case report

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Cryptococcal meningitis in an immunocompetent patient with primary myelofibrosis on long-term ruxolitinib: report of a rare case and review of literature

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Summary Ruxolitinib is a Janus kinase (JAK) 2 inhibitor that is an effective therapeutic agent for primary myelofibrosis (PMF), which helps significantly to reduce constitutional symptoms and spleen size. However, this drug has significant immunomodulatory effects that may lead to various opportunistic infections. Reactivation of tuberculosis and certain viral infections have been well documented. Although a few reports of patients with pulmonary cryptosporidiosis on ruxolitinib exist, an extensive literature review shows only one previously reported case of cryptococcal meningoencephalitis in an immunocompetent patient on ruxolitinib, with a history of avian exposure. Here we report another extremely rare incidence of cryptococcal meningitis in a fully immunocompetent male patient on ruxolitinib, with no history of contact with birds. Although this is an approved and effective therapy for PMF, careful evaluation, screening, and prophylaxis in susceptible individuals should be considered before starting therapy.

Keywords Ruxolitinib · Primary myelofibrosis · Cryptococcal meningitis · Opportunistic infections · Immunocompetent

Introduction

Primary myelofibrosis (PMF) is a myeloproliferative neoplasm (MPN) that is characterized by cytopenia and massive hepatosplenomegaly as a result of extramedullary hematopoiesis. It is a chronic debilitating disease with allogeneic hematopoietic cell transplantation as the only known cure. However, other immune-modulating agents as well as chemotherapy have been found to be effective for reducing spleen size and improving other constitutional symptoms. Such agents are generally used in patients for whom transplantation may not be an option [1]. A dysregulation in the Janus kinase (JAK) signal transducer and activator of transcription (STAT) signaling pathway is found to be present in the majority of patients with PMF [2]. Ruxolitinib is a potent JAK1 and JAK2 inhibitor that is an approved therapy for patients with PMF. It is found to be effective in treating MF by reducing the spleen size and ameliorating debilitating symptoms, thereby improving the quality of life and overall survival [3, 4]. It can also be used in other MPNs such as polycythemia vera (PV) and certain hematologic malignancies.

The JAK-STAT pathway has significant immunomodulatory effects, which includes alterations in T cells as well as natural killer and dendritic cells, hence effecting immune development and signal transduction [1]. Ruxolitinib inhibits the JAK-STAT pathway, thereby exerting immunosuppressive activities by downregulating several cytokines, such as interleukins (ILs), interferon-gamma, and tumor necrosis factor-alpha (TNF-α; [5]). Such immunosuppressive activity of ruxolitinib predisposes the patient to several opportunistic infections, which includes pulmonary and extrapulmonary tuberculosis, *Pneumocystis jirovecii* pneumonia, *Cryptococcus neoformans* pneumonia, progressive multifocal leukoencephalopathy (PML), disseminated herpes virus infection, and hepatitis B virus reactivation [1].

Here, we report an extremely rare case of cryptococcal meningitis in an immunocompetent adult male patient on long-term ruxolitinib therapy for MF. An extensive review of the literature shows just one previ-

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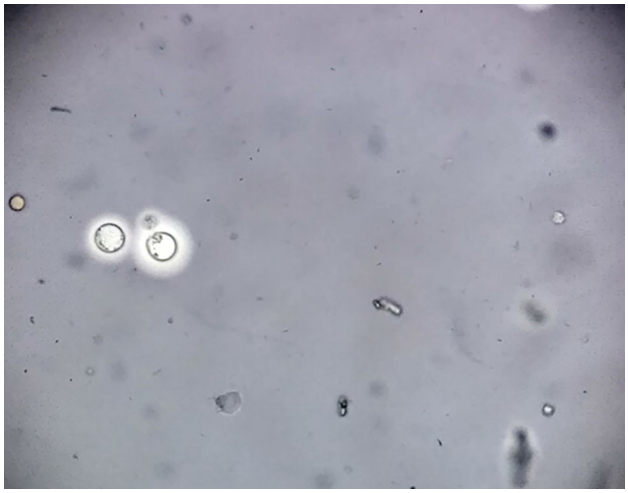

Fig. 1 India ink preparation showing Cryptococcus

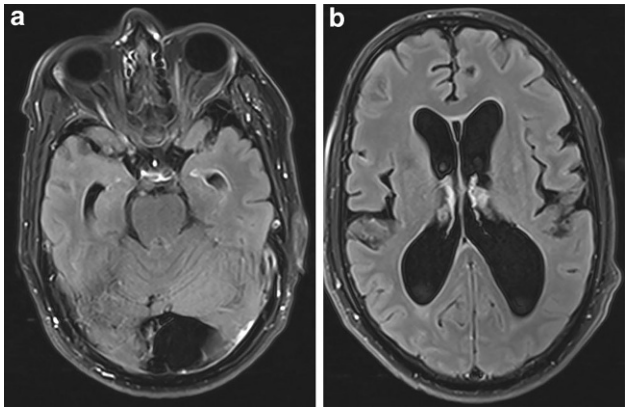

Fig. 2a,b Axial T2 FLAIR post-contrast images depicting communicating hydrocephalus along with thin diffuse leptomeningeal enhancement and mild enhancement of the ependymal lining of the bilateral temporal horns of the lateral ventricles

ously reported case of meningoencephalitis with concurrent ruxolitinib therapy [6], although a few cases of pulmonary cryptococcosis have been reported [5, 7, 8]. Investigations to determine the patient's immune status included CD4 count; T- and B-cell subset studies revealed mildly reduced absolute CD4 counts, while absolute CD8 counts and serum immunoglobulin G(IgG) levels were normal and he was seronegative for human immunodeficiency virus (HIV).

Ruxolitinib was temporarily discontinued and the patient was treated with antifungals along with other supportive therapy, to which he responded well. Ruxolitinib was restarted once the patient recovered.

Case report

Here we report an extremely rare incidence of cryptococcal meningitis in a fully immunocompetent 60-year-old male patient who was diagnosed with PMF and started on ruxolitinib 2 years earlier. He was initially started on a 20-mg dose, which was reduced to 15 mg after 6 months of therapy based on his platelet count. Bone marrow evaluation was confirmatory of high-risk PMF and JAK2 was detected by polymerase chain reaction. His past medical history was significant for a history of tuberculosis 8 years previously, for which he had undergone 9 months of antitubercular therapy. After 2 years of continuing the drug, he presented with a 2–3-month history of headache, which was aggravated over the last 20 days, along with visual disturbances, fatigue, and gait abnormalities. Following admission, investigations carried out showed cerebrospinal fluid (CSF) cell count of 149 cells/mm^3, with 80% neutrophils and 20% lymphocytes. The CSF glucose level was reduced, at 20 mg/dl, while protein was elevated with a value of 207 mg/dl. Potassium hydroxide (KOH) mount showed no fungal elements, while CSF tested positive for cryptococcal antigen, which was confirmed by the presence of encapsulated budding yeast cells morphologically resembling Cryptococcus on an India ink preparation (Fig. 1). He was HIV-1 and -2 seronegative. We conducted T-cell enumeration studies, which yielded the following results:

- T helper cells (CD4$^+$, CD3$^+$) absolute count: 312 cells/mm^3
- T suppressor cell (CD8$^+$, CD3$^+$) absolute count: 239 cells/mm^3
- T cells (CD3$^+$) absolute count: 589 cells/mm^3
- T helper cells: suppressor ratio: 1.31
- CD4$^+$ CD3$^+$ % of T lymphocytes: 53%
- CD8$^+$ CD3$^+$ % of T lymphocytes: 41%

Furthermore, the IgG level was measured, which was found to be within normal range: 1,279 mg/dl.

During this episode, the patient's Hb level was 11.4 mg/dl, platelets were $140 \times 10^3/\mu$l, and white blood cell count was $12.40 \times 10^3/\mu$l.

Magnetic resonance imaging (MRI) of the brain showed diffuse abnormal leptomeningeal and bilateral temporal ependymal enhancement with communicating hydrocephalus suggesting meningitis (Fig. 2a and b).

He was started on treatment with intravenous fluconazole. Ruxolitinib was discontinued temporarily. The patient recovered eventually; his symptoms were completely alleviated and he was discharged in a hemodynamically stable condition. In the follow-up outpatient department visits, ruxolitinib was restarted at reduced doses of 10 mg, as his disease was well controlled.

Discussion

Ruxolitinib is commonly used in the treatment of MF and has been found to significantly reduce constitutional symptoms and enlarged spleen size, due to inhibition of JAK1 and JAK2, leading to decreased STAT 3 and STAT 5 activation. This subsequently results in anti-inflammatory effects by affecting den-

dritic cell function, reduced cytokine production, and decreased expression of antigen-specific T-cell activation [9]. Ruxolitinib affects T cells by reducing their numbers, thereby impairing cytokine production and halting differentiation to T helper cells type 1 (Th1), Th17, and regulatory T cells [10]. It also reduces NK cell numbers, thereby increasing the risk for viral infections [11]. These effects on cell-mediated immunity may result in severe immunodeficiency, hence predisposing the patient to high risks for infectious complications.

Several publications have been reported citing severe infections in ruxolitinib-treated patients. Although reactivation of tuberculosis with ruxolitinib is well documented, there have been few reported cases of pulmonary cryptococcosis in ruxolitinib-treated patients [5, 7]. However, an extensive literature review shows only one previously documented incidence of long-term ruxolitinib treatment associated with cryptococcal meningoencephalitis, as reported by Chen et al. [6]. Moreover, this case describes close contact with chickens that subsequently led to the development of cryptococcal infection with concomitant ruxolitinib use.

In our report, we describe a case of cryptococcal meningitis in a fully immunocompetent male patient with no history of exposure to birds. Moreover, IgG levels were normal whereas T-cell subset studies showed no clinically significant immunosuppression. Other reported cases of opportunistic infections in patients on ruxolitinib also show normal CD4 and absolute lymphocyte counts. Dioverti et al. [1] report two cases presenting with AIDS-defining illnesses, including cytomegalovirus retinitis and PML, despite normal CD4 counts. Therefore, immunological studies are not reliable for assessing and predicting such infections in patients on ruxolitinib [2]. Furthermore, a few major trials comparing treatment with ruxolitinib and placebo did not show significantly increased opportunistic infections in the former, as studied by Vanunucchi et al. [7], who report 41.8% cases of herpes zoster in patients treated with ruxolitinib as compared with 36.9% in patients receiving standard therapy, out of a total of seven patients. Favorable responses of ruxolitinib, however, led to improvement in leucopenia and decreased risk of infection [1, 12]. Nevertheless, initiation of ruxolitinib warrants a thorough assessment for infectious risks and screening for certain viral infections such as cytomegalovirus, herpes simplex, and varicella zoster virus.

There are no clear guidelines as to the appropriate course of therapy once an opportunistic infection is diagnosed in a patient on ruxolitinib. Discontinuation of the drug has been most commonly reported, whereas some have restarted therapy. Heine et al. in their study report that the risk of developing infections may be dose dependent, as an increase in dosage may lead to reactivation or development of an infection, which resolve with subsequent dose reduction [1, 13].

Conclusion

Ruxolitinib is a JAK2 inhibitor that is used for the treatment of PMF and has been found to significantly reduce constitutional symptoms and spleen size. However, patients on long-term ruxolitinib are at a higher risk of developing opportunistic infections due to immunosuppressive actions of this drug. Hence, treating physicians should be vigilant and consider the possibility of such infections for prompt diagnosis and management in order to improve patient outcomes. Past medical history, risk of reactivation of infections, drug interactions and history of exposure to opportunistic infections should be considered prior to starting therapy.

Conflict of interest A. Chakrabarti and N. Sood declare that they have no competing interests.

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