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Case Report

Miliary Tuberculosis during R-MPV Therapy in an Elderly Patient with Primary Central Nerve System Lymphoma: A Case Report

Yushiro Take[a] Mitsuaki Shirahata[a] Jun Sakai[b] Yuichi Kubota[c] Tomonari Suzuki[a] Jun-ichi Adachi[a] Shigefumi Maesaki[b] Kazuhiko Mishima[a] Ryo Nishikawa[a]

[a]Department of Neurosurgery/Neuro-oncology, Saitama Medical University International Medical Center, Saitama, Japan; [b]Department of Infectious Diseases, Saitama Medical University Hospital, Saitama, Japan; [c]Department of Neurosurgery, TMG Asaka Medical Center, Saitama, Japan

Keywords
Primary central nervous system lymphoma · Latent tuberculosis infection · Miliary tuberculosis · Tuberculosis reactivation · Chemotherapy

Abstract
Most elderly patients with tuberculosis (TB) have previously been infected with *Mycobacterium tuberculosis*, which remains dormant in the body for decades and may reactivate when their immunity declines due to underlying diseases. Elderly cancer patients are at a high risk for TB, and the treatment of TB reactivation in these patients is challenging. Among cancer patients, the incidence of TB reactivation is the highest in lymphoma patients. However, the impact of chemotherapy on TB reactivation in lymphoma patients is unknown. We report the case of an immunocompetent elderly patient with primary central nervous system lymphoma (PCNSL) having no prior history of TB, who developed miliary TB during multiagent chemotherapy consisting of rituximab, high-dose methotrexate, procarbazine, and vincristine (R-MPV therapy). Retrospectively, the chest computed tomography showed calcification of the pleura, suggesting that the patient had a latent tuberculosis infection (LTBI) and developed miliary TB from the reactivation of TB triggered by the R-MPV therapy. Our case emphasizes that when chemotherapy is administered to patients with PCNSL, interferon-gamma release assay (IGRA) should

Correspondence to:
Mitsuaki Shirahata, mitsira@gmail.com

be performed if there are findings on chest examination suggestive of LTBI, such as pleural calcification, and if IGRA is positive, chemotherapy should be given concurrently with LTBI treatment.

Introduction

Tuberculosis (TB) is a prominent infectious disease, with 10 million new cases diagnosed worldwide in 2019 [1]. In developed countries, most TB cases occur in the elderly [1]. Approximately 90% of TB cases in the elderly are due to reactivation of previous TB infection, and the risk factors for TB reactivation include malignancy, immunosuppression, diabetes, poor nutritional status, and chronic renal failure [2]. Miliary TB is the most severe form of TB, caused by large numbers of *Mycobacterium tuberculosis*, resulting in hematogenous dissemination of lymph fluid and embolization in the vascular beds of various organs, with mortality rates reaching 20–30% [3].

Primary central nervous system lymphoma (PCNSL) is a type of extranodal non-Hodgkin's lymphoma that represents diffuse large B-cell lymphoma, confined to the central nervous system. It has been suggested that acquired immunosuppression is involved in the development of PCNSL, with patients infected with human immunodeficiency virus (HIV) and organ transplant recipients being more commonly affected. Recently, the number of immunocompetent PCNSL patients has been increasing, particularly among the elderly with a median age at diagnosis of 67 years [4]. High-dose methotrexate (HD-MTX)-based chemotherapy has become the mainstream treatment strategy in PCNSL patients [5]. Especially, R-MPV therapy (rituximab, HD-MTX, procarbazine, and vincristine) has shown favorable results in PCNSL and is currently widely used as a practical treatment for elderly patients [5]. Of particular concern is the risk of infection; however, there have been few reports of TB developing during chemotherapy in PCNSL [5].

We report the first case of miliary TB during R-MPV therapy in an immunocompetent elderly patient with PCNSL who had no medical history of TB. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000530711) [6].

Case Presentation

Consent for the publication of this case report was obtained from the patient. A 72-year-old immunocompetent female patient with no medical history of TB presented to a nearby hospital with right hemiparesis. Magnetic resonance imaging (MRI) revealed multiple homogeneous enhanced mass lesions in the left superior frontal gyrus and left middle frontal gyrus (Fig. 1a). For histological diagnosis, she underwent removal of the tumor in the left superior frontal gyrus, and the diagnosis was made with CD20-positive diffuse large B-cell lymphoma. The patient was transferred to our center for adjuvant chemotherapy. Upon admission to our center, she had no symptoms except for right hemiparesis and no comorbidities. She had a history of depression, but her condition had stabilized without medication. The HIV-1 and HIV-2 antigen/antibody tests were negative. Pre-chemotherapy MRI showed a resection scar in the left superior frontal gyrus and a residual tumor in the left middle frontal gyrus (Fig. 1b). After confirming that her general

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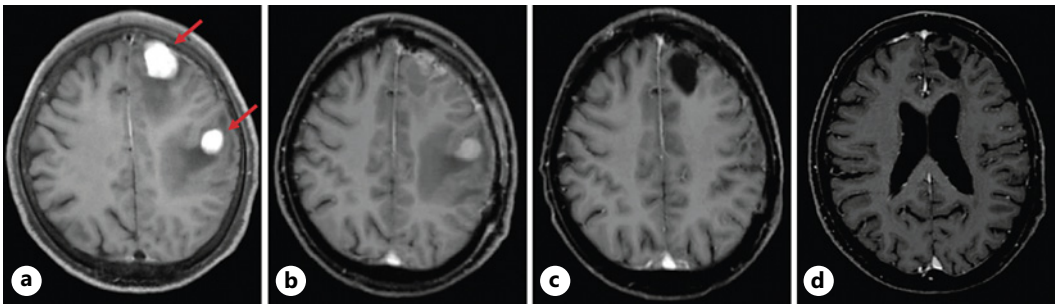

Fig. 1. The clinical course of the PCNSL. Gadolinium-enhanced T1-weighted magnetic resonance imaging (MRI) showing multiple homogeneous enhancing mass lesions (arrows) in the left superior frontal gyrus and left middle frontal gyrus (**a**), resection scar in the left superior frontal gyrus and residual tumor in the left middle frontal gyrus before chemotherapy induction (**b**), complete response (CR) after two cycles of chemotherapy (**c**), and CR was maintained for 3 years after two cycles of chemotherapy (**d**).

condition, as well as bone marrow and major organ functions, were suitable for chemotherapy induction, R-MPV therapy was administered (day 0). The patient's right hemiparesis improved after the first cycle. However, due to a worsening mental state, we withheld chemotherapy and prioritized medical treatment for depression. Two months later, her mental status improved, and the second cycle of chemotherapy was resumed (day 57). The MRI showed complete response (day 73) (Fig. 1c). The third cycle of chemotherapy was planned, but she had a fever in the 37°C range. Chest computed tomography (CT) demonstrated diffuse miliary shadows in both lung fields, suggestive of miliary TB (day 104) (Fig. 2a). The polymerase chain reaction of sputum and the sputum culture test detected *M. tuberculosis*, which was found to be susceptible to all anti-TB agents. We reviewed the pretreatment chest X-ray and CT scans and found no evidence of pneumonia or active TB in the lung field, but found calcification of the pleura (Fig. 2b, c). She was diagnosed with miliary TB and was transferred to a hospital specializing in TB treatment. R-MPV therapy was discontinued. She recovered from miliary TB after 1 month of inpatient treatment with HREZ (isoniazid, rifampin, ethambutol, and pyrazinamide), and completed TB treatment with 9 months of outpatient treatment with isoniazid and rifampin. Regarding PCNSL, a complete response was maintained for 3 years after two cycles of R-MPV without additional treatment (Fig. 1d).

Discussion

In the present case, despite the absence of a medical history of TB, pretreatment chest X-ray and CT scan showed calcification of the pleura, a typical finding of latent or inactive TB [7]. No other findings suggestive of a past TB infection, such as calcification of the lymph nodes, were observed in this case. In general, it is difficult to detect past TB infections using imaging techniques. A meta-analysis revealed that the sensitivity of imaging findings for past TB infections was approximately 15% [7]. Furthermore, similar findings were detected in approximately 10–60% of uninfected patients, depending on TB prevalence [7]. Calcification of nodules, pleural thickness, and fibrous scarring are observed in various other diseases, such as sarcoidosis, pulmonary infections, malignancies, and occupational lung diseases [7]. Since the patient had no history of diseases or medications related to immunodeficiency, we determined that she had a latent TB infection, and R-MPV therapy may have induced TB reactivation.

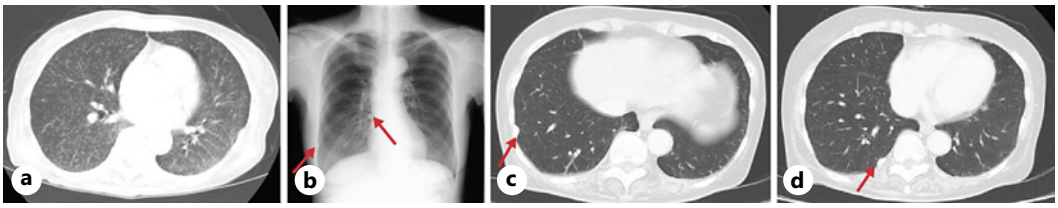

Fig. 2. Chest images before and after the development of miliary TB. **a** Chest CT scan showing diffuse miliary shadows in both lung fields, suggestive of miliary TB. **b** Pretreatment chest X-ray showing no evidence of pneumonitis or active TB in the lung fields, but calcified lesions of the pleura (arrows) are present. **c**, **d** Pretreatment chest CT scan showed pleural calcification (arrows).

Latent tuberculosis infection (LTBI) is defined as the absence of clinical manifestations of TB but the presence of an immune response to infection with *M. tuberculosis* [8]. One-third of the world's population is estimated to be infected with *M. tuberculosis* [8]. According to the LTBI guidelines, it is important to evaluate TB infection with interferon-gamma release assay (IGRA) or tuberculin skin test (TST) when a chest X-ray or CT scan shows findings indicative of previous or latent TB [8]. Our experience emphasizes the importance of careful evaluation of the chest examination in ruling out LTBI prior to induction of chemotherapy, even in patients with no history of TB, and that when calcifications are found, they should not be underestimated, and a TB test should be performed proactively. IGRA has higher specificity than TST and is not affected by the *Bacille de Calmette et Guérin* or non-TB mycobacteria vaccination [9]. The sensitivity of the IGRA is high (80–90%) [9]; therefore, immunocompromised cancer patients may benefit more from IGRA than TST. Of note, sensitivity tends to decrease in the elderly, and the risk of false negatives cannot be excluded [9]. The guidelines recommend LTBI treatment for patients at high risk of developing TB, including patients infected with HIV, preparing for organ or hematologic transplantation, who have had TB within the past 2 years, with untreated TB, on dialysis, taking biologics or immunosuppressive drugs, and patients with silicosis [8].

A population-based study of cancer patients showed that the cumulative incidence of TB following cancer diagnosis was highest in lymphoma (154.1/100,000 patients) [10]; however, the impact of chemotherapy for lymphoma on TB reactivation has not been fully elucidated, and the incidence of TB reactivation during chemotherapy in patients with PCNSL remains unknown. CD20-positive B-cell lymphoma is often treated with rituximab, which is a risk factor for TB reactivation. However, some studies showed that rituximab did not increase adverse events of infection [11]. Because rituximab is rarely used as a single agent in the treatment of lymphoma, the direct risk of TB reactivation with rituximab remains unclear [12]. The impact of multidrug chemotherapy on TB reactivation and whether rituximab should be withheld from PCNSL patients at a high risk of TB reactivation are issues for future research.

Herein, the patient developed severe miliary TB while PCNSL was in remission; thus, we prioritized the treatment of TB and withheld chemotherapy for PCNSL. Fortunately, the tumor did not recur, and TB was cured. Although some studies have shown that anticancer drugs do not reduce the efficacy of anti-TB drugs for TB [13], simultaneous treatment of cancer and TB is challenging because the simultaneous administration of antitumor and anti-TB drugs requires consideration of drug interactions and the side effects of multiple drug use, particularly in the elderly. Of the 32 cancer patients who developed TB, chemotherapy was delayed by 53%, and three died of TB [14]. Currently, there is no consensus regarding whether chemotherapy should be initiated during LTBI treatment for elderly patients with PCNSL and suspicious latent TB findings. However, our case suggests that patients with chest findings suggestive of TB should be tested by IGRA or TST, even if they have no medical history of TB, and if positive, chemotherapy should be administered concurrently with LTBI treatment.

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The LTBI guidelines recommend 6 months of isoniazid monotherapy. Alternative therapies include rifapentine and isoniazid weekly for 3 months, or 4 months of daily rifampin [15]. When chemotherapy for cancer and anti-TB treatment for LTBI are administered simultaneously, the possibility of drug-drug interactions must be considered. Rifampin induces hepatic drug-metabolizing enzymes, such as CYP3A4, which may affect vincristine metabolism [15]. Isoniazid and rifampin are associated with the risk of hepatic and renal impairment as adverse effects. The incidence of hepatic dysfunction with isoniazid use ranges from 3.7% to 11.4%, and, although rare, mortality has been reported [15]. Adverse events related to multidrug therapy should be carefully monitored, particularly in the elderly.

Conclusion

When starting chemotherapy for patients with PCNSL, oncologists/clinicians should be aware of the pleura. In addition, TB infection should be tested using IGRA before immunosuppressive therapy or administration of biological drugs. If positive, the initiation of chemotherapy during LTBI treatment should be considered, with careful monitoring for adverse events and TB reactivation.

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Statement of Ethics

Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Yushiro Take and Mitsuaki Shirahata: conceptualization, data curation, formal analysis, investigation, resources, visualization, writing – original draft, and writing – review and editing. Jun Sakai, Tomonari Suzuki, Jun-ichi Adachi, Shigefumi Maesaki, Kazuhiko Mishima, and Ryo Nishikawa: supervision and writing – review and editing. Yuichi Kubota: resources and writing – review and editing.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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