

Feeling it in my bones...

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Introduction

- Case presentation
- Review of pertinent points in regards to vOM
 - Laboratory markers
 - MRI findings
 - Bone biopsy
 - Microbiology
 - Long-term follow-up and relapse

Mrs MC – 76 year old

- PHx
 - Grave's disease (ophthalmopathy) Dx 2007 (no Rx since Sept 07)
 - OP
 - PVD
 - Right popliteal to PTA bypass 10 years ago
 - Hypercholesterolaemia
 - AF
- Medications
 - Warfarin, atenolol, pravastatin
- Soc Hx
 - Originally victim of Kinglake bushfires
 - Recently moved into new unit, son in same complex

HOPC

- Admission 12/12/10 – 06/01/11
- 2 – 3/52 history of severe, constant lumbar back pain
 - Gradual onset with increasing severity
 - Exacerbated by movement
 - Only comfortable on lying completely still
 - Difficulty sleeping
 - Acute deterioration 3/7 prior
- Associated 2/52 diarrhoea and LOA
- No fevers, sweats, rigors, myalgias, arthralgias

On examination

- Afebrile, haemodynamically stable
- Comfortable at rest
- Generalised abdominal tenderness
- Neurology: reduced lower limb strength (3–4/5) – limited by pain
- WCC 12.2, neut 10.6, CRP163, blood cultures taken
- Urine negative
- Empirically commenced on ceftriaxone, ampicillin, metronidazole

MRI 13/12 – T1 and T2



- ❑ L5/S1 discitis / OM (? L2/3, L3/4 and L4/5)
- ❑ Diffuse perivertebral soft tissue oedema L3/4 to L5/S1
- ❑ No epidural abscess, significant canal stenosis
- ❑ Severe degenerative compromising exiting left L5 nerve root

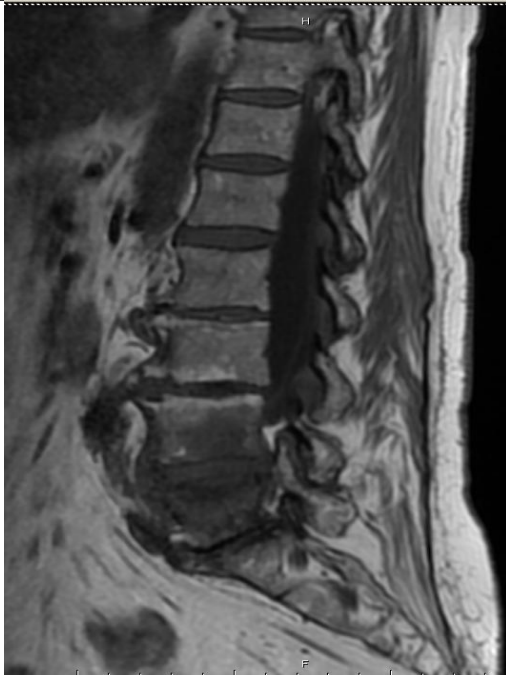
Progress 1

- Changed to Tazocin / vancomycin 13/12
- Urgent biopsy planned 14/12
 - Warfarin reversed
 - Enoxaparin given on morning of procedure - cancelled
- Blood cultures
 - 12/12 – prior to antibiotics
 - Anaerobic bottle grew *Streptococcus intermedium*
 - Etest MIC penicillin <0.016, ceftriaxone 0.125, vancomycin 1.0
 - 13/02 x3 (alternate times), 14/02, 15/02 – negative
- Ongoing severe back pain

Progress 2

- Bone biopsy 21/12
 - 12 fragments received
 - Histology: active haemopoietic marrow with slight increase in myeloid elements
 - No growth
 - TB PCR negative
 - Negative 16S rRNA
- Commenced rifampicin / fusidic acid 28/12/10 (vancomycin ceased)
- Autoimmune screen negative

MRI 31/12 – T1 and T2



- Discitis and osteomyelitis at L4/5
- L5-S1 disc shows no evidence for hyperintensity
- Diffuse perivertebral soft tissue oedema more pronounced esp left
- 1.2 cm, 1.3cm and 0.2cm collections around L4/5 disc

BECC rehabilitation 06/01 – 24/01/11

- Continued Tazocin / rifampicin / fusidic acid given clinical and inflammatory marker improvement (WCC normal, CRP 30) and stable neurology
- Plan for early reimaging

ID OP review 24/01

- Widespread, erythrodermic rash causing distress
- Tazocin ceased (Day 49)
- Ciprofloxacin 750mg bd commenced
- Recommended direct admission

TNH 24/01 – 16/02

- Issues on admission 24/01
 - Day 35 rifampicin / fusidic acid
 - Troublesome erythrodermic rash present for 2 – 3 weeks
 - Eosinophilia up to 4.6
 - Persistent diarrhoea
 - Faecal culture negative
 - Sigmoidoscopy mild colitis
 - Ongoing severe back pain

MRI 27/01- T1 and T2



- Very marginal progression in the changes at L4-5
- New annular tear in the disc in left posterolateral location at L5-S1 with peripheral enhancement – too small to differentiate inflammatory vs infection

Progress

- 03/02
 - Nauseated, vomiting
 - Ceased ciprofloxacin 03/02
 - Continued rifampicin / fusidic acid
- Very slow improvement pain, nausea / diarrhoea and rash
 - D/C 16/02 on rifampicin / fusidic acid (week 7)
 - Plan for 6 – 12 months of treatment
 - WCC, CRP within normal limits

Outpatient review

- Resolution of erythrodermic rash
- Resolution of pain
- Improved appetite
- Bowels have settled
- Continued on rifampicin / fusidic acid

Pyogenic Vertebral Osteomyelitis

Features

- Epidemiology
 - Men > females – mean age 60 – 62 years
 - Common sites of infection
- Risk factors
 - Recent or current infection; DM; renal insufficiency; immunosuppression, prior surgery / trauma; IDC / IVC; advanced age
- Aetiology
 - Haematogenous spread
 - Contiguous focus of infection (adjacent area in contact)
 - Those associated with peripheral vascular disease
 - Approx. 40% have no obvious source of infection



Laboratory markers

At presentation

- Leukocytosis in only 42 - 50% of cases
- Elevated alkaline phosphatase
- Elevated ESR and CRP in 90 – 100%
 - Used for monitoring
- Positive blood cultures in 20 - 50% of haematogenous vOM

Prediction of clinical outcomes

- Prospective study of WCC, ESR, CRP levels in 45 pts with culture positive (PC) or culture negative (NC) vOM
- No significant difference in WCC or ESR levels
- CRP values
 - Higher at day 1: PC 12.9 g/dL, NC 5.1 g/dL (p=0.007)
 - Normalisation in NC (53.6 d) > than PC (25.9 d) p=0.005
- At 4 weeks post-antibiotics patients with ESR > 55mm/h, CRP 2.75mg/dL had higher rates of treatment failure (OR = 5.15, p=0.037)

Imaging

Imaging

□ CT

- Diffuse moth-eaten bone destruction; intervertebral disc and paravertebral osseous and soft tissue involvement
- Does not detect epidural abscesses

□ Three-phase bone scan

- Reported sensitivity as high as 90% but is not specific
- Does not differentiate active from inactive VO

Imaging

□ MRI

- Sensitivity of 96%, specificity of 92% and accuracy of 94%
- T1: gadolinium-enhanced vertebral body and disc
- T2: increased signal intensity of adjacent vertebral and intervertebral disc
- Changes can occur at multiple levels and thus there is a preference for whole spine imaging

MRI appearances of early vOM and discitis

- Early presentation may result in the MRI having non-specific changes
- Retrospective review of spinal infection database over 2 years in patients with positive microbiology and clinical picture of vOM
- Non-specific endplate subchondral changes seen at baseline
- Follow-up MRI 17 days (8 – 22 d) later showing typical features of vOM and discitis after antibiotic treatment

Follow-up MRI and prognosis

- Retrospective cohort study from Mayo Clinic using repeat MRI 4 and 8 weeks after completion of therapy
- Repeat MRI findings at 4-8 weeks correlated with lack of microbiologically-confirmed treatment failure at 1 year
 - Improved: 100%
 - Equivocal: 89% (95% CI, 74%-96%)
 - Worse: 56% (95% CI, 24%-83%) (p=0.004)

Follow-up MRI and prognosis

- Retrospective cohort study from Mayo Clinic using repeat MRI 4 – 8 weeks after completion of therapy with respect to baseline

	Baseline	4 – 8 weeks	p value
Loss of vertebral height	14/33 [47%]	26/33 [79%]	P<0.001
Epidural enhancement	29/33 [88%]	19/32 [59%]	P<0.008
Epidural canal abscess	15/33 [45%]	3/32 [9%]	P<0.001
Epidural canal compromise	19/33 [58%]	10/32 [31%]	P<0.008

- Overall: 21/32 (66%) improved, 5 (16%) equivocal, 6 (19%) worse
- Soft tissue findings rather than bony findings should be the focus of follow-up MRI scans

Biopsy

Yield by biopsy

- Gold standard for diagnosing OM is a bone biopsy
- Percutaneous yield biopsy reported as 31 – 70%
 - 92 radiologically and clinically consistent cases with 30.4%
 - 133 Danish vOM patients - 31% had biopsies with 40% positive
- When infection is not suggested radiologically then only 5% positive
- Negative or inconclusive results warrant repeat procedure

Surgical vs radiological biopsy

	Endoscopic discectomy and drainage*	CT-guided percutaneous biopsy#
No of patients	20 patients	32 patients
Culture positive	18/20 (90%)	15/32 (47%) [^]

*performed by a surgeon; #performed by a radiologist; [^] p=0.002; min F/U 12 months

	Open biopsy	Percutaneous biopsy
No of patients	15 patients	32 patients
Culture positive	14/15 (93%)	14/29 (48%) [^]

[^] p=0.003

Prebiopsy antibiotics in vOM

- Previous studies had suggested that the diagnostic yield may be diminished by antecedent antibiotics
- Retrospective cohort study of 150 inpatients (2003 – 2007)
- 60 (65%) had received antibiotics in preceding 14 days as they presented more clinically unwell
- 92 (61%) underwent biopsy
 - 60 (65%) needle
 - 32 (35%) open
 - more likely to present more clinically unwell, had neurological deficit on examination or chart / biochemical abnormalities

Results

	Open biopsy	Needle biopsy	P value
Total Bx pts	35% (32/92)	65% (60/92)	
Total cultures positive#	91% (29/32)	53% (32/60)	p<0.001
Prior antibiotics*	95% (20/21)	59% (23/39)	p=0.003
No antibiotics	82% (9/11)	43% (9/21)	p=0.06

pathogens found in 66% (61 pts) total *median duration 4 days (1-37)

- Multivariate regression model to predict a positive biopsy culture previous antibiotic exposure was not associated with significant negative culture results (aOR, 2.3; 95% CI, 0.8–6.2; p=0.1)
- THUS prior antibiotic treatment should not preclude biopsy

Pre-antibiotics and biopsy

- Retrospective cohort study Jan 2003 – Dec 2005
- 65/100 patients with haematogenous vOM biopsies with 69.2% receiving antibiotics in the preceding 14 days
 - Only 23/42 empirically treated with an antibiotic matching the susceptibility pattern of the recovered pathogen
- Thus performing a bone biopsy and obtaining the organism helps improve antibiotics selection
- No difference in pathogen recovery with / out antibiotics (p=1.0)

PCR and biopsy cultures

- Molecular diagnosis can be made with 16S rDNA PCR with a high concordance with biopsy cultures
- Helps with prior antibiotics and presence of fastidious organisms eg. *Kingella kingae*, anaerobes and *Streptococcus* species
- Caveat is contamination from skin flora

PCR vs standard techniques

- Pathogen recovery
 - 19/19 of PCR cases
 - 14/19 cases standard microbiological techniques
- Comparison of PCR in 18 culture-positive patients vs 20 non-infectious bone biopsies
 - Specificity of culture 95% vs PCR with 100%
 - True culture positivity seen in 9/18 vs 11/18 of PCR
 - Combined positivity in 13/18 (72%)
 - Prior antibiotic treatment
 - Culture: positivity until 7 days
 - PCR: positivity until 16 days

Microbiology

Microbiology and sources

- Microbiological diagnosis is found in only 2/3 of cases
- Single organism in 85%, polymicrobial in 9%
- Anaerobic < 3%

Site	Likely organism
Haematogenous	Staphylococcus (MSSA 33%, MRSA 22%)
Surgical site and post-operative	Staphylococci, Streptococcal spp, Propionibacterium acnes
Spinal surgery, urinary tract instrumentation, immunocompromised	GNB - E. coli, Pseudomonas spp, Proteus spp
IVDU, catheter-related	Pseudomonas aeruginosa, Serratia, candida
Immunocompromised	Fungal, mycobacterial

Bhavan KP and Kirmani N. Mo Med. 2009 Jul-Aug;106(4):277-82. Review. Jaramillo-de la Torre *et al* Neurosurg Clin N Am 17 (2006) 339 – 351; Mylona E *et al*. Semin Arthritis Rheum 2008; 39:10-17; Conterno and da Silva. Cochrane database syst rev. 2009 Jul 8 (3):CD004439; Bhavan KP *et al*. BMC Infectious Diseases 2010, 10:158; Jorge LS *et al*. Braz J Infect Dis 2010; 14(3):310-315

Bacteraemia is important

- 74 cases of microbiologically-confirmed vOM aetiology with a higher yield from blood cultures than bone biopsy
- 21 (28.4%) had a preceding bacteraemia in the prior yr
 - 9/10 recurrent bacteraemias had identical antibiogram (all *Staphylococcus*)
- Outlining importance of adequate treatment of bacteraemia

Treatment

Medical treatment

- Mortality dropped from 25 – 56% to less than 5% with antibiotics
- Clinical success in approximately 75 - 84% of patients
- No randomised trials exist as a guide to selection of appropriate route, duration or agent or therapy
- Practice is based on retrospective case series, expert opinion and data extrapolated from animal and laboratory data

Empirical treatment

- Negative cultures necessitate use of empirical antibiotics for Gram negative and Gram positive organisms
- Australian guidelines:
 - Di/flucloxacillin
 - Ceftriaxone
- Sanford guidelines:
 - MRSA possible: vancomycin
 - MRSA unlikely: nafcillin / oxacillin

Penicillin-based therapy

- Review of 133 consecutive Danish patients with *S.aureus* vOM from 1980 – 1990
- Increased rate of recurrence
 - Lower dosed penicillinase-stable penicillin (eg flucloxacillin)based regimen ($p < 0.01$)
 - Shorter duration of treatment (20d vs 83 days $p < 0.01$)
- Patients who received cumulative dose of 100g of penicillin
 - 18 received IV alone; 10 oral alone; 61 IV(weeks) / oral IV
 - Rates of failure did not differ significantly between groups

Continued

- With penicillin-based and fusidic acid combination compared with penicillin alone
 - Lower mortality, recurrence ($p < 0.05$) and rate of therapeutic failure (24% vs 53%)
- Conclusions
 - Duration of treatment should be at least 8 weeks
 - Daily dosing of penicillin-based treatment should be not less than 4g/day
 - Suggests as long as dose right then can have different modalities of treatment

Levofloxacin and rifampicin

- Empirical treatment of spondylodiscitis in 48 patients
 - High-dose levofloxacin (500mg bd - normalised to renal function and monitored)
 - Rifampicin 600mg daily
- Mean treatment duration 15.1 weeks, follow up 9 months
- Response rate
 - 77.1% ITT
 - 84.1% in those who completed Rx (n=44)
 - 96.3% in documented levofloxacin-sensitive isolates
 - Not relapse at end of follow up

Other recommendations

- Early conversion to oral antibiotics should be avoided until endocarditis has been ruled out
- Clindamycin and fluoroquinolones are noted for good oral bioavailability and bone penetration and are potential options for oral treatment
- It is postulated that with orals
 - Better compliance
 - Avoids potential complications of long term IV catheters
 - Need to monitor closely to ensure adequate absorption and adherence

Long-term follow-up and relapse

Long-term follow up

- Retrospective study of 253 patients with long-term F/U of 6.5 years (2 days – 38 years)
 - 11% died, residual disability > 1/3; 14% relapsed
- Independent risk factors for adverse outcome (death or qualified recovery)
 - neurologic compromise, time to diagnosis, and hospital acquisition of infection (P<.0004)
 - Severe vertebral destruction / abscesses
 - Recurrent bacteremia, paravertebral abscesses, and chronically draining sinuses independently associated with relapse (P <0 .001).

Overall Conclusions

Overall conclusions

- Poorly researched areas with retrospective analyses that could lead to significant bias in the trials
- Treatment is still based on clinical experience and the organism isolated
- Use of antibiotics should not preclude biopsy
- Improved yield with open biopsy may be related to better sampling technique but is an invasive procedure
- CRP, ESR and repeat MRI findings at 4 – 8 weeks can help predict outcome