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Disseminated Tuberculosis With an Atypical Cutaneous Manifestation in a Hematopoietic Cell Transplant Patient in the Early Posttransplant Period: Case Report and Review of the Literature

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We describe an unusual case of posttransplant tuberculosis reactivation in a man who underwent allogeneic hematopoietic cell transplant. Concomitant with disseminated adenovirus infection, reactivation of tuberculosis manifested as disseminated, nonfollicular pustules on day +49. Skin biopsy was obtained on day +50. Initial histopathologic evaluation did not suggest mycobacterial infection, but tissue stain showed acid-fast organisms, which were subsequently identified as *Mycobacterium tuberculosis*. Shortly after the cutaneous presentation of tuberculosis, the patient died on day +52. Our case is among a paucity of reports describing tuberculosis reactivation in hematopoietic cell transplant patients in the early posttransplant period. It highlights the difficulty of diagnosing contemporaneous systemic infections, and it presents a rare and atypical cutaneous manifestation of tuberculosis in a hematopoietic cell transplant patient. Our case and review of the literature emphasize the need for further research to elucidate risk factors associated with early posttransplant reactivation of tuberculosis, and the importance of remaining vigilant for active tuberculosis in hematopoietic cell transplant patients with epidemiologic risk factors.

Keywords. cutaneous tuberculosis; disseminated tuberculosis; hematopoietic cell transplant; tuberculosis pustules; tuberculosis reactivation.

CASE REPORT

A 68-year-old male who underwent allogeneic hematopoietic cell transplantation (HCT) was admitted after 2 weeks of intermittent fevers with disseminated adenovirus (ADV) infection and cytomegalovirus (CMV) DNAemia. He subsequently developed progressive, multifocal, nonfollicular pustules on his trunk and extremities.

The patient had a history of high-risk myelodysplastic syndrome (MDS), treated with 4 cycles of azacitidine. After treatment with azacitidine, he was tested for exposure to tuberculosis (TB) with an interferon-gamma release assay (IGRA) (T-SPOT), which was negative. However, the patient reported a remote positive tuberculosis skin test (TST), for which he had not received treatment. Screening chest imaging showed right lung calcified granulomata.

The patient was born in Southeast Asia and immigrated to the United States in the 1980s. He reported history of Bacillus Calmette-Guerin (BCG) vaccination. The patient had not traveled back to Southeast Asia for more than a decade preceding transplant. He had frequent occupational exposure to plants and soil.

For MDS, he underwent nonmyeloablative haploidentical peripheral blood HCT. He was CMV seropositive, toxoplasma seronegative, and hepatitis B core antibody positive. He received conditioning with fludarabine, cyclophosphamide, and total body irradiation 400 cGy. He received graft-versus-host disease (GVHD) prophylaxis with cyclophosphamide, mycophenolate mofetil, and tacrolimus. He received standard antimicrobial prophylaxis for alphaherpesviruses and hepatitis B, serial monitoring for CMV, and initiation of pneumocystis prophylaxis on day +21. His pre-engraftment course was complicated by persistent neutropenic fevers, for which he was started on broad-spectrum antibacterials and posaconazole empirically. Infectious work up, including blood cultures, serum fungal biomarkers, and blood polymerase chain reaction (PCR) for CMV, Epstein-Barr virus, and human herpesvirus 6, was negative. Fevers subsequently resolved

Accepted 28 November 2022; published online 29 November 2022

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https://doi.org/10.1093/ofid/ofac643

and were attributed to noninfectious causes. He had neutrophil engraftment on day +19 and platelet engraftment on day +25. Antibacterials were discontinued, and posaconazole was changed to itraconazole for ongoing prophylaxis due to costs. T-cell chimerism on day +28 showed 100% donor.

Fevers recurred beginning day +30. On day +34, the patient was found to have CMV DNAemia, for which he was started on ganciclovir 5 mg/kg intravenously every 12 hours. On day +39, the patient was found to have ADV DNAemia. A computed tomography (CT) chest image at that time showed increasing mediastinal adenopathy and stable calcified pulmonary granulomata without new infiltrates. The patient then developed dysuria with ADV qualitative PCR positive in the urine. He was admitted for inpatient management of disseminated adenovirus on day +44.

On admission, the patient was afebrile, hemodynamically stable, and on room air. His exam was notable for blood-tinged urine without clots. Laboratory analysis was notable for white blood count 11.86 K/cu mm, absolute neutrophil count 10.80 K/cu mm, and absolute lymphocyte count 0.27 K/cu mm. Serum creatinine (1.1 mg/dL), aspartate aminotransferase (33 U/L), and alanine aminotransferase (58 U/L) were not significantly changed from recent prior results. Plasma ADV PCR was 139 592 copies/mL (log 5.14), increased from 38 000 copies/mL (log 4.58) on day +39. Plasma CMV PCR was 4160 IU/mL (log 3.62), stable from 2510 IU/mL (log 3.40) on day +35 when ganciclovir was initiated.

For disseminated ADV, he was started on cidofovir 5 mg/kg per week and intravenous immunoglobulin 0.4 mg/kg for 5 doses. He continued (1) ganciclovir and (2) hepatitis B, pneumocystis, and antifungal prophylaxis. Although afebrile on admission, fevers recurred on day +45. On day +47, he developed productive cough and hypoxia requiring supplemental oxygen. The CT chest image showed new diffuse bilateral ground-glass opacities and increasing mediastinal adenopathy (Figure 1). He was started on cefepime empirically. A respiratory pathogen panel was positive for ADV. The patient was not able to provide a sample for respiratory culture, and bronchoscopy was deferred given concern for precipitating worsening respiratory failure requiring periprocedural intubation.

On day +49, he developed nonpainful, nonpruritic, nonfollicular pustules on his face, neck, and chest (Figure 2). On day +50, the pustules progressed to involve the trunk and extremities, and skin biopsy with tissue culture was obtained. Late on day +50, the patient developed multisystem organ failure, including encephalopathy requiring intubation for airway protection. The skin biopsy showed a neutrophil rich pustule involving the entire epidermis and superficial dermis without necrotizing granulomas or significant histiocytic infiltrates (Figure 3). Although histopathology was not suggestive of mycobacterial infection, tissue smear was positive for acid-fast organisms. The patient was recommended to start rifampin 600 mg/day, isoniazid 300 mg/day, pyrazinamide 2 g/day, and ethambutol 1.6 g/day on day +51. Despite life support measures, the patient died on day +52. *Mycobacterium tuberculosis* PCR from the skin biopsy specimen was positive. Subsequent Ziehl-Neelsen stain on dermatopathology confirmed many acid-fast positive organisms (Figure 3). Ultimately, the skin tissue culture grew pan-sensitive *M tuberculosis*. Mycobacterial cultures were not obtained from other sources. The donor did not report exposure to TB, and donor TST was negative. The patient was diagnosed with disseminated TB due to reactivation of latent disease.

DISCUSSION

We describe a 68-year-old man who underwent allogeneic HCT with a posttransplant course complicated by an atypical presentation of TB reactivation. In the early posttransplant period, TB manifested as disseminated, nonfollicular pustules on day +49. Other signs and symptoms of TB were confounded by concurrent disseminated ADV infection. Diagnosis was made with skin biopsy obtained on day +50. Initial dermatopathology was not typical for mycobacterial infection, but identification of acid-fast organisms on tissue stain led to the diagnosis. The patient precipitately developed multisystem organ failure and died on day +52. This case is a rare presentation of TB reactivation manifest as cutaneous pustules with nonclassic dermatopathology in the early post-HCT period.

Reactivation of TB is overall rare. It is more common in HCT recipients compared with the general patient population, but less common compared to solid organ transplant recipients [1]. In 22 cohort studies published in 2000 to present, the incidence of active TB infection (ATBI) in HCT recipients ranged 0%–3.1% (excluding Munoz et al [2] due to small sample size) and tended to positively correlate with TB endemicity (Table 1). Reactivation of latent TB infection (LTBI) versus de novo (or less likely donor derived) TB infection in the posttransplant period can be difficult to distinguish in areas of high TB endemicity, because both false-positive TST due to BCG vaccination, and false-negative TST or IGRA due to immunosuppression can occur [3]. In the United States, where there is low TB prevalence, ATBI in HCT recipients likely reflects TB reactivation, where incidence ranged 0%–0.7% (Table 1).

To attempt to mitigate risks of developing post-HCT ATBI, many centers seek to diagnose and treat LTBI [1, 4]. Diagnosis of LTBI in immunocompromised hosts can be hindered by reduced sensitivity of IGRA and TST. We suspect our patient's IGRA was falsely negative due to immunosuppression with azacitidine, and that his prior TST was truly positive given his birth in an area with high TB endemicity and calcified pulmonary granulomata consistent with prior TB. Furthermore, although limited by small sample size, treatment of LTBI seems to decrease post-HCT ATBI. In two pooled studies that treated

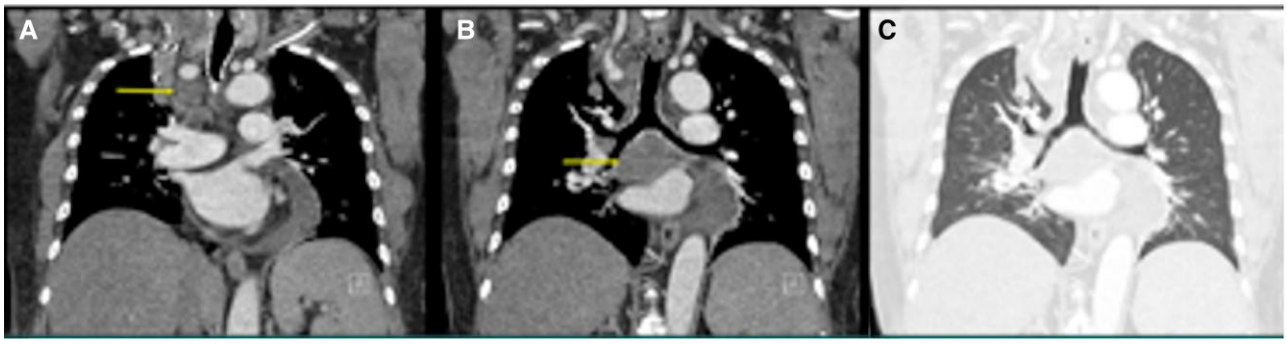

Figure 1. Computed tomography chest image obtained on day +47. (*A* and *B*) Arrows showing mediastinal adenopathy. (*C*) Diffuse bilateral ground-glass opacities.

LTBI posttransplant (timing of LTBI treatment not further specified), none of the 62 recipients who had HCT and were treated for LTBI (of 198 total LTBI) developed ATBI [5, 6]. In contrast, in three pooled studies, among recipients who had HCT with untreated LTBI, 10 of 181 (5.5%) developed ATBI [5–7].

The range of median times from HCT to ATBI was 1.3 to 14.9 months (Table 1). Because TB reactivation typically occurs months after HCT, LTBI treatment is often started weeks to months posttransplant. Before transplant, drug interactions or overlapping toxicities between TB antimicrobials and chemotherapy regimens can complicate or even preclude LTBI treatment. In the early posttransplant period, LTBI treatment is often deferred until possible adverse effects of TB antimicrobials can more easily be differentiated from other drug toxicities, engraftment syndrome, hepatic veno-occlusive disease, and acute GVHD, but before the window when TB reactivation typically occurs. Our institutional practice is to initiate LTBI therapy on or after day +60. Although various treatment regimens for LTBI are available, LTBI in transplant patients is most often treated with isoniazid for 6–9 months due to longstanding clinical experience with isoniazid, and interactions between rifamycins and immunosuppressants used for GVHD prophylaxis and treatment [1].

Our patient developed early TB reactivation before LTBI therapy was initiated, and a minority of other case reports describe early TB reactivation within the first 100 days post-HCT (Table 1). TB reactivation is more common among allogeneic HCT recipients compared to autologous HCT recipients (Table 1). Other reported risk factors include GVHD [5, 8–11] and a history of pretransplant ATBI that was previously treated and inactive at the time of HCT [12, 13]. Our patient received an allogeneic HCT, but otherwise did not have these risk factors. Before transplant, our patient was treated with 4 cycles of azacitidine, which is a demethylating agent and antimetabolite that has been associated with an increased incidence of bacterial and viral infections [14]. However, other than one other case report describing a patient with chronic myelomonocytic leukemia receiving azacitidine [15], TB reactivation has not been reported with azacitidine. Our patient also had concurrent infections with disseminated ADV and CMV DNAemia, suggesting profound lymphocyte dysfunction. Because control of LTBI requires cytotoxic T cells [16], this evidence of lymphocyte dysfunction was likely an additional risk factor for TB reactivation. One study did not show a significant difference in the incidence of CMV DNAemia in patients post-HCT who developed ATBI versus those who did not [13]. However, synergistic and immunomodulatory effects of CMV with other viruses in relationship to TB is not well defined.

For our patient, we initially suspected that disseminated adenovirus was causing recurrent fevers, mediastinal adenopathy, hematuria, and then pulmonary infiltrates. Although this may have been true, the subsequent diagnosis of disseminated TB raises the question of whether TB contributed to these symptoms and findings. It is an important reminder to be vigilant for contemporaneous infections in HCT recipients, and especially those who are clinically declining on therapies for known infections.

Furthermore, manifestations of ATBI in transplant recipients differ from those in immunocompetent hosts. Although pulmonary TB is the most common form of disease in transplant recipients and non-transplant recipients, disseminated TB is more common in transplant recipients [17]. Disseminated TB can spread hematogenously to infect any organ, including the skin. Cutaneous presentations of disseminated TB are rare, and even more rare in HCT recipients [18–20]. Cutaneous TB can manifest as diffuse erythematous papules, pustules, and nodules [21]. However, as far as we are aware, our patient is the only report describing a HCT recipient with disseminated TB manifest as pustules. Our patient's skin biopsy showed a neutrophil dense pustule expanding the entire epidermis and superficial dermis. This is distinct from reported histopathologic descriptions of cutaneous TB in other patient populations that report focal dermal microabscesses containing neutrophils and occasional lymphohistiocytes and plasma cells, sometimes with surrounding macrophages or giant cells [22–24]. Thereby, TB was not considered

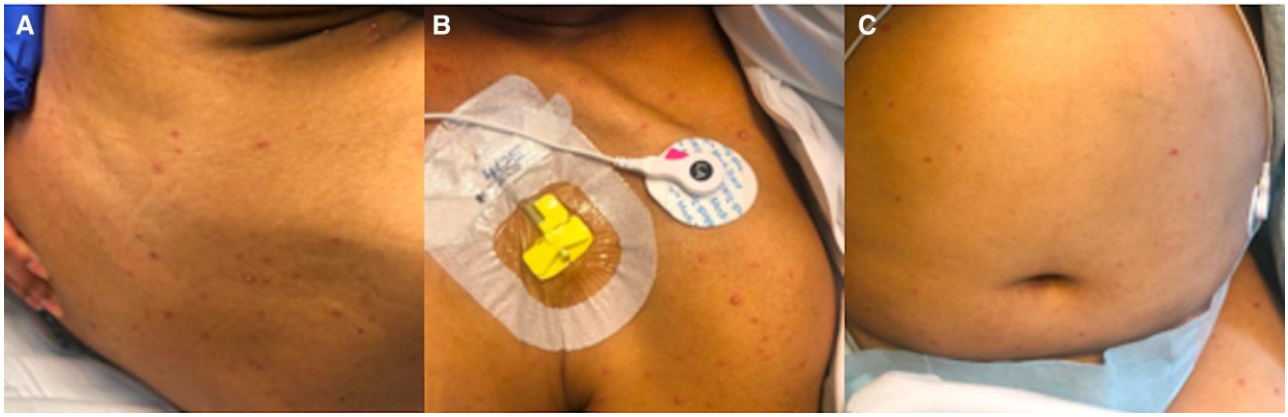

Figure 2. Multifocal, nonfollicular pustules on (*A*) back, (*B*) left shoulder, and (*C*) abdomen.

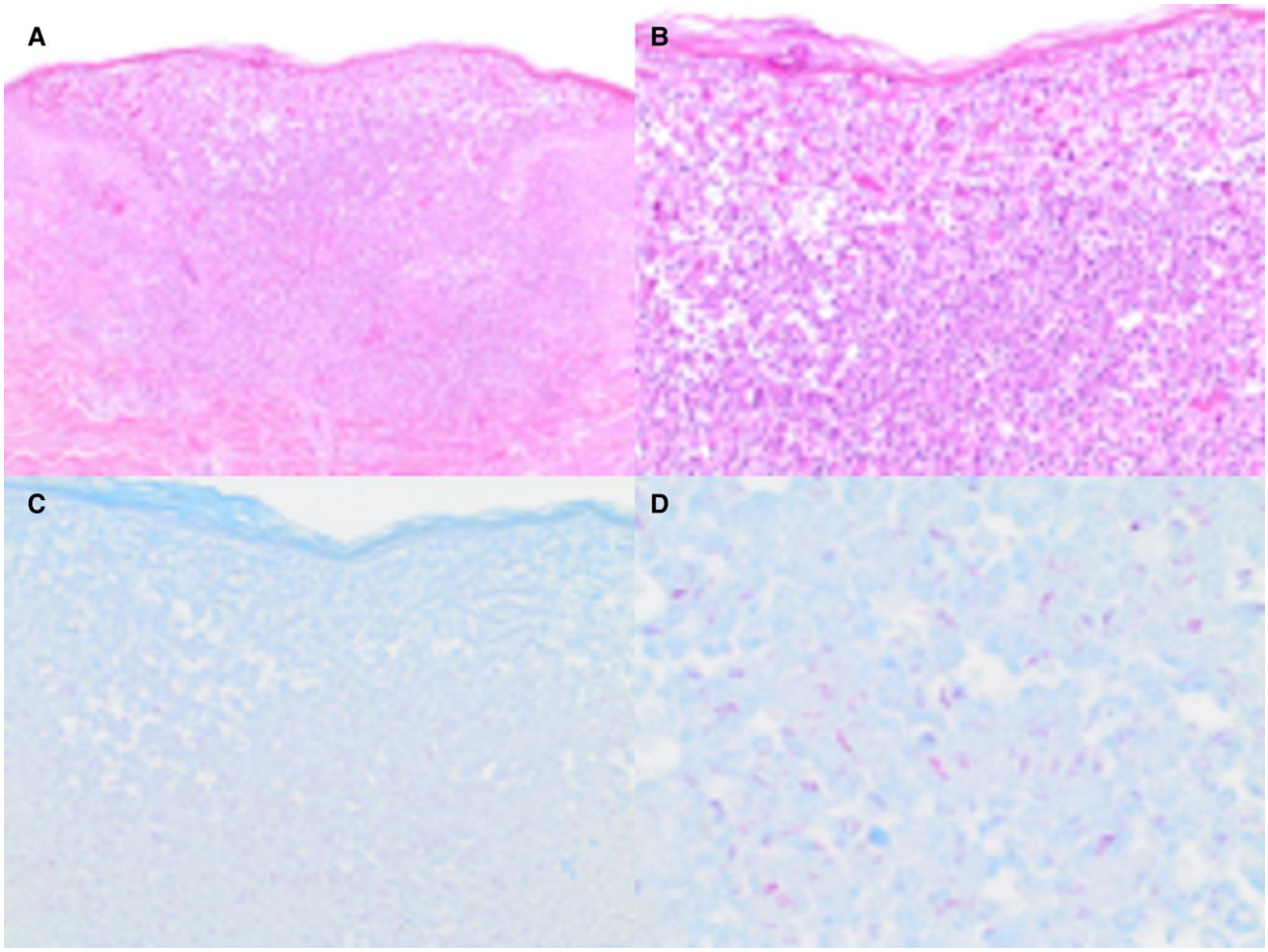

Figure 3. Biopsy of skin pustule. (*A*) ×4 magnification, hematoxylin and eosin (H&E) stain. Pustule exuding into dermis. (*B*) ×10 magnification, H&E stain. Pustule filled with neutrophils and scattered histiocytes. (*C*) ×10 magnification, Ziehl-Neelsen (ZN) stain. Many acid-fast organisms. (*D*) ×40 magnification, ZN stain. Acid-fast organisms at higher power.

Table 1. Published Studies Describing Tuberculosis in Hematopoietic Cell Transplant Patients

Publication	Country of Cohort Study	Prevalence of LTBI Among HCT Patients	Treatment for LTBI Among HCT Patients	ATBI Cases Following HCT/HCT Cohort	Time From HCT to ATBI	Site of ATBI	Outcomes[a]	Duration of Follow up
Agrawal et al [8]	India	Unknown	Unknown	5/175 (2.9%) All alloHCT	Median 8.5 mo	Pulm 3/5 ExPulm/Diss 2/5	0/5 TB cohort died 91/175 (52%) no-TB cohort died	Median 36 mo, range 21–45.7 mo for TB cohort Median 26.5 mo, range 5.5–59.7 mo for alive patients in no-TB cohort
Aki et al [26]	Turkey	224/493 (45.4%) LTBI determined by TST (in a country that administers BCG vaccine)	151/558 (27.1%) All treated post-HCT	1/558 (0.2%) 0/271 alloHCT 1/287 (0.3%) autoHCT ATBI in 1 patient after second autoHCT with negative TST	4 mo	Pulm 1/1	1/1 successful TB treatment 375/558 (67.2%) total cohort alive at follow up	Median 29 mo, range 3–133 mo
Al-Anazi et al [27]	Saudi Arabia	Unknown	Unknown	3/103 (2.9%) 3/82 (3.7%) alloHCT 0/21 autoHCT	Median 5 mo, range 1–12 mo	Pulm 2/3 ExPulm/Diss 1/3	1/3 (33.3%) failed TB treatment	Unknown
Garces Ambrossi et al [28]	USA	Unknown	Unknown	4/577 (0.7%) All alloHCT 4/92 (4.4%) foreign born and 0/485 US-born alloHCT recipients developed TB posttransplant 372/577 received T-cell depleted alloHCT 2/4 TB pts with T-cell depleted 2/4 TB pts with GVHD	Median 4.2 mo, range 2–9.8 mo	Pulm 3/4 ExPulm/Diss 1/4	1/4 TB cohort died	Unknown
Bourlon et al [29]	Mexico	58/290 (20%) LTBI determined by TST (in a country that administers BCG vaccine)	53/58 (91%) All treated pre-HCT w/ median time from initiation of INH to HCT 70 d	0/290 (0%) 125 alloHCT 165 autoHCT	NA	NA	NA	12 mo
Budak-Alpdogan et al [30]	Turkey	36/116 with TST reaction size >10 mm (in a country that administers BCG vaccine) Study did not delineate TST reactions at 5 mm	77/351 None of these patients developed posttransplant TB	5/351 (1.4%) All alloHCT	Median 12 mo, range 10–47 mo	Pulm 4/5 ExPulm/Diss 1/5	0/5 TB cohort died	Unknown
Cheng et al [31]	USA	91/2531 (3.6%), of which 48 (52.7%) were foreign born LTBI determined by TST, QuantiFERON-TB Gold, and/or T-SPOT	58/91 (63.7%) 24 pts treated before HCT, and 34 treated after HCT	0/2531 (0%) 1252 autoHCT 1279 alloHCT	NA	NA	NA	6981 person years

Table 1. Continued

Publication	Country of Cohort Study	Prevalence of LTBI Among HCT Patients	Treatment for LTBI Among HCT Patients	ATBI Cases Following HCT/HCT Cohort	Time From HCT to ATBI	Site of ATBI	Outcomes[a]	Duration of Follow up
Cordonnier et al [32]	14 countries: Austria, Australia, Belgium, France, Germany, Hungary, Italy, Portugal, Slovenia, Spain, Sweden, the Netherlands, Turkey, United Kingdom	Unknown	Unknown	20/4525 (0.4%) 16/1513 (1.1%) alloHCT 4/3012 (0.1%) autoHCT	Mean 10.7 mo±SD 10.8 mo, median 6.0 mo	Pulm 12/20 ExPulm/Diss 7/20	3/20 (15%) TB cohort died	Unknown
De la Camara et al [9]	Spain	Unknown	Unknown	20/8013 (0.25%) 12/2866 (0.4%) alloHCT 8/5147 (0.2%) autoHCT	Median 10.7 mo, range 0.4–109.7 mo 4/20 patients had ATBI before day+ 100 posttransplant	Pulm 16/20 ExPulm/Diss 4/20	11/20 (55%) TB cohort died	Median follow up of TB group 36.1 mo, range 6.9–73.6 mo
De Oliveira Rodrigues et al [5]	Brazil	11/126 (8.7%) alloHCT in cohort 1 6/48 (12.5%) alloHCT with cGVHD in cohort2 LTBI determined by TST and/or QTF-GIT	11/11 cohort 1 patients treated posttransplant 0/6 cohort 2 patients treated	0/126 alloHCT withOUT cGVHD in cohort 1 2/58 (3.4%) alloHCT with cGVHD in cohort 2 1 with TB had negative or indeterminate QFT-TB 1 with TB had positive QFT-TB	Unknown	Unknown	1/2 TB cohort died	Both cohorts followed for up to 18 mo
Fan et al [10]	Taiwan	Unknown	Unknown	39/2040 (1.9%) 32/1336 (2.4%) alloHCT 7/665 (1.1%) autoHCT	Median 14.6 mo, range 0.7–55.6 mo	Pulm 34/39 ExPulm/Diss 5/39	20/39 (51.3%) TB cohort died 781/2001 (39.0%) no-TB cohort died	Median 22.8 mo, IQR 6.4–53.7 mo
Ku et al [33]	Taiwan	Unknown	Unknown	8/350 (2.3%) 8/255 (3.1%) alloHCT 0/95 autoHCT	Median 3.8 mo, range 1–33.5 mo	Pulm 5/8 ExPulm/Diss 3/8	4/8 TB cohort died	Mean 25 mo ±SD 22 mo
Lee et al [12]	Korea	Unknown	Unknown	9/295 (3.1%) 7/156 (4.5%) alloHCT 2/139 (1.4%) autoHCT 28 patients with a prior history of ATBI, 8 of which developed recurrent ATBI after HCT	Median 2.8 mo, range 1.5–5.4 mo	Pulm 7/9 ExPulm/Diss 2/9	5/9 (55.6%) failed TB treatment	Median 39.6 mo, range 2–90.3 mo
Lee et al [7]	Korea	45/391 (11.5%) LTBI determined by QFT-TB	None	8/391 (2%) All alloHCT 5 with TB had negative or indeterminate QFT-TB 3 with TB had positive QFT-TB	Median 4.6 mo, range 2.6–25.8 mo, IQR 3.3–9.1 mo	Pulm 3/8 ExPulm/Diss 5/8	4/8 TB cohort died	Median 15.6 mo, IQR 7.2–27.6 mo
Liu et al [11]	Taiwan	Unknown	Unknown	6/422 (1.4%) All alloHCT	Median 10.6 mo, range 0.7–31.1 mo	Pulm 5/6 ExPulm/Diss 1/6	3/6 TB cohort died	Median 33.8 mo, range 0.3–150.6 mo
Maeda et al [19]	Japan	Unknown	Unknown	3/113 (2.7%) All unrelated cord blood HCT	Median 1.3 mo, range 1.1–2.0 mo	ExPulm/Diss 3/3	2/3 TB cohort died	1/3 living patients with ATBI followed until day+ 180

Table 1. Continued

Publication	Country of Cohort Study	Prevalence of LTBI Among HCT Patients	Treatment for LTBI Among HCT Patients	ATBI Cases Following HCT/HCT Cohort	Time From HCT to ATBI	Site of ATBI	Outcomes[a]	Duration of Follow up
Munoz et al [2]	Spain	8/26 LTBI determined by TST and QFT-GT	None	1/26 (3.8%) 1 patient with TB received alloHCT	3 mo	ExPulm/ Diss 1/1	1/1 TB died 7/25 no-TB cohort died	Median 47.5 mo, IQR 27–57.5 mo
Park et al [6]	Korea	181/1162 (15.6%) Determined by QFT-TB	51/181 (28%) All treated post-HCT	21/1162 (1.8%) All alloHCT 15 with TB had negative or indeterminate QFT-TB 6 with TB had positive QFT-TB and did NOT receive LTBI treatment	Median 7.4 mo, IQR 3.9–10.8 mo	Pulm 10/ 21 ExPulm/ Diss 11/ 21	7/21 (33.3%) TB cohort died Overall cohort mortality 469/1162 (40%)	Median 20.1 mo, IQR 7.4–24.0 mo
Yang et al [25]	China	Excluded patients with pretransplant positive T-SPOT	NA	14/730 (1.9%) All alloHCT	Median 6.4 mo	Pulm 12/ 14 ExPulm/ Diss 2/ 14	6/14 (42.9%) TB cohort died	Median follow up of survivors 23.6 mo, range 3.9–88.2 mo
Yoo et al [34]	Korea	Unknown	Unknown	7/230 (3.0%) All alloHCT	Median 14.9 mo, range 5.8–24.1 mo	Unknown	0/7 died	Unknown
Yoo et al [35]	Korea	Unknown	Unknown	13/1266 (1.0%) All alloHCT	Unknown	Unknown	4/13 (30.7%) TB cohort died	Unknown
Zeng et al [13]	China	Unknown	Unknown	33/6236 (0.5%) All alloHCT 11/33 patients that developed posttransplant ATBI had a history of pretransplant ATBI	Median 4.4 mo, range 2.3–6.8 mo	Pulm 26/ 33 ExPulm/ Diss 7/ 33	Nonrelapse mortality at 2 y after HCT in TB cohort 7.2% versus no-TB group 9.8% (P= .807)	Median 38.9 mo, IQR 22.1–41.5 mo for TB cohort Median 26.3 mo, IQR 11.6–41.5 mo for no-TB group

Abbreviations: AlloHCT, allogeneic hematopoietic cell transplant; AutoHCT, autologous hematopoietic cell transplant; ATBI, active tuberculosis infection; BCG, Bacillus Calmette-Guerin; cGVHD, chronic graft versus host disease; d, days; Diss, disseminated; ExPulm, extrapulmonary; HCT, hematopoietic cell transplant; INH, isoniazid; IQR, interquartile range; LTBI, latent tuberculosis infection; mo, month; pts, patients; Pulm, pulmonary; NA, not applicable; QTF-GT, QuantiFeron TB gold in tube; SD, standard deviation; TB, tuberculosis; TST, tuberculin skin test; y, years.

[a]Unless otherwise stated, mortality includes all-cause mortality.

based on the initial histopathology alone, highlighting the importance of concurrent tissue stains and cultures in HCT recipients who exhibit a new rash, even when the cutaneous findings are subtle. Because of the varied presentation of TB in HCT recipients, diagnosis is often delayed, invasive procedures are often required, and mortality is as high as 55% in HCT recipients with ATBI [9, 10, 12, 17, 25].

CONCLUSIONS

This case describes an uncommon presentation of TB reactivation in the early post-HCT period. It highlights our incomplete understanding of risk factors that predispose patients to early post-HCT TB reactivation, difficulty diagnosing concomitant systemic infections, and variable presentations of ATBI in this population. Improved understanding of these aspects would be important to prompt earlier treatment for LTBI in patients with risk factors and/or heightened monitoring for signs and symptoms of ATBI post-HCT.

Acknowledgments

Financial support. This work was funded by the National Institute of Allergy and Infectious Diseases (Division of Intramural Research, MMC; K08AI156021 to AHK). Open access publication was funded by the Sherrilyn and Ken Fisher Center for Environmental Infectious Diseases.

Potential conflicts of interest. AHK reports receiving consulting fees from Roche. TJ reports institutional research support from CTI Biopharma, Syneos Health, Incyte; Consultancy with Targeted Healthcare Communications; and advisory board participation with Care Dx, Bristol Myers Squibb, Incyte, Abbvie, and CTI.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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