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Case Report

CNS-invasive aspergillosis following ibrutinib therapy

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Abstract

Ibrutinib is Bruton's tyrosine kinase inhibitor that now become the standard of care for the treatment of CLL (chronic lymphocytic leukemia) and other lymphoid cancers. With its increasing usage, oncologists must become more aware of their potential side effect profile. Ibrutinib is typically thought to be less immunosuppressive than standard immunotherapy; however, can still cause devastating side effects. We present a case of CNS-invasive aspergillosis in a patient with Waldenstrom's macroglobulinemia being managed with ibrutinib. We hypothesize that treatment with ibrutinib can resemble those with X-gammaglobulinemia, thus putting our patient at risk of developing such an invasive fungal infection. Traditional risk factors for CNS-invasive aspergillosis include neutropenia, systemic glucocorticoid treatment, mastoidectomy, spinal anesthesia and paraspinal glucocorticoid injections. Oncologists need to weigh the risks and benefits of ibrutinib therapy in certain populations and more data in the future may suggest potentially adding empiric antifungal coverage with its usage.

Background

Bruton's Tyrosine Kinase (BTK) allows B-cell to enter the S phase of the cell cycle through control of cyclin-D2 expression and calcium release, which is necessary for proliferation. In addition, it serves an essential role in B-cell receptor cross-linking on antigen binding, as well as BCR class switching [1,2]. Congenital lack of BTK is the cause of X-linked Agammaglobulinemia, which presents as a lack of serum and mucosal antibodies due to a lack of B-cells. This presents as recurrent sinopulmonary infections by 2-3 months of life [3]. Thus, mature B-cells rely on BTK for proliferation and activation, and most mature B-cell malignancies are dependent on BTK for proliferation. Ibrutinib, an inhibitor of the kinase activity of BTK has become nearly ubiquitous in the treatment of mature B-cell malignancies, especially in CLL where it is approved as a first-line treatment but also as a novel therapeutic for Waldenstrom's macroglobulinemia, marginal zone lymphoma, mantle cell lymphoma, graft vs. host disease and relapsed follicular lymphoma [4]. Use in CLL has continued to increase, as the long-term findings of the RESONATE trial have shown superior progression-free survival with a low-risk profile [5]. However, due to the essential nature of BTK, and increasingly widespread use, case studies suggest that in certain individuals, atypical infections have become a rare but persistent side effect. Here we document another case of CNS aspergillosis as a result of ibrutinib therapy and discuss the potential mechanisms and potential considerations of ibrutinib therapy.

Case presentation

A 64-year-old male presented to the hospital with new onset fevers, chills, and headaches for three days. The patient's medical history was significant for a history of insulin-dependent type II diabetes, atrial fibrillation, peripheral vascular disease, coronary artery disease status post CABG, Waldenstrom's macroglobulinemia on ibrutinib and a history of transformed diffuse large B-cell Lymphoma status post ICE/BEAM chemotherapy and subsequent hematopoietic stem cell

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transplant in 2013. The patient was hospitalized for 2 weeks with bacterial pneumonia with superimposed influenza A that was treated with vancomycin and cefepime and then augmentin. Two days later, the patient was re-presented to the hospital with worsening severe headaches, fevers and chills. A lumbar puncture was performed. Cerebral spinal fluid analysis revealed a WBC count of 595/mcL predominantly neutrophils with gram stain positive for white blood cells but without growth of an organism on culture. The patient was empirically started on vancomycin and meropenem for 2 weeks.

MRI (Magnetic Resonance Imaging) of the head obtained during the hospitalization showed an abnormal mass-like signal and enhancement along the ependymal surface/periventricular white matter of the anterior horn left lateral ventricle, with an abnormal signal in the dependent left occipital horn and along the junction of the right atria and temporal horn. He had a repeat lumbar puncture done after the 2 weeks which continued to show an unexplained pleocytosis and a repeat MRI which showed persistent findings. Fungitell was eventually found to be elevated to 326 pg/mL; however, serologies for Histoplasmosis, Blastomycosis, Aspergillosis and Coccidiosis antibodies were negative. HIV, Hepatitis, Quantiferon Gold, and urine streptococcus pneumonia antigen and Histoplasma antigen testing were all negative. CSF cytology was negative and CSF infectious workup was negative for H. influenza, Listeria, N. gonorrhea, S. pneumococcus, CMV, enterovirus, HSV1/2, HHV6, and Cryptococcal antigen, but did test positive for aspergillosis. The patient was started on IV voriconazole and micafungin empirically and began to improve clinically after 48 hours. Biopsy was not pursued based on multi-disciplinary discussion between the primary bone marrow transplant team, infectious disease, neurosurgery and family wishes. The patient was discharged to pursue 8 weeks of IV antifungal treatment but elected to pursue hospice care thereafter.

Discussion

Ibrutinib is a small molecular inhibitor that binds permanently to protein: Bruton's tyrosine kinase (BTK), which ultimately leads to blocking signaling in the B-cell leading to inhibition of cellular migration, protective tumor microenvironment, and eventually apoptosis [6]. The drug has revolutionized the treatment of CLL and now is being used very frequently. Ibrutinib is generally considered to be less immunosuppressive than standard immunotherapy in general and no prophylactic antifungal therapy is typically prescribed. The most common side effects of ibrutinib similar to other immunotherapy include autoimmune side effects. The most typical side effects of ibrutinib include diarrhea, fatigue, arthralgia, bleeding, atrial fibrillation, rashes and infections [8,9]. The effects are proposed to occur due to off-target effects with other cellular kinases. Diarrhea may be a result of EGFR off-target inhibition, due to similar events with EGFR inhibitors, and is often a self-limited reaction early in therapy, occurring in up to 50% of individuals. Arthralgias and myalgias are other common side effects without an obvious mechanism and bleeding occurs due to the inhibition of glycoprotein VI on platelets [10]. Atrial fibrillation is another well-studied side effect occurring in around 16% of patients [11]. Finally, the risk of infection is known to be increased due to the issues we have highlighted in suppressing BTK activity in B-cells. In addition, BTK inhibits IL-2-inducible T-cell kinase, which may additionally inhibit the cellular immune response [12]. Aspergillosis is a known issue in ibrutinib therapy, occurring in approximately 2.5% of patients on clinical trials [13] and was the most common infectious agent, occurring in approximately 81% of infections in one study, with as many as 40% of cerebral localizations in those instances, though that amounted to only 10 patients total [14].

CNS aspergillosis is a very rare presentation that is usually only seen in immunocompromised patients and has a mortality rate exceeding 90% [15]. Fungal infections with the use of ibrutinib have been increasingly identified with the increased use of the drug for CLL. In mice, BTK deficiency has been linked to increased susceptibility to *Aspergillus* infections [16]. In humans, the loss of BTK has been postulated to resemble individuals with X-linked agammaglobulinemia, which results in a decreased amount of B-cells leading to an increased risk of infection from encapsulated bacteria, fungi and viruses [17]. A 2018 study published in Clinical Infectious Diseases conducted a retrospective analysis at a NY hospital that found 41 out of 378 patients with "lymphoid cancer," which included both Waldenstrom's macroglobulinemia and CLL, developed serious infections. Out of this population, 16 patients were determined to have invasive aspergillosis with two cases involving the brain similar to our patient. The majority of infections seemed to correlate within the first year of initiation of ibrutinib, specifically the first thirty days within initiation, but could also range up to a maximum of 1082 days. This same population usually had received more than three treatments of ibrutinib as well. These patients did not show any signs of neutropenia, or lymphopenia, or have recent steroid use, which delves into the complexity of making a more clinical diagnosis based on symptoms [18]. Our patient also had a history of diabetes, coronary artery disease and immunosuppressed from Waldenstrom's and prior bone marrow transplantation which are known risk factors for aspergillosis [19]. Our patient also presented with the development of mild cognitive defects and delirium as a result but was relatively asymptomatic initially with nothing to suggest an invasive fungal infection involving the brain laboratory-wise or clinically. In addition, a study in Blood from 2018 conducted a retrospective analysis concluding similar results but found a strikingly high incidence of CNS invasive aspergillosis [14]. Voriconazole has been shown to have good CNS penetration and has been shown in a recent retrospective study to have a complete or partial response in 35% of patients with a survival rate of 31% [20].

Invasive aspergillosis is an extremely difficult diagnosis to make given its high mortality rate affecting high-risk groups with neutropenia and hematological malignancies. A retrospective analysis published in a 2014 study from the Journal of Clinical Microbiology evaluated the sensitivity and specificity of the whole body or serum PCR for aspergillosis. The study analyzed twenty-five studies with a total of 2595 patients that met their study criteria and found the collective pooled sensitivity and specificity of the PCR test was 84%

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(95% Confidence Interval [CI], 75 to 91%) and 76% (95% CI, 65 to 84%), respectively. However, when two samples were collected, the sensitivity and specificity rose to a specificity of 95% and sensitivity of 64% with a likelihood ratio of 12.8. Based on this, their analysis concluded that two positive PCR samples indicated a very high likelihood of confirming invasive aspergillosis [21]. Brain biopsy is thought to be the gold standard of diagnosis in CNS-invasive aspergillosis, but usually cannot be performed in immunosuppressed and thrombocytopenic hematological malignancy patients on active treatment. Although our patient did not have a biopsy-proven specimen confirmed CNS aspergillosis, the patient improved clinically after receiving IV voriconazole and micafungin empirically after 48 hours. With the increasing use of ibrutinib for CLL and other cancers, more research must be done to look into the mechanism of why ibrutinib raises the propensity for fungal infection and whether we should consider prophylactic antifungal treatment in this population. Oncologists and primary care physicians should also be aware of the possible correlation between ibrutinib and invasive fungal infections and have a lower threshold for further workup if warranted.

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