An Intramuscular Heroin Abuser with an Uncommon Cause of Renal Failure

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Case History

- Mr Chan, 58/M
- Chronic smoker, social drinker
- Work as a driver
- Good past health
1-2 Months’ Symptoms

- Subjective weight loss
- Poor appetite
- Progressive lower back and left hand pain
- History of intakes of unknown herbal medications
- Found renal impairment with Cr 350 (from 200+ within weeks) by private nephrologist
- Referred to us for further management
He is an active intramuscular heroin abuser
Significant Physical Abnormalities

- 1+ alb in urine dipstix
- Pallor
- A tender subcutaneous swelling over dorsum of left hand with mild increased temperature
- Smooth nontender **hepatomegaly** around 2 cm under the costal margin
- Smooth nontender **spleen tip**
- Local tenderness over **lumber region** of the spine
Basic Investigations

- Normocytic normochromic anemia, Hb~8, WBC and Plt normal
- High ESR~90 and CRP ~30
- Urea 13, Cr 309, Na and K both normal
- Alb 35, ALP 309 (bone origin), with normal Ca, PO4, AST, ALT and bilirubin
- Spot glucose and urate normal
- CPK normal
- ABG: mild metabolic acidosis with appropriate respiratory compensation, HCO~ 17
MSU: scanty RBC with normal morphology, scanty WBC and culture negative after 4 days of incubation

Bedside USG kidneys: NAD

CrCl: 15 ml/min and 24 hr TP: 0.79g daily
Clinical Problems

- IM heroin abuse
- Severe renal impairment with low grade proteinuria, equivocal urinary sediment and normal USG kidneys
- Subacute systemic symptoms with mild hepatosplenomegaly and raised ESR and CRP
- Left hand dorsum and lower back pain
- NCNC anemia and increased ALP of bone origin
Serological Work Up

- Hepatitis C +ve, HBsAg –ve, HIV-ve
- VDRL, ANF, RF-ve
- C3, C4, clotting normal
- Urine and serum protein electrophoresis: no paraprotein
- ANCA –ve, ASOT-ve
Radiological Work Up

- CXR: clear
- XR lumbar spine: degenerative changes
- XR left wrist and hand: unremarkable
USG Abdomen

- Mild **hepatomegaly** with normal echotexture
- **Splenomegaly**, 17 cm
- Both kidneys appear normal in echogenicity and size
MRI Lumbar Spine

- Multiple foci of abnormal signals are seen in the lumbar spine
- DDX includes early infection, metastasis and lymphoma
- The involvement of L3/4 disc favours infection
Subcutaneous swelling over Dorsum of Left Hand

- Aspiration performed
- Microscopy: scanty WBC
- No urate crystal
- No growth after 4 days of incubation
What would be the next investigation?
Renal Biopsy: LM

- Glomeruli: NAD
- Interstitium: marked inflammatory infiltrates composed predominantly of lymphocytes, associated with mild oedema. Eosinophils are focally found. In area, there is granuloma surrounding a central microabscess containing eosinophils and neutrophils.
- Tubules: focal tubulitis and tubular epithelial cell flattening and degeneration.
- Vessels: unremarkable with no evidence of vasculitis.
- Ziehl-Neelsen stain: multiple acid fast bacilli in the granuloma.
Renal Biopsy

- IF: -ve for IgA, IgG, IgM, C3, C1q and fibronogen
- EM: not done
Summary of Renal Biopsy

Mycobacterial Infection with acute Interstitial nephritis
Progress

- EMU culture: **AFB positive** after 6 days of culture

- Hand subcutaneous swelling aspiration: **AFB positive** after 7 days of culture

- ? Diagnosis
Surprising Final Diagnosis

After identification of the AFB: both EMU and aspirate grown *mycobacterium chelonae*
Mr Chan, 58 yr old gentleman, with history of active intramuscular heroin abuse and HCV infection, suffered from systemic mycobacterium chelonae infection with radiological evidence of spinal, possibly liver and spleen involvements, microbiological evidence of left hand subcutaneous infection and finally histological and microbiological evidence of renal infection, causing acute granulomatous interstitial nephritis.

There may be contribution of his renal impairment due to herbs induced interstitial nephritis.

No apparent impairment of cell mediated immunity to explain the widespread disease, although the needles for injection probably increase chances of blood born spread of the organisms.
Progress

- His clinical status and renal function are relatively stable even without specific treatment.
- He is started on typical anti-TB treatment after initial positive Ziehl Neelsen stain on the renal biopsy.
Sensitivity Pattern of the M. Chelonae

- Sensitive to amikacin, tienem, klaccid, resistant to ciprofloxacin and septrin

- He is switched to IV tienem for 6 weeks and also oral Klaccid, plan for 6 months
After One Month

- He is well, his hand’s swelling and lower back pain subside
- Renal function improving although slow, Cr ~235
- ALP decrease to 132 and alb normalised
- ESR and CRP both decreased
- MSU : NAD and culture negative
Follow Up Imaging

- USG abdomen and MRI spine are booked to see the progress of the liver, spleen and bone disease
End of Case Presentation

Questions?
After Literature Search through Medline, Pubmed and Google

There is no single report on mycobacterium chelonae infection in native kidney biopsy!
Rapidly Growing Mycobacteria—M. Chelonae

- Nontuberculous mycobacteria (NTM)
- Classified in the Runyon group IV, rapidly growing mycobacteria
- Found in natural and processed water sources as well as in sewage
- Distribution probably worldwide
Clinical Diseases

- Lung disease
- Local cutaneous disease, osteomyelitis, joint infections, and ocular disease (eg, keratitis or corneal ulcers) may occur after trauma
- Rare cause of isolated lymphadenitis
- Disseminated disease, usually with disseminated skin and soft tissue lesions, occurs almost exclusively in the setting of immunosuppression, especially AIDS
- Endocarditis has also been documented
- Surgical site infections due to *M chelonae* are well documented, especially in association with cardiothoracic surgery and augmentation mammoplasty. Frequently, the source is contamination of the wound, directly or indirectly, with colonized tap water
- Other nosocomial infections: infections of implanted devices (eg, catheters) and injection-site abscesses
Mortality/Morbidity: localized: rare. Death may result from extensive pulmonary or disseminated disease

Race: No clear racial predilection

Sex: No sexual preference

Age: In general, no known age preference exists. Lung disease in a younger patient (<50 y) strongly suggests a primary underlying lung disorder. Isolated lymphadenitis primarily occurs in children
Symptoms

- Patients with skin disease may have a nonhealing but nonspreading wound or skin ulcer
- Patients with lung disease may have a chronic cough
- Easy fatigability, occasional fever, night sweats, and weight loss occur with pulmonary or disseminated disease, although less commonly than with tuberculosis
Physical Findings

No physical examination findings are pathognomonic for *M. chelonae*. Findings depend on infection site.

- **Skin**: Ulcerative lesions and/or subcutaneous nodules may be present. Deep infection may lead to draining fistulas.
- **Eye**: Corneal ulcers or keratitis may be present.
- **Lungs**: Rales or rhonchi may be present.
- **Heart**: Valvular murmur with endocarditis may be present.
- **Abdomen**: Diffuse tenderness with peritonitis may be present, similar to that associated with peritoneal dialysis.
Causes

Trauma or injection - Skin lesions, subcutaneous lesions, ocular lesions, and osteomyelitis

- Disseminated disease - Immunosuppression, especially AIDS or corticosteroid use

- Lung disease - Achalasia and bronchiectasis
Differentials

Actinomycosis
Blastomycosis
Coccidioidomycosis (Infectious Diseases)
Coccidioidomycosis (Pulmonology)
Cryptococcosis
Histoplasmosis
Mycetoma
Mycobacterium Fortuitum
Mycobacterium Gordonae
Mycobacterium Haemophilum
Mycobacterium Kansasii
Mycobacterium Marinum
Mycobacterium Xenopi
Nocardiosis
Sporotrichosis
Tuberculosis
Wound Infection
Diagnosis

- **Bacteriological**
  - Smear and culture
  - Identification:
    - Biochemical & phenotypical
    - Others
      - HPLC
      - Molecular:
        1. Nucleic acid probe
        2. PCR-restriction enzyme analysis
        3. Hybridization
  - Susceptibility testing

- **Histological**
Smear and Culture

- **Smear:**
  - Conventional basic fuchs in method/fluorochrome method
  - Acid fast
  - Generally pleomorphic

- **Culture:**
  - Solid media
  - Broth media: radiometric and non-radiometric system
  - Rate: after 2-4 day of incubation, up to 7 days
  - Also grow on blood agar, MacConkey agar
### Identification

**TABLE 4. Laboratory phenotypic features of the 12 most clinically important species of nonpigmented or late-pigmenting RGM**

<table>
<thead>
<tr>
<th>Species or complex</th>
<th>Prior designations</th>
<th>Pigment</th>
<th>3-Day aryl-sulfatase</th>
<th>Nitrate reduction</th>
<th>Iron uptake</th>
<th>Utilization of:</th>
<th>5% NaCl</th>
<th>Unique PRA (hop65)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>M. chelonae-abscessus group</em></td>
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<tr>
<td><em>M. abscessus</em></td>
<td><em>M. chelonae subsp. abscessus</em></td>
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<tr>
<td><em>M. chelonae</em></td>
<td><em>M. boritense, M. chelonii, M. chelonae subsp. chelonae</em></td>
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<tr>
<td><em>M. immunogen</em></td>
<td><em>M. immunogen</em></td>
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<tr>
<td><em>M. fortuitum group</em></td>
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<tr>
<td><em>M. fortuitum</em></td>
<td><em>M. ranae, M. fortuitum biovar fortuitum</em></td>
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<tr>
<td><em>M. peregrinum (type 1)</em></td>
<td><em>M. fortuitum biovar peregrinum (pipemidic acid susceptible)</em></td>
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<tr>
<td><em>M. peregrinum (type 2)</em></td>
<td><em>M. fortuitum biovar peregrinum (pipemidic acid resistant)</em></td>
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<tr>
<td><em>M. fortuitum third biovariant complex</em></td>
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<tr>
<td><em>M. houstonense (proposed)</em></td>
<td><em>M. fortuitum third biovar sorbitol positive</em></td>
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<tr>
<td><em>M. bonickei (proposed)</em></td>
<td><em>M. fortuitum third biovar sorbitol negative</em></td>
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<tr>
<td><em>M. mucogenicum</em></td>
<td>MCLO</td>
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<tr>
<td><em>M. smegmatis group</em></td>
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<tr>
<td><em>M. smegmatis sensu stricto</em></td>
<td><em>M. smegmatis</em></td>
<td>±</td>
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<tr>
<td><em>M. wolinskyi</em></td>
<td><em>M. smegmatis</em></td>
<td>±</td>
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<tr>
<td><em>M. goodii</em></td>
<td><em>M. smegmatis</em></td>
<td>±</td>
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</tbody>
</table>
Susceptibility Testing-Rx

- **Purpose**
  - Identification
  - Treatment

- **Indication:**
  - Clinically significant isolates
  - Isolates that recovered after Rx failure/relapse

- **Method:**
  - Broth Microdilution MIC (Gold standard)
  - Others: Agar disk diffusion, Agar disk elution, E test

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**TABLE 5. Suggested broth microdilution breakpoints for susceptibility testing of RGM**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Susceptible</th>
<th>Intermediate</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>≤16</td>
<td>32</td>
<td>≥64</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>≤16</td>
<td>32–64</td>
<td>≥128</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>≤1</td>
<td>2</td>
<td>≥4</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>≤2</td>
<td>4</td>
<td>≥8</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>≤1</td>
<td>2–8</td>
<td>≥16</td>
</tr>
<tr>
<td>Imipenem</td>
<td>≤4</td>
<td>8</td>
<td>≥16</td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td>≤32</td>
<td>8</td>
<td>≥64</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>≤4</td>
<td>8</td>
<td>≥16</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Susceptible</th>
<th>Intermediate</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone</td>
<td>≤16</td>
<td>32</td>
<td>≥64</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>≤2</td>
<td>4</td>
<td>≥8</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>≤2</td>
<td>4</td>
<td>≥8</td>
</tr>
<tr>
<td>Linezolid</td>
<td>≤8</td>
<td>16</td>
<td>≥32</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>≤1</td>
<td>2</td>
<td>≥4</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>≤4</td>
<td>8–16</td>
<td>≥32</td>
</tr>
</tbody>
</table>

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*a Drugs and breakpoints recommended by NCCLS document M24-T2 (218).
*b Imipenem MICs are not reported for *M. chelonae*-abscessa group isolates due to lack of reproducibility.
*c MIC end point is 80% inhibition of growth (218).
*d Tobramycin MICs recommended to be reported only for isolates of *M. chelonae*.
*e Non-NCCLS-approved mycobacterial drugs and their breakpoints. Breakpoints are those recommended for aerobic organisms in NCCLS Mi100-S11, 2001 (112), except those for linezolid, which were recently proposed for mycobacteria by Wallace et al. (195).
Histological findings

- Chronic inflammatory infiltrates including lymphocytes, plasma cells and epithelioid histiocytes are commonly seen, though not universally present
- Caseous/non-caseous granulomatous inflammation +/- Langhans’ giant cells
- Extensive fibrin material deposition or suppurative inflammation may be discerned in some cases
- Ziehl-Neelsen stain demonstrates acid-fast bacilli
Treatment

- Most species of RGM have a unique drug susceptibility pattern
- Usually resistant to first line anti-TB drugs
- Lack of consensus due to absence of large controlled clinical trials
- Case reports and in vitro susceptibility tests only
Prolonged antibiotic therapy is generally required for *M. cheloneae* infections. *Intravenous* (IV) therapy is preferred for *serious* illness or *disseminated* disease, at least initially. Frequently, 2-6 weeks of parenteral therapy is administered, followed by a long course of oral antibiotics.

Antibiotic therapy with *2 drugs* is preferable in most patients. Test all initial isolates for antibiotic sensitivity to guide therapy because the sensitivity patterns between given isolates can vary considerably.
- **Amikacin** is the preferred aminoglycoside for treating rapidly growing mycobacteria; however, **tobramycin** may also have activity against *M cheloneae*

- **Cefoxitin** is probably the beta-lactam of choice for both *M cheloneae* and *M abscessus*

- **Imipenem** also has activity against *M cheloneae* and *M abscessus*, but it is reportedly less active against them than it is against *M fortuitum*
- **Ciprofloxacin** and **levofloxacin** have activity against these organisms. Of these, ciprofloxacin use has been reported most often, but levofloxacin has the better activity in vitro. **Gatifloxacin** and **moxifloxacin** also have good in vitro activity, but no clinical experience is reported.

- **Clarithromycin** and **azithromycin** have both been used successfully and are more active than erythromycin, which no longer should be considered.

- **Doxycycline** has activity against some isolates. **Tigecycline** has good in vitro activity against both *M. chelonae* and *M. abscessus*, but no clinical data exist on its use; tigecycline should be considered only in the absence of other options.
Trimethoprim apparently adds little, if anything, to the activity of SMZ. However, the trimethoprim-sulfamethoxazole (TMP-SMZ) fixed-dose combination is a readily available form of the sulfa drug, and the combination has been used successfully.

Linezolid has good in vitro activity against *M chelonae* and has been used successfully alone and in combination to treat infections with this organism.

Topical amikacin and ciprofloxacin have been reported as useful for ocular disease. Topical quinolones may also be effective.
No standard duration of therapy is reported. Treatment usually lasts for many months, and courses that are 6 months or longer are not unusual.

Administer drugs long enough to allow for a complete resolution of clinically apparent lesions. How much additional therapy is needed to prevent relapse is unclear.
Disseminated Infection with Rapidly Growing Mycobacteria (Christopher et al, CID, 1993)

- Only 4 cases of M. cheloneae over last 14 yrs in Duke University Medical Center, together with 17 other cases by review of the medical literature since 1960

- Underlying diseases and use of IS drugs are frequent risk factors (renal transplant, CTD, lymphoma, leukemia, CRF on dialysis)

- Fever and rash are common, positive blood and bone marrow cultures are also common

- Hepatosplenomegaly with histological evidence of diffuse granulomatous infection reported
The best antibiotic treatment is controversial and is likely remained so because of the rarity of these infections.

The success rate of treatment depends on the degree and reversibility of the immunosuppressive state.

Multiple combinations of antibiotics had been used, and difficult to compare the response rate as all patients have different antibiotic regime and degree of underlying disorders and immunosuppression.
Surgery

- Adequate surgical debridement of all affected tissues or infected foreign bodies if possible

- Incomplete removal of infected tissues would result in re-emergence of infection even up to months after surgery
Thank You

End
Surgical Treatment

- Adequate surgical debridement of all affected tissues
- Removal of only sparse tissue would result in re-emergence of infection even up to 3 months after surgery
M. chelonae-abscessus group

- Clarithromycin as cornerstone of therapy

M. chelonae:

- Skin infection (Dermatologic Therapy, 2004)
  - clarithromycin +
    doxycycline or ciprofloxacin (25% isolates sensitive to doxycycline and ciprofloxacin)
  - acquired resistance to drug will be decreased by combination therapy
Newer potential drugs for use in combination with clarithromycin:

- 8-methoxyfluoroquinilone
  e.g., gatifloxacin
- Gatifloxacin inhibited 90% of M. chelonae isolates at $\leq 4$ ug/ml
• Linezolid (an oxazolidinone)
  • 94% isolates of *M. cheloneae* inhibit at concentrations of \( \leq 16 \text{ ug/ml} \), including strains with acquired clarithromycin resistance

• As a macrolide companion drug