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Letter to the Editor

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Malignant syphilis in HIV negative patient treated with ibrutinib

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Sir,

Ibrutinib is a drug that irreversibly inhibits *Bruton Tyrosine Kinase* (BTK) - an enzyme involved in the development, activation, function, and survival of B-lymphocytes [1]. It is therefore a useful therapeutic option in neoplasms of this cell lineage (i.e. chronic lymphocytic leukaemia, Waldeström's macroglobulinaemia, mantle lymphoma and marginal zone lymphoma). The drug is easy to administer (orally), the response is fast and long-lasting, and it is generally well tolerated by the patient. However, several types of side effects such as haemorrhagic diathesis, atrial fibrillation, skin lesions, diarrhoea and opportunistic infections have been reported [2,3]. The main opportunistic infections described in patients treated with ibrutinib are classical bacterial (mainly capsular), fungal (*Aspergillus* spp. and *Pneumocystis jirovecii*) and viral (*Herpesvirus* family) infections [4-7]. However, the incidence, severity and type of microorganism are influenced by other factors such as the type of haematological malignancy, previous use of other drugs or concomitant use of immunosuppressive medication [4,5,8,9]. In this paper we report the association of ibrutinib treatment with malignant syphilis, a rare and severe manifestation of sexually transmitted infection.

A 51-year-old Caucasian man with a history of primary hypogonadism under replacement therapy and unprotected sexual relations with multiple partners. He was diagnosed with Waldenström's macroglobulinemia, receiving a first line of treatment with 6 cycles of cyclophosphamide, dexamethasone and rituximab, with poor clinical response. Subsequently, a second line of 6 cycles of bortezomib, dexamethasone and rituximab were administered, despite of that, a sudden increase in the monoclonal component was observed so it was finally decided to start treatment with ibrutinib, with an excellent initial response.

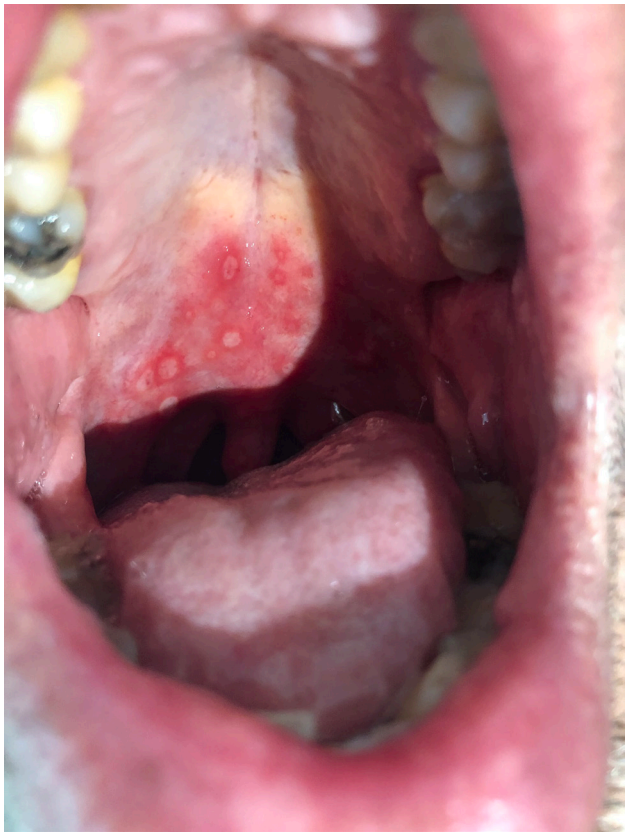

Figure 1 | **Oral Herpes simplex virus type 1 infection**

Five months after starting treatment the patient was referred to the outpatient infectious diseases unit relating a two-months multiple painful ulcerative lesions on the soft palate, without neither genital nor other areas affected. He was afebrile. Physical examination revealed multiple erythematous

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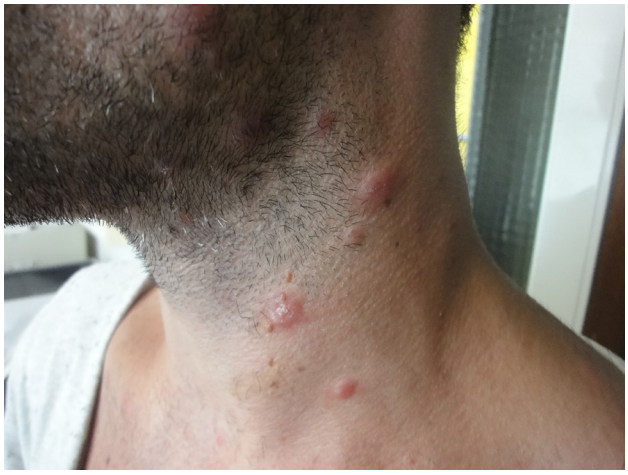

Figure 2 | **Malignant syphilis**

non-exudative aphthae on the soft palate without pillars or uvula involvement (Figure 1). One of the lesions was cultured, *Herpes simplex* virus type 1 was isolated and treated with valacyclovir with a good outcome. It should be noted that the patient had previous positive herpes simplex virus serology. Two months later, he returned to the clinic with a two-week course of fever, myalgia and the appearance of disseminated lesions (face, calotte, neck, chest, limbs, genitals and palms of the hands). These lesions were in different stages of evolution, some of them crusted (Figure 2). Direct microbiological examination of the lesions did not report bacteria, fungi or viruses. Serology showed RPR titres of 1:64 and HIV serology was repeatedly negative. With the diagnosis of malignant syphilis, treatment with penicillin was started and the lesions solved completely. One month later, he came for a check-up reporting two-week duration yellowish diarrhoea with non-pathological products, six stools per day approximately, without fever. The coproparasitic study showed *Giardia intestinalis* cysts and treatment with tinidazole was started, with resolution of the diarrhoea. HIV serology remained negative. Two years after the last event, the patient did not report new infectious complications.

Ibrutinib is a covalent inhibitor of several tyrosine kinase-active enzymes of the Tec (*transient erythroblastopenia of childhood*) family [3]. The effect on B-lymphocyte-derived neoplasms derives mainly from action on Bruton's tyrosine kinase (BTK) acting in the B-cell receptor (BCR) signalling pathway. It is therefore logical that the use of ibrutinib is associated with infections by capsulated bacteria and enteroviruses, such as in X-linked congenital agammaglobulinemia [10]. However, ibrutinib, unlike other BTK inhibitors (covalent or not), also exerts this effect on other Tec family enzymes such as BMX (*bone marrow tyrosine kinase on chromosome X)*, ITK (*interleukin 2-inducible T cell kinase*), RLK (*resting lymphocyte kinase*) and TEC (*tyrosine kinase expressed in hepato-cellular carcinoma*). T lymphocytes express three of these kinases (ITK, TEC and RLK), so complication of ibrutinib treatment with intracellular infections (especially fungal and viral) is possible [11].

Two factors are involved in the pathogenesis of any infectious disease: the causative agent and the host's defense mechanisms. In the patient described in this study, three infectious diseases were observed in a short period of time. Initially, a reactivation of herpes simplex type 1, with more aggressive features than the forms appearing in immunocompetent subjects. Afterwards, he developed a clinical and biological condition corresponding to malignant syphilis. This syndrome is characterised by the appearance of crusty ulcerated skin lesions accompanied by systemic manifestations such as fever, headache, myalgia, lymphadenopathy or visceral involvement [12,13]. Malignant syphilis is rare in immunocompetent individuals and has been described especially immunosuppressed patients (mainly in HIV co-infected and occasionally in association with immunosuppressive treatment [12,14]. Furthermore, the patient suffered from a *Giardia intestinalis* enteritis, probably related to risky sexual practices [15].

The above data suggest on the one hand that, although the association with skin lesions and diarrhea are well described nonspecific manifestations in patients receiving ibrutinib, it seems justified to look for associated infectious factors that can be specifically treated before attributing them to drug toxicity. On the other hand, we should really consider STI prevention in patients receiving ibrutinib.

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None to declare

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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