Abstract  [Objective] The incidence rate of nontuberculous mycobacterial (NTM) infection has been increasing globally in recent years. However, reports of osteoarticular NTM infection are relatively rare. We report the characteristic clinical features of patients with osteoarticular NTM infection. [Patients and Methods] We examined 14 patients with osteoarticular NTM infection (mean age, 68 years) were treated in our hospital in the 20 years between 1995 and 2015. [Results] The rate of osteoarticular NTM infection in whole osteoarticular infection during the same period in our hospital was 2.7%. The NTM species isolated from the 14 patients included *Mycobacterium avium* (n = 7), *M. intracellulare* (n = 5), *M. fortuitum* (n = 1), and *M. kansasii* (n = 1). Twelve patients had spinal involvements, and their levels were categorized as thoracic (n = 3), lumbar (n = 4), thoracolumbar (n = 1), and cervicothoracic (n = 4), with an average number of affected vertebrae of 4.4. Nine patients had pulmonary lesions, including fibrocavitary (n = 5) and nodular/bronchiectatic types (n = 4). Nine patients had lesions in sites other than the spinal and pulmonary regions, including the skin (n = 6), rib (n = 2), ilium (n = 2), humerus (n = 2), ulna (n = 1), wrist (n = 1), knee joint (n = 1), femur (n = 2), tibia (n = 1), toe (n = 1), and kidney (n = 1). In the initial examination, 11 patients were misdiagnosed, which delayed the final diagnosis in 7 patients. Six patients received chemotherapy with rifampicin, ethambutol, and clarithromycin, and 8 patients received other macrolide-based therapy. Five patients underwent surgical treatments in former hospitals, and 8 patients underwent surgical treatments (including salvage surgeries) in our hospital. With regard to outcome, 9 patients achieved healing, 2 patients with relapse were healed after retreatment, 1 patient was undergoing treatment, 1 patient had interrupted treatment, and 1 patient died during the treatment period. [Discussion] Osteoarticular NTM infection presented widely spread lesions in the spine and other various locations, mostly developed as a part of disseminated infection. Most patients were aged or immunosuppressed, but some patients were healthy individuals with no relevant medical history. Thus, if a patient is diagnosed with disseminated NTM infection, examination for possible lesions in other sites, including the bone and joint, should be performed. Cutaneous lesions, including subcutaneous abscess, were also characteristic. It is worth mentioning that such lesions can develop even under chemotherapy. Given the increasing trend in the overall incidence of NTM infection, awareness that NTM is a causative organism of osteoarticular infection is important.

Key words: Nontuberculous mycobacterial infection, Osteomyelitis, Spondylitis, Arthritis, Disseminated infection

Introduction

The incidence of nontuberculous mycobacterial (NTM) infection has been increasing globally, including Japan. Its prevalence in Japan is estimated to be 33–65 cases per 100,000 individuals, which is considered one of the highest in the world\(^1\). The pathophysiological mechanism and treatment of NTM have not been clarified yet. Especially osteoarticular NTM infection, which is usually reported as a part of the pathology of disseminated NTM infection, is relatively rarely reported in case series. We report the characteristic clinical features of 14 patients with osteoarticular NTM infection who were treated in our department.

Patients and Methods

We examined 14 patients with osteoarticular NTM infection (age: range, 52–86 years; mean, 68 years) who were treated in our department within the 20 years between 1995 and 2015. Seven of the 14 patients were male. Diagnosis of osteoarticular NTM infection was made based on the detection of bacteria

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ASSOCIATION BETWEEN A pMAH135 PLASMID AND THE PROGRESSION OF PULMONARY DISEASE CAUSED BY *MYCOBACTERIUM AVIUM*

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Abstract  [Background] Pulmonary disease caused by nontuberculous mycobacteria has a variable clinical course. Although this is possibly the result of not only host factors, but also bacterial factors, many questions remain to be answered regarding these manifestations. [Methods] To assess the relationship between the progression of pulmonary *Mycobacterium avium* disease and bacterial factors, we performed variable number tandem repeats (VNTR) typing analysis of *M. avium* tandem repeats (MATR) in *M. avium* isolates from 46 patients with different clinical courses, and furthermore, examined the association between disease progression and a pMAH135 plasmid derived from *M. avium*. [Results] In patients whose treatment was initiated because of worsened chest radiograph findings and/or clinical symptoms within 18 months after being diagnosed with pulmonary *M. avium* disease, the detection rate of 6 genes located in pMAH135 was 35.3–47.1% for 17 isolates. However, in untreated patients with a stable condition, these rates were 10.3–13.8% in 29 isolates. MATR-VNTR typing analysis showed that isolates from patients with worsened disease and those with stable disease are clustered differently. In cluster II, the number of isolates from patients with worsened disease was higher than that from patients with stable disease (p=0.019), and furthermore, the number of isolates carrying pMAH135 genes was higher than that not carrying pMAH135 genes (p≤0.001). [Conclusion] These results indicate an association between the progression of pulmonary *M. avium* disease and pMAH135. The presence of pMAH135 genes might be a useful prognostic indicator for pulmonary *M. avium* disease and may serve as one criterion for treatment initiation.

Key words: *Mycobacterium avium* subsp. *hominissuis*, Disease progression, Variable number tandem repeats, pMAH135 plasmid

Introduction

Nontuberculous mycobacteria (NTM) infection is thought to be caused by NTM residing in the environment, including residential soil or bathrooms1,2,3, and the prevalence of NTM disease is increasing worldwide. In Japan, the prevalence per 100,000 population has increased greatly from 0.82 in 1971 to 5.9 in 2001.4 Today, the rate is estimated to be around 15.0, which is substantially higher than the rates seen in the United States and Europe.4-6

Pulmonary disease caused by NTM is divided into two major disease types, the nodular bronchiectatic type and the fibrocavitary type, with the former being more prevalent.7-9 However, the mechanisms involved in the development and exacerbation of pulmonary NTM disease have yet to be elucidated. Although some patients remain stable without treatment, others have deteriorating symptoms despite drug therapy, demonstrating the disease’s diverse clinical course.8-9 Therefore, it would be helpful from the viewpoint of treatment if the clinical course of pulmonary NTM disease could be predicted. The establishment of pulmonary NTM disease or the variable clinical course involves bacterial factors in addition to host-related risk factors including decreases in the levels of estrogen, a major female sex hormone, or the presence of polymorphisms in *NRAMP1* (encoding natural resistance-associated macrophage protein 1)10,11.

With regard to mycobacterial plasmids, previous studies isolated pVT212 and pLR740 from *M. avium*. Given their relatively small size of 4.8–16 kb and their lack of virulence genes, the significance of these plasmids is currently unknown. Our previous study has shown the presence of a circular plasmid derived from *M. avium* strain TH135, designated pMAH135.13 This novel plasmid codes genes that are associated with pathogenicity of mycobacteria and its resistance

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TUBERCULOSIS AND LUNG CANCER

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Abstract The occurrence of pulmonary tuberculosis (PTB) and lung cancer as comorbidities has been extensively discussed in many studies. In the past, it was well known that lung cancer is a specific epidemiological successor of PTB and that lung cancer often develops in scars caused by PTB. In recent years, the relevance of the two diseases has drawn attention in terms of the close epidemiological connection and chronic inflammation-associated carcinogenesis. In Japanese case series studies, most lung cancer patients with tuberculous sequelae received supportive care alone in the past, but more recently, the use of aggressive lung cancer treatment is increasing. Many studies on PTB and lung cancer as comorbidities have revealed that active PTB is noted in 2–5% of lung cancer cases, whereas lung cancer is noted in 1–2% of active PTB cases. In such instances of comorbidity, many active PTB cases showed Type II (non-extensively cavitary disease) and Spread 2–3 (intermediate–extensive diseases) on chest X-rays, but standard anti-tuberculosis treatment easily eradicates negative conversion of sputum culture for M. tuberculosis; lung cancer cases were often stage III–IV and squamous cell carcinoma predominant, and the administration of aggressive treatment for lung cancer is increasing. The major clinical problems associated with PTB and lung cancer as comorbidities include delay in diagnosis (doctor’s delay) and therapeutic limitations. The former involves two factors of radiographic interpretation: the principles of parsimony (Occam’s razor) and visual search; the latter involves three factors of lung cancer treatment: infectivity of M. tuberculosis, anatomical limitation due to lung damage by tuberculosis, and drug–drug interactions between rifampicin and anti-cancer drugs, especially molecularly targeted drugs. The comorbidity of these two diseases is an important health-related issue in Japan. In the treatment of PTB, the possibility of concurrent lung cancer should be kept in mind, while in the treatment of lung cancer, the possibility of concurrent PTB should also be considered.

Key words: Tuberculosis, Lung cancer, Comorbidity, Epidemiology, Scar cancer, Doctor’s delay, Therapeutic limitation

1. Introduction

The occurrence of pulmonary tuberculosis (PTB) and lung cancer as comorbidities was first described in an autopsy record by Bayle in 1810, followed by the first case report by Penard in 1846, and has subsequently been discussed in many studies. In Japan, the comorbidity of these two diseases has drawn attention since the mid-20th century. Japan is a middle-ranked country for PTB prevalence, and lung cancer is the leading cause of cancer death in Japan. Furthermore, the proportion of elderly patients affected by both diseases is high. Therefore, the comorbidity of these two diseases is an important issue in Japan.

In this review, we introduce epidemiological studies focusing on the relationship between previous tuberculosis and lung cancer development, as well as etiological studies investigating the relationship between tuberculosis-related lesions and lung carcinogenesis. We then document case series studies in terms of various pathological conditions related to the comorbidity of PTB and lung cancer.

2. Epidemiological studies

In epidemiological studies of lung cancer in patients with previous tuberculosis, long-term surveys in England/Wales and Australia since the early 1900s have shown that the overall mortality rate for “tuberculosis + lung cancer” was constant, at approximately 20%. As this close relationship was not seen between other diseases, lung cancer appears to be a specific epidemiological successor of PTB. It was assumed that the reduced number of tuberculosis deaths in young individuals may be associated with the increased incidence of lung cancer in elderly patients. It is unclear...