Mycobacterium tuberculosis infection in cancer patients at a tertiary care cancer center in Japan

J Infect Chemother 20 (2014) 213–216

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Original article

Mycobacterium tuberculosis infection in cancer patients at a tertiary care cancer center in Japan

Takahiro Fujita, MD [a,b,*], Masahiro Endo, MD, PhD [c], Yoshiaki Gu, MD [d], Tomoaki Sato [e], Norio Ohmagari, MD, MSc [f]

[a] Department of Infectious Disease, Tokyo Women's Medical University, Tokyo, Japan
[b] Department of Infectious Diseases, Shizuoka Cancer Center, Nagaizumi, Shizuoka, Japan
[c] Division of Diagnostic Radiology, Shizuoka Cancer Center, Nagaizumi, Shizuoka, Japan
[d] Department of Regional Cooperation for Infectious Diseases, Tohoku University Graduate School of Medicine, Sendai, Japan
[e] Department of Clinical Laboratory, Yamagata University Hospital, Yamagata, Japan
[f] Disease Control and Prevention Center, National Center for Global Health and Medicine Hospital, Tokyo, Japan

ARTICLE INFO

Article history:
Received 12 May 2013
Received in revised form
10 October 2013
Accepted 4 November 2013

Keywords:
Tuberculosis
Cancer
Anti-tumor agents
Immunocompromised host

ABSTRACT

The characteristics of active tuberculosis in cancer patients in Japan and the effects of this infection on cancer treatment have not yet been clarified. The records of all consecutive patients with microbiologically documented *Mycobacterium tuberculosis* infection diagnosed between September 2002 and March 2008 at Shizuoka cancer center (a 557-bed tertiary care cancer center in Japan) were reviewed. There were 24 cancer patients with active tuberculosis during the study period. Of these, 23 had solid-organ tumors, and the most common site of the underlying malignancy was the lung. Most of the patients had pulmonary tuberculosis. Among 15 patients followed up for more than 2 months prior to the diagnosis of pulmonary tuberculosis, 12 had healed scars suggestive of old tuberculosis lesions, as shown by chest imaging obtained at the time of the initial evaluation. Discontinuation of cancer therapy or more than a month's delay in surgery occurred in 10 patients with pulmonary tuberculosis. Development of active tuberculosis can delay cancer treatment in Japanese centers. Cancer patients with scars suggestive of old tuberculosis disease lesions as shown by chest imaging should be screened for active tuberculosis and carefully followed up. In some cases, prophylactic treatment should be considered.

1. Introduction

Malignancy is a known risk factor for the development of active tuberculosis [1]. At the same time, immunosuppressive anti-tumor treatment is widely used among cancer patients in those countries with high rates of tuberculosis infection. Previous reports from the United States, which has a low prevalence of tuberculosis infection, showed that US-born cancer patients with an underlying solid tumor had the same tuberculosis rate as US-born patients without cancer [2–4]. Because the incidence of tuberculosis is affected by the prevalence of tuberculosis in the cancer patient population, we need to consider the locally specific data to establish the ideal strategies for screening, early detection, and treatment of latent tuberculosis infections. However, the characteristics of active tuberculosis in cancer patients in Japan and the effects of this infection on cancer treatment have not yet been clarified. This is partly because of the absence of infectious disease departments in Japanese cancer center hospitals. Here, we describe the characteristics of cancer patients with active *Mycobacterium tuberculosis* infection at a tertiary cancer center hospital in Japan, and consider the suitable management strategies for cancer patients in a country that is intermediately endemic for tuberculosis.

2. Patients and methods

2.1. Definitions

We reviewed the records of all consecutive patients with microbiologically documented *M. tuberculosis* infection

* Corresponding author. Department of Infectious Disease, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan. Tel.: +81 3 3353 8111; fax: +81 3 3358 8995.
E-mail address: fujita.takahiro@twmu.ac.jp (T. Fujita).

1341-321X/$ – see front matter
http://dx.doi.org/10.1016/j.jiac.2013.11.005

diagnosed between September 2002 and March 2008 at the Shizuoka cancer center (a 557-bed tertiary care cancer center in Japan). The patients were identified from a microbiology database previously established for patients with *M. tuberculosis* isolated from any body site. Patient information was obtained from electronic medical records.

2.2. Definition of tuberculosis patients

Microbiologically documented *M. tuberculosis* infection was defined when clinical specimens were found to be positive by culture or polymerase chain reaction (PCR; Roche AMPLICOR MTB test®).

2.3. Neutropenia and lymphopenia

Neutropenia was defined as an absolute neutrophil count lower than 500/μL at the time when samples growing *M. tuberculosis* were obtained. Lymphopenia was defined as an absolute lymphocyte count of lower than 500/μL at the time when samples growing *M. tuberculosis* were obtained.

2.4. Systemic corticosteroid use

Systemic corticosteroid use was defined at a dose of more than 1 mg/(kg day) of prednisone or an equivalent dose of another corticosteroid given within the 4 weeks before diagnosis of infection.

2.5. Radiographic findings

Radiographic findings were reviewed by 2 investigators (M. Endo and T. Fujita), including a radiology specialist (M. Endo).

2.6. Deaths attributable to Mycobacterium infections

Deaths were attributed to *M. tuberculosis* if the patient died with progressive tuberculosis within 4 weeks of infection diagnosis.

Table 1
Patient characteristics.

Patient characteristics	No. of patients (%)
Underlying cancer	
Lung	6 (25)
Esophagus	3 (13)
Colon	3 (13)
Stomach	2 (8)
Prostate	2 (8)
Pharynx	2 (8)
Pancreas	2 (8)
Breast	2 (8)
Thyroid	1 (4)
Non-Hodgkin lymphoma	1 (4)
Site of infection	
Lung	21 (88)
Lymph node	2 (8)
Intestine	1 (4)
Clinical presentation	
Fever	11 (46)
Sputum	11 (46)
Cough	8 (33)
Asymptomatic	7 (29)
Asymptomatic and abnormal chest radiograph	6 (25)
Weight loss	4 (17)
Dyspnea	3 (13)
Lymph node adenopathy	2 (8)

3. Results

3.1. Patients and disease characteristics (Table 1)

There were 24 cancer patients with active tuberculosis during the period studied. Eighteen patients (75%) were men and 6 (25%) were women. The median age was 72 years (range, 56–89 years). Twenty-three patients had solid-organ tumors. The one patient with hematological malignancy had non-Hodgkin lymphoma. The most common site for the underlying malignancy was the lung (6 patients). Four patients (17%) had received systemic corticosteroids. Four patients had lymphopenia, and 1 had concomitant neutropenia. Twenty-one patients (88%) had pulmonary tuberculosis, 2 (8%) had tuberculous lymphadenitis, and 1 (4%) had intestinal tuberculosis. Among symptomatic patients, the most common symptoms were fever (11 patients) and sputum (11 patients). The tuberculosis that developed in 7 patients during or within 30 days of chemotherapy was found to be pulmonary tuberculosis. No patients had ever received anti-tuberculosis drugs. Seven patients were asymptomatic, and 6 of these only had abnormal findings on plain chest radiography or pulmonary computed tomography (CT). One patient was found on CT to have lymph node adenopathy, which was considered metastatic pancreas cancer. The antimicrobial susceptibility status of 21 *M. tuberculosis* isolates was available. All strains tested were found to be susceptible to isoniazid, rifampin, pyrazinamide, and ethambutol. Among 21 pulmonary tuberculosis patients, 16 were diagnosed by sputum, 3 by bronchoalveolar lavage (BAL), 1 by both sputum and BAL, and 1 by lung biopsy. Twelve patients (54%) had smear-positive sputum. Of the 7 patients who developed active tuberculosis during or within 30 days of chemotherapy, 4 (57%) were smear-positive.

Fifteen patients received follow-up for more than 2 months prior to the diagnosis of tuberculosis (range, 2–35 months). Of these patients, 12 (12/15: 80%) had healed scars suggestive of old tuberculosis lesions as shown by plain chest radiography or CT obtained at initial evaluation at presentation to our hospital.

All 7 patients who developed active tuberculosis during or within 30 days of chemotherapy had pulmonary tuberculosis. Of these patients, 5 had healed scars suggestive of old tuberculosis lesions, 1 had chronic bronchitis, and 1 patient had old nonspecific pleurisy on chest radiography or chest CT taken before the initiation of chemotherapy. Six patients were diagnosed with simultaneous active tuberculosis and malignancy. Three patients had been followed by another institute for cancer and were referred to our hospital for further investigation, where they were diagnosed with tuberculosis. Of the 12 patients who had healed scars suggestive of old tuberculosis lesions, 7 (58%) had no history of tuberculosis.

Death was attributed to *M. tuberculosis* diseases in 1 patient who developed the disease during chemotherapy for pancreatic cancer, and then developed acute respiratory distress syndrome. Delay of cancer therapy (discontinuation of chemotherapy, or more than a month's delay in surgery) was necessary in 10 patients with pulmonary tuberculosis.

4. Discussion

To the best of our knowledge, this is the first report in English to detail the characteristics of patients with tuberculosis and cancer in a Japanese tertiary cancer center hospital. The present study demonstrated that patients with tuberculosis at our Japanese tertiary care cancer center who had lung cancer as their most common underlying disease were older than similar patients in the United States [2,3]. Seven (29%) patients were asymptomatic and had no identifiable risk factors other than malignancy such as corticosteroid administration. During initial evaluation at our institute, we

commonly observed healed scars suggestive of old tuberculosis lesions. Thirteen (54%) patients were smear-positive and had to be transferred to other specialty tuberculosis hospitals, as specified by Japanese law. In some patients, cancer therapy was delayed during tuberculosis treatment.

While lung cancer was the most common underlying malignancy noted at our institute, several other previous reports, in similar institutes, describe a more diverse set of underlying malignancies. In Korea, for example, the most common underlying malignancy has been shown to be stomach cancer [5,6], while in the United States, hematological malignancies were the most common underlying malignancy [2]. These differences might depend on the type of cancer patients treated at each institute. In Japan, for instance, 1% of lung cancer patients also have pulmonary tuberculosis. This reported rate is 25 times higher than that in the general population [7]. This value could also be influenced by repeat radiographic evaluation of lung cancer patients, which could increase the number of these cases being reported.

Patients diagnosed with active tuberculosis at our institute were, on average, older than their counterparts in the United States [2,3]. This reflects the fact that half a century ago, tuberculosis was an endemic disease in Japan. In European and North American countries, tuberculosis is a disease of immigrants, especially those emigrating from endemic areas. By contrast, in Japan, a rapidly developing country over the last few decades, tuberculosis is a disease of elderly people. The affected individuals survived the endemic era before the introduction of anti-tuberculosis drugs. Therefore, in Japan, tuberculosis patients with cancer share characteristics with other tuberculosis patients in Japan: they are of advanced age and their pulmonary tuberculosis is a reactivation, often of a disease that has been previously "healed". The estimated prevalence of tuberculosis infection in the aging Japanese population (>70 years) has been estimated at >60%. This value is increasing with advancing age and shows a rapid decline in the generation born after 1945 (following the end of World War II), a positive turning point in Japanese public health status [8].

The healed scar suggesting previous tuberculosis on chest radiography was characteristic of cancer patients with active tuberculosis at our institute. Because many older patients do not present with respiratory symptoms [9], radiographical evaluation is critical to detecting pulmonary tuberculosis in patients with cancer. In Korea, it has been reported that most cancer patients with pulmonary tuberculosis have healed scars suggesting previous tuberculosis on chest radiography [5,6]. In a case series where Kim reported the characteristics of solid-organ malignancy patients with pulmonary tuberculosis, healed scars suggesting previous tuberculosis on chest radiography were found in most patients, regardless of whether they had received anti-TB chemotherapy [6]. This suggests that the disease was caused by reactivation of latent infection. However, patients not receiving anti-cancer chemotherapy were also found to have healed scars. Thus, this reactivation may reflect the immunodeficiency effect of the malignant disease itself. In this report by Kim, the proportion of patients who received anti-cancer chemotherapy among 305 patients with healed scars is unclear. It is known that latent tuberculosis patients with healed scars have a high risk of reactivation [10]. The additive effect of anti-cancer chemotherapy on reactivation of tuberculosis in solid-organ cancer patients with old radiographic lesion is not well defined.

The characteristics of tuberculosis patients described in this report are suggestive of high-risk patients who need careful estimation of tuberculosis risk and assessment of the necessity of latent tuberculosis treatment before or during immunosuppressive therapy of their malignant diseases. In the present study, we found that old radiographic changes, identified at initial evaluation and before commencement of cancer treatment, were common in Japanese tuberculosis patients. Therefore, we propose that it is important to carry out pulmonary radiographic evaluation prior to treatment. Changes in chest radiography findings, especially in case of fibronodular disease, is a risk factor for the development of active tuberculosis [11]. Cancer patients exhibiting these radiographic changes should be considered for further evaluation through interferon-gamma release assays (IGRA) or treatment of latent tuberculosis infection (LTBI) infection before or during anti-cancer chemotherapy. Guidelines issued by the Japanese Society for Tuberculosis regarding treatment for LTBI do not effectively discuss possible risk factors in cancer patients for developing active tuberculosis nor do they indicate that cancer patients are possible candidates for LTBI treatment [12]. The diversity in the immunocompromised status among cancer patients makes it challenging to determine a common strategy for diagnosis and treatment of LTBI across all types of cancer. Therefore, more elderly cancer patients, for example, could be further evaluated according to other individual risk factors such as concomitant diabetes or corticosteroid administration to best determine their need for LTBI treatment. It is unclear whether the benefit of treating latent tuberculosis infection exceeds the risk of drug side effects in cancer patients receiving anti-cancer chemotherapy. Tuberculosis reactivation during anti-cancer chemotherapy can be safely treated [5]. Therefore, close observation of patients to ensure early detection is also a clinically relevant option.

Our study showed that tuberculosis could be a reason for the delay in cancer treatment. Because the Japanese law mandates that smear-positive patients be transferred to a tuberculosis ward, surgery and chemotherapy in such patients were postponed until their discharge. Smear-negative patients and smear-positive patients who were discharged from tuberculosis wards were treated at our institute by physicians specializing in infectious diseases. Anti-cancer therapy was restarted only after at least 2 weeks, when infectivity is considered to be decreased. If anti-cancer chemotherapy or surgery could be safely postponed, we withheld anti-cancer therapy until 2 months after initial anti-tuberculosis treatment was completed. Although the prognostic effect is unclear, this approach might negatively affect prognosis because treatment delay might result in cancer progression. Early re-initiation of cancer therapy is crucial and can be achieved by coordination between infectious disease specialists and oncologists. To reduce the delay in cancer treatment for tuberculosis patients, all cancer hospitals in Japan should have an infectious disease department.

This study has several limitations. First, this is a retrospective study at a single center, with a relatively small number of patients. Prospective multicenter investigations in cancer hospitals in Japan are required to allow for better comparison between nationwide tuberculosis epidemiology and that of cancer. Furthermore, there was a lack of information on purified protein derivative treatment, IGRA performance, and Bacillus Calmette–Guerin vaccination status, because patients were recruited on the basis of microbiological examination. Although these data are not essential for the diagnosis of active tuberculosis, cases diagnosed only on the basis of clinical suspicion might not be included in this study. Finally, we did not collect data regarding cancer progression, such as TNM stage and histopathological classification. Cancer progression is associated with tuberculosis development because patients with advanced cancer have compromised immunity. There are currently no global guidelines to distinguish between the terms "advanced" and "non-advanced" cancer with regard to immunosuppression status. Hence, the risk of tuberculosis reactivation associated with cancer progression must be assessed on a case-by-case basis using best clinical judgment.

In conclusion, we believe that cancer patients presenting evidence of healed scars on chest images, suggestive of old tuberculosis disease lesions, should be screened for active tuberculosis and carefully followed up. In some cases, prophylactic treatment should be considered. Further prospective studies are needed to clarify whether high-risk cancer patients would benefit from screening, including IGRA, and from treatment of latent tuberculosis infection before or during their anti-cancer treatment.

Conflict of interest

All authors declare no conflicts of interest.

Acknowledgments

Part of this study was presented as a poster (poster number K-1406) at the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)/Infectious Disease Society of America (IDSA) annual meeting on October 2008, in Washington DC, USA.

References

[1] Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society. MMWR Recomm Rep 2000;49:1–51.
[2] Aisenberg GM, Jacobson K, Chemaly RF, Rolston KV, Raad II, Safdar A. Extrapulmonary tuberculosis active infection misdiagnosed as cancer: *Mycobacterium tuberculosis* disease in patients at a Comprehensive Cancer Center (2001–2005). Cancer 2005;104:2882–7.
[3] De La Rosa GR, Jacobson KL, Rolston KV, Raad II, Kontoyiannis DP, Safdar A. *Mycobacterium tuberculosis* at a comprehensive cancer centre: active disease in patients with underlying malignancy during 1990–2000. Clin Microbiol Infect 2004;10:749–52.
[4] Kamboj M, Sepkowitz KA. The risk of tuberculosis in patients with cancer. Clin Infect Dis 2006;42:1592–5.
[5] Kim DK, Lee SW, Yoo C-G, Kim YW, Han SK, Shim Y-S, et al. Clinical characteristics and treatment responses of tuberculosis in patients with malignancy receiving anticancer chemotherapy. Chest 2005;128:2218–22.
[6] Kim H-R, Hwang SS, Ro YK, Jeon CH, Ha DY, Park SJ, et al. Solid-organ malignancy as a risk factor for tuberculosis. Respirology 2008;13:413–9.
[7] Sugino K, Homma S, Miyamoto A, Takaya H, Sakamoto S, Kawabata M, et al. Clinical analysis of lung cancer complicated by pulmonary tuberculosis. Jpn J Lung Cancer 2007;47:97–103.
[8] Statistics of TB. Available at: http://www.jata.or.jp/rit/rj/data_tp.html [accessed 18.09.08].
[9] Ohmori M, Wada M, Mitarai S, Hoshino H, Yanai H, Yoshiyama T, et al. Studies on the process of discovery of the hospitalized elderly TB patients. Kekkaku 2004;79:243.
[10] Groth-Petersen E, Knudsen J, Wilbek E. Epidemiological basis of tuberculosis eradication in an advanced country. Bull World Health Organ 1959;21:5–49.
[11] Landry J, Menzies D. Preventive chemotherapy. Where has it got us? Where to go next? Int J Tuberc Lung Dis 2008 Dec;12:1352–64.
[12] Kato S, Nishimura N, Takanashi S, Igari H, Inagaki T, Izumi S, et al. Treatment guidelines for latent tuberculosis infection. Kekkaku 2013;88:497–512.