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DIAGNOSTIC AND THERAPEUTIC CHALLENGE IN USUAL INTERSTITIAL PNEUMONITIS DUE TO CHEMOTHERAPEUTICS

General Medicine

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ABSTRACT

The Recognition of drug-induced lung disease is difficult because the clinical, radiological, and histological findings are nonspecific. The development of inflammatory damage and toxicities by the drugs are hard to recognize which poses challenge in early recognition and management of the patients. Drugs have been associated with various pulmonary complications like interstitial inflammation ,fibrosis, bronchospasm, pulmonary edema and pleural effusions. Main treatment is the avoidance of further exposure of drugs and administering systemic corticosteroids in patients with progressive or disabling disease.

KEYWORDS

INTRODUCTION

The lungs have a larger surface area and is a site for metabolism of the certain chemotherapeutic substances. Chemotherapeutics induced injury may involve the airways, lung parenchyma, mediastinum, pleura, pulmonary vasculature, and neuromuscular system. Chemotherapy-induced lung injury have the incidence of 2.8% as per many studies held around the world. Most commonly implicated chemotherapeutic drugs in lung toxicity are bleomycin, carmustine, busulfan, and cyclophosphamide.

Bleomycin is widely studied for the cause of ILD. Symptoms may develop earlier than 4 weeks or later than 10 weeks after chemotherapy and the lung base is the most commonly affected part. Around10% of patients receiving bleomycin complicate with pneumonitis and carries a mortality risk of 10%-20%, also survival of patients is uncertain. The mechanisms of bleomycin toxicity are multifactorial like genetic predisposition, oxidative damage, release of inflammatory cytokines and deficiency of the bleomycin hydroxylase enzyme in the lungs. There is no proper data available on management of BIP and permanent discontinuation of bleomycin is the mainstay of the treatment.

CASE REPORT

A 60yr female patient, known case of hypertension since 10years and diagnosed of stage III Hodgkin's lymphoma since 4 months was on chemotherapy ABVD regimen (Adriamycin, Bleomycin, Vinblastine, Dacarbazine). Total 4 cycles of chemotherapy were completed, the last dose was given 18 days prior to the admission. Patient presented with breathlessness, non-productive cough, chest tightness since 5 days which gradually progressive in nature. Blood pressure was normal, tachycardia present, echocardiograph was within normal limit. On examination patient was fully conscious oriented with bilateral normal vesicular breath sounds on respiratory auscultation but had decreased chest expansion, tachypnoeic, respiratory rate 32/ minute on 98% saturation with simple venturi mask. In the view of respiratory distress and tachypnoea the Non-invasive ventilation support was given. Her ABG analysis showed respiratory alkalosis with compensatory metabolic acidosis, complete hemogram showed normal HB, platelet and total count which was mildly neutrophilic. Inflammatory markers such as CRP, ESR and ferritin was on higher side, chest radiograph was showing multiple patch haziness indicating likely of infective etiology initially.

Patient was put on the treatment for community acquired pneumonia with IV antibiotics, atypical bacteria coverage, MRSA coverage as she was immunocompromised and frequent hospital visitor. Her oxygen saturation began to fall with normal leucocytes on day3 after admission so antiviral therapy, steroids, low-molecular heparin were started, RTPCR for n-COVID19 and H1N1 sent which resulted in negative. HRCT was done which showed diffuse interstitial ground glass opacities in all lobes involving 80% of lung and tractional bronchiectasis in lower lobes. Serum procalcitonin, beta-galactomannan, D-glucan levels, serology markers for Hep B, C and HIV virus were in normal indicating bacterial and fungal less likely.

SL no.	Investigations	Day 1	Day 3	Day 6
1	HB	11.6	10.5	10.4
2	Total count	4600	10,800	16,300
3	Platelets	2.54	1.62	1.67
4	Creatinine	1.1	1.3	1.5
5	ESR	40	62	76
6	CRP	102	146	163
7	PCT		0.2	
8	Serum ANA, p-ANCA, c-ANCA, Beta-Galactomannan and glucan levels	No significant elevated titres		
9	Blood cs, urine cs, sputum cs	No organism isolated		
10	Serology: HIV, HBSAG, HCV	Negative and non-reactive		

She was gradually deteriorating, became drowsy and tachypnoeic on day6 so was intubated, was put on invasive mode of ventilation. Repeat chest radiograph showed increased haziness all over lung field. Patient was worsening inspite of covering anti-inflammatory and anti-infective therapy with elevated inflammatory markers, so usual interstitial pneumonitis due to chemotherapeutics drug bleomycin was suspected and high dose steroid were started. But patient gradually deteriorated over next 2days and expired.

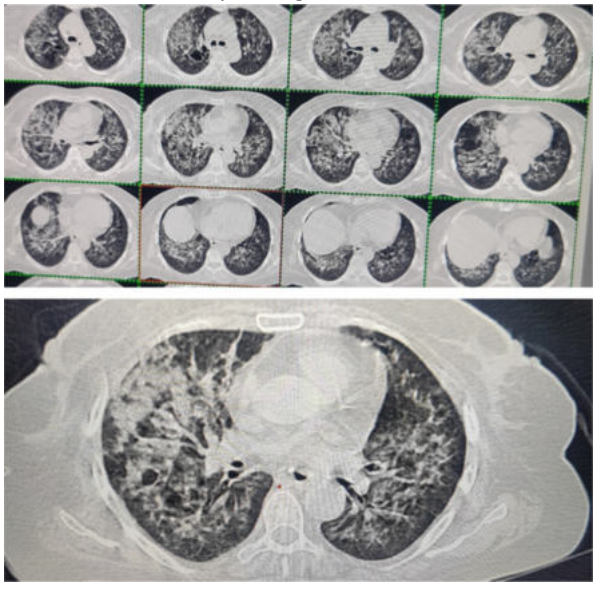

Fig.1: HRCT thorax showing diffuse area of ground glass opacities, approximately 80% involvement with bronchiectatic changes in upper and lower lobes.

Discussion with experts of respiratory, infectious diseases,

radiologists regarding alternative diagnoses and approaches to management were taken in the hospital course. In the setting of severe disease unresponsive to antimicrobial and glucocorticoid therapy, all impressions of the clinical, laboratory and radiological features were pointing towards a diagnosis of bleomycin induced pneumonitis.

DISCUSSION

Bleomycin-induced pneumonitis is challenging to manage because it is a difficult condition to diagnose, patients often present late in the disease process and evidence to guide treatment is lacking. Apart from discontinuation of bleomycin and a trial of glucocorticoids, there are no proven effective therapies for severe BIP.

Studies have shown that inflammatory mediators, such as tumor necrosis factor alpha (TNF-α) are seen in the pathophysiology of BIP. The TNF-α inhibitor infliximab has demonstrated an ability to protect against BIP by its anti-inflammatory and antifibrotic properties in many clinical studies. Hence compared to administration of bleomycin alone, pretreatment with infliximab resulted in significantly reduced serum levels of inflammatory biomarkers and histological evidence of fibrosis in some studies. Tyrosine kinase inhibitors (imatinib) and Transforming growth factor beta (pirfenidone) are other agents which had shown efficacy in the management of BIP. Drug induced complications are markedly reduced when these agents are given in the early inflammatory phase of BIP, reducing the progression to end-stage pulmonary fibrosis. Preventative strategies such as patient age selection, dose reduction particularly in renally impaired patients, avoidance of concurrent mediastinal radiation therapy, as well as close monitoring of pulmonary function should be considered for better outcomes in chemotherapeutic drug therapies.

Early diagnosis is challenging in drug induced pneumonitis. Early high-resolution CT scans may show only scattered or diffuse areas of ground-glass opacity. Later, findings of fibrosis (traction bronchiectasis, honeycombing) predominate in a basal distribution. The predominance feature on HRCT is fibrosis that leads to subpleural cystic airspaces with thick walls that is known as “honeycombing”. Ground glass abnormalities, increased attenuation of the lung tissue without distortion of the underlying blood vessels or bronchi, are absent or minimal in classic UIP. Bronchoscopy with bronchoalveolar lavage (BAL) can also be useful in evaluating patients.

Better prognosis is seen if the diagnosis is made early in acute Drug induced ILD. Therefore, a full recovery could be achieved. On the other hand, failure to recognize a drug-mediated lung disease can lead to significant morbidity and mortality. The specific drug, underlying clinical, physiologic and pathologic severity of the lung disease are all that affects the prognosis.

CONCLUSION

With an increasing number of therapeutic drugs available for use, the list of drugs that is responsible for severe pulmonary disease also grows. Therefore, it is important for physicians to be familiar with iatrogenic diseases for which their patients are at risk. With the current understanding of BIP, the use of TNF-α inhibitors, TGF beta inhibitors and other treatments in early stage of disease have better outcomes than in late-stage disease. Further researches regarding prevention and management of advanced chemotherapeutics induced pneumonitis are required.

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