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Bevacizumab-related pulmonary and renal adverse reactions: A case report

Savya Kurian[1], Betcy C Byju[1], Lakshmi R[1]*, Madhu CS[2], Aditya V Boney[2]

1 Department of Pharmacy Practice, St. Joseph's College of Pharmacy, Cherthala, Kerala, India.
2 Department of Oncology, Lourdes Hospital, Post Graduate Institute of Medical Science & Research, Kochi, Kerala, India.

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ABSTRACT

Bevacizumab is a recombinant humanized monoclonal antibody directed against the vascular endothelial growth factor (VEGF). Binds all isoforms of VEGF-A. VEGF is a pro-angiogenic growth factor overexpressed in many solid human cancers, including colorectal cancer.Due to the inhibition of angiogenesis, many adverse reactions such as GI perforations, life-threatening pulmonary bleeding, and increased risk of thromboembolic events have been described[1]. However, its association with pneumonitis and nephrotic syndrome is rarely reported in the literature. We report a case of a 78-year-old woman with stage 4 ovarian cancer who presented with hypertension, pedal edema, nephrotic syndrome, breathlessness, SpO2 fall, and persistent cough after initiation of 3 doses of Bevacizumab. CT scan revealed pneumonitis features, persistent cough, breathlessness on minimal exertion, and dropping SpO2 level. Due to the temporal relationship with the initiation of Bevacizumab, she was suspected to have developed Bevacizumab-induced pneumonitis and nephrotic syndrome. The repeat CT chest showed a good response to steroids.

INTRODUCTION

Bevacizumab, a humanized monoclonal antibody targeting vascular endothelial growth factor (VEGF) A, was the first anti-angiogenic drug approved by the US FDA for cancer treatment. Generally, it is well tolerated, with its side effects typically differing from traditional chemotherapy. Due to its unique mechanism of action, Bevacizumab presents a distinct adverse event profile. While most side effects are mild and manageable, some can lead to significant morbidity and, in rare cases, mortality[2]. Competitively inhibiting VEGF prevents its binding to receptors on nearby endothelial cells. Consequently, various adverse reactions, such as hypertension, thromboembolism, proteinuria, and impaired wound healing, have been linked to its use. Established pulmonary complications include hemoptysis and pulmonary hemorrhage[3]. This case report highlights a rare instance of bevacizumab-induced pneumonitis and nephrotic syndrome in an ovarian cancer patient receiving Gemcitabine and Bevacizumab.

CASE HISTORY

A 78-year-old woman was diagnosed with stage IV ovarian cancer, as evidenced by CT scans revealing primary ovarian malignancy with omental and peritoneal nodules, along with enlarged para-aortic lymph nodes. Ascites fluid cytology confirmed malignancy, with a markedly elevated serum CA 125 level of 1347 U/mL (normal range: 0-35 U/mL). Given her age and poor health, she commenced chemotherapy with carboplatin + paclitaxel, at reduced doses. Following six cycles, her CA 125 levels decreased, prompting cytoreductive surgery. Due to surgical complexities, only left ovariotomy and peritoneal biopsy were feasible.

Subsequently, she underwent alternative chemotherapy comprising Gemcitabine (1.6g), carboplatin (300mg), and bevacizumab (10mg/kg or 800mg) starting on 21-02-2023. The second course was administered on 14-03-2023, followed by the third on 11-04-2023 (fig1). Encouragingly, a notable biochemical response was evidenced by a decline in CA 125 levels.

After three doses of Bevacizumab on 25-04-2023, she

Table 1 : Laboratory Investigations during the time of admission.

TEST	ADMISSION LAB VALUES
HB	8.3gm/dl
PLT	60000 lakhs/m
TC	7590/mm
ESR	40mm/hr
Creatinine	0.92 mg/dl
Albumin	2.60 gm/dl
Total protein	4.14 gm/dl
Sodium	129 Mmol/L
Potassium	4.00 Mmol/L
FBS	109 mg/dl
BP	170/100 mmHg

developed thrombocytopenia (platelet count of 70,000 cells/mm3), leading to the discontinuation of carboplatin. Subsequently, she experienced hypertension, breathing difficulties, pedal edema in both legs and signs of nephrotic syndrome, characterized by proteinuria and hypoalbuminemia (table 1). These adverse effects occurred despite her lack of previous exposure to Bevacizumab. A CT scan revealed pneumonitis, a persistent cough, breathlessness upon minimal exertion, and a drop in SpO2 levels. Treatment commenced with parenteral methylprednisolone at a dose of 62.5mg intravenously twice daily, which was gradually tapered to 40mg twice daily, then 20mg twice daily, and finally 16mg orally twice daily. A follow-up CT scan of the chest indicated a favorable response to steroids, prompting the recommendation for a cautious tapering of the medication.

Upon admission, the patient's blood work revealed hypoalbuminemia (fig 3) and proteinuria (fig 4). A CT scan indicated features consistent with pneumonitis (fig 2). Empirical broad-spectrum antibiotic therapy was initiated with intravenous faropenem 1.5g three times daily due to clinical and radiological findings suggestive of pneumonia. However, subsequent sputum culture results for common infectious agents, including bacteria, fungi, and viruses, were negative, leading to the discontinuation of intravenous antibiotics after a four-day course.

On the second day of hospitalization, the patient commenced treatment with parenteral methylprednisolone 62.5mg intravenously twice daily, with a gradual tapering to 40mg twice daily, then 20mg twice daily, and finally 16mg twice daily, resulting in an improvement in the patient's condition. Additionally, due to bilateral pedal edema, the patient was advised to receive 100ml of 20% human albumin intravenously over 4-6 hours.

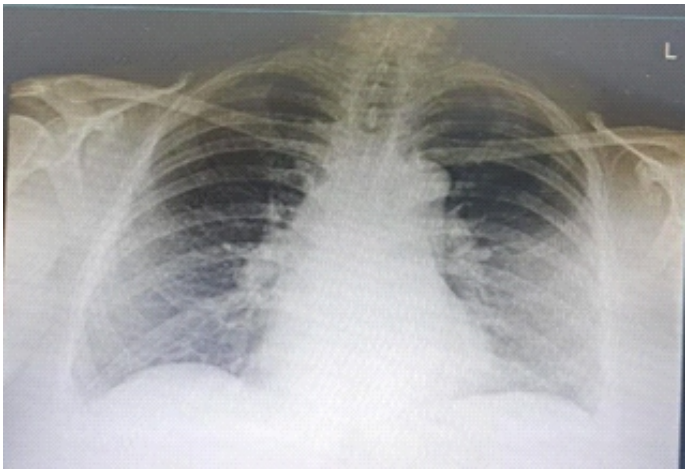

Figure 1 : Chest X-ray before taking bevacizumab

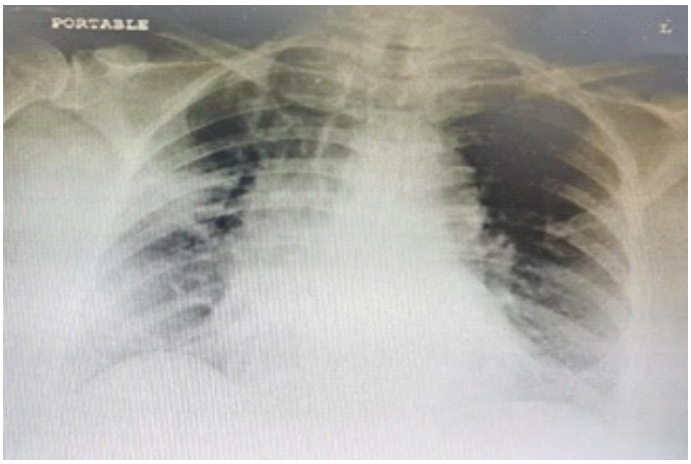

Figure 2 : Chest Xray on admission showing Subpleural consolidation with partial collapse middle lobe with adjacent faint ground glass opacity.

The patient underwent chest physiotherapy and a regimen including 20% 100ml human albumin, Inj. Faropenem, Inj. Methylprednisolone, Tab.Montelukast10mg with Fexofenadine 120mg once a day, Tab. Acebrophylline 100mg BD, Syp. Levocloperastine 5ml three times a day and steam inhalation for additional support. Following this treatment, the patient's condition improved, leading to the administration of a fourth course of D1 Salvage chemotherapy with Inj. Gemcitabine 1.6g. After three weeks of hospitalization, the patient responded positively to the treatment and was discharged.

Subsequent CT imaging of the thorax revealed subpleural interstitial thickening with faint ground glass opacity scattered in both lungs, predominantly in the basal segments. There were no areas of consolidation or infiltratory nodular lesions observed. Minimal nodular fissure thickening was noted on the left side, without any pleural effusion or thickening. An increased amount of mediastinal and epicardiac fat pad was observed, but there was no evidence of mediastinal or hilar lymphadenopathy or any other mass lesion. Compared to the previous scan, the current one showed significant resolution of interstitial thickening and ground glass opacity in both lungs. A minimal focal increase in

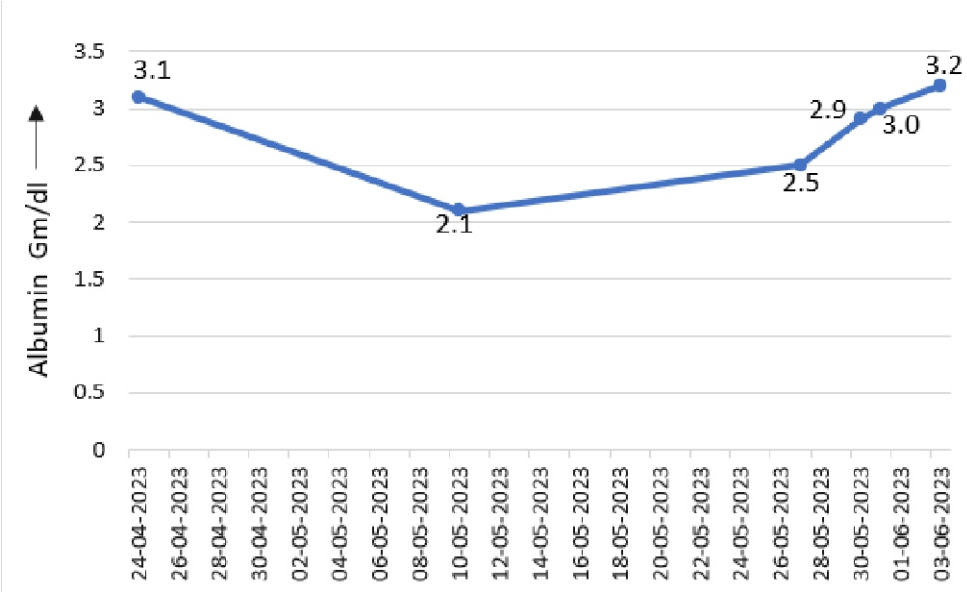

Figure 3 : Graphical Representation of Hypoalbuminemia

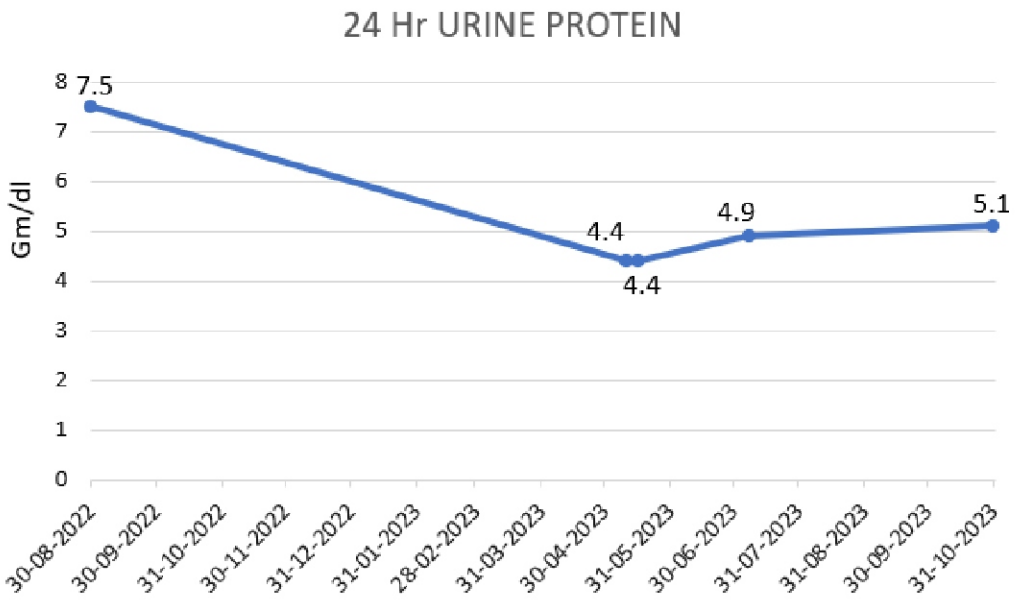

Figure 4 : Graphical Representation of Proteinuria

fibrosis was noted in the posterior segment of the right upper lobe, with no evidence of metastatic lesions.

A causality assessment was conducted, determining that the observed adverse drug reaction (ADR) was classified as "probable" according to the Naranjo ADR probability scale and "Certain" according to the World Health Organization Causality Assessment scale. The severity of the reaction was assessed using Hartwig's Severity Assessment Scale, which categorized it as a Level 5 severe reaction. Subsequently, the ADR was reported to the pharmacovigilance center as part of the National Pharmacovigilance Program in India.

DISCUSSION

The case is unique and interesting due to the close association of acute symptoms exhibited by the patient after administering a vascular endothelial growth factor inhibitor.

In a case report describing Bevacizumab-induced pneumonitis, the patient developed cough and dyspnea on exertion the day after the initiation of Bevacizumab. She had started the combination of Capecitabine and Bevacizumab and

received the first dose of Bevacizumab one week after starting Capecitabine. Bilateral air space opacities were observed on imaging, and infectious and cardiogenic etiologies of dyspnea were ruled out. Due to the temporal relationship with the initiation of chemotherapy, she was suspected to have developed Bevacizumab-induced interstitial pneumonitis. She was managed with broad-spectrum antibiotics and IV Methylprednisolone 60mg every 8 hours; subsequently, her condition improved, and she was extubated within two days of corticosteroid therapy initiation and was transitioned to daily oral Prednisone 40 mg[3].

In another case, interstitial pneumonitis was reported in a patient with metastatic breast cancer treated with the combination of Bevacizumab and pegylated Liposomal Doxorubicin. Cough and dyspnea started after three courses of treatment[4].

In a case report, a 71-year-old white man diagnosed with pancreatic cancer experienced nephrotic syndrome following Bevacizumab treatment. Initially, he underwent adjuvant chemotherapy with Gemcitabine for two months, followed by Capecitabine. Subsequently, due to disease progression, he received an additional four months of single-agent Gemcitabine. When the disease progressed further, the patient was prescribed a combination of Bevacizumab and Gemcitabine. After three doses of Bevacizumab, the patient developed hypertension and hypoalbuminemia[5].

In our patient, the emergence of reversible hypoalbuminemia, proteinuria, and pneumonitis strongly suggests drug-induced adverse effects. Although Bevacizumab is widely used and generally considered safe, rare but serious adverse reactions such as chronic lung injuries and nephrotic syndrome have been reported. Our patient received only three doses of Bevacizumab and subsequently developed a persistent cough, worsening shortness of breath, and nephrotic syndrome. Additionally, she was concurrently receiving Gemcitabine and Carboplatin. Carboplatin was discontinued due to the development of thrombocytopenia, leaving Gemcitabine and Bevacizumab as the remaining treatments. Notably, our patient and others reported to have Bevacizumab-associated proteinuria were also receiving other chemotherapeutic agents. Therefore, it is conceivable that Gemcitabine treatment initially caused injury, which was then exacerbated by the addition of Bevacizumab, and the adverse reactions improved following Bevacizumab discontinuation.

Patients with ovarian cancer had significantly higher odds of exhibiting proteinuria than those with colorectal cancer. A previous study suggested that ovarian cancer is a risk factor because the bevacizumab dose used for ovarian cancer is higher than that used for colorectal cancer (5 or 7.5 mg/kg). Advanced age and low serum albumin were significant risk factors for developing adverse reactions. Risk factors associated with pneumonitis during chemotherapy include older age, low-performance status, and decreased normal lung area on a chest CT scan, as shown in a retrospective cohort study, which compares the incidents of adverse reactions from the most frequently used monoclonal antibody[6].

Mechanisms of Bevacizumab-associated nephrotic syndrome include:Bevacizumab can affect the filtration function of the glomeruli in the kidneys. This may result from alterations in the renal microvasculature. Podocytes are specialized cells in the kidney that help maintain the filtration barrier. Disruption of VEGF signaling can lead to podocyte dysfunction, potentially contributing to proteinuria. Thrombotic microangiopathy is characterized by blood vessel damage and blood clots in small vessels, which can affect kidney function[7].Mechanisms of Bevacizumab-induced pneumonitis include: It may affect the immune system, leading to an abnormal lung inflammatory response.Inhibition of VEGF can lead to endothelial cell dysfunction, potentially causing vascular leakage and inflammation in the lung tissue.Disruption of normal angiogenesis can lead to hypoxia and ischemia, which can contribute to lung injury.

Depending on the severity of adverse effects, the administration of Bevacizumab should be discontinued temporarily or permanently. In cases with moderate to severe proteinuria or uncontrolled hypertension, Bevacizumab therapy should be temporarily discontinued until stabilization of the patient's condition. Clinicians should be aware of the important complication of Bevacizumab because this agent has been used with increased frequency to treat patients with various malignancies.

CONCLUSION

The patient developed pneumonitis and nephrotic syndrome following the administration of three doses of Bevacizumab, as evidenced by findings on chest CT scan and clinical indicators such as hypoalbuminemia and proteinuria. Enacting corticosteroid treatment resulted in clinical improvement of pneumonitis, indicating that acute respiratory failure was driven by lung inflammation. It's worth noting that pneumonitis and nephrotic syndrome associated with Bevacizumab are rare adverse reactions, highlighting the importance of early detection and preventive measures to mitigate potential morbidity and mortality risks.

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