

# Taxane induced pneumonitis in a case of carcinoma esophagus treated with chemo-radiation: Case report and review of literature

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## ABSTRACT

Taxanes are the preferred chemotherapy (CT) modality in treatment of carcinoma esophagus. Taxane use is associated with toxicities such as myelosuppression, neuropathy and musculoskeletal effects. Pneumonitis arising with the use of taxanes is a relatively rare and less explored entity. The present case report addresses this phenomenon in a patient who received Neoadjuvant and concurrent treatment with taxane and presented with symptoms and signs of pneumonitis. Patient initially presented with flu like symptoms and dyspnea that was unresponsive to antibiotic treatment. She presented 12 days after, the completion of concurrent CT-Radiotherapy. Despite all the measures, she ultimately succumbed to the pneumonitis. In any such case of development of pneumonitis/interstitial lung disease/fibrosis related symptoms and signs in relation to CT-RT, taxane induced pneumonitis should be kept in the differential diagnosis. Clinicians should be aware of this entity to appropriately manage such a rare and life-threatening occurrence.

**Key words:** Carcinoma esophagus, concurrent chemotherapy-radiotherapy, pneumonitis, taxane

## INTRODUCTION

Carcinoma esophagus (CE) is the eighth most common cancer and causes the sixth highest cancer-related mortality world-wide.<sup>[1]</sup> The advantages of adding chemotherapy (CT) to the treatment of CE are potential tumor down-staging prior to surgery, targeting micrometastases and decreasing the risk of distant metastasis.<sup>[2]</sup> Definitive CT-radiotherapy (RT) has been established as a curative option in select subset of patients with CE and its clinical efficacy has expanded.<sup>[3]</sup> The regulatory approval of Docetaxel to treat patients with metastatic or advanced Gastro Esophageal (GE) cancers in 2006 has established the role of taxanes in its management.<sup>[4]</sup> The most frequent dose-limiting toxicities of taxanes include

myelosuppression, neuropathy and musculoskeletal effects.<sup>[3]</sup> In addition, drug-induced adult respiratory distress syndrome and interstitial pneumonitis, has sporadically been reported as a serious toxic effect of taxanes.<sup>[4-6]</sup>

A 63-year-old female presented to our hospital as a case of metastatic CE who was treated with induction CT with Docetaxel for six cycles followed by concurrent weekly Paclitaxel with RT under image guidance. 12 days following the completion of RT she presented with symptoms of fever, dry cough, chest pain and dyspnea.

## CASE REPORT

### Patient characteristics and chief complaints

A 63-year-old female, a proven case of CE lower third with pulmonary and hepatic metastases who had been treated with primary CT (Docetaxel based) presented to us for adjuvant RT for local residual disease as seen on a post therapy positron emission tomography (PET) scan. At presentation, she was in a good general condition with an Eastern Co-operation Oncology Group (ECOG) performance status (PS) one.

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### History of presenting illness

Patient had complaints of dysphagia, weight loss (20 kg) and anorexia since July 2012. She underwent a computerized tomography (CAT) scan that revealed an ulcero proliferative growth measuring 2 cm × 1.8 cm in the distal esophagus and GE junction involving the entire wall circumferentially besides a metastatic lesion in the lung and liver. Biopsy from the growth was reported as invasive moderately differentiated non-keratinizing squamous cell carcinoma. She then received CT with injection Docetaxel, Cisplatin and 5 fluorouracil from September to December 2012 with good symptomatic relief. An interim check CAT scan carried out after four cycles of CT showed significant reduction in the thickening at the GE junction and near complete resolution of the liver and pulmonary metastasis. After completion of six cycles CT, she underwent a PET-CAT scan that revealed non-fluoro deoxy glucose (FDG) avid thickening at the primary site with no other site of FDG avidity in the whole body.

### COURSE

At presentation, she was largely asymptomatic and in a good general condition with no other systemic abnormality. She had a locally advanced disease and the PET-CAT had suggested the possibility of sub-clinical residual disease. She was advised locoregional RT and was treated with image guided RT to a total dose of 5000 centigray (cGy) in 25 fractions along with weekly concurrent CT with Paclitaxel and Carboplatin. At completion of therapy, she maintained a good general condition, with essentially normal systemic examination and ECOG PS of 1.

After 12 days of after the completion of treatment, she presented with complains of dry cough, chest pain and dyspnea. A chest X-ray revealed prominent broncho-vascular markings in bilateral lung fields. Bilateral lower zone haze was also seen. Linear opacities were seen in the peripheral right mid zone [Figure 1]. A CAT scan carried out revealed bilateral lung fields showing multi-focal areas of ground-glass density with interlobular septal thickening and few air space lesions randomly distributed [Figure 2].

On suspicion of a possible RT induced pneumonitis, her RT plans were checked and revealed that the radiation dosage delivered were modest (2500c Gy) to small volumes (30%) of normal lungs [Figure 3] and any association with radiation related lung morbidity was ruled out. Keeping in mind the possibility of a taxane induced pneumonitis; she was started on steroids with needful supportive and symptomatic management. She

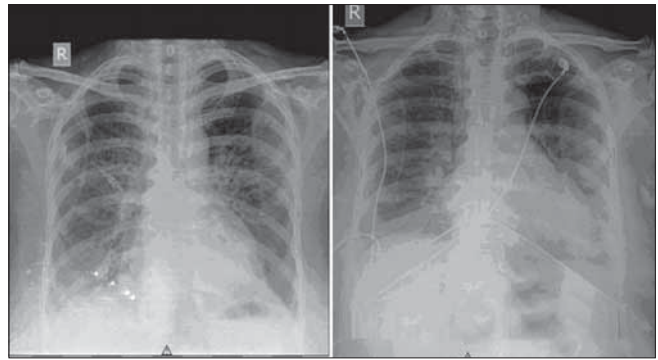


Figure 1: Chest X-ray posterior-anterior view

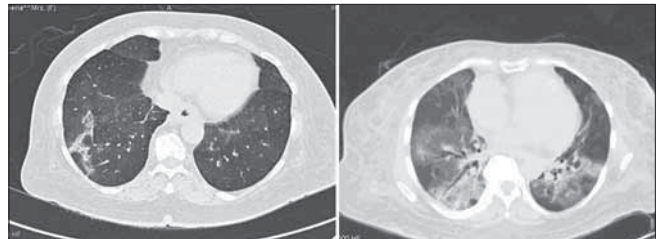


Figure 2: High resolution computerized tomography scan

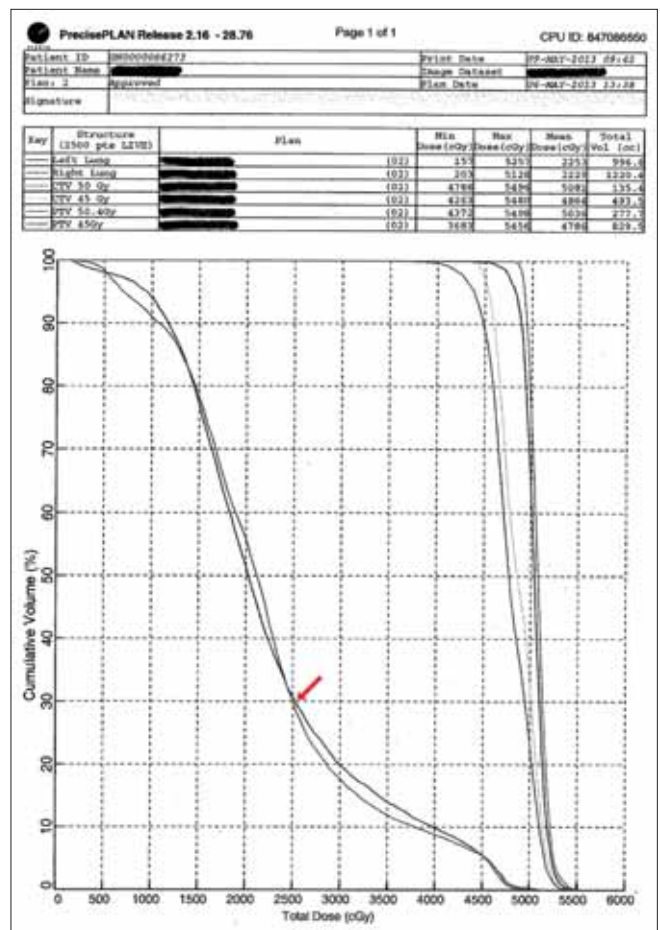


Figure 3: Dose volume histogram showing 30% lung receiving 2500 cGy (Red arrow)

responded equivocally to the treatment and succumbed within a fortnight.

## DISCUSSION

Drug-induced infiltrative lung disease is the most common form of anti-neoplastic agent-induced respiratory disease that involves interstitial, eosinophilic and/or hypersensitivity pneumonitis, pulmonary fibrosis or organizing pneumonia.<sup>[7]</sup> In the background of RT, pneumonitis causes a diagnostic dilemma and can be mistaken to be radiation associated. A number of CT drugs are well-known to cause various Histopathological patterns of lung injury. The incidence of CT-induced infiltrative pneumonitis is rare and the diagnosis is difficult due to the non-specific clinical and radiological presentations that have the potential to cause significant morbidity and mortality in cancer patients. This however is a rare probability in esophageal irradiation given the fact that the modern high precision RT delivery systems are capable of limiting dose to the critical structures and treat with real time image guidance, safeguarding against any possible lung overdosage.

Looking retrospectively at the dose volume histograms of the patient, it was confirmed that 30% of the lungs received a dose of 2500 cGy while 20% received 3000 cGy. The mean dose received by bilateral lungs was 22 Gy. These modest doses do not warrant for the pulmonary insult.<sup>[8-10]</sup> In addition, Radiation Pneumonitis (RP) takes place usually within 1-6 months after completion of RT<sup>[10]</sup> while this patient became symptomatic in less than 2 weeks. Wang *et al.* analyzed clinical and dosimetric factors in CE patients treated with definitive CT-RT and their relationship to the development of RP and reported that dosimetric factors were not associated with the development of symptomatic pneumonitis and that induction CT administered before concurrent CT-RT significantly increased the development of pneumonitis among patients with CE.<sup>[11]</sup>

Taxanes are found to be associated with pulmonary toxicity and an additional side-effect unique to docetaxel is fluid retention and pleural effusion secondary to capillary leak syndrome. Docetaxel induced pneumonitis is characterized by a later onset of respiratory deterioration and a longer duration of symptoms. In the present case as well, patient had received injection docetaxel in a neoadjuvant setting for six cycles. Docetaxel has been found to be associated with the expression of specific pulmonary antigen that may cause the proliferation of cytotoxic T-cells and reactive oxygen metabolites causing direct lung injury. In addition, this also indicates the immunomodulatory

effects of taxanes, with the resulting pulmonary insult lasting the life span of the leukocytes.<sup>[12]</sup>

## CONCLUSION

Radiosensitization has been reported to increase therapy efficacy, but it may also increase therapy-induced toxicity. The practice of advanced techniques of RT that include 3D conformal RT, intensity modulated RT and even more precise image guided RT that has the advantage of real time image guidance are the technical advancements that aim to reduce acute and late treatment-associated toxicity.

The high effectiveness and easiness of administration have made taxanes a widely used CT agent. Although it is generally well-tolerated, patients must be carefully monitored with chest X-rays, pulmonary function tests and CT scans when unexpected respiratory symptoms and pulmonary infiltrates appear. Discontinuation of the therapy, until diagnosis of the cause is available, is recommended. If infection and tumor spread in the lungs are excluded, an aggressive pulmonary support and use of corticosteroids must be attempted.

Although pneumonitis is a rare side-effect of taxane administration, clinicians should be aware of this entity to diagnose and appropriately manage such a rare, but life-threatening occurrence.

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