57, early diastolic murmur, chest clear, pitting edema to knees, no stigmata of infective endocarditis
Modified Duke criteria

Major clinical criteria

• Blood cultures
  • Persistently positive
    • For typical organisms – at least two cultures, ideally >12 hours apart
    • For common contaminants – three or a majority of ≥4 cultures (at least one hour between first and last sample)
  • Single positive culture for *Coxiella burnetii* or phase I IgG antibody titre >1:800

• Evidence of endocardial involvement
  • Echocardiogram finding of vegetation or abscess or new partial dehiscence of prosthetic valve
  • New valvular regurgitation – increase in or change in pre-existing murmur not sufficient

Typical organisms:
- *Staph. aureus*
- viridans streptococci
- *Strep. gallolyticus* (previously *S. bovis*)
- HACEK group
- *Enterococcus sp.* in the absence of a primary focus
Modified Duke criteria

Minor clinical criteria

• Predisposition – IVDU or predisposing heart condition (prosthetic valve or valve lesion with significant regurgitation/turbulence)
• Fever
• Vascular phenomena – arterial/pulmonary emboli, mycotic aneurysm, intracranial bleed, conjunctival bleed, Janeway lesions
• Immunologic phenomena – glomerulonephritis, Osler nodes, Roth spots, positive rheumatoid factor
• Microbiologic evidence – positive cultures not meeting major criteria

Osler nodes – O for Ouch, spider in OStralia
Definite endocarditis

• Pathologic criteria
  • Pathologic lesions – vegetation or intracardiac abscess demonstrating active endocarditis on histology
  • Microorganisms – on culture or histology of a vegetation or intracardiac abscess

• Clinical criteria
  • Two major criteria
  • One major and three minor criteria
  • Five minor criteria
What does Duke say?

• Major clinical criteria
  • Blood culture
    • Persistently positive ✗
    • Single positive *Coxiella burnetii* culture or phase I IgG >1:800 ✗
  • Evidence of endocardial involvement

• Minor clinical criteria
  • Predisposition ✗
  • Fever ✗
  • Vascular phenomena ✗
  • Immunologic phenomena ✗
  • Microbiologic evidence ✗
Operation report

- Bicuspid aortic valve
- Vegetation on left cusp
- Destruction of left leaflet at the base
- Mechanical prosthesis implanted
- Surgeon – ‘there definitely is endocarditis’
- Antibiotics recommenced post-op pending further ID input
What’s cooking in the lab? (histology conveniently not requested)

<table>
<thead>
<tr>
<th>MICROBIOLOGY - CULTURE</th>
<th>Tissue valve aorta</th>
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<tbody>
<tr>
<td>Polymorphs</td>
<td>Nil seen</td>
</tr>
<tr>
<td>Squam/Epith</td>
<td>Nil seen</td>
</tr>
<tr>
<td>Organisms</td>
<td>Nil seen</td>
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</tbody>
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Comment: NO GROWTH at 48 hrs. (Further incubation proceeding) No further report unless significant growth occurs.
Time to start digging

 Causes of culture-negative endocarditis?

- ANA, anti-phospholipid antibodies negative
- Legionella serology negative
- Brucella serology negative
- Bartonella serology negative
- Serum Q fever PCR negative
Need a plan

• Ceftriaxone -> benzylpenicillin (planned for 4 weeks total)
• Transferred back to Armidale Hospital for convalescence
• 16s RNA PCR requested on valve tissue (ICPMR Westmead)
• The 16s ribosomal RNA:
  • is a component of the 30s subunit of prokaryotic ribosomes
  • is highly conserved (ie very slow rate of evolution within a species)
  • can classify down to genus, and often down to species level
  • is useful for identifying slow-growing or fastidious organisms
Microbiology calls two weeks later...

16s RNA PCR on valve tissue positive for *Tropheryma whipplei* – confirmed on *T. whipplei*-specific PCR!
A diagnosis!
Whipple’s disease

- George Whipple (1907). *A hitherto undescribed disease characterised anatomically by deposits of fat and fatty acids in the intestinal and mesenteric lymphatic tissues.* Johns Hopkins Hospital

- Index case – a man with ‘gradual loss of weight, stools consisting chiefly of neutral fat and fatty acids, indefinite abdominal signs, and a peculiar multiple arthritis’

- Initially named ‘intestinal lipodystrophy’

- ‘Rod-shaped organisms resembling the tubercle bacillus’ were noted
Whipple’s disease

• 1949 – classic histological findings of Periodic acid-Schiff (PAS)-positive macrophages were described
• 1952 – successful treatment with chloramphenicol
• 1991 – organism named *Trophyrema whipplei* (‘trophe’ = nourishment, ‘eryma’ = barrier in Greek)
• 1999 – organism successfully cultured
• 2003 – immunohistochemistry techniques confirm the presence of *T. whipplei* in Dr Whipple’s original autopsy sample from 1907!
Tropheryma whipplei

• Gram positive bacillus related to Actinomycetes
• Ubiquitous – found in sewage water and the saliva of >30% of healthy people
• Disease is extremely rare – ~30 cases annually worldwide (this is likely an under-estimation from before the widespread use of PCR)
• Predilection for middle-aged Caucasian male farmers
Pathogenesis

• Unclear at present
• Tissue samples classically show no inflammation despite large amounts of *T. whipplei*
• *T. whipplei* does not seem to be cytotoxic to host cells
• Defective host immunity may be a major factor
  • ~70% of healthy individuals have IgG antibodies against *T. whipplei*
  • Patients seem to have reduced *T. whipplei*-specific Th1 responses
  • n.b. these patients do not seem to be more susceptible to other pathogens!
Clinical manifestations

• Classically:
  • Arthralgias – non-deforming
  • Weight loss
  • Diarrhoea + abdominal pain

• Bonus:
  • Lymphadenopathy
  • Skin pigmentation
  • CNS – dementia, gaze palsy, cerebellar ataxia, oculomasticatory myorhythmia
  • Pulmonary – pleural effusion, chronic cough, pulmonary hypertension
  • Endocarditis
Diagnosis

• Exclude alternative (and common) diagnoses first!
• PAS stain, PCR, and immunohistochemistry can be performed on duodenal biopsy or other tissue/fluid samples
• PAS-positive macrophages in duodenal biopsy are classic for Whipple’s disease
• Caveat – PCR on non-invasive samples could just reflect environmental exposure, not disease
• Culture requires special media which are not commonly available
• Serology currently NOT helpful – more on this later
Treatment

- Whipple’s disease was previously a fatal diagnosis!
- Treatment guidelines are empirical
- Induction – iv ceftriaxone or benzylpenicillin for 2 to 4 weeks
- Consolidation – trimethoprim/sulfamethoxazole (Bactrim) OR doxycycline + hydroxychloroquine for 12 months
- Controversies:
  - Feurle et al found that 3 months of Bactrim was non-inferior to a 12-month course (open-label, non-randomised trial)
  - Didier Raoult’s group found a higher failure rate with Bactrim c.f doxycycline + HCQ – also recommend lifelong doxycycline prophylaxis
Whipple’s endocarditis

• First confirmed as an etiology via 16s PCR in 1997
• ~100 cases reported in literature so far (majority from Germany, France, and Switzerland)
• Is it more common than we think?
  • Geißdörfer et al reported on a series of 1135 patients (878 unselected, 257 with possible endocarditis) undergoing valve replacement in two German centres
    • 255 cases of endocarditis were diagnosed on culture/PCR/FISH/histopath
    • *T. whipplei* was found in 16 (6.3%) cases – most common pathogen after *Streptococcus*, *Staphylococcus*, *Enterococcus*
Whipple’s endocarditis

• As with systemic Whipple’s, has a predilection for middle-aged male farmers of European descent
• Can occur in isolation
• Most commonly affects the aortic valve
• Heart failure is the dominant (70%) presenting feature
• Fever is uncommon
• Arthralgia can be variable – 21 of 28 (75%) in French series vs 2 of 16 (13%) in German series
Diagnostic difficulty

• Patients usually do not meet Duke criteria prior to valve excision
• Hard to differentiate carrier state vs disease state without an invasive sample
• Serum PCR is not sensitive – only 5 out of 16 patients with tissue-confirmed Whipple’s endocarditis tested positive in French series
More on serology

• The lack of a serological response in patients with active Whipple’s was first reported by Bonhomme in 2009

• French group have been working on Western Blot assays in the diagnosis of active disease:
  • 2009 – 56/60 (93%) of patients with classic Whipple’s vs 5/26 (19%) of carriers had a Western Blot profile consistent with infection (defined as lack of reaction or decrease in reaction after deglycosylation of antigen GpTw110)
  • 2013 – Not helpful in endocarditis series: 10 had negative or weakly positive profile, 8 had frankly positive profile
Local research

• Dr Stephen Graves

• Hypothesis – if a patient has positive serology to Whipple’s, he or she DOES NOT have active Whipple’s disease. Therefore, a positive Whipple’s serology can be used to exclude Whipple’s from the list of differentials

• If you have a patient with definite Whipple’s disease, please contact Dr Graves at Graves.Rickettsia@gmail.com
Back to our patient

• Further history:
  • Intermittent arthralgias
  • Episode of mono-articular knee arthritis 12 months prior – attributed to gout
  • ~25kg weight loss in the 6 months prior to presentation

• Progress:
  • Commenced on oral trimethoprim/sulfamethoxazole with no issues
  • Short stay in peripheral hospital for post-op rehab
  • Regained 10kg of weight in 3 months

• Whipple’s serology:
  • IgA not detected (<1:128)
  • IgM 1:256
  • IgG not detected (<1:128)
Take home messages

• Live by the Duke criteria – not every patient with bacteremia needs an echocardiogram (e.g. beta-hemolytic streptococci, Gram-negative bacteria)
• When the surgeon swears that ‘it looks like infection’, tread carefully
• Whipple’s endocarditis is like Schrodinger’s cat – the only way to find out is to open the chest

Osler nodes – O for Ouch, spider in OStralia