Open Forum Infectious Diseases

BRIEF REPORT

Recurrent *Mycobacterium chelonae* Skin Infection Unmasked as Factitious Disorder Using Bacterial Whole Genome Sequence Analysis

Sarah Flohr,[1,a] Alban Ramette,[2,a] Philipp K. A. Agyeman,[1] Andrea Duppenthaler,[1] Cordula Scherer,[3] Peter M. Keller,[2] and Christoph Aebi[1]

[1]Division of Pediatric Infectious Disease, Department of Pediatrics, University of Bern, Bern, Switzerland, [2]Institute for Infectious Diseases, University of Bern, Bern, Switzerland, [3]Department of Pediatric Surgery, Bern University Hospital, Inselspital, University of Bern, Bern, Switzerland

Mycobacterium chelonae infections usually resolve with adequate therapy. We report the case of an adolescent with a chronic and progressive *M chelonae* infection refractory to combined antimicrobial and surgical therapy. Whole genome sequence analysis of consecutive isolates distinguished reinfection from recurrence and contributed to the diagnosis of a factitious disorder.

Keywords. factitious disorder; *Mycobacterium chelonae*; pediatrics; psychiatry; whole genome sequencing.

A 14-year-old previously healthy female adolescent presented with an inflammatory skin lesion of her left lower limb to a peripheral emergency center. She stated that the lesion resulted from a trivial wood splinter wound to her left ankle in December 2018 with local redness, swelling, and pain (Figure 1, no. 1; Supplementary Figure 1). Physical examination was otherwise unremarkable. Local incision and wound inspection failed to reveal any debris. Bacterial secondary infection was suspected.

Amoxicillin/clavulanate was prescribed for 7 days. Six weeks later, the patient presented to another emergency center with additional lesions located proximally to the primary site. Despite restarting amoxicillin/clavulanate, the lesions continued to deteriorate. Thus, the patient was referred to our institution 2 months after the onset of her illness. On admission, she was afebrile and well appearing. Her physical examination was unremarkable except for 3 partly confluent, tender, raised, erythematous, and poorly demarcated lesions on the medial aspect of the left calf (Figure 1, nos. 2 and 3). The skin surface was intact. Her peripheral white blood cell count (WBC) was 7.9×10^9/L, C-reactive protein (CRP) was <3 mg/L, and the erythrocyte sedimentation rate was 19 mm/hour. Histopathology of a skin biopsy revealed granulomatous inflammation and a routine culture grew *Enterobacter cloacae*. She was discharged from the hospital with oral ciprofloxacin for 7 days. Two weeks later, she was readmitted, because her left lower leg lesions progressed (Figure 1, nos. 3 and 5). She was started on cefepime, the lesions were debrided, and vacuum-assisted wound therapy was administered for 8 days. Histopathology revealed fibrotic tissue with moderate, nonspecific inflammation. Mycobacterial culture from a biopsy specimen grew *Mycobacterium chelonae* (isolate MCHE08). The diagnosis of a mycobacterial skin and soft tissue infection with a sporotrichoid pattern was made. Oral therapy with clarithromycin and moxifloxacin was initiated empirically. In accordance with the results of the susceptibility testing (Supplementary Table 1), the latter was subsequently replaced by tobramycin. A right-arm midline catheter was inserted for outpatient therapy. Five days later, the patient presented with acute-onset fever, chills, and myalgias. Her WBC count was 13.6×10^9/L, CRP was 26 mg/L, and a peripheral blood culture grew α-hemolytic streptococci considered irrelevant. Four days later, she again presented with fever to 40°C and required readmission. Her midline catheter was removed, and she defervesced promptly without additional antimicrobial therapy. A blood culture drawn through this line yielded *Acinetobacter* species, *Stenotrophomonas maltophilia*, and *Enterococcus faecalis*. Two repeat blood cultures within 24 hours as well as the catheter tip culture remained sterile. Because of local tenderness on her right forearm, Doppler sonography was performed and revealed radial vein thrombosis. Subcutaneous enoxaparin was initiated and switched to low-dose therapy after 3 weeks for a total of 6 weeks. Clarithromycin was continued, tobramycin was replaced by oral linezolid.

Two weeks later, a new lesion appeared. The patient was readmitted, and the lesion, together with scar tissue from previous surgery, was removed (Figure 1, no. 5). Microscopy revealed acid-fast bacilli, but mycobacterial culture yielded no growth. Histology revealed granulomatous, partly necrotizing inflammation at multiple biopsy sites. During her 6-day admission, she received oral clarithromycin and tobramycin, which was replaced by clofazimine, when she was discharged. The lesions gradually improved during the subsequent 2 months. In August 2019, multiple new lesions appeared (Figure 1, no. 8), which were initially diagnosed as erythema nodosum. These lesions gradually improved over 2 months with topical

Received 12 August 2020; editorial decision 12 October 2020; accepted 14 October 2020.

[a]S. F. and A. R. contributed equally to this manuscript.

Correspondence: Christoph Aebi, MD, Division of Pediatric Infectious Disease, Department of Pediatrics, Bern University Hospital, Inselspital, University of Bern, CH-3010 Bern, Switzerland (christoph.aebi@insel.ch).

Open Forum Infectious Diseases®2020

DOI: 10.1093/ofid/ofaa506

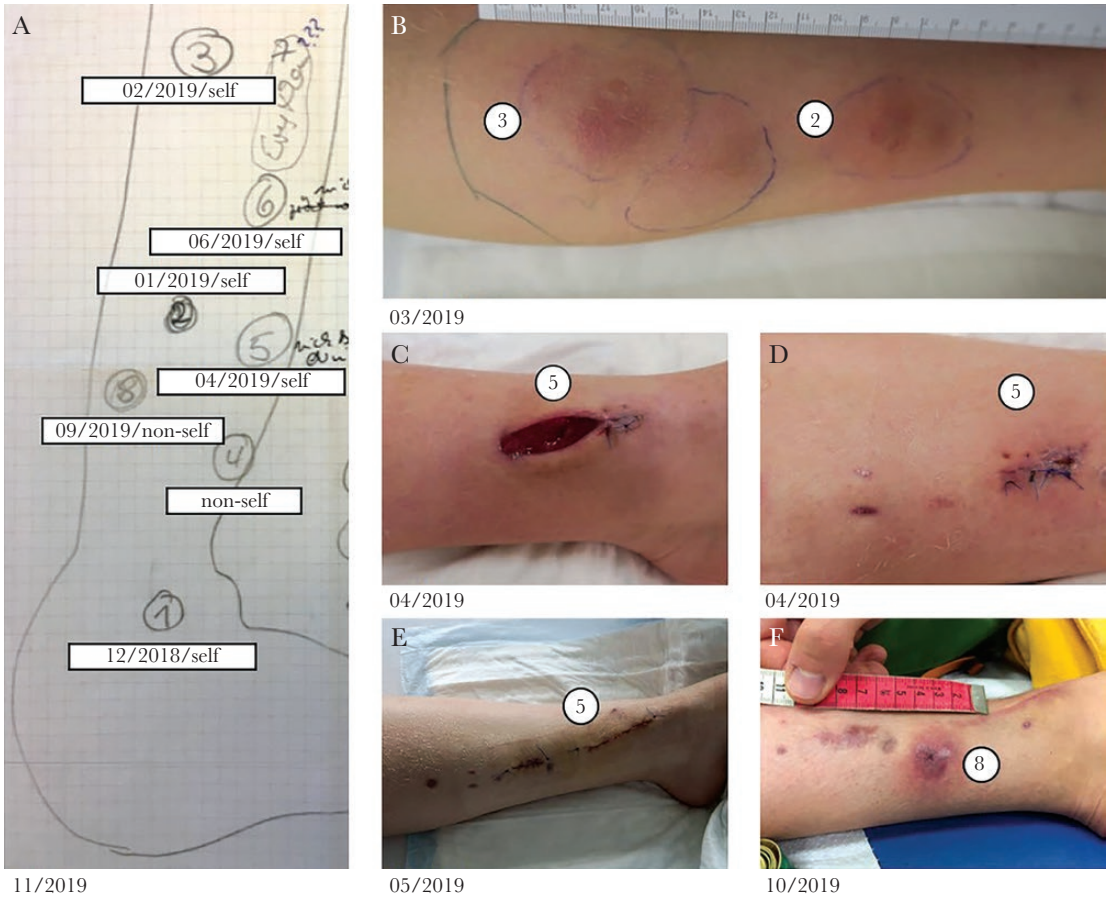

Figure 1. (A) "Leg map" sketch drawn by the patient and annotated by the authors indicating the approximate dates of self-injection and of spontaneously appearing lesions reported by the patient; (B–F) clinical presentation at different time points as indicated, numbers in circles correspond to those in A.

corticosteroid therapy. In October 2019, yet another erythema nodosum-like lesion appeared. Excisional biopsy again revealed granulomatous inflammation and mycobacterial culture again grew *M chelonae* (isolate MCHE42), now revealing resistance to clarithromycin (Supplementary Table 1), which was replaced by minocycline. Comparative deoxyribonucleic acid sequence analysis of the of the *rrl* gene of the 2 available isolates revealed the appearance of the point mutation A2059G, which confers macrolide resistance presumed to have resulted from prolonged clarithromycin exposure. As had first been done 7 months earlier, we confronted the patient with our suspicion of self-harm, but she denied it. Genomic analysis of the 2 available isolates using next-generation whole genome sequencing (WGS) was subsequently performed (Supplementary Tables 2–5) and revealed that the 2 isolates, MCHE08 and MCHE42, were genetically highly diverse and clonally unrelated (Supplementary Figure 2 and Table 6). The 2 isolates showed some genomic similarities and shared identical taxonomic classification as *M chelonae*, but unambiguous differences at both the single-nucleotide variant (SNV) and genomic organization level including a plasmid and other genomic elements (Supplementary Figure 2) indicated that the 2 genomes were evolutionarily unrelated to each other.

At approximately the time when these results became available, the patient revealed to her psychotherapist, who had followed her for the past 5 months, that the lesions appeared after multiple intentional self-injuries. She explained that she repeatedly self-injected up to 30 mL tap water that had been stagnant for weeks at a time in a plastic drinking bottle on the windowsill of her bedroom. She presented a "leg map" drawn from memory with the approximate injection sites and dates (Figure 1A).

Patient Consent Statement

Oral informed consent was obtained from the patient and her family as required by the University Hospital for case reports. The Cantonal Ethics Committee, Bern, Switzerland, declared nonresponsibility.

DISCUSSION

Factitious disorders (FDS) are rare, challenging to manage, and usually incur long diagnostic delays dotted with unnecessary, misleading, and potentially harmful interventions. Factitious disorders also occur in children and adolescents [1]. Clinicians suspecting factitious behavior induced by the patient or another

person (Munchausen syndrome by proxy) often fail to collect physical evidence corroborating illness falsification [1] for extended periods of time. In our case, clinical suspicion arose for the first time when polymicrobial, catheter-related bacteremia complicated by an arm vein thrombosis occurred 6 months before FD was finally ascertained.

Self- or proxy-induced infections are a major subgroup of FD [1] and often involve skin manifestations [2]. Remarkably, nontuberculous mycobacteria (NTM) and, specifically, *M chelonae* have rarely been implicated as pathogens in FD despite being ubiquitous environmental organisms known to contaminate soil and water [3]. To our knowledge, only 3 cases of FD resulting in NTM infections have been reported, all presenting with bloodstream infections due to *Mycobacterium mucogenicum* [4, 5] or *Mycobacterium fortuitum* [6]. Thus, this report is the first to describe an FD presenting as NTM infection induced by repetitive self-inoculation of stagnant drinking water using a hypodermic needle. It is interesting to note that all NTM species previously reported are rapidly growing mycobacteria. Factitious panniculitis, presumably with similar clinical appearance, was reported as FD induced by cupping or milk injections.

We entertained the diagnosis of a naturally evolving and relapsing *M chelonae* infection for many months, because the patient adhered reliably to therapy, endured adverse effects, presented with a seemingly sporotrichoid pattern of progression well described for *M chelonae* infections [7], and experienced apparently treatment-related emergence of a *rrl* gene mutation conferring clarithromycin resistance (Supplementary Data). Because difficult-to-treat *M chelonae* infections are primarily encountered in immunocompromised patients [8], we even planned a diagnostic work-up for genetic Mendelian susceptibility to mycobacterial disease [9].

Genomic comparison of the 2 isolates (MCHE08 and MCE42) recovered from 2 distant lesions sampled 7 months apart unequivocally established that reinfection rather than relapse had occurred and that clarithromycin resistance did not result from a single mutational event in the *rrl* gene of the original isolate, but it reflected the primary genotype of the second one. We cannot rule out the possibility that both isolates may have been present from the outset rather than sequentially, but we expect that we would have identified different strains in culture and WGS analysis [10]. Genomic comparison revealed that the 2 isolates were genetically diverse and clonally unrelated (Supplementary Material). This notion is clearly supported by clinical studies in *Mycobacterium abscessus*, a closely related species, demonstrating that within-patient isolates typically differ by less than 50 SNV [11, 12], which is far less than what we observed.

Within-patient WGS has emerged as a precise tool to distinguish between relapse and reinfection in patients with tuberculosis [13], *Mycobacterium ulcerans* [14], *M abscessus* [12], and various non-mycobacterial infections. It is also used in forensic medicine. However, to our knowledge, it has not been described in *M chelonae* infection or as a diagnostic tool to support the diagnosis of FD-associated infection of any etiology. Whole genome sequencing of *M chelonae* for other purposes included its identification in an outbreak of tattoo infections related to contaminated ink and water [15] and in nosocomial infection chains complicating cosmetic surgery.

Whole genome sequencing can thus be a powerful tool for diagnosing FD as the cause of seemingly chronic infections, but several limitations remain. First, establishing plausibility for repetitive self-inoculation requires a multidisciplinary approach including psychiatric exploration. Molecular diagnostics can have an important supportive role for subsequent psychotherapy not only by unmasking the pathogenesis, but also by fostering lasting confidence in the accuracy of the diagnosis of FD. Second, as in any microbiologic analysis, erroneous interpretation of WGS comparison may occur if an isolate is a contaminant rather than a pathogen at the sampling site. This could easily occur with an environmental organism such as *M chelonae*, but it appears improbable in the present case. Surgical sites with intact skin surfaces were sampled, histopathology yielded granulomatous inflammation at each site, and WGS ruled out a clonal origin of the isolates. Third, distinguishing between within-host microevolution and reinfection may not always be as obvious as in this case, particularly when the number of SNV is small. On the other hand, the identification of few genomic differences between consecutive within-host isolates cannot be considered as decisive proof against reinfection by the same environmental isolate. Ultimately, bacterial WGS is currently an expensive research tool, and its costs are not generally covered by healthcare insurances.

CONCLUSIONS

Comparative genomic analysis using WGS of sequential clinical isolates from a given patient may differentiate between relapse and reinfection and provide robust evidence for clinically suspected FD presenting as chronic or recurrent infection. Sequence analysis of individual antimicrobial resistance genes may erroneously indicate treatment-induced emergency of resistance when in fact reinfection with a different strain had occurred.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

We thank the patient and her family for their cooperation and trust and Antonya Eggert, psychotherapist of the patient, for sharing her insights.

Disclaimer. The sponsor had no role in the design, execution, interpretation, or writing of the study.

Potential conflicts of interest. A. R. received travel grants from Oxford Nanopore Technologies to attend scientific conferences. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Libow JA. Child and adolescent illness falsification. Pediatrics **2000**; 105:336–42.
2. Harth W, Taube KM, Gieler U. Facticious disorders in dermatology. J Dtsch Dermatol Ges **2010**; 8: 361–72; quiz 73.
3. Gomez-Alvarez V, Revetta RP. Whole-genome sequences of four strains closely related to members of the *Mycobacterium chelonae* group, isolated from biofilms in a drinking water distribution system simulator. Genome Announc **2016**; 4:e01539–15.
4. Fonteyn N, Wauters G, Vandercam B, et al. *Mycobacterium mucogenicum* sepsis in an immunocompetent patient. J Infect **2006**; 53:e143–6.
5. Kwon Y, Koene RJ, Cross C, et al. Fatal non-thrombotic pulmonary embolization in a patient with undiagnosed factitious disorder. BMC Res Notes **2015**; 8:302.
6. Hashimoto A, Takayama Y, Matsushita R, et al. [A case of Münchausen syndrome with recurrent bacteremia and PR3-ANCA positivity]. Kansenshogaku Zasshi **2007**; 81:189–93.
7. Kemp DM, Govind AG, Kang J, et al. Sporotrichoid-like spread of cutaneous *Mycobacterium chelonae* in an immunocompromised patient. Case Rep Dermatol Med **2017**; 2017:8219841.
8. Wallace RJ Jr, Brown BA, Onyi GO. Skin, soft tissue, and bone infections due to *Mycobacterium chelonae* chelonae: importance of prior corticosteroid therapy, frequency of disseminated infections, and resistance to oral antimicrobials other than clarithromycin. J Infect Dis **1992**; 166:405–12.
9. Bustamante J. Mendelian susceptibility to mycobacterial disease: recent discoveries. Human Genet **2020**; 139:993–1000.
10. Shaw LP, Doyle RM, Kavaliunaite E, et al. Children with cystic fibrosis are infected with multiple subpopulations of *Mycobacterium abscessus* with different antimicrobial resistance profiles. Clin Infect Dis **2019**; 69:1678–86.
11. Davidson RM, Hasan NA, Reynolds PR, et al. Genome sequencing of *Mycobacterium abscessus* isolates from patients in the United States and comparisons to globally diverse clinical strains. J Clin Microbiol **2014**; 52:3573–82.
12. Bryant JM, Grogono DM, Rodriguez-Rincon D, et al. Emergence and spread of a human-transmissible multidrug-resistant nontuberculous mycobacterium. Science **2016**; 354:751–7.
13. Bryant JM, Harris SR, Parkhill J, et al. Whole-genome sequencing to establish relapse or re-infection with *Mycobacterium tuberculosis*: a retrospective observational study. Lancet Respir Med **2013**; 1:786–92.
14. Wynne JW, Stinear TP, Athan E, et al. Low incidence of recurrent Buruli ulcers in treated Australian patients living in an endemic region. PLoS Negl Trop Dis **2018**; 12:e0006724.
15. Griffin I, Schmitz A, Oliver C, et al. Outbreak of tattoo-associated nontuberculous mycobacterial skin infections. Clin Infect Dis **2019**; 69:949–55.