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Case Report

Docetaxel induced subacute interstitial lung disease in a patient with prostate cancer

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ABSTRACT

Interstitial lung disease (ILD) is a collective term for a group of disorders that result in inflammation and scarring of the lung interstitium. Although majority of the cases of ILD are idiopathic, some of the etiologies can range from viral infections; connective tissue disorders or drug injury. Docetaxel is an anticancer agent of taxoid family that can rarely cause pulmonary toxicity. It can be occasionally used for the management of advanced prostate cancer. The adverse effects of the medication are mediated by type I and type IV hypersensitivity reactions. Here, we reported a case of 68-year-old man with advanced prostate cancer who completed six cycles of chemotherapy with docetaxel and presented with shortness of breath, low-grade fever and cough two weeks after completion of scheduled regimen. Clinical examination revealed diffuse wheeze and decreased air entryon auscultation, oxygen desaturation and an ulcerative lesion on the left forearm. All his routine serum, sputum and autoimmune profile were inconclusive. The inflammatory markers (CRP, ESR) were raised but procalcitonin was in normal range. Pulmonary function tests were indicative of restrictive lung disease. Digital chest X-ray revealed diffuse opacification with prominent bronchovascular markings and HRCT of thorax reported bilateral scattered honeycomb appearance, subpleural opacities, centrilobular nodules with air trapping. Docetaxel induced interstitial lung disease (DILD) was diagnosed and the patient was advised with high dose systemic and inhalational steroids along with external oxygen support. Rapid clinical improvement was seen and the patient was eventually discharged with tapering doses of oral steroids, physiotherapy and close follow-up.

Keywords: DILD, Docetaxel, Dose, Steroids, Prostate cancer

INTRODUCTION

Interstitial lung disease (ILD) is a collective term for a cluster of disorders that cause inflammation and destruction of the interstitium of the lung. The interstitium of the lung is an area between the alveolar membrane of the alveolar epithelium and endothelial lining of the alveolar blood vessels.[1] Thus, scarring in this area causes restriction in alveolar expansion and oxygen exchange, which results in hypoxia as well respiratory distress. Although the majority of the cases of ILD do not have any known cause, some of them are triggered by a number of medical or environmental stimulus.[2] They can be viral infections like Coronavirus disease-19 (COVID-19), atypical bacterial pneumonias, connective tissue disorders like rheumatoid arthritis, sarcoidosis, systemic lupus erythematous (SLE), systemic sclerosis or due to inhalation of toxic substances, drug injury from certain antibiotics, antiarrhythmic and chemotherapeutic agents. Docetaxel is a chemotherapeutic drug used in the management of various types of cancer like breast, prostate, gastric adenocarcinoma and lung cancer. In

prostate cancer, the management of choice is prostatectomy with orchiectomy and lymph node dissection. In advanced disease where the malignancy has spread to the vertebrae, spinal cord or distant organs, radiotherapy and chemotherapy with docetaxel, paclitaxel or estramustine can be used. Adverse effects of docetaxel include hematological manifestation like pancytopenia, granulocytopenia, gastrointestinal distress, nausea, vomiting or diarrhea and alopecia. Some studies have reported on the pneumo-toxicity but it is very rare accounting for only 4.6% of the total adverse effects of docetaxel.[3] Among the cases of pulmonary toxicity, only <1% of the cases have been reported as ILD. Here we report a case of subacute ILD following docetaxel chemotherapy in a 68 years old male with advanced prostate cancer.

CASE REPORT

A 68 years old male presented to the emergency department with grade 3 dyspnea and intermittent episodes of fever for the past four days. Detailed history taking revealed that the patient's dyspnea was gradual in onset and progressive in nature. It was associated with cough with mild expectoration as well as chest pain. It caused slight limitations in his daily life activities and he was unable to finish a complete sentence while talking. There was no history of palpitations, orthopnea, paroxysmal nocturnal dyspnea, hemoptysis, and pedal edema. He had intermittent episodes of low grade fever (100-101°F) for the past four days; associated with chills, anorexia and nausea. The patient has a significant medical history of advanced prostate cancer with spinal metastasis. He underwent prostatectomy with bilateral orchiectomy. He had a history of percutaneous transluminal coronary angioplasty five years ago and is on medications for diabetes as well as hypertension. Considering the age of the patient, comorbidities and the progression of the cancer to distant sites, six cycles of medium-dose chemotherapy with docetaxel (50 mg/m^2 or 90 mg IV) was advised. However after ten days of her last scheduled cycle of chemotherapy, he developed diarrhea, vomiting followed by cough and dyspnea.

Clinical examination demonstrated an apprehensive look and the patient was in significant respiratory distress. The left forearm had a grade II ulcerative lesion on its dorsal aspect (as shown in Figure 1). Pulse oximetry revealed oxygen saturation of 76% on room air with heart rate of 108 beats per minute. The patient was tachypneic, blood pressure was 126/82 mmHg with mercury thermometer reading of 100°F on presentation. On auscultation, the air entry was decreased on bilateral lung bases with wheezing and occasional crepitations throughout the lungs. Other systemic examinations were within normal limits. At the emergency, patient was put on non-rebreather mask (NRBM) at 15 l/min of oxygen supply and was nebulised with 1.25 µg of levosalbutamol. Considering the current status of the patient, his co-morbidities and the burden of COVID-19 in India at that point of time; he was admitted in the intensive care unit for monitoring with a provisional diagnosis of lower respiratory tract infection. Complete blood count, serum electrolytes and urinalysis were within normal limits. Chest X-ray demonstrated diffuse opacification throughout the lung field with prominent bronchovascular markings and mild pleural effusion on the right side. Sputum analysis for routine microbiological examination, acid fast bacilli, RT-PCR for COVID-19 and respiratory pathogen panel test were ordered. Inflammatory markers like C-reactive protein (CRP) and ESR were raised to eight-to-nine folds of their normal values. Pulmonary function testing (PFT) corroborated with findings of restrictive lung pattern showing decreased forced vital capacity (FVC), forced expiratory volume (FEV1) but a near normal FEV1/FVC ratio. High resolution computed tomography (HRCT) of the chest reported scattered honeycomb appearance, bilateral sub-pleural opacification with centrilobular nodules and air-trapping.

Sputum examination did not show any evidence of microbiological growth or positive stain. There were mildly increased eosinophil in the sputum. Serum anti-nuclear antibodies (ANA), angiotensin converting enzyme (ACE) and calcium were within the laboratory reference range. Serum procalcitonin levels were normal. Hence, a restrictive lung disease (RLD) of non-infectious and non-autoimmune etiology was considered as a diagnosis. Thus, it was concluded that the RLD occurred due to exposure of the patient to some pneumotoxic agent, which in this case was most likely to be the chemotherapeutic drug, docetaxel. The patient was immediately started on systemic steroids with intravenous methylprednisolone 1 mg/kg once daily for one week period. Continuous oxygen supply with NRBM, nebulisation with levosalbutamol and budesonide was continued. Intravenous cefpodoxime 1 g was added as a prophylactic antibiotic therapy. Rapid clinical improvement was seen in two days of time and the artificial oxygen requirement was reduced and eventually terminated on day 4 of steroid therapy. On stabilization, the patient was shifted to the general ward and eventually was discharged home on tapering doses of oral steroids. Furthermore, close follow-up visits were arranged for the patient and he was advised with oral calcium, vitamin D3 tablets as well as regular home glucose and blood pressure monitoring. He was further advised with chest physiotherapy and programmed aerobic exercise for a faster recovery.

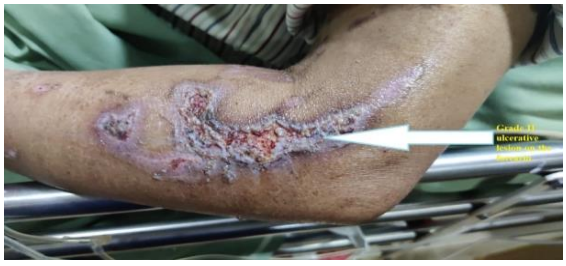

Figure 1: Grade II ulcerative lesion on the left forearm (as a result of docetaxel toxicity).

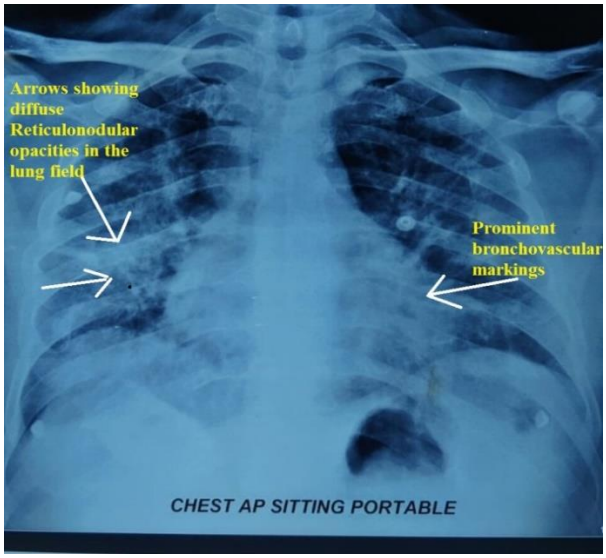

Figure 2: Digital chest X-ray showing diffuse reticulonodular opacities in the lung field with prominent bronchovascular markings as marked by arrow.

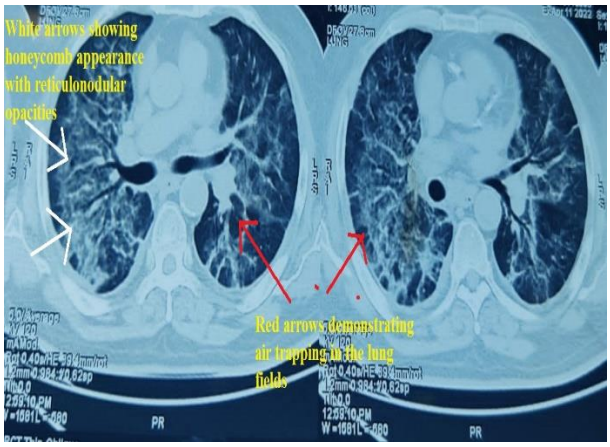

Figure 3: HRCT of the thorax showing honeycomb appearance with air trapping and diffuse opacities (as marked by arrow).

DISCUSSION

Docetaxel is an antineoplastic drug of the taxoid family and a more potent congener of paclitaxel. It inhibits the growth of potent cancerous cells by binding to the luminal side of β tubulin and enhancing its polymerization to form excess microtubules. These microtubules are stabilized and their depolymerization is prevented thereby halting the anaphase of the mitotic cycle. Of the many other adverse effects of the drug as discussed earlier, ILD is one of the rare ones. Patients with prior lung disease are shown to have higher chances of lung injury when exposed to docetaxel. In a study conducted by Hettiarachchi et al reported that patients with prior lung anomaly were shown to have increased risk of ILD.[4] The incubation period between the administration of the drug and the onset of lung injury is mostly unpredictable but most studies have reported a mean time gap of about 15±3 days. In a study by Manuprasad et al conducted on 477 patients, the median time gap from administration of last dose to onset of symptoms and median hospital stay were 16 days (8-28 days) and 8.5 days (7-18 days) respectively.[5]

The lung injury is mostly mediated by immediate hypersensitivity (type I) and cell mediated reaction (type IV hypersensitivity). In certain trials of paclitaxel and docetaxel, 30-40% patients developed type I hypersensitivity reactions. It is proposed that complement activation or activation of mast cell or basophil directly by IgE and antigen is responsible for this side effect.[6] The mechanism of DILD differs between cytotoxic and immune mediated pulmonary injuries.[7] Cytochrome oxidase is a monooxygenase group of enzymes and is shown to cause cytotoxic pulmonary injury, mostly related to drug concentration and metabolism in individuals like promoting free radical metabolites. Immune mediated mechanism is due to drug allergy mainly. In a study conducted by Anoop et al taxane rechallenge was done on 41 patients who recovered from docetaxel toxicity with systemic steroids. They reported that 49% subjects did not have any recurrence of pneumonia and oral steroids were given to the subjects as a safety measure.[8]

The study also advised against re-challenge of drugs in patients with residual lung abnormalities after steroids. A study conducted by Hoshina et al and Takei et al showed an occurrence of case of ild in a patient undergoing treatment with anthracycline induced chemotherapy.[9] The same study also cited that 14 patients out of 25 patients experienced DILD several times after the administration of paclitaxel or docetaxel following anthracycline. In yet another case treated and presented by Wang et al stated a patient with squamous cell carcinoma received relatively low dose docetaxel (30 mg/m^2) on day one after premedication with dexamethasone (10 mg). The patient developed cough and dyspnea three days after the start of treatment.[10] It indicated the variability as well as the unforeseeable nature of drug dosing and development of DILD. Studies also indicated that patients on a weekly schedule of docetaxel are more vulnerable to pneumonitis than tri-weekly schedule. However, the weekly schedule of docetaxel reported lower incidence of myelosuppression than the tri weekly schedule.[11] This also shows that incidence of ILD due to docetaxel is more related to delivery schedule rather than its dose.

Docetaxel is a non-ionic surfactant belonging to the family of polysorbate 80. Polysorbate 80 is known to cause many different types of acute hypersensitivity reactions. Hence researchers have developed a cremophor-free formulation of paclitaxel in which nanoparticles are conjugated to albumin molecules. Unfortunately, no similar formulations have been derived for docetaxel that is free of polysorbate. The pathophysiology of the disease has been explained above as in Figure 4.[7] Generally, use of docetaxel is well tolerated by patients with minimal and non-fatal side effects. Occurrence of DILD, though rare

but a harmful side effect of the drug which must be kept in mind while using it. Patients must be kept in close watch for any lung abnormality and close monitoring with relevant radiological imaging and laboratory evaluation is required to screen for any abnormality.

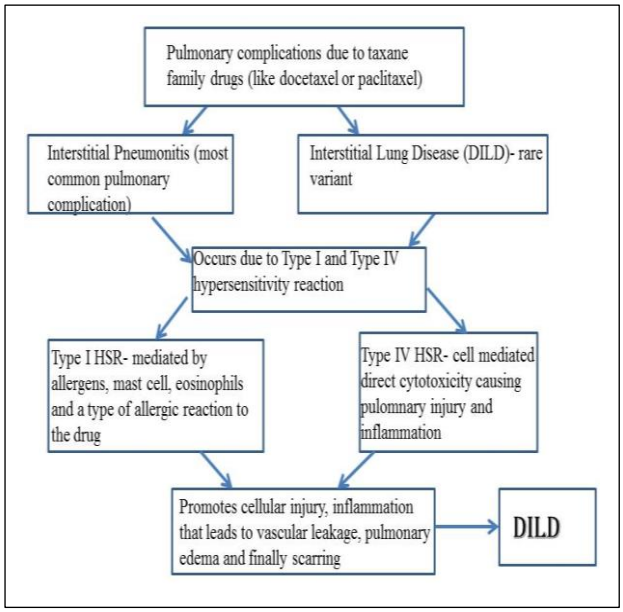

Figure 4: Pathophysiology of DILD.[7]

CONCLUSION

With the advent and success of radiotherapy, the decision to use chemotherapy in prostate cancer is subjective and vary on a case to case basis. Clinicians should consider the age of the patient, comorbidities, side-effects of the drug and clinical status of the individual prior to administering anti-neoplastics. Lung injury with docetaxel is a rare but fatal complication that should be kept in mind while administering it. The occurrence of DILD is independent of the dose of docetaxel. Hence, systemic corticosteroids shall be considered as a prophylactic agent and as a concomitant agent along with the cycles of anti-neoplastic drug schedule. Appropriate screening with the correct clinical and imaging modality as well as timely intervention for the management of the condition can improve the overall morbidity and mortality with optimal improvement in healthcare.

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