Case report

A case of familial hot tub lung

Yoshihiro Kitahara[*], Yusuke Araki, Kikuo Nakano

Department of Respiratory Medicine, National Hospital Organization Kure Medical Center and Chugoku Cancer Center, 3-1 Aoyama-cho, Kure, 737-0023, Japan

ABSTRACT

Hot tub lung is a lung disease caused by *Mycobacterium avium* complex. We report the first case of familial hot tub lung appearing simultaneously in a husband and wife. Our case supports the consideration that hot tub lung is a hypersensitivity pneumonitis rather than an infectious lung disease. It also suggests that the state of hot tub lung changes seasonally depending on temperature variations, in a manner similar to summer-type hypersensitivity pneumonitis. This case demonstrates similarities between hot tub lung and summer-type hypersensitivity pneumonitis in regards to familial occurrence and seasonal changes in the disease state.

© 2016 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

It has recently been recognized that a hypersensitivity pneumonitis-like lung disease, which has been termed hot tub lung, can occur with exposure to *Mycobacterium avium* complex (MAC), composed of *M. avium* and *M. intracellulare* [1]. Despite an increasing number of reported hot tub lung cases, a familial case has never been reported [2,3]. Here, we describe the first case of familial hot tub lung occurring simultaneously in a husband and wife.

2. Case reports

A 79-year-old man and his 72-year-old wife were admitted to the National Hospital Organization Kure Medical Center and Chugoku Cancer Center (Kure, Japan) on 23 October 2013 with a chief complaint of dyspnoea on effort and cough, which had been present for one month. Although the husband had been treated for diffuse panbronchiolitis with a macrolide antibiotic and his wife had been treated for atypical pneumonia with a quinolone antibiotic, their symptoms did not improve. Their house was mouldy and wooden, and they had no pets. The husband had a history of hypertension and hyperuricemia and his wife had a history of colon cancer.

On admission, the husband's and wife's temperatures were 36.4 °C and 36.6 °C, respectively. Both patients had bilateral coarse crackles on auscultation of the lungs, an increased respiratory rate (30 breaths/min), and increased respiratory accessory muscle activity. The husband was hypoxemic with a percutaneous oxygen saturation (SpO_2) of 88% while the wife maintained a SpO_2 of 96% on room air. Bilateral ground glass opacities were observed on chest radiography and computed tomography in both patients (husband, Fig. 1a and b; wife, Fig. 2a and b). In addition, nodular shadows were present in both lung fields in the husband (Fig. 1a and b), and in right upper lung lobe (right S^2) in the wife (Fig. 2a and b).

The serum Krebs Von Den Lungen-6 (KL-6) levels were elevated at 839 U/mL and 721 U/mL in the husband and wife, respectively (normal range, <500 U/mL) (Fig. 3) [4]. The possibility of summer-type hypersensitivity pneumonitis was considered based on their symptoms, physical findings, radiological findings, and elevations in serum KL-6 levels [5,6]. However, the serum immunoglobulin G antibody against *Trichosporon asahii* was negative in both patients with a corrected absorbance index of 0.03 and 0.00 in the husband and wife, respectively.

Transbronchial lung biopsy revealed a small noncaseating granuloma with a lymphocytic infiltration of the alveoli. *M. intracellulare* was isolated from the bronchoalveolar lavage fluid of the husband, which was obtained from the right upper lung lobe (right S^3a) where the nodular shadow existed; however, MAC species were not isolated from the wife's bronchoalveolar lavage fluid obtained from the right S^2 segment where the nodular shadow existed. Their symptoms improved without any intervention within ten days after admission. Chest computed tomography findings at three weeks after admission showed improvement of the bilateral ground glass opacities in both patients (husband,

---

* Corresponding author.
  E-mail address: mayunachinase@gmail.com (Y. Kitahara).
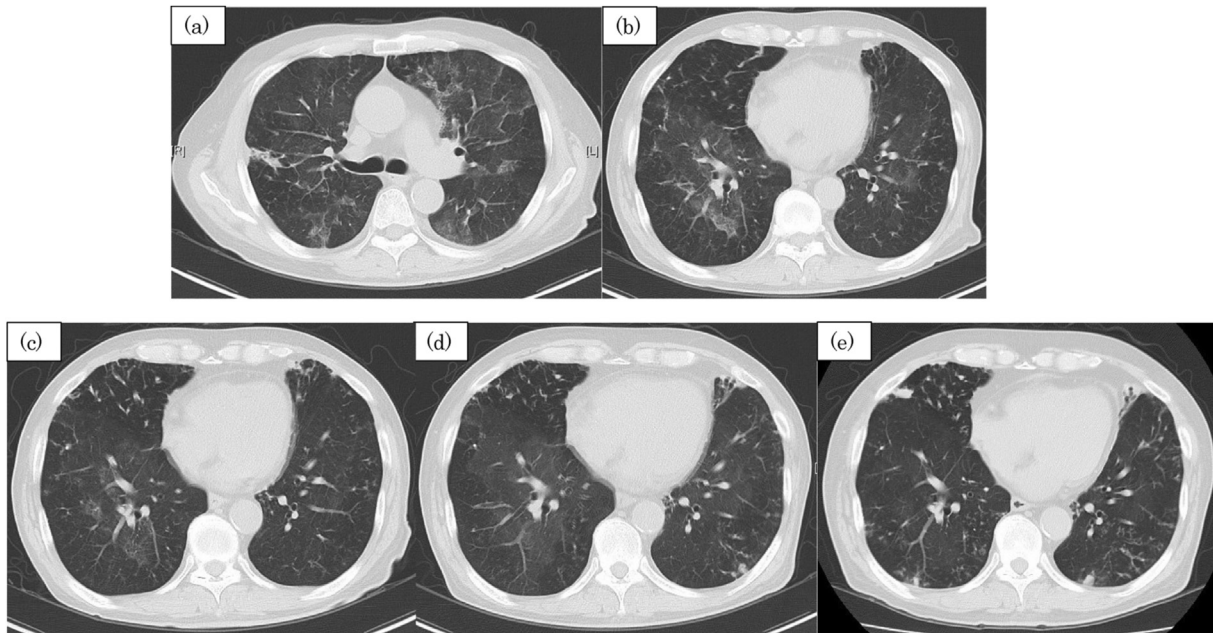
Fig. 1. Serial computed tomography (CT) findings in the husband. (a), (b); CT scan at first admission in October 2013 shows bilateral ground glass opacities and nodular shadows in both lung fields. (c); CT scan 3 weeks after the first admission shows remarkable improvement in the ground glass opacities. (d); CT scan at the second admission in June 2014 once again shows bilateral ground glass opacities. The bilateral nodular shadows have increased in comparison to the first admission and bronchiectasis has appeared in the left lingual lobe. (e); CT scan from August 2015 shows minimal persistence of the bilateral ground glass opacities. Diffuse bilateral nodular shadows persist.
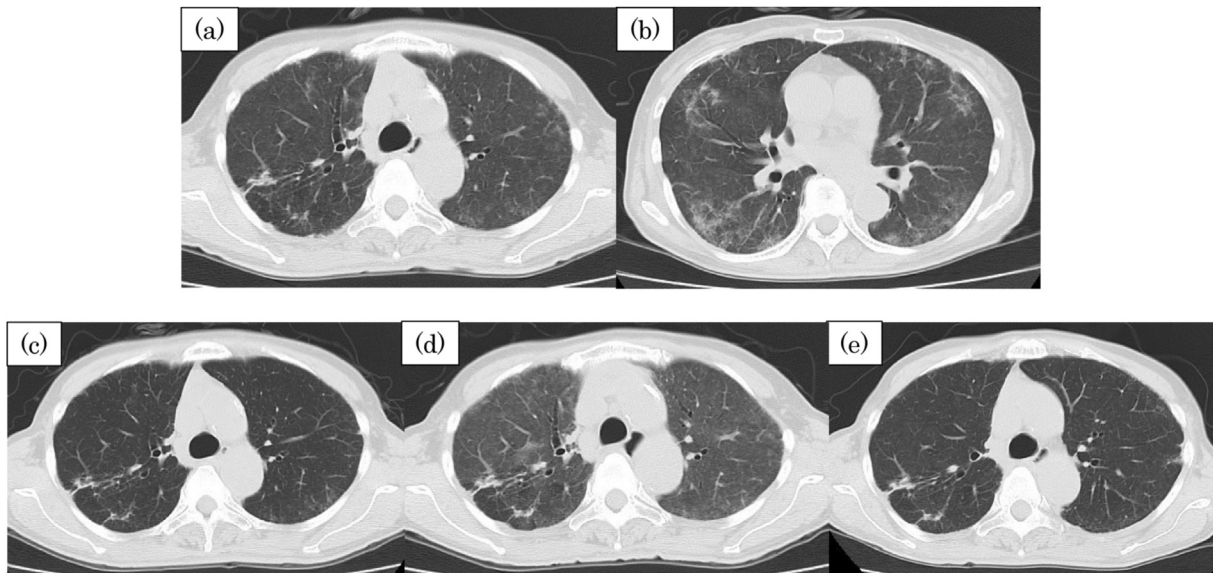

Fig. 2. Serial computed tomography (CT) findings in the wife. (a), (b); CT scan at first admission in October 2013 shows nodular shadows in the right upper lung lobe (right S^2) in addition to bilateral ground glass opacities. (c); CT scan 3 weeks after the first admission shows remarkable improvement in the ground glass opacities. (d); CT scan at the second admission in June 2014 once again shows the presence of bilateral ground glass opacities. (e); CT scan from August 2015 show minimal persistence of the bilateral ground glass opacities. The nodular shadows in the right S^2 have remained stable throughout the entire clinical course.

Fig. 1c; wife, Fig. 2c). Serum immunoglobulin A antibodies to the glycopeptidolipid core, derived from the *M. avium* complex by enzyme-linked immunosorbent assay (Capilia™ MAC Ab ELISA, TAUNS Laboratories, Inc., Izunokuni, Japan), were positive in the husband (corrected absorbance index >10.0), but not in his wife (corrected absorbance index <0.05) [7]. Although we recommended that the patients clean their house or move to a new house because of the suspicion of hot tub lung, they remained in the same house and did not clean it.

During the winter and spring, they had no respiratory symptoms, such as dyspnoea on effort or cough, and serum KL-6 levels declined (Fig. 3). However, on 18 June 2014, they were re-admitted to our hospital due to dyspnoea on effort and cough. Bilateral ground glass opacities were observed once again on chest
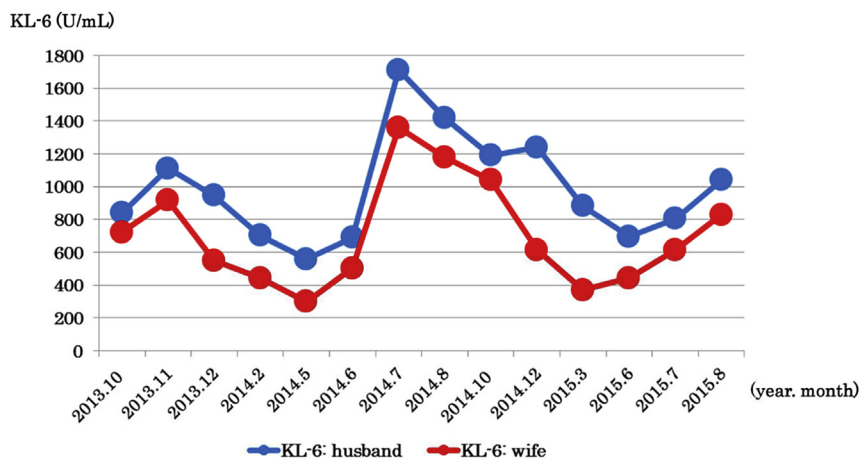
Fig. 3. Changes in serum Krebs Von Den Lungen-6 (KL-6) levels. In both the husband and wife, serum KL-6 levels declined from winter to spring and were elevated from summer to autumn.

radiography and computed tomography in both patients (husband, Fig. 1d; wife, Fig. 2d). In the husband, the bilateral nodular shadows had increased in comparison to the first admission, and bronchiectasis had appeared in left lingual lobe. The husband was hypoxic with a SpO$_2$ of 90% while the wife maintained a SpO$_2$ of 96% on room air. Although the wife recovered without any intervention, the husband required oxygen therapy and intravenous corticosteroids for several days for acute respiratory failure. The highest serum KL-6 level was 1710 U/mL in the husband and 1360 U/mL in the wife, and these levels declined gradually (Fig. 3). After the second discharge, we investigated their house for microorganisms on 8 August 2014. A mouldy rotten wood sample obtained from under the sink tested positive for *M. intracellulare* on polymerase chain reaction, and *M. avium* was cultured from a sludge sample

Fig. 4. Mouldy rotten wood from under the sink in the patients' house. A mouldy rotten wood sample obtained from under the sink tested positive for *M. intracellulare* on polymerase chain reaction.

from the bath overflow (Fig. 4).

Human leukocyte antigen (HLA) phenotypes were tested in both patients. HLA-A2 and HLA-DR4 were both positive in the husband and wife. Moreover, HLA-A24, HLA-B35, HLA-B60, and HLA-DR9 were positive in the husband, while HLA-A31, HLA-B46, HLA-B55, and HLA-DR8 were positive in the wife.

Since spring 2015, the patients began to open the windows in their house during the daytime hours. As of 19 August 2015, they had no respiratory symptoms and no decrease in SpO$_2$, despite an elevation in serum KL-6 levels at 1040 U/mL and 828 U/mL in the husband and wife, respectively. The appearance of bilateral ground glass opacities on computed tomography was minimal in both patients (husband, Fig. 1e; wife, Fig. 2e). The nodular shadow in the right S^2 segment of the wife's lung had not changed. The nodular shadows were widely spread in both lung fields of the husband, suggesting an exacerbation of MAC infectious disease.

Both patients provided informed consent for all study procedures mentioned above and for the publication of this study's findings.

3. Discussion

Although several cases of familial summer-type hypersensitivity pneumonitis have been previously reported [8], to the best of our knowledge, this is the first report of familial hot tub lung. We believe there are two particularly interesting points regarding this report.

First, there was a seasonal change in the state of hot tub lung; a seasonal trend in the occurrence of hot tub lung has not been previously reported. The respiratory symptoms and imaging findings in both patients worsened with the elevation of serum KL-6 levels from summer to autumn, but improved with a decline in serum KL-6 levels from winter to spring. Their clinical course was similar to that of summer-type hypersensitivity pneumonitis, during which seasonal variations in serum KL-6 levels are greater than those for other types of interstitial lung disease [5,6].

Nontuberculous mycobacteria can grow in a wide range of temperatures; the optimal temperature for most nontuberculous mycobacteria cultures is 28–37 °C [1]. Falkinham has reported that both *M. avium* and *M. intracellulare* can grow in natural or drinking water at 10–45 °C [9]. We speculated that because the average air temperature during winter in Kure, the city where they lived, was <10 °C, MAC could not grow optimally, leading to an improvement
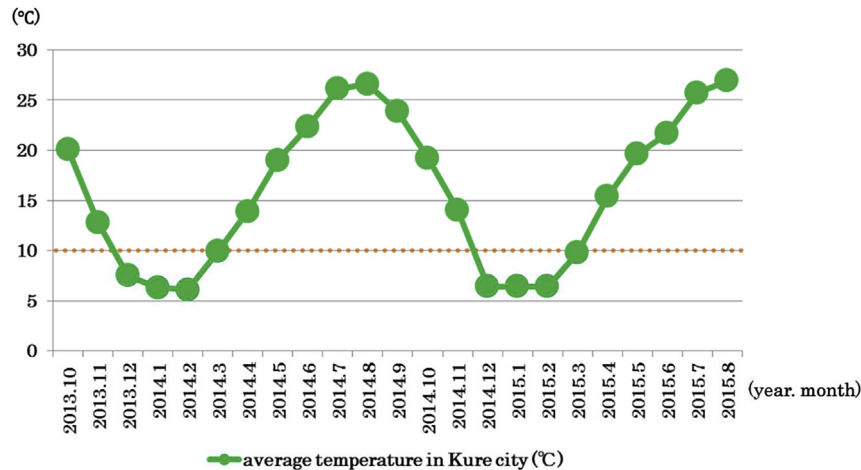
Fig. 5. Average air temperature in Kure city. The average air temperature was <10 °C (orange dotted line) during winter.

in hot tub lung during winter and spring (Fig. 5) [10]. Although the appearance of respiratory symptoms and the ground glass opacities in summer improved with the opening of the house's windows in our cases, it still remains unclear whether environmental improvements (i.e., house cleaning and room ventilation) can prevent the worsening of hot tub lung from summer to autumn; further studies are necessary to clarify this point.

The second interesting point was that hot tub lung occurred with MAC infection in the husband, but without MAC infection in the wife. Although the presence of nodular shadows was observed in similar lung regions in both patients, we diagnosed MAC infection only in the husband based on the isolation of MAC from bronchoalveolar lavage fluid and the results of Capilia™ MAC Ab ELISA. The fact that nodular shadows worsened only in the husband, but not in the wife, also supports our impression that MAC infection was not present in the wife. Because of this, we believe that hot tub lung can occur in the absence of MAC infection and that it is likely to be a hypersensitivity pneumonitis rather than an infectious lung disease as suggested in previous reports [11].

The degree of the respiratory disturbance was more severe in the husband than in the wife during both admissions. An exacerbation of MAC infectious disease present in the husband may partly explain this phenomenon. In addition, we speculate that chronic MAC infection in the lung might have led to continuous MAC exposure and severe respiratory failure in the husband because the human body temperature, 37 °C, is suitable for MAC growth year round. However, considering that the disease state and serum KL-6 levels showed similar seasonal changes in both patients, it may be the case that MAC infection does not necessarily worsen the severity of hot tub lung.

Previously, an association between HLA phenotypes and MAC infection have been reported. According to a study by Takahashi and colleagues, the frequencies of HLA-A33, HLA-DR6 antigens, and haplotype A33-B44-DR6 were significantly increased in pulmonary MAC patients compared to that of a control population [12]. In a study by Kubo and colleagues, HLA-DR6 and HLA-DQ4 were significantly more frequent in patients with MAC infection than in controls, and HLA-A26 was significantly more frequent in deteriorated patients than in controls [13]. In contrast, HLA-A2 and HLA-DR4 were positive in both the husband and wife in our case. The significance of our patients' HLA findings may reflect a difference in the disease mechanisms between MAC infection and hot tub lung; further studies are warranted to clarify the association between hot tub lung and HLA phenotypes.

Based on our case, clinicians should be cognizant of the fact that

similar to summer-type hypersensitivity pneumonitis, hot tub lung can occur simultaneously in family members, and the disease state can change seasonally depending on temperature variations.

Conflict of interests

There are no conflicts of interest to declare.

Funding information

No funding was received for this study.

References

[1] D.E. Griffith, T. Aksamit, B.A. Brown-Elliott, A. Catanzaro, C. Daley, F. Gordin, et al., An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases, Am. J. Respir. Crit. Care Med. 175 (4) (2007) 367–416.

[2] V. Hanak, S. Kalra, T.R. Aksamit, T.E. Hartman, H.D. Tazelaar, J.H. Ryu, Hot tub lung: presenting features and clinical course of 21 patients, Respir. Med. 100 (4) (2006) 610–615.

[3] T.K. Marras, R.J. Wallace Jr., L.L. Koth, M.S. Stulbarg, C.T. Cowl, C.L. Daley, Hypersensitivity pneumonitis reaction to Mycobacterium avium in household water, Chest 127 (2) (2005) 664–671.

[4] N. Kohno, S. Kyoizumi, Y. Awaya, H. Fukuhara, M. Yamakido, M. Akiyama, New serum indicator of interstitial pneumonitis activity. Sialylated carbohydrate antigen KL-6, Chest 96 (1) (1989) 68–73.

[5] M. Ando, M. Suga, Y. Nishiura, M. Miyajima, Summer-type hypersensitivity pneumonitis, Intern. Med. 34 (8) (1995) 707–712.

[6] H. Ohnishi, S. Miyamoto, S. Kawase, T. Kubota, A. Yokoyama, Seasonal variation of serum KL-6 concentrations is greater in patients with hypersensitivity pneumonitis, BMC Pulm. Med. 14 (2014) 129, http://dx.doi.org/10.1186/1471-2466-14-129.

[7] S. Kitada, K. Kobayashi, S. Ichiyama, S. Takakura, M. Sakatani, K. Suzuki, et al., Serodiagnosis of Mycobacterium avium-complex pulmonary disease using an enzyme immunoassay kit, Am. J. Respir. Crit. Care Med. 177 (7) (2008) 793–797.

[8] A. Nakajima, T. Saraya, T. Mori, R. Ikeda, T. Sugita, T. Watanabe, et al., Familial summer-type hypersensitivity pneumonitis in Japan: two case reports and review of the literature, BMC Res. Notes 6 (2013) 371, http://dx.doi.org/10.1186/1756-0500-6-371.

[9] J.O. Falkinham 3rd, Mycobacterial aerosols and respiratory disease, Emerg. Infect. Dis. 9 (7) (2003) 763–767.

[10] Japan Meteorological Agency website. http://www.jma.go.jp/jma/indexe.html. Accessed September 03, 2015.

[11] J. Embil, P. Warren, M. Yakrus, R. Stark, S. Corne, D. Forest, et al., Pulmonary illness associated with exposure to Mycobacterium-avium complex in hot tub water. Hypersensitivity pneumonitis or infection? Chest 111 (3) (1997) 813–816.

[12] M. Takahashi, A. Ishizaka, H. Nakamura, K. Kobayashi, M. Nakamura, M. Namiki, et al., Specific HLA in pulmonary MAC infection in a Japanese population, Am. J. Respir. Crit. Care Med. 162 (1) (2000) 316–318.

[13] K. Kubo, Y. Yamazaki, M. Hanaoka, H. Nomura, K. Fujimoto, T. Honda, et al., Analysis of HLA antigens in Mycobacterium avium-intracellulare pulmonary infection, Am. J. Respir. Crit. Care Med. 161 (4 Pt 1) (2000) 1368–1371.