

Case Report

Phenytoin-induced acute hypersensitivity pneumonitis

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ABSTRACT

Lungs are target organs for toxic effects of various drugs due to many reasons. Diphenylhydantoin (DPH) is reported to have many extrapulmonary side effects. We are presenting a case of acute hypersensitivity pneumonitis (HP) secondary to DPH, presenting with respiratory failure. Acute HP with respiratory failure is an uncommon drug side effect of the DPH therapy and is a diagnosis of exclusion. It requires detailed workup and exclusion of other causes along with evidence of improvement in the patient's condition after withholding DPH.

KEY WORDS: Diphenylhydantoin, drug-induced hypersensitivity pneumonitis, hypersensitivity pneumonitis

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INTRODUCTION

The lungs remain common targets for toxic effects of drugs due to their large surface area and elaborate dual circulation from pulmonary and bronchial arterial systems. The number of drugs causing lung disease is increasing and more than 380 drugs have been reported to cause lung disease.^[1] Diphenylhydantoin (DPH) use is reported to result in various extrathoracic complications.^[2] Mediastinal lymphadenopathy is the commonest intrathoracic manifestation while lung parenchymal involvement is rare. Drug hypersensitivity secondary to DPH is well-known to present as rashes, lymphadenopathy, and fever but interstitial pneumonitis is rarely seen.^[2]

We are reporting a case of acute hypersensitivity pneumonitis (HP), secondary to the DPH therapy.

CASE REPORT

A 38-year-old man, nonsmoker, presented with a history of progressive breathlessness for 2 weeks, along with low-grade fever and cough with minimal expectoration. He was on antiepileptics (phenytoin- 100 mg TDS and

levetiracetam- 750mg BD) since the past 6 months, for an episode of generalized tonic-clonic seizure (GTCS). Results of the magnetic resonance imaging (MRI) and electroencephalogram (EEG) of brain done then were normal. He had no significant family history. He had no history of exposure to environmental, domestic, or agricultural pollutants or allergic diathesis or drug hypersensitivity reaction in the past.

On examination, the patient was of average built, moderately nourished, with no anemia, icterus, clubbing, cyanosis, peripheral lymphadenopathy, or skin rashes. There was no abnormality on general physical examination. His pulse rate was 90/min, rate of respiration patient was Tachypnoic 24 breaths/min, blood pressure was 110/70 mmHg, and body temperature was 37.4 celcius. His resting oxygen saturation was 88% on room air. Examination of respiratory system revealed bilateral vesicular breath sound with few basal inspiratory crackles. Results of other systemic examinations were unremarkable.

Hematology and biochemistry profile was within normal limits. Hematology and biochemistry profile was within normal limits. Chest X-ray (CXR) revealed bilateral diffuse haziness with prominent interstitial markings in the mid and lower zones [Figure 1]. His electrocardiogram (ECG) report was normal ECHO was done, which revealed an ejection fraction of 50% and left ventricular (LV) diastolic dysfunction grade 1. Results of serological tests for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), and fever profile were negative. Serum precipitins were negative to molds.

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10.4103/0970-2113.168126

Antinuclear antibody (ANA) and other autoimmune profiles including extractable nuclear antigen (ENA), rheumatoid factor (RF), anti-citrullinated protein antibody (ACPA), and anti-neutrophil cytoplasmic antibody (ANCA) were negative. Findings from sputum smears and culture examinations for pathogenic organisms, mycobacteria, and fungi were also negative. His arterial blood gas analysis revealed pH - 7.43, partial pressure of oxygen (pO₂)- 50, partial pressure of carbon dioxide (pCO₂)- 33, HCO₃ 21.9, oxygen saturation- 86%, base excess-1.7. His spirometry revealed normal ventilatory parameters, with FVC -3.65 L (80% of the predicted), FEV₁ -3.10 L (81% of the predicted), FEV₁/FVC ratio - 85% and diffusion was mildly reduced to 71. Oxygen saturation test of the patient revealed significant desaturation from 90% to 75%. Walk distance covered was 396 meters (60.74% of the predicted).

High resolution computed tomography (HRCT) scan of thorax revealed areas of ground glass haze bilaterally and consolidation along with well-demarcated areas of lucency, resulting in a mosaic pattern in the upper lobe that is more profound in the lower lobes [Figure 2]. The bronchi were not dilated. No pleural effusion or cardiomegaly was seen. The HRCT features were compatible with constrictive bronchiolitis. Fiber-optic bronchoscopy did not reveal any endobronchial abnormality. The bronchoalveolar lavage (BAL) analysis revealed mixed inflammatory cells, with no malignant cells, or cells with abnormal morphology or organisms (i.e., bacteria, acid-fast bacilli, fungi, *Pneumocystis carinii* pneumonia(PCP), *Nocardia*).

Transbronchial lung biopsy (TBLB) showed marked interstitial inflammation and poorly formed granulomas in the interstitium and around terminal bronchioles consistent with the diagnosis of “Hypersensitivity pneumonitis” [Figure 3]. The patient was initially managed with oxygen therapy, broad-spectrum antibiotics, steroids (prednisolone 40mg/day), and bronchodilators, along with supportive therapy. Fever and breathlessness improved but did not subside. In the absence of any other history of exposure to allergens, it was considered to be related to the DPH therapy. Hence, phenytoin therapy was stopped and the doses of other antiepileptic drugs were increased in addition to phenobarbitone by the neurophysician. Rest of the treatment was continued as before. This resulted in an alleviation of symptoms with complete defervescence of fever and breathlessness over the next few days. His baseline oxygenation increased to 96% with insignificant desaturation to 93% on 6-min walk test (6MWT) (distance = 470 m, 72.08%). Repeat CXR [Figure 4] showed clearing of lung fields.

The patient was discharged in a stable condition with normal oxygenation and diffusion capacity and steroids tapered over next 2 weeks. On a follow-up, the patient is doing well with no relapse or reoccurrence of symptoms.

DISCUSSION

Various previous studies Earlier studies have mentioned abnormal chest Xrays in 84% patients receiving Phenytoin

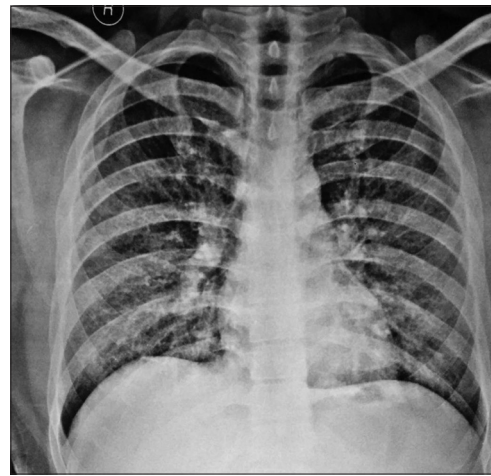


Figure 1: Chest X-ray on admission: Reticular shadows with GGO



Figure 2: CT chest showing areas of GGO and areas of air-trapping, more profound on expiratory scan

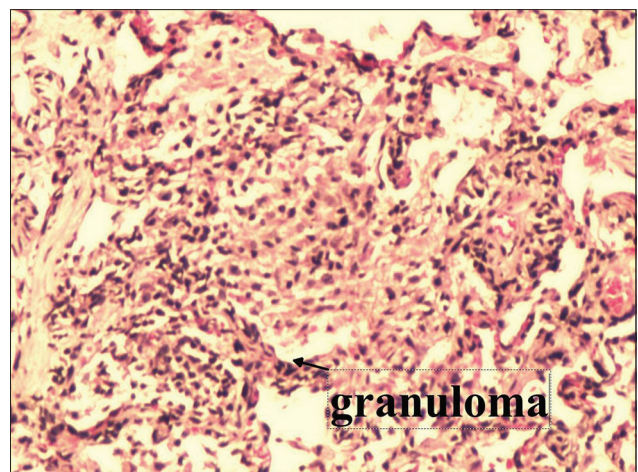


Figure 3: Histopathology: Interstitial inflammation and ill-formed granulomas in interstitium as well around terminal bronchioles

for two or more years^[3] and another study showed abnormal pulmonary functions in 45% patients receiving the drug for same period.^[4] have reported occasional minimal lung involvement.^[5]

Interstitial pneumonitis on transbronchial lung biopsy has been reported after 1 month of treatment with DPH.^[6] Lymphocytic interstitial pneumonia, organizing pneumonia, eosinophilic pneumonia, and pulmonary vacuities are other features reported in the past.^[7]

Acute reversible pulmonary disease has been reported in patients presenting with fever, cough, breathlessness, and hypoxia that is managed with steroids and drug cessation.^[8] Acute respiratory failure has been shown to be caused by an overdose of DPH. Our patient presented with a normal serum phenytoin level after 6 months of DPH therapy.

Generally, acute clinical presentation begins with fever, followed by shortness of breath, lung infiltrates, and peripheral and parenchymal eosinophilia.^[9] In our case, there was no peripheral or lung eosinophilia (negative BAL eosinophilia). Although, eosinophilia is more common with drug induced acute eosinophilic pneumonia, absence of eosinophilia does not rule out drug induced pulmonary toxicity. Our case presented with symptoms of acute HP without eosinophilia.

Clinical signs of drug induced pulmonary disease are nonspecific. Bilateral basal crackles with absent clubbing or evidence pulmonary artery hypertension only indicate acute nature of the disease as in our case. His ECHO findings were normal and there was no evidence of pulmonary hypertension. Generally, routine investigations are noncontributory to establish the diagnosis,^[10] and are insignificant as in our case. Negative profile for infection and autoimmune diseases helped us to rule out such causes that have similar presentation.



Figure 4: Chest X-ray on follow-up visit after 15 days showing significant resolution of reticular shadows

HRCT is more sensitive than chest radiograph (74%) in delineating radiological abnormalities but is not specific to any drug induced etiology.^[10] Generally, it is difficult to infer the histopathological diagnosis on the basis of imaging studies.

The “head cheese” sign is a combination of normal lung parenchyma, ground-glass opacity (GGO), and mosaic perfusion, and is accentuated in expiratory scans in patients with mixed obstructive and infiltrative disorders, wherein obstruction is manifested by mosaic perfusion and infiltration that is seen as GGO. A majority of these patients have HP. Our patient’s CT scans showed this sign.^[11,12] Commonly HP pattern is reported with use of cyclophosphamide, sulfonamides, or nonsteroidal anti-inflammatory drugs (NSAIDs)^[10] [Table 1]. Our patient had no history of using any other drug besides DPH. There was a history of use of levetiracetam that does not seem to be an offending drug. The patient is still continuing on it and had no recurrence of symptoms despite being off steroids.

Pulmonary function in HP varies from normal dynamic lung function to restriction or mixed ventilatory defect with reduced diffusion capacity and exercise induced hypoxia.^[13] In our case, the lung functions were compatible with diffuse parenchymal lung disease (DPLD), especially HP, and the patient also had hypoxia as seen in his arterial blood gas (ABG) analysis.

Bronchoscopy with BAL is useful in evaluation of certain DPLD, though it is infrequently diagnostic. When compatible clinical and radiological findings are present, BAL can help in the diagnosis.^[14] BAL lymphocytosis in the absence of other causes, e.g., tuberculosis and sarcoidosis, makes the diagnosis of HP^[12] easier. BAL in our case was within normal limits. The specimen obtained on TBLB was small but adequate to establish the diagnosis of drug induced pulmonary disease in 76%.^[15] Moreover, correlation of histology and radiology using HRCT contributed further to clarify the diagnosis. In our case, TBLB revealed airway centered poorly formed granuloma with lymphocytic infiltrate and loose epithelioid cell granulomas in the interstitium, which, in the absence of tuberculosis, established the diagnosis of HP. Drug induced HP was inferred after exclusion of all other known causes of HP.

Table 1: Common drugs causing HP

Azathioprine
6-Mercaptopurine
Beta-blockers
Busulfan
Fluoxetine
Nitrofurantoin
Procarbazine

HP: Hypersensitivity pneumonitis

The primary goal of treatment in HP is to suppress the inflammation and prevent progression of fibrosis by discontinuing the offending drug. Further, if the disease is severe or appears to progress or does not improve, empirical corticosteroids are recommended as was done in our case. Although on rechallenge the offending drug may be tolerated, still if an alternative drug is available it is advisable not to use the offending drug again.

Prognosis of drug induced pulmonary disease is variable. Prognosis is not linked to the severity of the disease at presentation but is related to the specific drug causing it.^[16]

Since there are more than 480 drugs leading to drug induced interstitial lung disease (ILD). No consensus for the definite diagnostic criteria and approach for suspected drug induced lung disease exists. Such cases have no pathognomonic clinical and radiological features that can distinguish them from other causes of DPLD. Physicians need to be familiar with iatrogenic diseases. Early detection and stopping of drug leads to better prognosis as well these cases respond well to steroid treatment. Regular follow-up, initially monthly and subsequently at 3-6 months with functional assessment and radiological evaluation, is advised for 1 year.

To summarize, in our case, the history of intake of DPH, prior to the onset of symptoms, and showing a temporal relationship raised possibility of drug induced pulmonary toxicity. These findings were further supported by laboratory and radiological studies, BAL and lung biopsy, thereby confirming the diagnosis of HP and excluding other causes. The cessation of DPH administration resulted in complete resolution; further established the diagnosis of DPH induced acute HP, which is an uncommon presentation of DPH.

Removal of the offending drug is crucial to the proper management of drug induced pulmonary disease, it is important to recognize these offending drugs. A quick reference to dedicated website may be the only opportunity to prevent further progression of the disease (www.pneumotox.com).

ACKNOWLEDGMENT

We thank Dr. Charul Dabral, M.D., for her prompt services and diligent efforts as pathologist.

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How to cite this article: Periwal P, Joshi S, Gothi R, Talwar D. Phenytoin-induced acute hypersensitivity pneumonitis. *Lung India* 2015;32:631-4.

Source of Support: Nil, **Conflict of Interest:** None declared.