Rare disease

Closed trauma, *Mycoplasma hominis* osteomyelitis, and the elusive diagnosis of Good's syndromeAmanda Noska,¹ Rawad Nasr,² David Neville Williams³¹Department of Internal Medicine, Hennepin County Medical Center, Minneapolis, Minnesota, USA²Department of Rheumatology, University of Minnesota Fairview, Minneapolis, Minnesota, USA³Department of Infectious Diseases, Hennepin County Medical Center, Minneapolis, Minnesota, USA

Correspondence to Dr Amanda Noska, noska003@umn.edu

Summary

Mycoplasma hominis septic arthritis has a well-established association with hypogammaglobulinaemia, but is rarely seen in immunocompetent hosts. An association also exists with a closed trauma and a predisposition to *M hominis* bone infections. In this clinical case report, a patient with *M hominis* osteomyelitis following a closed trauma was diagnosed using 16S ribosomal studies, and led to the diagnosis of a severe underlying immunodeficiency syndrome known as Good's syndrome.

BACKGROUND

Infections with *Mycoplasma* species outside the genito-urinary, respiratory and central nervous systems (CNS) are uncommon. Numerous case reports of central nervous system (CNS) infections with *Mycoplasma pneumoniae* have been reported among children and, less commonly, among adults, though the exact mechanism of infection has yet to be clearly defined.^{1–6} *Mycoplasma hominis* infections of the CNS have also rarely been implicated in neonatal meningitis and encephalitis.^{7–8} Individuals with *M pneumoniae* CNS infections commonly have residual neurological deficits despite appropriate antibiotic therapy, but uncommonly warrant further evaluation for possible underlying hypogammaglobulinaemia.⁹ A rare but well-established relationship exists between hypogammaglobulinaemia and *Mycoplasma* infections, particularly in the setting of malignancy, immunosuppression after liver or renal transplant, or congenital immunodeficiency.^{10–13} Extragenital, extrapulmonary and non-CNS infections with *Mycoplasma* species should prompt evaluation of underlying immunodeficiency as these infections are exceedingly rare in immunocompetent individuals.

Good's syndrome is a rare form of cellular and humoral immune dysfunction seen with adult-onset-associated thymoma. Organisms such as *Mycobacterium tuberculosis* and *Staphylococcus aureus* have been implicated in osteomyelitis following closed trauma likely related to earlier haematogenous dissemination. These organisms have a capacity for intracellular survival, and *M hominis* may share the same capacity for intracellular survival and chemotaxis in the evolution of closed trauma osteomyelitis. When appropriate cultures are sterile in situations where a high degree of clinical suspicion for infection exists, 16S ribosomal sequencing studies can be used for identifying pathogens and guide an anti-infective treatment. The following case illustrates these principles in a greater detail.

CASE PRESENTATION

The patient was a 63-year-old man with Crohn's disease, who had not received immunosuppressive therapy, and was with a history of thymectomy for a benign thymoma. Two months prior to admission, he fell at home and sustained a closed fracture of the fourth digit of his right foot. He presented to the hospital with a 2-week history of fever, swelling, redness and increased pain in the right foot at the site of the previous closed trauma. He had no open wounds. His admission examination and imaging were consistent with osteomyelitis (figure 1). He underwent debridement and resection of the fourth metatarsal head on the third day of hospitalisation. Tissue histopathology showed evidence of chronic osteomyelitis with granulation tissue and lymphocytic inflammation. Bacterial, fungal and anaerobic tissue cultures taken from the site of debridement were sterile. Tissue samples sent for 16S rRNA sequencing and gene amplification studies because of the concern for an infectious aetiology returned strongly positive (100% analytic sensitivity) for *M hominis*. Because of the patient's history of thymoma and the isolation of an unusual pathogen, immunodeficiency test reports were obtained.

INVESTIGATIONS

The patient's CD4 T-cell count returned at 122 cells/mm³ (490–1436/mm³), CD8 197 cells/mm³ (274–662/mm³), CD19 0 cells/mm³ (16–409/mm³), CD56 9 cells/mm³ (98–325/mm³) and H/S ratio 0.6 (1.2–3.0). Serum immunoglobulin levels were also profoundly low: IgG 80 mg/dl (681–1648 mg/dl), IgM <25 mg/dl (48–312 mg/dl) and IgA 5 mg/dl (87–474 mg/dl). The HIV antibody screen was non-reactive.

TREATMENT

The patient was started on oral doxycycline 100 mg twice daily for 6 weeks to treat *M hominis* osteomyelitis and a

Figure 1 Admission x-ray of patient's right foot. Red arrow: bone destruction of the fourth metatarsal consistent with osteomyelitis.

subsequent improvement was found in his symptoms and signs. After the laboratory and immunodeficiency test reports were obtained, he was diagnosed with Good's syndrome and was started on monthly IVIG (intravenous immunoglobulin) to treat his underlying IgG deficiency and a daily single-strength tablet of trimethoprim-sulphamethoxazole for prophylaxis, given his low CD4 count.

OUTCOME AND FOLLOW-UP

The patient responded well to doxycycline and monthly infusions of IVIG, with recovery of his immune function and no recurrence or new infections over the subsequent 2 years of follow-up.

DISCUSSION

M. hominis osteomyelitis has not, to our knowledge, previously been reported. However, *M. hominis* septic arthritis has been documented in isolated case reports in association with hypogammaglobulinaemia.^{10 14–16} *M. hominis* is a highly unusual cause of infection of the bone. If detected in a presumably healthy host, *Mycoplasma* bone or joint infections should prompt further work-up for hypogammaglobulinaemia. In our patient, once *M. hominis* osteomyelitis was diagnosed using 16S ribosomal RNA

Figure 2 CT imaging of the patient's chest. Red arrow: mediastinal mass measuring 9 cm × 6.7 cm × 8.0 cm in the anterior mediastinum. The pathology later confirmed a benign thymoma.

amplification studies, further investigation led to the discovery of a severe underlying immunodeficiency syndrome.

Good's syndrome was first described by Dr Robert Good in 1954. The syndrome is a rare adult-onset condition characterised by thymoma, hypogammaglobulinaemia and a low number of peripheral B cells.¹⁵ Although a unique clinical entity distinct from CVID (common variable immunodeficiency), Good's syndrome has many of the same defining characteristics, including: low IgG, recurrent sinopulmonary infections with encapsulated and atypical organisms, and an association with autoimmune disease.¹³ Unlike CVID, Good's syndrome (1) is associated with thymoma (figure 2), (2) is typically diagnosed in the fourth and/or fifth decades of life, (3) involves severe defects in both cellular and humoral immunity, (4) has an increased predisposition to opportunistic infections including *Herpes simplex*, *Candida* sp., *Haemophilus* sp., *Pseudomonas* sp., *Klebsiella* sp., *Mycoplasma* sp. and *Pneumocystis carinii* pneumonia and (5) generally has a poorer overall prognosis than CVID owing to a more profound immunodeficiency.¹³

Mycoplasmas and Ureaplasmas are the two genera that make up the family of Mycoplasmataceae, which are among the smallest free-living organisms in existence.^{14 17} Because Mycoplasmataceae lack a cell wall, visualisation on gram stain or isolation from the culture presents diagnostic challenges.^{14 17} Both Mycoplasmas and Ureaplasmas have a predilection for mucous membranes and, therefore, primarily cause disease in the respiratory and urogenital tracts. Increased colonisation by these microbes in patients with hypogammaglobulinaemia has been previously explained by a deficiency of protective antibodies at mucosal surfaces.^{1 17} In 1988, Kraus *et al*¹⁸

underscored the importance of maintaining a high clinical suspicion for *Mycoplasma* septic arthritis in hypogammaglobulinaemic patients so as to minimise joint destruction from progressive disease. Multiple case reports have validated this association since that time,^{14 17 19} although this remains a rare clinical entity.

In our patient, we suggest that his hypogammaglobulinaemia predisposed him to *Mycoplasma* infections because of a relative absence of antibodies at mucosal surfaces, thereby increasing his risk of developing *M hominis* infection within the genitourinary tract. In vitro work on the relationship between hypogammaglobulinaemia and *Mycoplasma* joint infections suggests that minor trauma common to large joints attracts neutrophils which are capable of taking up *Mycoplasma* species into phagocytic vacuoles.¹⁷ When the specific antibodies responsible for removal of these pathogens are absent at mucosal surfaces, these organisms can remain viable and subsequently invade distant joint spaces via neutrophil chemotaxis from genitourinary sites, causing infection.^{1 17} Research exploring the relationship between trauma and infectious osteomyelitis documented numerous case reports involving closed trauma and *Mycobacteria* species and *S aureus* osteomyelitis.^{20–26} The pathogenicities of both *M tuberculosis* and *S aureus* are largely due to haematogenous seeding and evasion of host defence mechanisms via intracellular uptake of these microbes.^{20 22 23 25 26} Like *M tuberculosis* and *S aureus*, *Mycoplasma* species are capable of intracellular host-defence evasion, further contributing to the overall pathogenicity.¹⁷

Ribosomal 16S rRNA gene sequencing studies are promising new ways to identify *Mycoplasma* species in the immunocompromised host because traditional bacterial cultures are invariably sterile. The precise role of 16S studies as a diagnostic tool is yet to be clearly defined. The most useful clinical situations to use 16S ribosomal gene sequencing and amplification studies are as follows: (1) identifying culture-negative pathogens from sterile sites in which a high degree of clinical suspicion for infection exists, (2) identifying new pathogens previously unknown to cause disease and (3) identifying microbes previously treated with antibiotics in critically ill or immunocompromised hosts with a low bacterial burden.^{27–30} The utility of 16S rRNA studies is limited to a diagnostic testing from closed, sterile body sites, because normal microbial flora from non-sterile sites cause interference signals from the 16S rRNA subunits which cannot be distinguished from true pathogens.^{27–30} The sensitivity and specificity of microbiological results from 16S rRNA amplification studies are relative to the size and reproducibility of the reference gene library, and therefore the results of these studies must be interpreted within the overall clinical context.^{27–30} According to most expert taxonomists, the per cent identity score must be greater than or equal to 97% to 99% to be reliably considered of diagnostic utility.²⁹ Difficulties with inadequate sensitivity and specificity arise when percent identities less than 97% are utilised for clinical purposes.

Learning points

- ▶ 16S studies have a useful but yet to be defined role as a diagnostic clinical tool.
- ▶ The association between hypogammaglobulinaemia and *Mycoplasma* bone and joint infections is rare but of clinical importance.
- ▶ Good's syndrome is a rare adult-onset condition characterised by thymoma and both cellular and humoral immunodeficiencies.
- ▶ Knowledge of atypical and/or unusual infectious diseases in unusual sites can serve as a sentinel indicator of underlying immunodeficiency.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. Bloom KA, Chung D, Cunningham-Rundles C. Osteoarticular infectious complications in patients with primary immunodeficiencies. *Curr Opin Rheumatol* 2008;**20**:480–5.
2. Narita M, Matsuzono Y, Togashi T, et al. DNA diagnosis of central nervous system infection by *Mycoplasma pneumoniae*. *Pediatrics* 1992;**90**:250–3.
3. Stamm B, Moshopulos M, Hungerbuehler H, et al. Neuroinvasion by *Mycoplasma pneumoniae* in acute disseminated encephalitis. *Emerg Infect Dis* 2008;**14**:641–3.
4. Tong CY, Menson E, Lin JP, et al. Prevalence of *Mycoplasma* encephalitis. *Lancet Infect Dis* 2011;**11**:425–6.
5. Tsiodras S, Kelesidis I, Kelesidis T, et al. Central nervous system manifestations of *Mycoplasma pneumoniae* infections. *J Infect* 2005;**51**:343–4.
6. Tunkel AR, Glaser CA, Bloch KC, et al. The management of encephalitis: clinical practice guidelines by the Infectious Disease Society of America. *Clin Infect Dis* 2008;**48**:303–27.
7. Hata A, Honda Y, Asada K, et al. *Mycoplasma hominis* meningitis in a neonate: case report and review. *J Infect* 2008;**57**:338–43.
8. Wolthers KD, Kornelisse RF, Platenkamp GJ, et al. A case of *Mycoplasma hominis* meningo-encephalitis in a full-term infant: rapid recovery after start of treatment with ciprofloxacin. *Eur J Pediatr* 2003;**162**:514–16.
9. Bitnun A, Ford-Jones EL, Petric M, et al. Acute childhood encephalitis and *Mycoplasma pneumoniae*. *Clin Infect Dis* 2001;**32**:1674–84.
10. Meyer RD, Clough W. Extragenital *Mycoplasma hominis* infections in adults: emphasis on immunosuppression. *Clin Infect Dis*. 1993;**17**(Suppl 1):S243–9.
11. Miranda C, Camacho E, Reina G, et al. Isolation of *Mycoplasma hominis* from extragenital cultures. *Eur J Clin Microbiol Infect Dis* 2005;**24**:334–7.
12. Rohner P, Schnyder I, Ninet B, et al. Severe *Mycoplasma hominis* infections in two renal transplant patients. *Eur J Clin Microbiol Infect Dis*. 2004;**23**:203–4.
13. Tarr PE, Sneller MC, Mechanic LJ, et al. Infections in patients with immunodeficiency with thymoma (Good syndrome). Report of 5 cases and review of the literature. *Medicine (Baltimore)* 2001;**80**:123–33.
14. Burdge DR, Reid GD, Reeve CE, et al. Septic arthritis due to dual infection with *Mycoplasma hominis* and *Ureaplasma urealyticum*. *J Rheumatol* 1988;**15**:366–8.
15. Kim SK. *Mycoplasma hominis* septic arthritis. *Ann Plast Surg* 1988;**20**:163–6.
16. Luttrell LM, Kanj SS, Corey GR, et al. *Mycoplasma hominis* septic arthritis: two case reports and review. *Clin Infect Dis* 1994;**19**:1067–70.
17. Furr PM, Taylor-Robinson D, Webster AD. *Mycoplasmas* and *ureaplasmas* in patients with hypogammaglobulinemia and their role in arthritis: microbiological observations over twenty years. *Ann Rheum Dis* 1994;**53**:183–7.
18. Kraus VB, Baraniuk JN, Hill GB, et al. *Ureaplasma urealyticum* septic arthritis in hypogammaglobulinemia. *J Rheumatol*. 1988;**15**:369–71.

19. **Vogel U**, Lüneberg E, Kuse ER, *et al.* Extragenital *Mycoplasma hominis* infection in two liver transplant recipients. *Clin Infect Dis* 1997;**24**:512–13.
20. **Chan ED**, Kong PM, Fennelly K, *et al.* Vertebral osteomyelitis due to infection with nontuberculous *Mycobacterium* species after blunt trauma to the back: 3 examples of the principle of Locus Minoris Resistentiae. *Clin Inf Dis*. 2001;**32**:1506–10.
21. **Clark RB**, Spector H, Friedman DM, *et al.* Osteomyelitis and synovitis produced by *Mycobacterium marinum* in a fisherman. *J Clin Microbiol* 1990;**28**:2570–2.
22. **Ellington JK**, Harris M, Hudson MC, *et al.* Intracellular *Staphylococcus aureus* and antibiotic resistance: implications for treatment of staphylococcal osteomyelitis. *J Orthop Res* 2006;**24**:87.
23. **Govender S**, Charles RV, Ballaram R, *et al.* Vertebral osteomyelitis after a closed fracture of the spine: a case report. *SAMJ* 1988;**73**:124–6.
24. **Greenberg DP**, Bayer AS, Cheung A, *et al.* Protective efficacy of protein A-specific antibody against bacteremic infection due to *Staphylococcal aureus* in an infant rat model. *Infect Immun* 1989;**57**:1113.
25. **Patel R**, Naik S, Melnikau B, *et al.* Clavicular tuberculosis following trivial trauma. *Southern Med Assoc* 2009;**102**:848–51.
26. **Webb LX**, *et al.* Osteomyelitis and intraosteoblastic *Staphylococcus aureus*. *J Surg Orthop Adv* 2007;**16**:73.
27. **Clarridge JE** 3rd. Impact of 16S rRNA gene sequence analysis for identification of bacteria on clinical microbiology and infectious diseases. *Clin Microbiol Rev* 2004;**17**:840–62.
28. **Kiratisin P**, Li L, Murray PR, *et al.* Identification of bacteria recovered from clinical specimens by 16S rRNA gene sequencing. *Eur J Clin Microbiol Infect Dis* 2003;**22**:628–31.
29. **Petti CA**. Detection and identification of microorganisms by gene amplification and sequencing. *Clin Infect Dis* 2007;**44**:1108–14.
30. **Woo PC**, Lau SK, Teng JL, *et al.* Then and now: use of 16S rDNA gene sequencing for bacterial identification and discovery of novel bacteria in clinical microbiology laboratories. *Clin Microbiol Infect* 2008;**14**:908–34.

Copyright 2012 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Noska A, Nasr R, Williams DN. Closed trauma, *Mycoplasma hominis* osteomyelitis, and the elusive diagnosis of Good's syndrome. *BMJ Case Reports* 2012;10.1136/bcr-2012-007056, Published XXX

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow