

**Sunitinib Use for Metastatic Renal cell Carcinoma
Associated with Necrotizing Cavitory Pulmonary
Aspergillosis with *Aspergillus flavus*: Case Report and
Review of Literature**

Abstract

Sunitinib associated chronic necrotizing cavitory pulmonary aspergillosis has rarely been reported in literature. This article describes a patient with biopsy proven papillary renal cell carcinoma initially treated by radical nephrectomy. He presented about 8 months later with progressively worsening abdominal pain, headache, weight loss of 40 pounds and investigation revealed extensive retroperitoneal and mediastinal lymphadenopathy with brain metastasis. He was evaluated by oncology and started on cycles of sunitinib with dexamethasone, which he took for about 6+ months. He presented to the hospital in respiratory distress requiring intubation and ICU admission and CT scan of thorax revealed a new large consolidation with necrosis and a cavity. Given suspicion of opportunistic fungal infection with sunitinib, he was started on empiric Vancomycin, Zosyn and Voriconazole. He underwent bronchoscopy,

bronchoalveolar lavage and cultures revealed *Aspergillus flavus*. Subsequently serum and BAL galactomannan were reported positive as well. Given poor prognosis, patient's family elected for comfort measures.

Keywords

Aspergillus flavus, pulmonary aspergillosis, Sunitinib, small molecule tyrosine kinase inhibitors, ibrutinib, metastatic renal cell carcinoma, immunocompromised

Introduction

Historically, the major risk factors for opportunistic invasive fungal infections include hematopoietic stem cell or solid organ transplant, prolonged neutropenia, graft versus host disease requiring immune suppression, chronic steroid therapy and cancer chemotherapy. Most of these risk factors increase the risk for IFI by direct and indirect effects on T cell and B cell function. The last decade has witnessed the approval of various highly sophisticated specific immune signal pathway inhibitors that has resulted in an unprecedented clinical success rates for treatment of cancer and other autoimmune diseases. Sunitinib is one such agent that belongs to a class of small molecule tyrosine kinase inhibitors (TKI, eg: imatinib, ibrutinib, tofacitinib and ponatinib). It is an indolin-2 analog with a broad

spectrum of action and inhibits multiple receptor kinases. Currently, it is indicated as primary therapy for patients with metastatic renal cell carcinoma and imatinib-resistant stromal tumors [1, 2]. Fungal and mycobacterial opportunistic infections have been reported from patients on TKIs [3, 4]. Pulmonary aspergillosis following treatment with sunitinib has been rarely reported. To our knowledge only two cases have been reported so far in literature [5, 6]. This article reports a case of necrotizing cavitary pulmonary aspergillosis in a patient who was on treatment with sunitinib for metastatic papillary renal cell carcinoma.

Case Report

A 69-year old male with past medical history of paroxysmal atrial fibrillation, hypertension and COPD initially presented in 5/2014 with diffuse abdominal pain, weight loss of 40 pounds and hematuria. Was evaluated by urology team, MRI revealed a large left renal mass. He underwent biopsy of the mass, pathology revealed papillary renal cell carcinoma and he underwent left radical nephrectomy in October 2016. It was a 12X11X8cm mass involving upper, middle and lower poles of the left kidney extending into the perinephric tissue and renal pelvis. Resection margins and lymph nodes were negative for carcinoma. A follow-up screening CT scan of thorax, abdomen and pelvis showed no evidence of metastasis except for a 1.5 cm pre-carinal lymph node. Hence there was no need for adjuvant chemotherapy and he was followed in outpatient clinic. He was

admitted again in June 2017 for abdominal pain, weight loss again, new onset tremors and partial seizures associated with abnormal gait. He was evaluated by neurology team, CT brain at that time showed a new 2.6 X 1.7 X 2.4 cm right parietal lobe brain mass and CT thorax and abdomen showed extensive paraaortic and retroperitoneal lymphadenopathy consistent with metastasis. He was seen by oncology team and started on sunitinib in June 2017 and was to follow with neurosurgery team for brain biopsy. However, he lost to follow up and was brought to emergency room in August 2018 with progressively worsening shortness of breath, dry cough with significant weight loss on sunitinib. He went into respiratory failure requiring intubation and admission to the intensive care unit. His chest X-ray and CT thorax showed a new large consolidation in right upper lobe with necrosis and cavitation with some necrotic areas noted in middle and lower lobes as well (figures 1 and 2). CT scan of brain was unchanged from 8 months ago with the same 2cm mass. He was started on empiric Vancomycin and Piperacillin-tazobactam intravenously.

Given that he had been on sunitinib monthly with dexamethasone, and suspicion for Aspergillosis, he was also started on voriconazole intravenously. He also underwent bronchoscopy and bronchoalveolar lavage (BAL). Bacterial cultures, AFB stain/PCR/culture, and pneumocystis DFA/cytology stain were all negative. Fungal cultures reported *Aspergillus flavus*, subsequently serum and BAL

galactomannan tests were reported positive. Family declined a brain biopsy and patient's condition continued to decline. Given critical clinical status with extensive metastasis and overall poor prognosis, family elected for comfort measures and patient expired. Autopsy was discussed but declined by family.

Discussion

Unlike acute invasive pulmonary aspergillosis, chronic necrotizing pulmonary aspergillosis is a distinct clinical entity reported in patients with chronic lung disease such as COPD, pulmonary fibrosis, bronchiectasis etc. especially patients on long term steroid therapy. Introduction of the novel small molecule Bruton tyrosine kinase inhibitors (TKI, eg: ibrutinib) and multi-receptor tyrosine kinase inhibitors (RTKI, eg: sunitinib) has revolutionized the management of certain cancers including mantle cell lymphoma, chronic lymphocytic leukemia, Waldenstroms macroglobulinemia, diffuse large B-cell lymphoma, primary central nervous system lymphoma, metastatic refractory renal cell carcinoma and imatinib-resistant stromal cancers, with durable response rates [3, 4]. Prolongation of survival with these agents comes with the cost of increased risk of bacterial and fungal infections. Among the TKIs, ibrutinib, tofacitinib, and dasatinib carry a black box warning for opportunistic infections including pneumocystis, aspergillosis, and reactivation of tuberculosis, varicella-zoster and cytomegalovirus infections [7-16]. Sunitinib specifically targets members of the split-kinase domain

family of receptor tyrosine kinases (RTKs) including the vascular endothelial growth factor receptors type 1 and 2 (VEGFR 1,2), platelet-derived growth factor receptors (PDGFR α,β), fibroblast growth factor receptor (FGFR1), FMS-related tyrosine kinase (FLT3), stem cell factor receptor (c-KIT), RET-kinase and colony-stimulating factor 1 receptor, resulting in direct and indirect B and T cell dysfunction at various levels [1, 2]. Despite such severe immune dysregulation/suppression, sunitinib related opportunistic infections is very rare. To our knowledge, only two cases of sunitinib related chronic necrotizing aspergillosis have been reported in literature.

Conclusion

Given that the use of TKIs has exponentially increased in the recent years, IFIs are still only rarely reported in these patients. Most of these patients also received high dose dexamethasone monthly with sunitinib therapy. Hence the risk for IFIs cannot be attributed to TKIs alone. It is likely that the risk for IFIs is multifactorial including genetic predisposition, concomitant steroid use, pre-existing chronic pulmonary disease and the specific immune target inhibited. It is essential for clinicians to have an insight into the mechanism of action of TKIs, immune pathways inhibited and the immunopathogenesis that would further help delineate the risk for specific bacterial, viral or fungal opportunistic infections. Enhanced clinical surveillance and implementation of prophylactic strategies based on risk

stratification would aid in the prevention, early diagnosis and management of these infections.

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Figure 1: Chest X-ray showing large Right upper lobe consolidation with necrosis and cavitation.

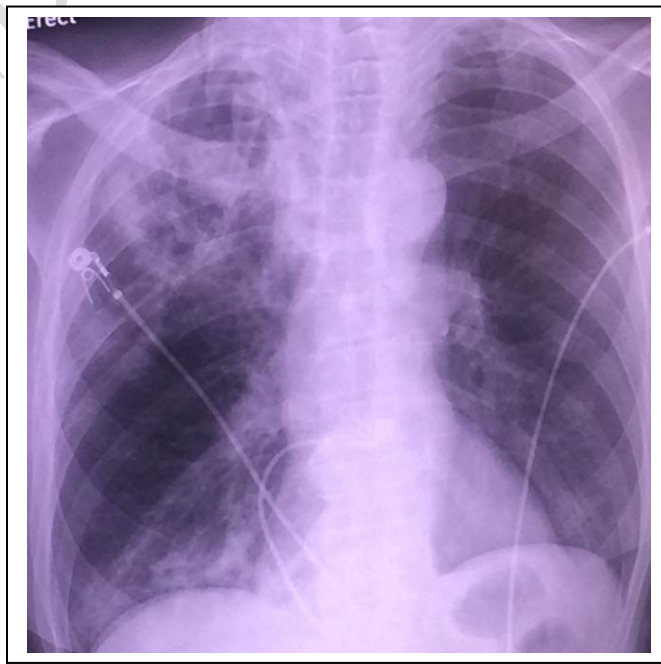


Figure 2: CT Thorax showing the Large right upper lobe necrotizing cavitory pneumonia.

