Lungs in White Induced by Docetaxel

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Taxanes, such as docetaxel and paclitaxel, are widely used chemotherapeutic agents for a wide range of malignancies. While paclitaxel is a derivative of the Pacific yew tree, docetaxel is a semi-synthetic compound. The principal mechanism of action of the taxane class of drugs is the disruption of microtubule function, thus taxanes are mitotic inhibitors. Taxanes have the potential to induce pulmonary injury through a variety of mechanisms; injuries can present as acute or subacute pulmonary damage [1]. In this case we report findings of interstitial pneumonitis in a 64 year old patient after three courses of docetaxel. Few studies have investigated interstitial lung disease (ILD) associated with docetaxel. The shortened time lag to initiate corticosteroid therapy in the treatment course of this case was dramatically effective and resolved interstitial pneumonitis in our patient. More severe outcomes such as pulmonary fibrosis and the need for mechanical ventilation could potentially occur in the case of delayed diagnosis.

PATIENT DESCRIPTION

A 64 year old man presented to our department complaining of dyspnea, dry cough, and a fever of 39°C lasting for 2 weeks. The patient reported that taking dipyrone (metamizole) helped to lower the fever but did not relieve the cough or shortness of breath. On admission to our department, the patient had a temperature of 36.8°C and an oxygen saturation of 84% in room air, 95% with an oxygen mask. Past medical history revealed known prostatic adenocarcinoma with a Gleason score of 9, which had been diagnosed via biopsy 1 year before his current admission with bone metastasis and without involvement of the lungs.

The patient was undergoing treatment with a docetaxel regimen (120 mg/3 weeks), with the last docetaxel administration 3 weeks prior admission. He had received a total of three courses of treatment. Treatment was withheld due to the onset of dyspnea and fever.

Physical examination revealed diffuse crackles in lung bases, no heart murmurs on auscultation, and pitting edema grade 2 in both legs. The patient was oxygen dependent with saturation values below 90% in room air with no cough. Respiratory rate was 22 breaths per minute. Blood tests were within normal limits, except for alkaline phosphatase of 205 IU/I, and lactate dehydrogenase (LDH) of 423 IU/I. A chest X-ray showed bibasilar reticulonodular infiltrates [Figure 1].

Empiric treatment with broad spectrum antibiotics ceftriaxone/roxithromycin was ineffective. Enoxaparin was administered for possible pulmonary embolism.

During hospitalization a nasal swab was negative for viruses. Computed tomography (CT) angiogram of the chest excluded pulmonary embolus but found bilateral milk glass opacification and plural thickness in the base of the left lung [Figure 2]. However, concern was raised for chemotherapy-related pneumonitis (specifically due to docetaxel), and therefore the drug was discontinued and treatment with prednisone was initiated. A dramatic improvement was noticed under this treatment.

The patient was seen by a pulmonologist and bronchoalveolar lavage was performed. Results showed 24% macrophages,

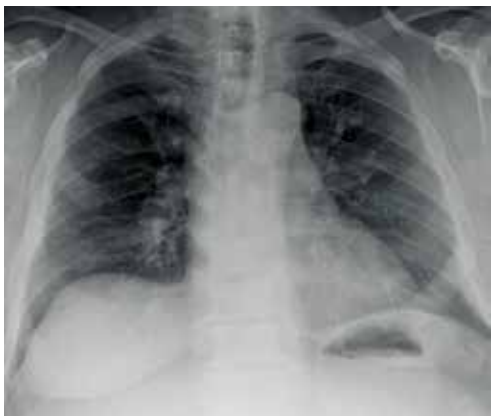

Figure 1. Chest X-ray showing bibasilar reticulonodular infiltrates

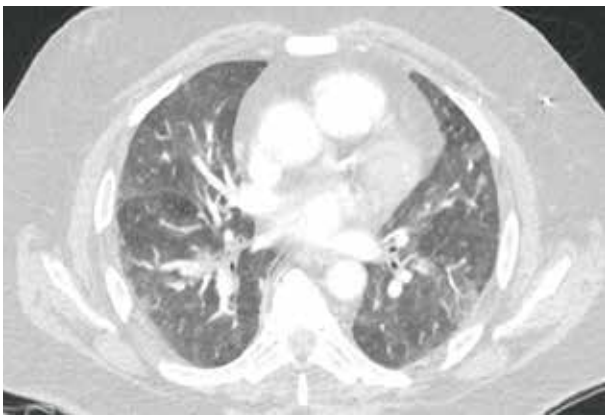

Figure 2. Computed tomography of the chest showing bilateral milk glass opacification and plural thickness in the base of the left lung

6% neutrophils, 70% lymphocytes, and a [TCD4+/ TCD8+] ratio of 0.6. Cultures of the bronchoalveolar lavage revealed *Serratia marcescens* resistant to penicillins and cephalosporins, and treatment was modified to include ertapenem.

Approximately 2 weeks later we noticed improvement in the dry cough as well as resolution of dyspnea. There was an increase in oxygen saturation value to 90% in room air, and the pitting edema was resolved. Since infection and pulmonary embolism were ruled out and a dramatic response to steroids was observed together with the results of the bronchoalveolar (BAL) fluid, chest X-ray and CT scan of the chest, drug induced pneumonitis was the diagnosis of choice.

COMMENT

Docetaxel is a taxane derived semisynthetically from the European yew tree (*Taxus baccata)*. It stabilizes microtubules against depolymerisation and thereby blocks cells undergoing metaphase of the cell cycle [1]. Several anti-neoplastic agents can cause pulmonary responses as part of their side effects. The most common agent is bleomycin-induced lung injury, and acute and chronic pneumonitis was observed in taxanes, methotrexate, and oxaliplatin, and in biological agents such as anti-epidermal growth factor receptor (EGFR), tyrosine kinase inhibitor (TKI), sunitinib and rituximab [2,3].

The main adverse effects of docetaxel are neutropenia, alopecia, asthenia, peripheral neuropathy, and peripheral edema. Paclitaxel, which is in the same class of drugs as taxane, is more commonly used than docetaxel to treat lung cancer, and has an incidence rate of approximately 3–12% of interstitial pneumonitis [2]. However, pulmonary toxicity induced by docetaxel alone is rare and not many cases have been reported [2]. Moreover, to the best of our knowledge, only a few cases have been reported in the case of prostate cancer [3]. The mechanism of taxane-induced interstitial pneumonitis is poorly understood, but the allergic type and the cell-mediated cytotoxic type have been suggested [3]. In addition, reactive oxygen metabolites have been associated with direct lung injury. Although these metabolites form spontaneously, it is felt that docetaxel could increase their production [4]. Moreover, the prolongation of docetaxel toxicity may indicate the immunomodulatory effects of taxanes, with the resulting pulmonary insult lasting the lifespan of the leukocytes [4].

Interstitial lung disease is caused by a misdirected immune or healing reaction to a number of factors, including infections of the lungs, toxins in the environment, certain medications, radiation therapy, and chronic autoimmune diseases. The docetaxel-induced lung toxicity in the cases that have been reported usually occurred after the second, third, or fourth course of chemotherapy, and was usually relieved with corticosteroid therapy [5]. Therefore, numerous diagnostic tests must be performed to confirm the disease. Among them, BAL fluid or transbronchial lung biopsy (TBLB) is necessary to exclude other etiologies. BAL fluid from drug-induced interstitial pneumonitis reveals lymphocytic alveolitis, an increase in the total number of cells, an increased proportion of neutrophils and eosinophils, and a decreased [TCD4+/TCD8+] ratio. A TBLB from drug-induced pneumonitis reveals edema and swelling of the alveolar septum, and interstitial/alveolar mononuclear cell infiltration with intraluminal organization/ aggregation of alveolar macrophages.

More severe interstitial pneumonitis has been reported in patients treated with docetaxel and gemcitabine in combination and also with concomitant thoracic radiation therapy [2,3]. Docetaxel has also been suspected of causing interstitial pneumonitis in a case in which it was used with doxorubicin and cyclophosphamide [5].

Awareness should be increased to both clinicians and patients for the possible pulmonary side effects of taxanes. When patients who have been treated with docetaxel show new respiratory symptoms and new pulmonary infiltrates, they must be carefully monitored with chest X-rays, pulmonary function tests and CT scans with high index of suspicion of pulmonary side effects of the drug. Discontinuation of the therapy until diagnosis of the cause is recommended. If infection and tumors spread in the lungs are excluded, an aggressive pulmonary support and use of corticosteroids must be attempted.

CONCLUSIONS

Early diagnosis of interstitial pneumonitis associated with docetaxel administration could prevent fatal prognosis. Research to discover pathophysiology to prevent docetaxel-induced interstitial pneumonitis is warranted. There is a correlation between administration of taxanes and pulmonary injuries. These injuries have been shown to occur not only with use of paclitaxel but also docetaxel, and whether it is used alone or in combination with other drugs. Therefore we report this case to demonstrate interstitial pneumonitis as a severe side effect of the drug docetaxel, and to stress the importance of early and aggressive treatment to avoid death due to interstitial pneumonitis. This information is especially relevant to those who are likely to encounter such patients, including emergency room physicians, internal medicine physicians, oncologists, radiologists, pulmonologists and general practitioners.

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