BMH MEDICAL JOURNAL

BMH Med. J. 2023;10(1):25-29. **Case Report**

Radiation Pneumonitis - A Case Report

Shilpa Chandran, Krishna Prasad, Ravindran Chetambath

Address for Correspondence: Dr. C Ravindran MBBS, MD, DTCD, Senior Consultant & Chief of Medical Services, Baby Memorial Hospital, Kozhikode, Kerala, India. Email: crcalicut@gmail.com

Abstract

Radiation-induced lung injury (RILI) encompasses any lung toxicity induced by radiation therapy (RT) and manifests acutely as radiation pneumonitis and chronically as radiation fibrosis. Because most patients with thoracic and breast malignancies are expected to undergo RT in their lifetime, and that too with curative intent, the population at risk is significant. Radiotherapy has proven satisfactory outcomes; however, adverse pulmonary effects, like pneumonitis, can be life-threatening. Fortunately, the incidence of serious pulmonary complications from RT has decreased secondary to advances in radiation delivery techniques. Understanding the temporal relationship between RT and injury as well as the patient, disease, and radiation factors that help distinguish RILI from other etiologies is necessary to prevent misdiagnosis. Here we report a case of life-threatening pneumonitis following RT in a case of a carcinoma breast.

Keywords: Radiation pneumonitis, radiation fibrosis, airspace consolidation

Introduction

Radiotherapy Induced Lung Injury (RILI) encompasses two phases: an early phase known as Radiation Pneumonitis (RP), characterized by acute lung tissue inflammation as a result of exposure to radiation; and a late phase called Radiation Fibrosis (RF), a clinical syndrome that results from chronic pulmonary tissue damage. Acute phase develops within 6 months, and the chronic phase after 6 months. Radiation pneumonitis typically develops between 4 and 12-weeks following completion of radiotherapy course, although they may be seen as early as one week, especially in patients receiving a high total dose and/or also having received chemotherapy [1-3]. Pneumonitis is caused by direct cytotoxic effect, oxidative stress, and immune-mediated injury. Radiation induces a loss of the alveolar barrier function by destroying epithelial and endothelial cells. The inflammatory response induces a cycle of increased inflammation, vascular permeability, and cytokine release within days or weeks. Macrophage accumulation and activation contribute to the development of hypoxia, stimulating the production of reactive oxygen species and reactive nitrogen species (ROS/RNS) and proinflammatory, profibrogenic and proangiogenic cytokines that perpetuate a non-healing tissue response that leads to chronic radiation injury. The challenge for diagnoses relies on the different clinical-radiological presentations and exclusion of alternative diagnoses.

Case Report

An elderly female, who was diagnosed to have carcinoma left breast treated with modified radical mastectomy, chemotherapy and radiotherapy was brought to the emergency department with high

grade fever, cough and shortness of breath of one day duration. She also had a history of irrelevant talk and behavioral changes. She was found to have hyponatremia and correction was given. Chest examination showed coarse crackles, bilaterally better heard on the left side. She was in distress and oxygen saturation was 82% which was corrected to 95% on 4 liter oxygen per minute. Her chest X-ray showed bilateral alveolar infiltrates more on the left side (**Figure 1a**). She was started on IV Piperacillin-Tazobactam. after sending the sputum for culture and sensitivity.

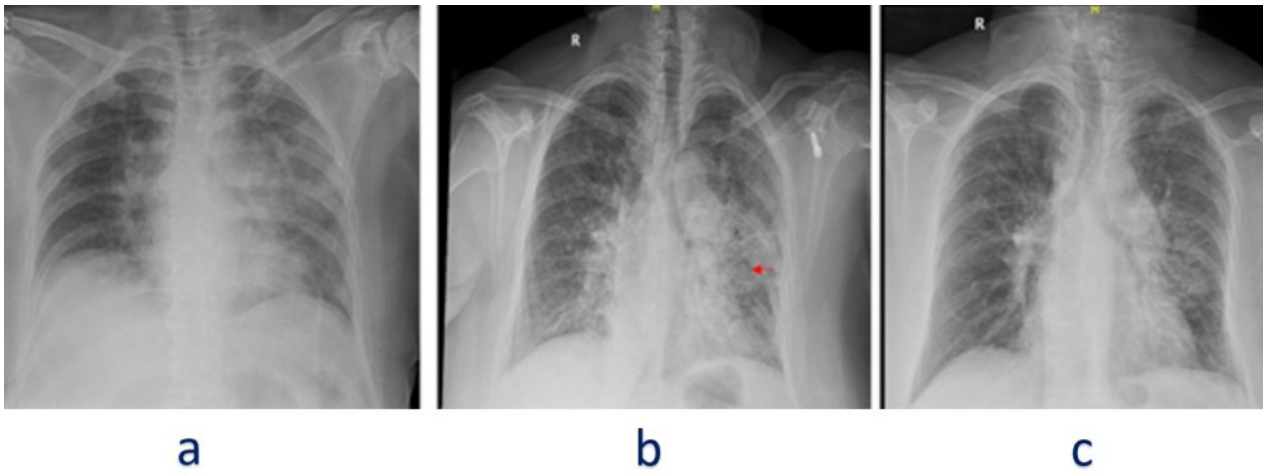

Figure 1: a) Initial x ray chest PA on presentation. **b)** X-Ray taken after 3 days of antibiotic therapy when the patient showed clinical deterioration. Red arrow showed a halo sign within a dense consolidation in the radiation field. Non homogenous opacities can be seen in the left lower zone and right mid zone. **c)** Showed partial clearance of shadows on the 4th day of steroid therapy.

Even after starting Piperazillin+tazobactam her fever persisted, and the X-ray after 3 days showed worsening (**Figure 1b**). Hence antibiotic was changed to Meropenem. Meanwhile the blood culture report came, and was sterile.

Her lack of response to antibiotics prompted us to consider a diagnosis of radiation pneumonitis. A detailed history was taken to understand the temporal relationship.

She was diagnosed with Ca breast six months earlier, and underwent modified radical mastectomy. Following surgery she was given 6 cycles of chemotherapy with Adriamycin, 5-Fluorouracil, and cyclophosphamide, with an interval of 21 days. After that she underwent radiotherapy. Total radiation was 42.5 Gy given as 16 fractions, 5 days continuously followed by 2 days interval. Last fraction of radiation therapy was given 10 days prior to the present symptoms. Patient was relatively asymptomatic after RT and was able to carry out her daily activities. But after 10 days she developed the present symptoms.

Bronchoscopy was performed, which showed slightly increased secretion in the left bronchial tree, Bronchoalveolar lavage was taken and sent for routine culture, fungal culture and cytology. She was started on IV Methylprednisolone 125 mg twice daily. After initiating systemic steroids, she started showing clinical improvement. Her dyspnea decreased, and 2 days later she was weaned off of O_2. Meanwhile her bronchioalveolar lavage routine culture yielded heavy growth of Klebsiella which was sensitive to Amikacin and Amoxicillin-Clavulanic acid. Antibiotic therapy was changed according to culture and sensitivity. Repeat chest X-ray after 4 days of steroid therapy showed significant resolution of shadows (**Figure 1c**). Steroid was tapered and the patient was discharged on a tapering dose of oral steroid.

Discussion

RP usually develops within 4-6 weeks of radiation. However, it can appear as early as 7 days following RT especially in patients receiving a high total dose of radiation or chemotherapeutic

agents concomitantly or prior to radiotherapy. Symptoms typically include cough, dyspnea, low-grade fever, chest discomfort and pleuritic pain [3].

The lungs are the most sensitive organ while irradiating the chest, and is the major dose-limiting factor. Radiation pneumonitis reflects the acute response of the lung to radiation and includes loss of type I pneumocytes [3], increased capillary permeability resulting in interstitial and alveolar edema and ingress of inflammatory cells into the alveolar spaces. When changes are seen in the non-irradiated lung, immune-mediated lymphocytic alveolitis has been postulated as the underlying cause [3].

Risk factors

RILI is usually reported in cases where thorax is exposed to RT. Common malignancies having a higher chance of RILI are lung cancer, breast cancer, mediastinal malignancies, esophageal cancer, mediastinal lymphoma and lower neck nodal disease.

Patients with a higher tumor volume receive significant lung and surrounding radiated volume. The percentage of radiated lung volume is a crucial factor that influences the development of RP [4,5]. There is evidence that smoking could play a protective role in patients who underwent radiotherapy. There is a higher incidence of RP in non-smokers compared to former smokers [6,7]. Patients with chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD) are more susceptible to RILI. COPD and ILD patients with RILI might be more symptomatic due to their impaired lung function [5,8].

Not all patients undergoing thoracic radiation develop RP. The risk factors leading on to the development RP include, total dose of RT administered (Invariably develops if it exceeds 40 Gy), degree of fractionation (if number of fractions are less to deliver total dose), prior chemotherapy with actinomycin D, adriamycin, bleomycin or busulfan, concurrent chemotherapy, reduced lung function and pulmonary hypertension [9].

Radiographic features

Although changes in the lung are usually confined to the irradiated region, changes in the remainder of the lung may also be seen [1,3]. Chest x-ray changes are nonspecific but confined to the irradiation region, with air space opacities being most common. Pleural effusions or atelectasis are also sometimes seen [1,10]. CT is able to delineate parenchymal changes, but often demonstrates changes localized to the irradiated field, making the diagnosis easier. With stereotactic ablative radiotherapy the shape of the irradiated field will not have straight edges or conform to the traditional conventional radiotherapy portals. As such it may be less obviously artificial in shape [11]. In cases of early or subtle radiation-induced pneumonitis, areas of ground-glass opacity may be evident on CT despite a normal chest x-ray [1,2]. The two most common findings are ground-glass opacities and/or airspace consolidation [1,2,12]. Unusual patterns of airspace opacities include halo sign (lung consolidation surrounded by ground-glass opacities) and reversed halo sign (ground-glass opacities surrounded by a crescentic or circumferential area of consolidation [12]. Additional features include nodule-like pattern, tree-in-bud appearances, crazy paving pattern and ipsilateral pleural effusion [12].

Differential diagnosis

If a clear demarcation conforming to the irradiation port is seen then there is little difficulty in making the diagnosis, especially when a history of chest radiotherapy is known. In cases where the distribution is atypical the differential depends on the dominant pattern of radiological features.

A knowledge of the time course of changes in relation to radiotherapy, total dose administered, administration of chemotherapy, and shape of the portal used can all have a significant impact on the differential, and thus should be sought if the referring clinician has not provided this information [12].

Treatment and prevention

Systemic corticosteroids reduce the severity of acute radiation pneumonitis. Depending on the degree of injury changes may be mild and spontaneously resolve or progress to adult respiratory distress syndrome with a high mortality rate [1,3]. Oral prednisone is prescribed at 1-2 mg/kg/day before tapering down over 3-12 weeks, is an option (13). In severe cases intravenous corticosteroids equivalent to methylprednisolone at 2-4 mg/kg/day tapered over six weeks is recommended. Pentoxifylline has immunomodulatory and anti-inflammatory properties mediated by the suppression of TNF-α and IL-1, which may play a role in treating of RF. The effects of pentoxifylline at a dose of 400 mg, taken orally three times a day for eight weeks, have proven to improve clinical signs, symptoms, and a reduction in lung fibrosis [14].

Amifostine is a radioprotector agent that functions through free radical scavenging. Two meta-analyses evaluated and verified the benefit of amifostine at reducing the risk of RP without affecting tumor response [15,16]. Angiotensin-converting enzyme inhibitors (ACE-inhibitors) exhibit significant antifibrotic activity against collagen accumulation in the lungs; [17,18]. Recently, nintedanib has emerged as a promising form of treatment and prophylaxis for RF, since it showed benefits reducing the annual FVC decline in patients with idiopathic pulmonary fibrosis that shares similar pathophysiology.

Conclusions

Radiation pneumonitis is a potentially life-threatening adverse event caused by treatment with radiotherapy targeting thorax. Multifactorial mechanism, and various risk factors have been identified which may help in implementing preventive strategies. However, there are gaps in our knowledge, particularly about the role of specific cytokines causing RP, the use of accurate diagnostic tests, and prophylactic and curative therapeutic strategies. Accurate assessment of risk factors, limiting the total dose within safety level, correct fractionation and regular follow up are few strategies which can reduce the incidence of RP in most of the cases.

References

1. Choi YW, Munden RF, Erasmus JJ et al. Effects of radiation therapy on the lung: radiologic appearances and differential diagnosis. Radiographics. 24 (4): 985-97. doi:10.1148/rg.244035160.

2. Ikezoe J, Takashima S, Morimoto S et-al. CT appearance of acute radiation-induced injury in the lung. AJR Am J Roentgenol. 1988;150 (4): 765-70.

3. Hassaballa HA, Cohen ES, Khan AJ et al. Positron emission tomography demonstrates radiation-induced changes to nonirradiated lungs in lung cancer patients treated with radiation and chemotherapy. Chest. 2005;128 (3): 1448-52. doi:10.1378/chest.128.3.1448.

4. Leprieur EG, Fernandez D, Chatellier G, Klotz S, Giraud P, Durdux C. Acute radiation pneumonitis after conformational radiotherapy for non small cell lung cancer: clinical, dosimetric, and associated-treatment risk factors. J Cancer Res Ther. 2013;9(3):447-51.

5. Ren C, Ji T, Liu T, Dang J, Li G. The risk and predictors for severe radiation pneumonitis in lung cancer patients treated with thoracic reirradiation. Radiat Oncol. 2018;13(1):69.

6. Kong F-MM, et al., Wang S. Nondosimetric risk factors for radiation-induced lung toxicity. Sem Radiat Oncol. 2015;25(2):100-9.

7. Jin H, Tucker SL, Liu HH, Wei X, Yom SS, Wang S, et al. Dose-volume thresholds and smoking status for the risk of treatment-related pneumonitis in inoperable non-small cell lung cancer treated with definitive radiotherapy. Radiother Oncol. 2009;91(3):427-32.

8. Sanuki N, Ono A, Komatsu E, Kamei N, Akamine S, Yamazaki T, et al. Association of computed tomography-detected pulmonary interstitial changes with severe radiation pneumonitis for patients treated with thoracic radiotherapy. J Radiat Res. 2012;53(1):110-6.

9. Marcelo F. Benveniste, Daniel Gomez, Brett W. Carter, Sonia L. Betancourt Cuellar, Girish S. Shroff, Ana Paula A. Benveniste, Erika G. Odisio, Edith M. Marom. Recognizing Radiation Therapy-related Complications in the Chest. (2019) RadioGraphics. 39 (2): 344-366. doi:10.1148/rg.2019180061

10. Chest radiology. edited by Jannette Collins, Eric J. Stern. Philadelphia : Wolters Kluwer Health/Lippincott Williams & Wilkins, c2008. ISBN:0781763142

11. Aoki T, Nagata Y, Negoro Y et-al. Evaluation of lung injury after three-dimensional conformal stereotactic radiation therapy for solitary lung tumors: CT appearance. Radiology. 2004;230 (1): 101-8. doi:10.1148/radiol.2301021226

12. Marcelo F. Benveniste, Daniel Gomez, Brett W. Carter, Sonia L. Betancourt Cuellar, Girish S. Shroff, Ana Paula A. Benveniste, Erika G. Odisio, Edith M. Marom. Recognizing Radiation Therapy-related Complications in the Chest. (2019) RadioGraphics. 39 (2): 344-366. doi:10.1148/rg.2019180061

13. Jain V, Berman AT. Radiation pneumonitis: old problem, new tricks. Cancers (Basel). 2018;10(7):1.

14. Ozturk B, Egehan I, Atavci S, Kitapci M. Pentoxifylline in prevention of radiation-induced lung toxicity in patients with breast and lung cancer: a double-blind randomized trial. Int J Radiat Oncol Biol Phys. 2004;58(1):213-9.

15. Mell LK, Malik R, Komaki R, Movsas B, Swann RS, Langer C, et al. effect of amifostine on response rates in locally advanced non-small-cell lung cancer patients treated on randomized controlled trials: a meta-analysis. Int J Radiat Oncol Biol Phys. 2007;68(1):111-8.

16. Sasse AD, de Oliveira Clark LG, Sasse EC, Clark OAC. Amifostine reduces side effects and improves complete response rate during radiotherapy: results of a meta-analysis. Int J Radiat Oncol Biol Phys. 2006;64(3):784-91.

17. Ghosh SN, Zhang R, Fish BL, Semenenko VA, Li XA, Moulder JE, et al. Renin-angiotensin system suppression mitigates experimental radiation pneumonitis. Int J Radiat Oncol Biol Phys 2009;75(5):1528-36.

18. Kharofa J Tomic R CEP, et al., Kharofa JTRCEP. Decreased risk of radiation pneumonitis with incidental concurrent use of angiotensin-converting enzyme inhibitors and thoracic radiation therapy. Int J Radiat Oncol Biol Phys. 2012;84(1):238-43.