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LETTER TO THE EDITOR

Atypical primary cutaneous cryptococcosis during ibrutinib therapy for chronic lymphocytic leukemia

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Dear editor,

Evidence about the role of Bruton's tyrosine kinase (BTK) inhibitor ibrutinib in predisposing patients with B-cell malignancies to fungal infections is growing, although a precise estimate of this clinical problem is still unknown [1].

Herein, we report an atypical case of primary cutaneous cryptococcosis (PCC) during ibrutinib treatment for chronic lymphocytic leukemia (CLL).

The patient was an 82-year-old woman, admitted to our hospital in September 2018 for edema and erythema of the left arm associated with a digital ulceration (Fig. 1a, b). Patient's medical history revealed CLL diagnosed in 2013: because of disease progression, in early 2016, she was enrolled in a phase 2 trial for treatment-naïve unfit patients, combining ibrutinib with 8 rituximab cycles (GIMEMA-LLC1114, NCT02232386).

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At admission, suspecting bacterial cellulitis, ceftriaxone and vancomycin were started and ibrutinib stopped. However, unexpectedly, *C. neoformans* grew on a swab of the digital ulcer, and the test for serum cryptococcal antigen was positive (1:16). A biopsy of the ulcer revealed granulomas and encapsulated yeasts (Fig. 1c) with the culture confirming the growth of *C. neoformans*. A lumbar puncture and a total-body CT scan ruled out central nervous system involvement and other localizations of the infection. Blood cultures and HIV test were negative and CD4 + T-cell count was normal.

Fluconazole was started obtaining fast clinical improvement. However, 5 weeks later, a new onset of sporotrichoid lymphangitis occurred on the arm (Fig. 1d). Given its persistence despite antifungal treatment, after 6 more weeks, a new biopsy was performed, still showing yeasts and granulomas. Fluconazole was continued for 8 months until the lymphangitis finally resolved. Currently, CLL is in remission and ibrutinib has not been reintroduced.

Invasive cryptococcosis has been classically associated to deficiency of CD4 + T-cells typical of AIDS or idiopathic CD4 + T-cell lymphocytopenia; less frequently it can affect patients with other types of impaired cellular immunity [2]. PCC is a rare entity, characterized by cutaneous localization of *Cryptococcus*, that can affect both immunocompromised and immunocompetent patients after environmental exposure [3].

CLL per se is not traditionally associated to cryptococcosis, with few cases reported after lymphocyte-depleting chemotherapy [4–6]. Interestingly, according to recent reports, ibrutinib seems an additional risk factor for opportunistic mycoses, and, since it was the only ongoing treatment for CLL in our patient, we wondered about its role in predisposing her to PCC [1].

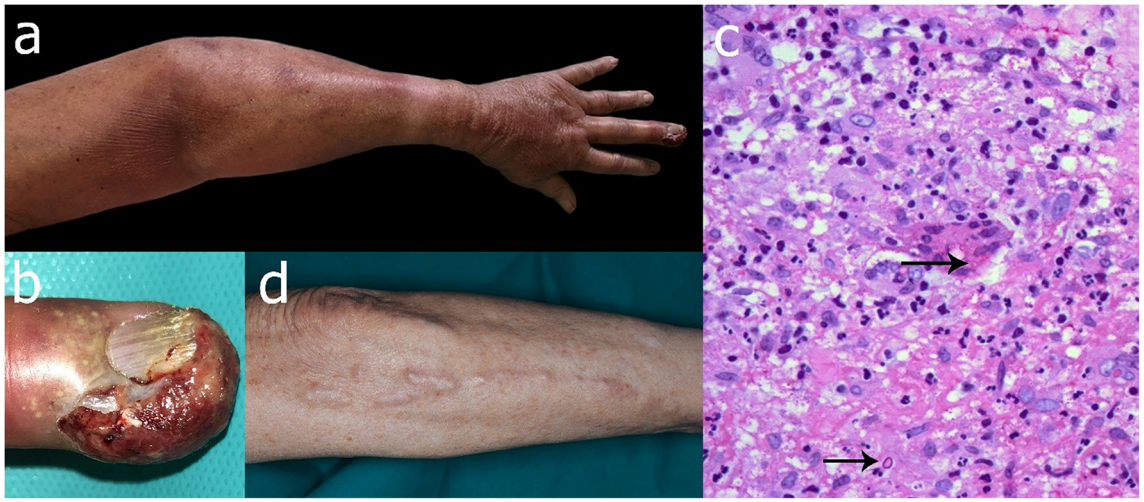

Fig. 1 **a** Patient's arm at presentation. **b** Ulcerated digital lesion at admission. **c** Digital biopsy showing granulomas with encapsulated yeast (arrows), periodic acid Schiff staining. **d** Nodular lymphangitis with sporotrichoid pattern

Ibrutinib inhibits BTK, fundamental for differentiation of B-lymphocytes [7]. Despite BTK is not expressed on T-cells, CD4 + T-cell function might be impaired by ibrutinib through some "off-target" effects such as inhibition of IL-2-inducible T-cell kinase [8]. Moreover, since BTK is expressed on monocytes and macrophages, ibrutinib can impair their function, including phagocytosis of fungal organisms [9, 10].

Of note, cryptococcosis is known to be associated to immune reconstitution inflammatory syndrome after early antiretroviral therapy in AIDS [2]: similarly, we speculate that the new onset of nodular lymphangitis after clinical improvement in our patient might be due to the recovery of monocyte-macrophage function after ibrutinib suspension, whose effects are still unknown.

Efforts to better understand mechanisms through which ibrutinib predisposes to fungal infections are warranted; moreover, we suggest that opportunistic mycoses should always be suspected in patients on ibrutinib who develop infections.

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Compliance with ethical standards

Conflict of interest AB has received personal fees including consultancy and travel grants from Gilead Sciences, Janssen Pharmaceuticals, ViiV Healthcare, Merck Sharp & Dohme, Nordic Pharma, Pfizer, and AbbVie. She has also received research grants from Gilead Sciences. FP has received honoraria for participating as a speaker at satellite symposia and educational meetings organized by Bioverativ, CSL Behring, Grifols, Novo Nordisk, Roche, Sanofi, Sobi, Spark Therapeutics, Sysmex, and Takeda. She is also member of the scientific advisory board of Sanofi. Other authors have no conflicts of interest to declare.

Ethical approval Not applicable since the paper does not contain any studies performed by the authors.

Consent for publication Written informed consent for publication of their clinical details and clinical images was obtained from the patient.

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