ORIGINAL RESEARCH LETTER

Pulmonary infection caused by *Mycobacterium marinum* in a patient with anorexia nervosa

To the Editor:

The global incidence of nontuberculous mycobacterial pulmonary disease (NTM-PD) has been increasing [1]. Recently popularised microbiology tests, including 16S rRNA sequencing and matrix-assisted laser desorption ionisation–time-of-flight mass spectrometry, have made it possible to identify rare nonmycobacterial species previously unidentifiable using conventional methods [2, 3]. Transmission of *Mycobacterium marinum* to humans is mainly through direct contact with domesticated fish or through pre-existing wounds or abrasions on limbs exposed to contaminated water [4]. *M. marinum* causes swimming pool or fish tank granuloma [4]. The organism grows well at 30–32°C, but poorly or not at all at 37°C [4]. Most *M. marinum* infections do not invade deeper than the superficial cooler regions of the skin, and pulmonary infections are rarely reported [4].

Anorexia nervosa is characterised by severe restriction of food intake, resulting in severe weight loss and malnutrition [5]. Malnutrition is an important and common risk factor associated with mycobacterial infection by both *M. tuberculosis* and nontuberculous mycobacteria [6]. In addition, increased susceptibility to mycobacterial infections has been reported in individuals with anorexia nervosa [7, 8].

A 46-year-old Japanese female office worker was admitted to the psychiatric ward in our hospital because of emaciation. Her physical condition had rapidly deteriorated in the 4 months preceding her admission, although she did not have any specific symptoms other than extreme weight loss. She was a nonsmoker with a 4-year history of restricting-type anorexia nervosa without bulimic episodes and no history of tuberculosis. No abnormalities had been detected in previous annual chest radiographs, suggesting that she had no pre-existing structural lung disease. She reported no recent contact with fish or contaminated water. She had not undergone bacille Calmette–Guérin vaccination. On examination, she was found to be emaciated, weighing 26 kg, with a body mass index (BMI) of 10.2 $kg \cdot m^{-2}$ and a body temperature of 35.3°C. She was not investigated for immunodeficiencies such as HIV infection or endocrine abnormalities. Respiratory symptoms, including cough and sputum, were not evident. Physical examination revealed bronchial breath sounds in both apices. The skin on all four limbs was intact. She did not have peripheral oedema, alopecia or cutaneous pigmentation. A chest radiograph on admission revealed cavities surrounded by infiltrates in both lung apices (figure 1a). Chest computed tomography revealed a large cavitating right upper lobe lesion and multiple thick-walled left upper lobe cavitary lesions (figure 1b). Laboratory tests revealed that the white blood cell count was 4700 $cells \cdot \mu L^{-1}$, with a lymphocyte count of 799 $cells \cdot \mu L^{-1}$, haemoglobin 9.5 $g \cdot dL^{-1}$, serum albumin 2.3 $g \cdot dL^{-1}$ and serum C-reactive protein 0.6 $mg \cdot dL^{-1}$.

The patient was initially suspected to have pulmonary tuberculosis and was transferred to the tuberculosis ward. Three out of four forced sputum samples revealed numerous acid-fast bacilli (AFB). She was initiated on 200 $mg \cdot day^{-1}$ isoniazid, 300 $mg \cdot day^{-1}$ rifampicin and 500 $mg \cdot day^{-1}$ ethambutol. A sputum culture grew *Mycobacterium* that formed smooth photochromogenic colonies that were negative for *M. tuberculosis* and *M. avium* complex on PCR assays. *M. marinum* was identified using a DNA–DNA hybridisation kit (DDH Mycobacteria; Kyokuto, Tokyo, Japan). Analysis of the 16S rRNA gene confirmed

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***Mycobacterium marinum* can cause pulmonary infection and can grow at ⩽32°C. Physicians should consider *M. marinum* when examining patients with pulmonary infection and low body temperature or anorexia nervosa, and grow the specimen at ⩽32°C.** https://bit.ly/3jkzBeq

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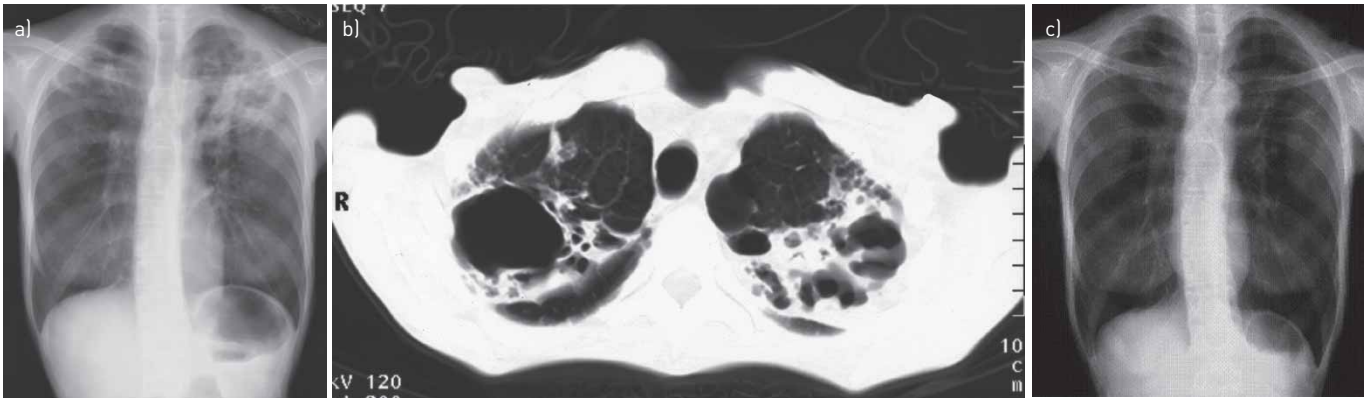

FIGURE 1 Chest imaging showing the patient's pulmonary lesions. a) Chest radiograph before initiating treatment showing bilateral cavities in the upper lobes of the lungs; b) chest computed tomography scan showing bilateral cavitary lesions surrounded by infiltrations in the apices of the lungs; c) chest radiograph 3 months after completing treatment showing a reduction in the size of the apical cavities.

that the mycobacteria was *M. marinum*, and the isolate was 100% consistent with that of *M. marinum* ATCC927^{T}. The primary culture grew on 2% Ogawa egg medium in a carbon dioxide incubator at 25°C and 32°C, but not at 37°C or 42°C. The minimum inhibitory concentrations of rifampicin and clarithromycin were $\leqslant$1.0 μg·mL^{-1} and 2.0 μg·mL^{-1}, respectively. Once the strain had been identified and its drug susceptibility characterised, combination therapy was changed to rifampicin 300 mg·day^{-1} and clarithromycin 200 mg twice daily. The patient's sputum expectoration resolved within several days after she began treatment. After initiating treatment, her body temperature temporarily decreased further and then gradually recovered, suggesting that her body temperature on admission was relatively pyretic due to mycobacterial infection. She was treated with this combination therapy for 6 months along with psychotherapy. A repeat chest radiograph 3 months after completing treatment revealed a reduction in the size of the apical cavities (figure 1c). 9 months after initiating treatment, her weight had increased to 30 kg and BMI was 11.7 kg·m^{-2}.

This case reveals four important clinical issues: 1) *M. marinum* can cause pulmonary infection; 2) it has the potential for acquisition *via* inhalation; 3) anorexia nervosa may increase susceptibility to pulmonary *M. marinum*; and 4) AFB culture at $\leqslant$32°C aids in identifying the pathogen.

As of September 2020, only two cases of pulmonary *M. marinum* infection have been reported in the English-language literature [9, 10], and only one of the case reports provided chest images. The radiological finding common to the two cases reported previously and this case is the presence of large cavities with infiltration in lung apices. This may be a characteristic radiological finding associated with *M. marinum*. In this case, the portal of entry by which the mycobacteria entered the lungs was unidentified, because the patient had no known marine exposure or contact with aquatic animals and did not have any injuries and wounds on the trunk or extremities. This suggests potential airway acquisition rather than direct transmission from an aquatic environment. The growth of *M. marinum* requires several weeks at a low temperature for primary cultivation *in vitro* [4]. The patient's hypothermia may have developed during the 4 months preceding her admission, providing an environment conducive to growth of the organism. This case suggests that *M. marinum* can grow in the human lung without producing symptoms.

In this case, the patient was extremely emaciated and had multiple risk factors for pulmonary mycobacterial infection. Low BMI is an independent risk factor for NTM-PD [11, 12]. Malnutrition increases susceptibility to pulmonary infection due to altered respiratory anatomy, mainly by reducing the clearance of inhaled pathogens from the airways as a result of respiratory muscle atrophy [6, 11, 12]. Low subcutaneous fat levels decrease production of adipokines, including leptin and adiponectin. Leptin is a hormone produced by white fat cells having immunomodulatory effects on T-lymphocyte differentiation, thereby enhancing phagocytosis and increasing tumour necrosis factor (TNF)-α production. In cases of malnutrition, cytokine is produced predominantly through the type 2 T-helper cell pathway, resulting in increased interleukin 4 production and decreased interferon (IFN)-γ production [5]. Because IFN-γ and TNF-α play critical roles in the defence against mycobacterial infection [6], individuals with anorexia nervosa would be expected to have an increased susceptibility to mycobacterial infection. It has been reported that patients with certain body morphotypes and immune phenotypes [13], corresponding to those of our patient, are more susceptible to NTM-PD. Furthermore, our patient had hypothermia on

admission, which may have conferred additional susceptibility because the primary culture of *M. marinum* isolated from the patient's sputum grew at ⩽32°C.

Anorexia nervosa sometimes presents with hypothermia [14] and the patient's anorexia nervosa-associated hypothermia may have contributed to the growth of *M. marinum* in her lower respiratory tract, leading to pulmonary infection. NTM-PD may produce few symptoms and the radiological changes are variable. Mycobacterium are not routinely cultured at ⩽32°C. Thus, *M. marinum* infection may be underdiagnosed under standard culture conditions. Physicians should consider *M. marinum* and culture samples for AFB at ⩽32°C, especially in patients with hypothermia or an underlying susceptibility to NTM-PD, especially in patients with apical cavitary disease, even if the patient has no known contact with fish or an aquatic environment.

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References

1 Brode SK, Daley CL, Marras TK. The epidemiologic relationship between tuberculosis and non-tuberculous mycobacterial disease: a systematic review. *Int J Tuberc Lung Dis* 2014; 18: 1370–1377.
2 Alcaide F, Amlerová J, Bou G, *et al.* How to: identify non-tuberculous *Mycobacterium* species using MALDI-TOF mass spectrometry. *Clin Microbiol Infect* 2018; 24: 599–603.
3 Kim SH, Shin JH. Identification of nontuberculous mycobacteria using multilocous sequence analysis of 16S rRNA, hsp65, and rpoB. *J Clin Lab Anal* 2018; 32: e22184.
4 Aubry A, Mougari F, Reibel F, *et al. Mycobacterium marinum. Microbiol Spectr* 2017; 5: doi:10.1128/microbiolspec.TNMI7-0038-2016.
5 Gibson D, Mehler PS. Anorexia nervosa and the immune system – a narrative review. *J Clin Med* 2019; 8: 1915.
6 McShane PJ, Glassroth J. Pulmonary disease due to nontuberculous mycobacteria: current state and new insights. *Chest* 2015; 148: 1517–1527.
7 Hotta M, Nagashima E, Takagi S, *et al.* Two young female patients with anorexia nervosa complicated by *Mycobacterium tuberculosis* infection. *Intern Med* 2004; 43: 440–444.
8 Hotta M, Minami Y, Itoda I, *et al.* A young female patient with anorexia nervosa complicated by *Mycobacterium szulgai* pulmonary infection. *Int J Eat Disord* 2004; 35: 115–119.
9 Lai CC, Lee LN, Chang YL, *et al.* Pulmonary infection due to *Mycobacterium marinum* in an immunocompetent patient. *Clin Infect Dis* 2005; 40: 206–208.
10 Velu PP, Fernandes SE, Laurenson IF, *et al.* Pulmonary *Mycobacterium marinum* infection: "fish tank granuloma" of the lung. *Scott Med J* 2016; 61: 203–206.
11 Griffith DE, Aksamit T, Brown-Elliott BA, *et al.* An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med* 2007; 175: 367–416.
12 Lake MA, Ambrose LR, Lipman MC, *et al.* "Why me, why now?" Using clinical immunology and epidemiology to explain who gets nontuberculous mycobacterial infection. *BMC Med* 2016; 14: 54.
13 Kartalija M, Ovrutsky AR, Bryan CL, *et al.* Patients with nontuberculous mycobacterial lung disease exhibit unique body and immune phenotypes. *Am J Respir Crit Care Med* 2013; 187: 197–205.
14 Miller KK, Grinpson SK, Ciampa J, *et al.* Medical findings in outpatients with anorexia nervosa. *Arch Intern Med* 2005; 165: 561–566.