Disseminated Infections with *Talaromyces marneffei* in Non-AIDS Patients Given Monoclonal Antibodies against CD20 and Kinase Inhibitors

Jasper F.W. Chan, Thomas S.Y. Chan, Harinder Gill, Frank Y.F. Lam, Nigel J. Trendell-Smith, Siddharth Sridhar, Herman Tse, Susanna K.P. Lau, Ivan F.N. Hung, Kwok-Yung Yuen, Patrick C.Y. Woo

Learning Objectives

Upon completion of this activity, participants will be able to:

1. Distinguish the clinical and epidemiologic characteristics of *T. marneffei* infection, based on a case series report
2. Discuss the recent emergence of disseminated *T. marneffei* infection in non-AIDS patients with hematologic malignant neoplasms treated with targeted therapies
3. Identify possible mechanisms of action underlying disseminated *T. marneffei* infection in non-AIDS patients with hematologic malignant neoplasms treated with targeted therapies

CME Editor

Thomas J. Gryczan, MS, Technical Writer/Editor, Emerging Infectious Diseases. Disclosure: Thomas J. Gryczan, MS, has disclosed no relevant financial relationships.

CME Author

Laurie Barclay, MD, freelance writer and reviewer, Medscape, LLC. Disclosure: Laurie Barclay, MD, has disclosed no relevant financial relationships.

Authors

Disclosures: Harinder Gill, MBBS; Frank Y.F. Lam, MBBS, MRCP(UK), FHKAM; Nigel J. Trendell-Smith, MBBS, FRCPath; Siddharth Sridhar, MBBS, MRCP(UK); Herman Tse, MBBS; Susanna K.P. Lau, MD; and Kwok-Yung Yuen, MD, have disclosed no relevant financial relationships. Jasper F.W. Chan, MBBS, FRCPath, FRCP(Edin), has disclosed the following relevant financial relationships: received travel grants from Pfizer Co. HK Ltd. and Astellas Pharma HK Co. Ltd. Thomas S.Y. Chan, MBBS(Hons), MRCP(UK), FHKAM(Med), has disclosed the following relevant financial relationships: served as a speaker or a member of a speakers bureau for Pfizer. Ivan F.N. Hung, MD, has disclosed the following relevant financial relationships: served as an advisor or consultant for Pfizer (Asia Pacific Capital Advisory Board). MSD; received conference sponsorships from AstraZeneca, Ferring. Patrick C.Y. Woo, MD, has disclosed the following relevant financial relationships: involved in Tigecycline Evaluation Surveillance Trial with Pfizer.

Author affiliation: The University of Hong Kong, Hong Kong, China

DOI: http://dx.doi.org/10.3201/eid2107.150138
Case-Patient 1
Patient 1 was a 56-year-old Filipino man with Waldenström macroglobulinemia, idiopathic thrombocytopenic purpura, and primary biliary cirrhosis. He had fever, night sweating, productive cough, and left facial pain for 1 week and bloody diarrhea for 2 days. He had previously received fludarabine, dexamethasone, and rituximab (mAb against CD20, 18 months earlier) for treatment of Waldenström macroglobulinemia (Table 1). The idiopathic thrombocytopenic purpura was controlled with intravenous immunoglobulin and maintenance prednisolone and mycophenolate sodium. A chest radiograph showed a small cavitary lesion in the right lower lobe. His symptoms and signs did not resolve after he received empirical intravenous imipenem/cilastatin and metronidazole (Table 2).

A colonoscopy showed multiple shallow ulcers at the terminal ileum (Figure 1). Histologic analysis of an ulcer biopsy specimen showed slough of an acutely inflamed ulcer but no microorganisms. However, histologic analysis of a specimen from a nasopharyngeal biopsy performed for persistent left facial pain showed abundant yeast cells engulfed by foamy macrophages (Figure 2). Culture of terminal ileal ulcer biopsy specimens, stool samples, and nasopharyngeal biopsy specimens yielded *T. marneffei*. A contrast-enhanced cranial computed tomography (CT) scan showed 2 lesions (3–4-mm) with rim enhancement and perifocal edema at the right occipital and left parietooccipital lobes. A thoracic CT scan showed 2 cavitary lesions (4–8 mm) in the right upper and lower lobes.

Immunologic testing showed that the patient was negative for HIV and autoantibodies against IFN-γ. His CD3+ and CD8+ counts were within references ranges, but he had mild CD4+ lymphopenia (Table 2). His fever and symptoms resolved with after 2 weeks of treatment with intravenous liposomal amphotericin B, followed by oral voriconazole. Reassessment colonoscopy (at 2 months) and CT scan (at 6 months) showed complete resolution of all lesions.

Case-Patient 2
Patient 2 was a 44-year-old Chinese man who had fever for 2 days. He had previously received chemotherapy and mAbs against CD20 (rituximab, 14 months earlier; obinutuzumab, concomitant) for refractory chronic lymphocytic leukemia (CLL) involving bone marrow (Table 1). He was empirically given intravenous piperacillin/tazobactam and anidulafungin (Table 2). Histologic analysis of a trophine biopsy specimen showed persistent CLL with plasmacytic differentiation, and Grocott staining showed yeasts with central septa in small clusters. Culture of peripheral blood and bone marrow aspirate yielded *T. marneffei*. A change in antifungal treatment to intravenous amphotericin B led to defervescence and clearance of fungemia. He was given oral itraconazole as maintenance therapy. He remained well until 2 months later when he was hospitalized for deteriorating CLL complicated by neutropenic fever with multiorgan failure caused by other opportunistic infections (Table 1). He died 5 months after the episode of disseminated *T. marneffei* infection.

Case-Patient 3
Patient 3 was a 63-year-old Chinese man with myelofibrosis and well-controlled diabetes mellitus. He had intermittent fever, right cervical lymphadenopathy, and productive cough for 4 months. He was given ruxolitinib (kinase

Infections with the fungus Talaromyces (formerly Penicillium) marneffei are rare in patients who do not have AIDS. We report disseminated *T. marneffei* infection in 4 hematology patients without AIDS who received targeted therapy with monoclonal antibodies against CD20 or kinase inhibitors during the past 2 years. Clinicians should be aware of this emerging complication, especially in patients from disease-endemic regions.

*T. marneffei* (formerly *Penicillium*) marneffei is a pathogenic, thermal dimorphic fungus that causes systemic mycosis in Southeast Asia. *T. marneffei* infection is characterized by fungal invasion of multiple organ systems, especially blood, bone marrow, skin, lungs, and reticuloendothelial tissues, and is highly fatal, especially when diagnosis and treatment are delayed (1,2). This disease is found predominantly in AIDS patients and occasionally those with cell-mediated immunodeficiencies involving the interleukin-12/interferon-γ (IFN-γ) signaling pathway, such as congenital STAT1 mutations or acquired autoantibodies against IFN-γ (1,3–6). The infection has rarely been reported among hematology patients, including those from disease-endemic regions (7,8).

At Queen Mary Hospital in Hong Kong, a 1,600-bed university teaching hospital that has a hematopoietic stem cell transplantation service, where a wide range of invasive fungal infections have been observed (9,10), only 3 cases of *T. marneffei* infection were encountered in >2,000 hematology patients in the past 20 years, despite the longstanding availability of mycologic culture and serologic testing (7,8,11,12). In contrast, the infection was commonly reported among AIDS patients (13).

In the past 2 years, we have been alerted by 4 unprecedented cases of disseminated *T. marneffei* infection among non-AIDS hematology patients given targeted therapies, including monoclonal antibodies (mAbs) against CD20 and kinase inhibitors, which are being increasingly used in recent years. We report details for these 4 hematology case-patients. The study was approved by the institutional review board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster in Hong Kong.

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Patient 1 was a 56-year-old Filipino man with Waldenström macroglobulinemia, idiopathic thrombocytopenic purpura, and primary biliary cirrhosis. He had fever, night sweating, productive cough, and left facial pain for 1 week and bloody diarrhea for 2 days. He had previously received fludarabine, dexamethasone, and rituximab (mAb against CD20, 18 months earlier) for treatment of Waldenström macroglobulinemia (Table 1). The idiopathic thrombocytopenic purpura was controlled with intravenous immunoglobulin and maintenance prednisolone and mycophenolate sodium. A chest radiograph showed a small cavitary lesion in the right lower lobe. His symptoms and signs did not resolve after he received empirical intravenous imipenem/cilastatin and metronidazole (Table 2).

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Patient 3 was a 63-year-old Chinese man with myelofibrosis and well-controlled diabetes mellitus. He had intermittent fever, right cervical lymphadenopathy, and productive cough for 4 months. He was given ruxolitinib (kinase
Inhibitor) 6 months before symptom onset because of transfusion-dependent myelofibrosis despite splenectomy 4 years earlier (Table 1). A chest radiograph and thoracic CT scan showed multiple cavitary lesions and consolidation. Bronchoalveolar lavage was negative for bacteria, fungi, and mycobacteria. A serum cryptococcal antigen test result was negative. He was empirically given intravenous imipenem/cilastatin and oral doxycycline, but his symptoms persisted. A right cervical lymph node culture yielded T. marneffei. His symptoms and radiologic abnormalities resolved after treatment with intravenous amphotericin B for 2 weeks, followed by oral voriconazole for 6 months.

Case-Patient 4

Patient 4 was a 67-year-old Chinese man with acute myeloid leukemia and hypertension. He had fever and malaise for 2 days without localizing signs. He had been given sorafenib (kinase inhibitor) 8 months earlier for chemotherapy-refractory acute myeloid leukemia (Table 1). His fever did not respond to intravenous meropenem. Subsequently,

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**Table 1. Characteristics of 4 case-patients with disseminated Talaromyces marneffei infection after targeted therapies**

| Characteristic | Case-patient 1 | Case-patient 2 | Case-patient 3 | Case-patient 4 |
|---------------|---------------|---------------|---------------|---------------|
| Age, y/sex    | 56/M          | 44/M          | 63/M          | 67/M          |
| Concurrent conditions | Waldenström macroglobulinemia, idiopathic thrombocytopenic purpura, primary biliary cirrhosis | Chronic lymphocytic leukemia | Myelofibrosis with splenectomy, diabetes mellitus | Acute myeloid leukemia, hypertension |
| Targeted therapy | Rituximab | Rituximab and obinutuzumab | Ruxolitinib | Sorafenib |
| Action of therapy | mAb against CD20 | mAb against CD20 | JAK-1/2 inhibitor | Multikinase inhibitor |
| Time interval, mo† | 18 | 14 (rituximab) and concomitant (obinutuzumab) | Concomitant | Concomitant |
| Cumulative dose before T. marneffei infection | 700 mg/dose iv x 4 doses | 700 mg/dose iv x 13 doses (rituximab) and 1,000 mg iv x 3 doses (obinutuzumab) | 10–20 mg 2×/d oral x 6.5 mo | 400 mg 2×/d oral x 8 mo |
| Other immunosuppressants (time interval, mo)† | Fludarabine and dexamethasone (39), prednisolone 10 mg/d and mycophenolate sodium 360 mg 2×/d (concomitant) | Fludarabine and cyclophosphamide (48), CHOP (36), bendamustine (13) | None | Mitoxantrone and etoposide (21), daunorubicin (20), clofarabine (18), azacitidine (15), decitabine (15), cytarabine (14) |
| Clinical manifestations | Terminal ileitis, cerebral abscesses, nasopharyngitis, and multiple cavitary lung lesions | Marrow infiltration and fungemia | Right cervical lymphadenitis and multiple cavitary lung lesions | Fungemia |
| Specimens positive for T. marneffei | Feces, and terminal ileal and nasopharyngeal biopsy specimens | Blood and bone marrow aspirate | Right cervical lymph node | Blood |
| Highest serum antibody titer against T. marneffei | 1:320 | <1:40 | 1:320 | <1:40 |
| Antifungal treatment (duration, mo) | Amphotericin B (2 weeks) and voriconazole (>21) | Amphotericin B (2 weeks) and itraconazole (5) | Amphotericin B (2 weeks) and voriconazole (>6) | Amphotericin B (2 weeks) and voriconazole (>5) |
| Other opportunistic infections | None | Bacteremia (Mycobacterium chelonae, Enterococcus faecalis, MRCNS), fungemia (Candida glabrata), HSV oral mucositis, PJP | Bacteremia (Klebsiella pneumoniae) | Herpes zoster at right occiput |
| Clinical outcome | Responded to antifungal treatment | Clearance of T. marneffei fungemia but died of MODS and multiple infections 5 mo after T. marneffei infection | Responded to antifungal treatment | Responded to antifungal treatment |

†mAb, monoclonal antibody; JAK, Janus kinase; IV, intravenous; CHOP, cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisolone; MRCNS, methicillin-resistant coagulase-negative Staphylococcus; HSV, herpes simplex virus; PJP, Pneumocystis jiroveci pneumonia; MODS, multiple organ dysfunction syndrome.
†Time interval between end of therapy and onset of symptoms for T. marneffei infection.
2 sets of blood cultures yielded *T. marneffi*. He was given intravenous amphotericin B for 2 weeks, followed by oral voriconazole. He remained well at follow-up 6 months after symptom onset.

**Discussion**

*T. marneffi* infection is an emerging complication in hematologic patients receiving targeted therapies. Historically, *T. marneffi* infection has rarely been seen in non-AIDS patients, even in disease-endemic regions. During 1994–2014, only 3 other cases were observed in our hematology patients (7, 8, 11). None of 47 patients with *T. marneffi* infection in another large local case series during 1994–2004 had hematologic disease (13). In the past 20 years, there has been no change in methods for laboratory diagnosis of *T. marneffi* infection or a marked increase
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in the number of hematology patients in our hospital. Therefore, these 4 cases indicate an increase in the incidence of T. marneffei infection in these patients. Although other immunosuppressants given to case-patients 1, 2, and 4 might have contributed to overall immunosuppression, none of these immunosuppressants, which have been used for years, have been associated with T. marneffei infection. Because use of targeted therapies is increasing in diverse patient groups, clinicians should be aware of this emerging complication, especially in patients from disease-endemic regions who have received these therapies with other immunosuppressants.

The exact mechanisms through which these targeted therapies lead to T. marneffei infection remain incompletely understood. Rituximab and obinutuzumab (used by case-patients cases 1 and 2) are mAbs against CD20 that predominantly target B cells. Unlike T cells, the role of B cell–mediated humoral response in T. marneffei infection is poorly defined. Although case-patient 1 had mild CD4+ lymphopenia probably related to concomitant use of prednisolone and mycophenolate sodium, T. marneffei infection is rarely seen in patients with CD4+ counts >300/µL (1). We postulate that B cell dysfunction might have impaired production of neutralizing antibodies against key virulence factors of T. marneffei or might involve impairment of cytokine-producing B cells, which are essential for T helper cell function (14).

More severe infections with fungemia and bone marrow involvement developed in case-patients 2 and 4, who had undetectable levels of serum antibodies against T. marneffei. Correspondingly, case-patients 1 and 3, who had antibody titers >1:320, did not have positive blood culture results (Table). Symptoms developed in case-patient 1 more than a year after he completed therapy with mAbs against CD20. This finding might be related to long-lasting B cell–depleting effects of mAbs against CD20 (15).

Regarding kinase inhibitors (used by cases-patients 3 and 4), ruxolitinib is a selective Janus kinase (JAK)-1/2 inhibitor that prevents signal transduction for type I/II cytokines, including IFN-γ, by interfering with the JAK-STAT signaling pathway. Use of ruxolitinib has been associated with opportunistic infections caused by intracellular pathogens, such as Mycobacterium tuberculosis and Cryptococcus neoformans (16,17). Similarly, patients with impaired JAK-STAT signaling, but not those with diabetes mellitus or splenectomy (case-patient 3), are predisposed to T. marneffei infection (6). Sorafenib is a multikinase inhibitor with various immunomodulatory effects, including impaired T-cell response and proliferation and reduced IFN-γ production (18). These immune defects have been associated with reactivation of latent tuberculosis and might also predispose patients to opportunistic infections caused by intracellular organisms such as T. marneffei (18).

The recognition of disseminated T. marneffei infection as an emerging complication in non-AIDS patients treated with targeted therapy has major public health implications.

Figure 1. Multiple, shallow, oozing ulcers at the terminal ileum (arrows) detected by colonoscopy on day 4 of hospitalization for case-patient 1, who had a disseminated infection with Talaromyces marneffei.

Figure 2. Nasopharyngeal biopsy specimen from case-patient 1, who had a disseminated infection with Talaromyces marneffei. A) Grocott silver staining showing abundant yeast cells (arrows) with central septa 4–5 µm in diameter. B) Hematoxylin and eosin staining showing necrotic material admixed with blood and fibrin with aggregates of foamy macrophages (arrow). Scale bars indicate 5 µm.
In regions to which *T. marneffei* infection is endemic, serologic surveillance for patients receiving targeted therapy might be useful in the early diagnosis of *T. marneffei* infection, as in the case of AIDS patients (19). In non-endemic regions, such as the United States, clinicians should be vigilant of this infrequent infection in at-risk hematology patients who have resided in or are returning from disease-endemic areas.

This study was partly supported by donations from the Hui Hoy and Chow Sin Lan Charity Fund Limited; the Health and Medical Research Fund (ref. no. 13121342) and HKM-15-M07 (commissioned study) of the Food and Health Bureau of Hong Kong Special Administrative Region Government; the Strategic Research Theme Fund, The University of Hong Kong; and a Croucher Senior Medical Research Fellowship.

Dr. Jasper F.W. Chan is a clinical assistant professor in the Department of Microbiology, The University of Hong Kong, Hong Kong, China. His research interests include emerging infectious diseases and opportunistic infections in immunocompromised hosts.

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Address for correspondence: Patrick C.Y. Woo, State Key Laboratory of Emerging Infectious Diseases, Department of Microbiology, Carol Yu Centre for Infection, The University of Hong Kong, University Pathology Bldg, Queen Mary Hospital Compound, Pokfulam Rd, Hong Kong, China; email: pcywoo@hku.hk