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Docetaxel-induced interstitial lung disease among patients with breast cancer: a case series and review of literature

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Abstract

Taxane-induced pneumotoxicity is rare. However, 1–5% of patients taking docetaxel may develop severe pneumotoxicity. This has been limited to case reports in the literature. We report seven breast cancer patients who developed docetaxel-induced diffuse parenchymal lung disease (DPLD) of an organizing pneumonia pattern on high-resolution computed tomography (HRCT). The patients presented with progressive breathlessness within four weeks of the final dose. All had an organizing pneumonia pattern on their HRCTs, without other evidence of infection. Restrictive lung disease with low carbon monoxide diffusing capacity (DLCO) was noted, with desaturation on a 6-min walk test (6MWT). They were started on prednisolone. Repeated HRCT after four to eight weeks from the commencement of steroid treatment showed marked improvement. The clinical and functional improvement were also significant. One patient succumbed to the illness as a result of severe lung involvement. Docetaxel-induced DPLD is a fatal adverse effect, which can be managed by the cessation of the drug and starting on steroids in adequate doses.

Introduction

Docetaxel has been a widely used agent against breast, non-small cell lung, gastric, head and neck, and prostate cancer since 1996, and included in many cancer treatment guidelines to date including European Society for Medical Oncology (ESMO) and National Institute for Health and Care Excellence (NICE) guidelines [1]. It is a semisynthetic taxane which acts by preventing depolymerization of cellular microtubules, resulting in inhibition of DNA, RNA, and protein synthesis. In addition, it inhibits angiogenesis and influences apoptosis pathways and gene expression pathways acting as a "broad-spectrum" anti-cancer drug [2]. Although bone marrow suppression, gastroenterological, hepatic, dermatological, endocrine, and neurological side effects are frequently reported, docetaxel/taxane-induced interstitial lung disease (ILD) is a relatively rare occurrence limited to case reports and case series. However, 1–5% of those who receive docetaxel may develop interstitial pneumonitis to a significant degree (i.e. grade 3–4 according to Common Terminology Criteria for Adverse Events, CTCAE version 5) [3–5].

All patients described here are breast cancer patients. They were relatively young, otherwise healthy patients who had been diagnosed at an early stage, with normal chest X-rays to begin with. Symptom onset brought the patient to the hospital early. They were referred to the National Hospital for Respiratory Diseases in a timely manner where swift and extensive investigations were possible.

Docetaxel-induced lung injury can vary in its pathology. The most common effect of docetaxel on the lung is interstitial pneumonitis. Patients may also present with non-cardiogenic pulmonary oedema, pleural effusions, and peripheral oedema as a result of capillary leakage syndrome. Hypersensitivity reaction with angioedema, stridor, or wheezing is also possible. However, ILD with organizing pneumonia pattern on high-resolution computed tomography

(HRCT) is a rare phenomenon in docetaxel exposure, but has been reported in the literature.

Case Series

Seven female patients (Table 1) diagnosed with invasive breast carcinoma who were treated with docetaxel in the preceding two to thirteen weeks presented with breathlessness, dry cough, and mild fever with progressive chest X-ray changes and HRCT changes from April to August 2020. Each of them had received between two to four cycles of docetaxel before the onset of symptoms. The total accumulated dose was in the range of 320–640 mg. None had undergone radiotherapy before the presentation.

The chest X-rays showed multifocal consolidations. All patients had organizing pneumonia pattern on the HRCTs involving bilateral upper and middle zones (Fig. 1). One patient had non-specific interstitial pneumonia (NSIP) pattern overlapping with organizing pneumonia pattern (NSIPOP) on HRCT. The pulmonary function tests (PFTs) were done in six out of the seven patients (except the one who passed away), which showed a restrictive pattern of lung disease.

In the 6-min walk test (6MWT), three of them (3/6) had significant desaturation (94% to 88%, 96% to 90%, and 92% to 88%). Another three had their resting saturations fluctuating between 94% and 96% and needed oxygen (28% Venturi mask) to maintain the saturation above 96%. However, they did not have significant desaturation on 6MWT. One patient had a late presentation with a significant resting desaturation (<90%) where the 6MWT was not possible. All of them needed supplementary oxygen to maintain oxygen saturation above 96% (via 28–40% Venturi masks according to the severity). Later, we were able to gradually taper off the supplementary oxygen.

Detailed investigations, which included full blood count, C-reactive protein (CRP), electrolyte sedimentation rate, sputum cultures, sputum for acid-fast bacilli, did not show evidence of pulmonary infection. Anti-nuclear antibodies (ANA) and rheumatoid factor (RF) were measured as a part of autoimmune screening and none of the patients had positive ANA or RF. The complete panel of extractable nuclear antigen antibodies was not done due to financial restraints.

As all the patients were symptomatic with dyspnoea and had comparatively low resting saturations as mentioned above, bronchoscopies were not offered. The decision of withholding bronchoscopy was also influenced by normal inflammatory markers, that is, erythrocyte sedimentation rate (ESR) and CRP with normal white cell counts as it reduced the suspicion of ongoing infection causing pneumonia. It was also decided not to perform lung biopsies after multidisciplinary discussions. Also, because performing lung biopsies in such respiratory compromised patients had led to severe complications in similar cases as reported in the literature.

Two patients were pulsed with methylprednisolone (after doing procalcitonin levels to further exclude the possibility of an infection) and started on oral prednisolone. Other patients were commenced on prednisolone at a dose of 1 mg/kg of ideal body weight, without methylprednisolone pulsing. There was clinical improvement within days.

One patient who had severe lung involvement needed mechanical ventilation and died after intensive immunosuppression.

The HRCT images showing the characteristic changes of DPLD at the time of diagnosis, and the HRCT images after treating with systemic steroids are shown in Figure 1. Significant resolution is seen after treating with systemic steroids. Residual fibrosis can also be seen in some patients.

Discussion

In Sri Lanka, the most common cancer among females is breast cancer. It has an annual incidence of over 3000 [6,7]. Both adjuvant and neoadjuvant chemotherapy for breast cancer consist of anthracycline (doxorubicin or epirubicin) and/or a taxane (docetaxel of paclitaxel). Currently, in Sri Lanka, non-small cell lung cancer (NSCLC) patients do not receive Docetaxel as the first-line treatment. Head and neck cancer patients are usually managed with surgical and radiological interventions and taxane use is infrequent in this group of patients in Sri Lanka. These may have contributed to the fact that breast cancer patients presenting as a cluster. Even though there are no identified pathophysiological links, there may be an epidemiological association as it is more commonly prescribed in breast cancer than others.

In 2001, Wang et al. described four patients who developed severe hypersensitivity pneumonitis following docetaxel treatment for NSCLC. They did not respond to steroids and had life-threatening complications [8]. At that time, the awareness regarding this adverse effect must have been low. In 2002, Read et al. described another four patients who received docetaxel for prostate, breast, and uterine cancer, developing DPLD and, two out of the four patients dying due to its severity [9].

An organizing pneumonia pattern in docetaxel-induced pneumotoxicity is even rarer in the medical literature. Up to 2012, there have only been a couple of reported cases. Hasskarl et al. in 2009 reported ILD in a 54-year-old male who had received docetaxel for NSCLC, which had improved rapidly following cessation of docetaxel and steroid treatment [10]. This supported our management as our patients also responded very well to steroids after the cessation of docetaxel.

Table 1. Patient characteristics, taxane regimes, time correlations, radiological appearance, and outcome of the patients in the case series.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age (years)	35	56	43	54	46	51	56
Taxane regime	Docetaxel 160 mg 3 weekly 29 January 2020 to 1 April 2020	Paclitaxel 300 mg 19 February 2020 Docetaxel 160 mg 3 weekly 11 March 2020 to 1 April 2020	Docetaxel 160 mg 3 weekly 2 February 2020 to 11 June 2020	Docetaxel 160 mg 3 weekly 3 June 2020 to 24 June 2020	Docetaxel 160 mg 3 weekly 26 February 2020 to 29 April 2020	Docetaxel 160 mg 3 weekly 4 April 2020 to 4 August 2020	Docetaxel 160 mg 3 weekly 9 April 2020 to 10 June 2020
Cumulative dose	640 mg	Paclitaxel 300 mg Docetaxel 320 mg	640 mg	320 mg	640 mg	640 mg	640 mg
Other agents given	Doxorubicin Cyclophosphamide (given five months back) Trastuzumab	Doxorubicin Cyclophosphamide (given five months back) Trastuzumab	Doxorubicin Cyclophosphamide (given five months back)	None	Doxorubicin Cisplatin	Doxorubicin Cyclophosphamide (given five months back)	Doxorubicin Cyclophosphamide (given five months back)
Symptom onset Time from the first dose (weeks)	11	11	13	13	13	14	13
Time from the final dose (weeks)	2	2	4	4	4	4	2
HRCT and respiratory MDTM diagnosis	NSIP /OP	Organizing pneumonia	Organizing pneumonia	Organizing pneumonia	Organizing pneumonia	Organizing pneumonia	Organizing pneumonia
Follow-up (HRCT done in four to 12 weeks)	Interval resolution (HRCT in four weeks)	Interval resolution (HRCT in six weeks)	Significant resolution (HRCT in six weeks)	Significant resolution (HRCT in six weeks)	Significant resolution (HRCT in six weeks)	Significant resolution (HRCT in eight weeks)	Died

HRCT, high-resolution computed tomography; MDTM, multidisciplinary team Meeting; NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia.

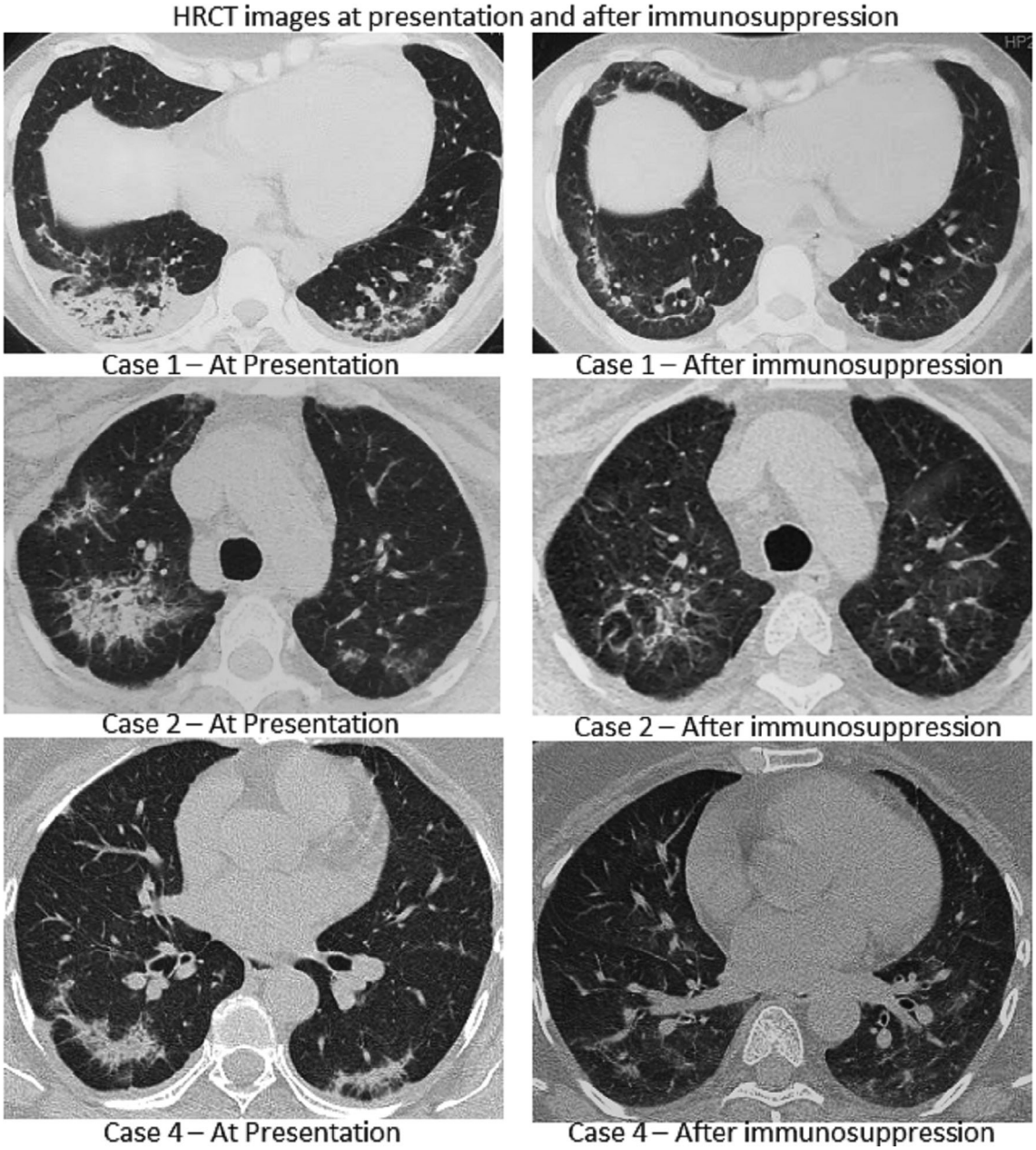

Figure 1. The high-resolution computed tomography (HRCT) on presentation and after treatment with systemic steroids.

Saradna et al. published in the *Chest* Journal in 2017 regarding a patient with paclitaxel-induced organizing pneumonia with intractable haemoptysis elaborating its rarity and response to steroid treatment [11]. Ochoa et al. described a patient who had pneumonitis and fibrosis following docetaxel treatment and, in their literature review, they elaborated on the rarity of organizing pneumonia due to taxane [12].

Although other agents such as cyclophosphamide, trastuzumab, and rarely doxorubicin could cause pulmonary toxicity, the distinct radiological evidence with the chronology of sequence of events strongly supported the docetaxel aetiology.

Cyclophosphamide pulmonary toxicity usually causes a reticular and/or nodular pattern (ground glass may present) more towards the periphery of upper zones and occurs from one to six months of treatment [13]. Trastuzumab pulmonary toxicity is also rare, and can occur within hours to months of the administration. It shows diffuse alveolar damage (DAD) in the acute stage,

and organizing pneumonia or hypersensitivity pneumonitis pattern when chronic. Quality and quantity of evidence in this regard are low as most of the patients had also been treated with other pneumotoxic agents and there are few case reports [14]. Doxorubicin can rarely cause pneumotoxicity in the form of organizing pneumonia. However, direct correlation is not proven and the incidence is very low.

A sudden rise of incidents of docetaxel-induced ILD within a few months is a phenomenon which needs investigation as the incidence is much higher than before. A change of regime, timing with other pneumotoxic agents, and change in quality or constituents of the preparation could be possible causes. Therefore, the particular batch of docetaxel was withdrawn from use until investigations were completed.

All our patients had received three weekly regimes, which have proven to be better than a weekly regime in reducing pneumotoxicity. Patients with lung malignancies, previous lung diseases, or those who have received radiotherapy are more vulnerable to docetaxel-induced ILD [15]. But, all our patients did not have any lung pathology in the past. They presented with breast carcinoma. None of them had received radiotherapy before chemotherapy.

The mechanisms of pneumotoxicity are believed to involve type I and type IV hypersensitivity. Timely identification and exclusion of other aetiologies are very important, as quick withdrawal of the drug and commencement of systemic steroids are essential to improve the outcomes of docetaxel-induced pneumotoxicity [15]. The importance of excluding infection before starting steroids in these already immunocompromised patients cannot be further highlighted. We performed blood investigations such as a full blood count, CRP, and ESR in all patients. Pro-calcitonin was checked only in a couple of patients, because it is not freely available in the state sector and was too costly for most patients.

Bronchoscopy and bronchial wash are justified given the organizing pneumonia pattern in HRCT. We weighed the risk and benefit on each patient and avoided doing bronchoscopy, because none of them had significantly elevated inflammatory markers or high-grade fever. Performing bronchial wash in a patient with significant desaturation and compromised respiratory reserve can be detrimental. The patients were closely monitored in high-dependency setups to detect any evidence of evolving infection but the clinical parameters improved with steroids. The inflammatory markers remained static. Repeated sputum cultures were also negative.

Our patients showed excellent improvement with steroids, timely oxygen supplementation, and intensive care with close monitoring. But, the outcomes of many reported cases and case series were poor with mortality being reported to be as high as 30% [15].

In conclusion, docetaxel-induced DPLD or ILD can have significant mortality and morbidity, if not identified and treated early. Out of various HRCT patterns, in lung involvement in docetaxel exposure, organizing pneumonia pattern is rarely reported in the literature. This cluster of patients is an eye opener to suspect, investigate, diagnose, and treat if similar cases arise in the future.

Disclosure Statement

Appropriate written informed consent was obtained for publication of this manuscript and accompanying images. Any details and images of patients have been appropriately anonymized.

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Author Contribution Statement

All authors actively engaged in managing these patients and contributed equally in writing the manuscript and proofreading the content and review of the literature.

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