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LETTER TO THE EDITOR

Invasive fungal infections after obinutuzumab monotherapy for refractory chronic lymphocytic leukemia

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Dear Editor,

Patient 1 was a 40-year-old man with refractory chronic lymphocytic leukemia (CLL), having received in the past 8 years R-CHOP, FCR, R-B, DHAP, BEAM, MINE (supplemental file), alemtuzumab, and radiotherapy. He was persistently neutropenic and had three septicemic episodes responding to broad-spectrum antibiotics. In January 2014, the anti-CD20 antibody obinutuzumab was administered via a named patient program (NPP) together with antifungal (itraconazole) and anti-pneumocytis (cotrimoxazole) prophylaxis. After the third dose of obinutuzumab, fever not responding to broad-spectrum antibiotics and echinocandin (micafungin) developed. Blood cultures were negative. Later, chest X-ray and computed tomographic scan showed diffuse ground-glass consolidations (Fig. 1a). Bronchoalveolar lavage yielded *Pneumocystis jirovecii*. Although high-dose cotrimoxazole was administered, fever persisted. A repeat blood culture showed *Candida krusei*. Despite high-dose liposomal amphotericin B, he died of multi-organ failure.

Patient 2 was a 38-year-old man with refractory small lymphocytic lymphoma/CLL, having received in the past 6 years FC (supplemental file), FCR, R-CHOP, and R-B. He was persistently neutropenic, but no septic episodes had occurred. In February 2014, obinutuzumab was administered via an NPP, with inhalational pentamidine prophylaxis. After the third dose of obinutuzumab, fever not responding to broad-spectrum antibiotics and echinocandin (anidulafungin) developed. Blood cultures were negative. Bone marrow examination showed septated fungi (Fig. 1b), confirmed by culture to be *Penicillium marneffei*. High-dose liposomal amphotericin B and itraconazole were administered. Fever failed to respond. His chest X-ray then showed bilateral shadowing (Fig. 1c), associated with progressive shortness of breath. It was highly suspicious of *P. jirovecii* infection, but severe thrombocytopenia precluded bronchoscopic confirmation. High-dose cotrimoxazole was given, resulting in resolution of fever and X-ray changes. A fourth course of obinutuzumab was administered under cotrimoxazole and itraconazole coverage.

Before obinutuzumab treatment, both patients had been heavily pre-treated with potent lymphodepleting/cytotoxic drugs, resulting in prolonged leucopenia. However, with appropriate prophylaxis, none of them developed opportunistic infections. Yet, once obinutuzumab was given, both patients developed invasive fungal infections (IFI).

In case 1, despite prophylactic cotrimoxazole, *P. jirovecii* infection still occurred. Furthermore, candidemia developed despite the use of itraconazole and micafungin. In case 2, an even more serious disseminated *P. marneffei* infection developed. *P. marneffei* infection is an acquired immunodeficiency syndrome (AIDS) defining condition [1]. Similar to case 1, despite prophylactic pentamidine, an infection highly likely due to *P. jirovecii* developed. The apparent failure of prophylaxis might be related to severe lymphopenia. In patient 1, the leucocyte counts were between 0.2 and 0.4×10^9/L, practically all of which were abnormal lymphoid cells. In patient 2, the CD4 T cell count at diagnosis of *P. marneffei* was 0.04×10^9/L. Hence, in both cases, the CD4 T cell counts would be lower than 0.05×10^9/L, which defined severe lymphopenia as occurring in AIDS.

IFI is rarely attributed to the type I anti-CD20 antibody rituximab [2]. For the type II anti-CD20 antibody obinutuzumab, trials in newly diagnosed CLL [3] and relapsed/refractory B cell lymphomas [4, 5] had not reported any IFI. Obinutuzumab is much more potent than rituximab in

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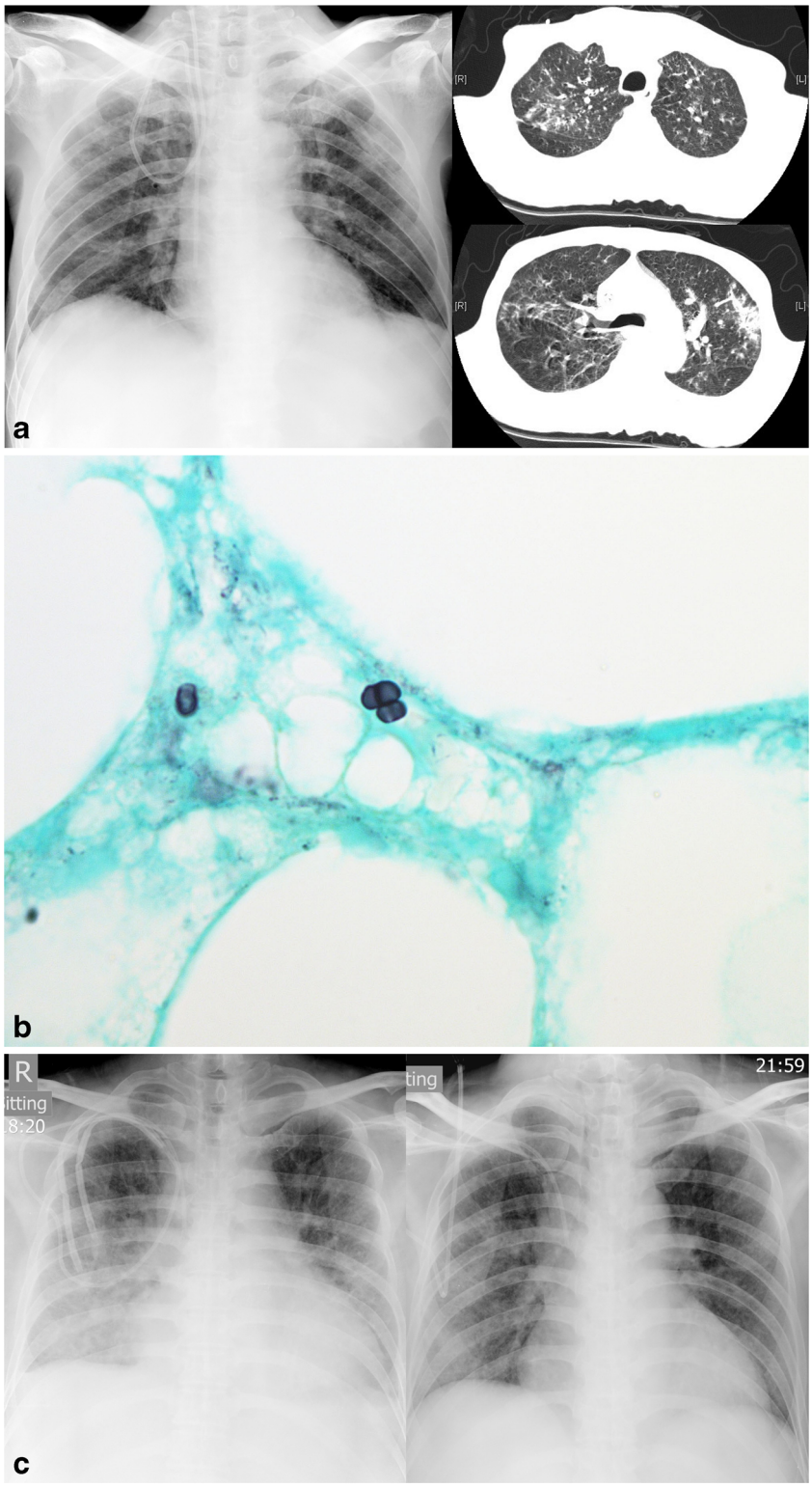

Fig. 1 Invasive fungal infections after obinutuzumab monotherapy. **a** Chest radiography showing bilateral diffuse shadowing. Computed tomography showed areas of consolidation and ground-glass opacities. **b** Grocott staining showing fungal elements (original magnification 1,000×). **c** Chest radiographs showing bilateral diffuse shadowing (*left*), which had largely resolved after 10 days of high-dose cotrimoxazole

depleting CD20-positive B cells [6]. Our cases showed that in heavily pre-treated patients who had received lymphodepleting drugs, although obinutuzumab might not be the sole risk factor, it did predispose to severe IFI. More ominously, IFI developed despite the use of otherwise effective prophylactic antifungal drugs.

IFI is conventionally attributed to prolonged neutropenia. However, T cells and B cells contribute to defense against IFI

[7]. Moreover, B cells, particularly B-regulatory cells that secrete cytokines [8], directly interact with T cells. Hence, B cell depletion impairs T cell immunity, increasing opportunistic infections. Physicians using obinutuzumab should be aware of the risks of IFI.

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Conflict of interest There are no conflicts of interest to declare.

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