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【 CASE REPORT 】

Disseminated Tuberculosis with Cholecystitis in a Patient after Cord Blood Transplantation

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Abstract:
The incidence of an active tuberculosis infection after allogeneic hematopoietic cell transplantation is high. We herein report the case of a patient with acute myeloid leukemia after cord blood transplantation (CBT). On day 36 after CBT, the patient developed fever, and a computed tomography scan on day 36 showed mild thickening of the wall of the gallbladder. Subsequently, a sputum specimen and a blood culture returned positive for the growth of *Mycobacterium tuberculosis*. After 2 months of administering combination therapy, both the symptoms and gallbladder findings improved. We therefore describe a case of disseminated tuberculosis with the gallbladder mimicking acute cholecystitis in a CBT recipient.

Key words: disseminated tuberculosis, latent tuberculosis infection, *Mycobacterium tuberculosis*, cord blood transplantation, hematopoietic cell transplantation, cholecystitis

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Introduction

The incidence of active tuberculosis after allogeneic hematopoietic cell transplantation (HCT) is high because the patient's immunocompromised situation due to intense conditioning regimens and the use of immunosuppressive drugs for prophylaxis and the treatment for graft-versus-host disease (GVHD) (1-5). Moreover, in cord blood transplantation (CBT), the limited cell dose of a single cord blood (CB) unit and the naïve phenotype of CB lymphocytes result in a higher incidence of infection compared with other graft sources (6) due to the occurrence of prolonged neutropenia and a delayed immune reconstitution. We report the case of a patient with acute myeloid leukemia (AML), who developed disseminated tuberculosis with cholecystitis after unrelated CBT.

Case Report

A 56-year-old Japanese man with AML following leukocytopenia was admitted to our hospital for unrelated CBT. A computed tomography (CT) scan before CBT revealed mediastinal lymphadenopathy and a gallbladder stone. Although the patient had no history of tuberculosis and an unknown history of bacille Calmette-Guérin (BCG) vaccination, T-SPOT.*TB*, an interferon-γ release assay (IGRA) established for diagnosis of latent tuberculosis infection (LTBI), was positive at 31 days before CBT. In his sputum specimens, Ziehl-Neelsen stain and the transcription-reverse transcription concerted (TRC) reaction (7) were negative for *Mycobacterium tuberculosis* at 28 days before CBT. Due to hypoplastic AML following leukocytopenia, the patient received unrelated single-unit CBT as an up-front treatment. The conditioning regimen consisted of 12 Gy of total body irradiation, cyclophosphamide 120 mg/kg, and granulocyte colony-stimulating factor combined with cytarabine 12 g/m^2; and prophylaxis for GVHD consisted of cyclosporine (CSP) and methotrexate, as we previously reported (8). The cord blood unit had 2-locus human leukocyte antigen (HLA) mismatches at a low resolution for HLA-A, -B, and -DR. The cryopreserved number of CB nucleated cells was 2.13×10^7/kg, and the cryopreserved number of CD34$^+$ cells was 1.55×10^5/kg. Neutrophil engraftment was achieved on day 20. On

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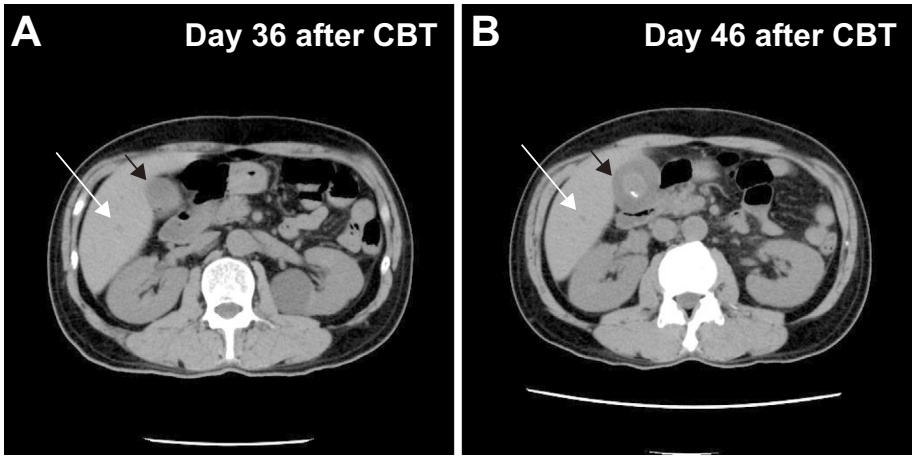

Figure. **An unenhanced computed tomography (CT) scan showing mild thickening of the wall of the gallbladder (black arrow), poorly marginated low-density areas (white arrow) on day 36 (A), and the enlargement and severe thickening of the wall of the gallbladder (black arrow) on day 46 (B).**

day 36, the patient developed a high-grade fever (>40°C) with a mild dry cough, and a CT scan on day 36 showed mild thickening of the wall of the gallbladder and poorly marginated low-density areas in the right lobe of the liver (Figure A), but no nodules in the chest. The fever persisted despite the administration of empiric meropenem, linezolid, and voriconazole treatments. In addition, ganciclovir treatment was also started for cytomegalovirus reactivation on day 35. In sputum specimens, Ziehl-Neelsen stain was negative, but the TRC reaction was positive for *M. tuberculosis* on day 39. Subsequently, a sputum specimen on day 39 and a blood culture on day 43 returned a positive finding for the growth of *M. tuberculosis*. Combination therapy with isoniazid, rifampicin, ethambutol, and pyrazinamide was initiated on day 43. A CT scan on day 46 showed the enlargement and severe thickening of the wall of the gallbladder (Figure B) and a small nodule in the chest. CSP treatment was tapered and finished on day 88 after CBT. After 2 months of these treatments, the patient's fever, and enlargement and thickening of the wall of the gallbladder had all improved.

Discussion

Previous studies have shown that the incidence of active tuberculosis after allogeneic HCT is around 2% at a median time of approximately 2.4 to 4.6 months (3). However, given that Japan has an intermediate burden of tuberculosis, the incidence of active tuberculosis after HCT could be around 2%. In fact, Maeda et al. reported that 3 of 113 (2.7%) patients developed active tuberculosis on 34, 41, and 61 days after CBT in Japan (5). Based on these cases (5) and our case, CBT might contribute to the early onset of active tuberculosis after HCT.

Abad et al. found that fever was the most frequent symptom of tuberculosis in patients after HCT. Around half of these patients presented with pulmonary tuberculosis (42.6%), but extra-pulmonary tuberculosis (34%) and disseminated tuberculosis (23.4%) were also relatively common (3). In our case, T-SPOT.*TB* was positive before CBT. Fever was the main symptom along with a positive blood culture for *M. tuberculosis.* Moreover, the enlargement and thickening of the wall of the gallbladder suggested gallbladder tuberculosis (9). All these findings indicated a diagnosis of disseminated tuberculosis after CBT.

Although monotherapy of isoniazid or rifampicin is commonly performed to prevent LTBI reactivation, these drugs are associated with hepatotoxicity and drug-drug interaction with CSP among HCT recipients. Interestingly, Cheng et al. reported that LTBI reactivation did not occur immediately after HCT even without prophylaxis for tuberculosis (10). Park et al. showed that the incidence of tuberculosis in positive IGRA using the QuantiFeron (QFT)-TB without isoniazid prophylaxis was higher than in positive IGRA using the QFT-TB with isoniazid prophylaxis (p=0.09) (11). Our case experienced LTBI reactivation early after CBT. Therefore, even though whether or not it is possible to prevent LTBI reactivation after HCT remains controversial, isoniazid prophylaxis before conditioning regimen should be considered to prevent LTBI early after CBT in patients with positive IGRA results before CBT.

In conclusion, disseminated tuberculosis should be considered early after CBT for patients with an unexplained fever. Our case showed disseminated tuberculosis with a gallbladder mimicking acute cholecystitis in a CBT recipient. Further studies are warranted to clarify the efficacy of screening before allogeneic HCT using IGRA and to identify the optimal practice for the prevention of LTBI reactivation after allogeneic HCT.

The authors state that they have no Conflict of Interest (COI).

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