INVASIVE PULMONARY ASPERGILLOSIS FOLLOWING BEVACIZUMAB TREATMENT FOR NON-SMALL CELL LUNG CANCER

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ABSTRACT
Bevacizumab is a recombinant humanized monoclonal antibody targeting the vascular endothelial growth factor. It is approved for the treatment of unresectable, locally advanced and metastatic non-small cell lung cancer in association with chemotherapy and as maintenance therapy. Infection risk due to use of bevacizumab is a very rare event. Several cases of aspergillosis in patients treated with monoclonal antibodies have been reported, mostly following treatment with tumor necrosis factor-alpha blockers. We present a case of a 60-year-old patient treated for stage IV non-small cell lung cancer, who has been diagnosed with invasive aspergillosis following bevacizumab treatment, and, we postulate that bevacizumab may contribute to this infection.

KEYWORDS
Invasive aspergillosis, Bevacizumab

Introduction
Bevacizumab is a recombinant humanized monoclonal antibody targeting the vascular endothelial growth factor VEGF; it has been approved for the treatment of different malignancies, including non-small cell lung cancer, in association with chemotherapy or as maintenance therapy.

Infection is a rare adverse event of using bevacizumab; most likely occurring in association with chemotherapy.

Invasive Aspergillosis is a disease occurring most often in the context of immunosuppression. It has been related mostly to neutropenia or the use of steroids. Several cases of aspergillosis in patients treated with monoclonal antibodies have been reported mostly following tumor necrosis factors alpha blockers treatment [1].

In this article, we reported the case of a patient diagnosed with invasive pulmonary aspergillosis following treatment with bevacizumab for stage IV non-small cell lung cancer and postulated that bevacizumab may have contributed to its occurrence.

Case Report
A 60-year-old adult male, diagnosed with stage IV adenocarcinoma of the lung, he received 6 courses of paclitaxel-carboplatin-bevacizumab (15mg/kg every three weeks) with good tolerance and stable disease then he switched to bevacizumab alone as maintenance therapy. He received five injections without incident. At his sixth injection of bevacizumab, he reported a cough, fever, hemoptysis, and chest pain. The patient was not neutropenic. The white count was normal: 10^9/ul and the PMNs was: 6.12^9/ul.

The thoracoabdominal pelvic computed tomography (CT) scan was performed showing stabilization of the malignancy but identified a cavitary lesion is corresponding to an Aspergillus transplant (Figure 1A). An admission sputum culture grew Aspergillus fumigatus, the galactomannan assay did not perform
to our patient due to its no disponibility in our hospital. Itraconazole started, the patient remained afebrile for 5 days and was discharged home on itraconazole for three months. Treatment with bevacizumab was interrupted, after two months of treatment, a thoracic CT was performed showing favorable evolution (Figure 1B).

Discussion

Abnormal regulation of angiogenesis, defined as the process of formation of new blood vessel, has been implicated in the pathogenesis of several diseases, including cancer.

Vascular endothelial growth factor (VEGF)-A plays a significant role in the process of angiogenesis and tumor growth. It binds to the VEGF receptors, promotes endothelial cell migration and proliferation and increases vascular permeability [2]. As a result, anti-VEGF strategies have been developed to treat several malignancies.

Of the antiangiogenesis agents, bevacizumab, a monoclonal antibody targeting the vascular endothelial growth factor (VEGF)-A, inhibiting activation of the VEGF pathway and angiogenesis.

Bevacizumab has been approved for the treatment of renal-cell carcinoma, breast cancer, and colorectal cancer [3]. It is also, indicated in the first-line treatment of patients with unresectable, locally advanced, metastatic non-small cell carcinoma, in combination with chemotherapy and as maintenance therapy [4].

Such other anti-angiogenesis agents, several adverse events have been described with the usage of bevacizumab, including hypertension [5], congestive heart failure [6], arterial thrombosis [7], bleeding [8], proteinuria [9, 10] and gastrointestinal perforation [11, 12].

Additionally, infection has rarely been reported with bevacizumab treatment; 33,526 patients from 41 Randomized controlled trials, have been included in a recent meta-analysis to demonstrate the risk of infection when adding bevacizumab to the treatment of cancer patients; the incidence of all-grade infections was 7.8% (95%CI, 4.8–12.4%) and 3.0% (95%CI, 2.1–4.3%) for high-grade infections [13].

Invasive Aspergillosis is a disease frequently occurring in immunocompromised subjects, mostly in patients treated for hematologic malignancies or underwent hematopoietic cell or solid organ transplantation.

The pathogenesis of invasive aspergillosis remains poorly understood [14]. Actually, the major risk factors reported are severe or prolonged neutropenia secondary to chemotherapy treatment. Although, many patients who develop this condition have normal neutrophil counts, and high dose corticoid use is the second most important risk factor [15].

Several cases of aspergillosis in patients treated with monoclonal antibodies have been described, the tumor necrosis factor (TNF)-alpha blockers are the most agents reported [1].

The contribution of bevacizumab to this infection remains poorly understood.

Angioinvasion appears to have a significant role in the pathogenesis of invasive aspergillosis. Aspergillus hyphae invade the pulmonary alveolar endothelial cells, then the pulmonary arteries causing endothelial cell damage, proinflammatory cytokine release and activation of the coagulation cascade, resulting in tissue hypoperfusion, intravascular thrombosis and tissue necrosis [16; 17].

Those phenomena are potent inducers of vascular endothelial growth factors including VEGF [18], and high VEGF levels have been reported in the presence of aspergilloma [19].

VEGF is produced by many cell types including macrophages [20]. The first line of immune defense, the inhibition of the VEGF signal pathway (with bevacizumab) could affect the function of these immune cells, as a result, affecting the host response and facilitating the promotion of the infection [21, 22]. Indeed, in several reports, Aspergillus infections have been shown to secrete angiogenesis inhibitors, inducing ischemia and preventing neutrophil clearance of the fungal infection [23–24–25]. Aspergillosis associated with bevacizumab treatment have been reported in a very limited report.

A case of invasive aspergillosis has been described in a patient treated with bevacizumab for colon cancer [26]. The patient had neutropenia secondary to chemotherapy; he was receiving in combination with bevacizumab, contrary to our patient who had invasive aspergillosis when receiving bevacizumab alone. In a trial, a total of 99 were treated with bevacizumab to assess the efficacy of bevacizumab in non-small cell lung cancer. Two patients have developed invasive aspergillosis with no case being reported in the control group [4]. Additionally, in a single-institution phase II trial of radiation, temozolomide, erlotinib, and bevacizumab for initial treatment of glioblastoma, one patient from a total of 55 patients enrolled for efficacy analysis died of disseminated aspergillosis [27].

Conclusion

Bevacizumab is an active drug, widely used in several malignancies; in our case, we postulate that bevacizumab may be responsible for other side effects not yet clearly identified, including invasive aspergillosis, reporting these side effects can be crucial in the management of such drug.

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Competing Interests
Written informed consent obtained from the patient for publication of this case report and any accompanying images.

Abbreviations
TNF: tumor necrosis factor VEGF: vascular endothelial growth factor NSCLC: non-small cell lung cancer CT: computed tomography PMNs: polymorphonuclear leukocytes

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