A case report of phenytoin-induced eosinophilic pneumonia

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ABSTRACT

Eosinophilic pneumonia comprises a rare and potentially serious group of lung diseases characterized by abnormal accumulation of eosinophils in the lungs. Many medications including the anticonvulsant phenytoin, have been implicated in the development of eosinophilic pneumonia. Attributing eosinophilic pneumonia to a medication or toxin can be difficult and may only be achieved by exclusion. The process can be particularly challenging in polypharmacy and when there has been long-term use. Notwithstanding, the presence of a potential offending drug/agent, exclusion of other causes of eosinophilic pneumonia, clinical improvement after cessation of the offending agent, or return of eosinophilic pneumonia after re-challenge are strong indicators for a drug-induced diagnosis. We report a case of phenytoin-induced eosinophilic pneumonia that resolved after medication withdrawal. Considering drug toxicity as a possible etiology of eosinophilic pneumonia is important to allow for the prompt removal of the causative agent, which can result in clinical cure.

1. Introduction

Eosinophilic Pneumonia encompasses diverse lung diseases characterized by pulmonary eosinophilia, radiographic airspace opacities and frequently, peripheral blood eosinophilia. Many medications including anticonvulsants have been associated with the development of eosinophilic pneumonia. We report a case of phenytoin-induced eosinophilic pneumonia that resolved after medication withdrawal.

2. Case description

A 56-year old male with a history of emphysema, psoriasis, and Grand mall seizures who had taken phenytoin for 35 years, presented with dyspnea, wheezing and non-productive cough. He was an active smoker and reported having pneumonia 5 times over the last 10 years, as well as pleurisy, and an idiopathic pleural effusion that warranted a chest tube insertion 10 years prior. It was unknown if these pneumonias were infectious in nature. Nine months prior to presentation, he had an episode of pneumonia at which time the eosinophil count was elevated at 2700/μL (19% EOS). Allergy testing via skin scratch method was negative and the bronchoscopy was reportedly abnormal for elevated eosinophils. His other tests included negative ANCA, negative Strongyloides, negative PDGFR mutation, and normal bone marrow biopsy except for the elevated number of eosinophils (17%). He had no history of prolonged antibiotic use, antiarrhythmics, chemotherapy, herbal or nutritional supplements. Symptoms of wheezing and cough improved with corticosteroids but worsened with reduction of prednisone below 30mg/day. On presentation to our clinic, physical exam demonstrated an alert and well-nourished male with diminished breath sounds but no respiratory distress. His peripheral blood eosinophils were elevated at 1615/μL and test for Giardia was negative. Chest imaging (Fig. 1) demonstrated severe upper lobe emphysema, mild bronchial wall thickening, band-like opacities and lower lobe fibrotic changes not consistent with usual interstitial pneumonia.

Given the long history of respiratory symptoms, idiopathic pleural effusion, and eosinophilic pneumonia, we were highly suspicious of an adverse drug reaction to phenytoin. He was initially reluctant to discontinue use as prior efforts to stop phenytoin had resulted in exacerbation of seizure disorder. However, in working with a consulting neurologist, we were able to discontinue phenytoin with replacement with Brivaracetam, without recurrent seizures. A month after discontinuation of phenytoin, eosinophil counts normalized and clinical status improved (absolute EOS count 200/μL, EOS %, 1%). Prednisone was tapered off without return of symptoms and eosinophil count remained normal. Patient had been, and continues to be on inhaled corticosteroid for emphysema, which could affect eosinophil count. CT scan of the chest performed approximately 6 months after discontinuation of phenytoin showed resolution of airspace opacities. He continued to smoke about a half pack per day.

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Fig. 1. High Resolution Computed Tomography (HRCT) of the chest obtained at presentation that demonstrated upper lobe emphysema, bronchial wall thickening and band-like opacities.

3. Discussion

Eosinophilic pneumonias (EP) may be idiopathic or of known etiology. Loeffler’s syndrome, acute eosinophilic pneumonia (AEP), and chronic eosinophilic pneumonia (CEP) make up the idiopathic eosinophilic pneumonias [1]. Known causes of eosinophilic pneumonia include infections with various parasites, such as Ascaris, fungal and viral infections, inhalational exposure, such as cigarette smoke or cocaine, and medication/drug exposure, most frequently from antimicrobials such as daptomycin but include many others, antidepressants, and anticonvulsants [2,7]. Over 100 different medications including phenytoin have been implicated in eosinophilic pneumonia, but attributing eosinophilic pneumonia to a drug or toxin can be a challenging feat that is usually achieved by exclusion [4]. The process can be particularly challenging in polypharmacy and when there is long-term use, such as in the case presented here. Other providers had mentioned phenytoin as the possible cause of EP, but it was discounted due to the long-term use. The presence of a potential offending drug/agent, exclusion of other causes of eosinophilic pneumonia, clinical improvement after cessation of the offending agent, or return of eosinophilic pneumonia after re-challenge are strong indicators for a drug-induced diagnosis [4]. In our case, the persistent symptoms and exclusion of any other causes of EP led us to strongly suspect phenytoin as the causative agent. Additionally, from a review of the literature, studies had shown abnormal lung findings in patients on long term hydantoin therapy where the only explanation was a drug allergy reaction. In one study, abnormal lung findings were seen in 16 radiographic readings of 31 patients who had been on hydantoin therapy for 2 or more years [6]. Moreover, in our case, radiological and clinical abnormalities resolved after removal of the offending agent.

Although eosinophilic pneumonias are rare, anticonvulsants represent one of the most frequently implicated drug families [3,5]. Phenytoin is an important anticonvulsant drug that is effective and widely used in controlling a wide range of seizures with little to no effect on neurological function. However, like many anticonvulsants, long term use can lead to serious adverse effects. While the exact triggering factor of eosinophilic pneumonia from phenytoin and other anticonvulsants is unknown, serotonin and eotaxins which are known to have eosinophil chemotactrant properties may be related to the link between EP and this family of drugs [5]. The infrequent occurrence and potential seriousness of phenytoin-induced eosinophilic pneumonia make our case an important adverse drug reaction worth reporting. This case is novel in that, the patient was on phenytoin therapy for a prolonged duration without recognition as to the etiology of the eosinophilic pneumonia and eosinophilia. Further, there had been several attempts in the past to change Phenytoin to alternative anti-epileptics, but each time, after switching, patient had a recurrent Grand mal seizure and so was returned to phenytoin. Patient had pneumonia five times over 10 years. In retrospect, the 10-year history of recurrent pneumonias and idiopathic pleural effusion were likely related to adverse drug reaction which worsened over time, although we could only speculate that was the case. Patient had tried Topamax, gabapentin and Tegretol but always returned to phenytoin due to several episodes of seizures. Long-term reliance on phenytoin made the patient reluctant to discontinue for fear of breakthrough seizures. It is important that patients with similar reactions be monitored closely with a replacement anticonvulsant to avoid possible relapse of seizures.

4. Conclusion

Drug-induced adverse effects can be easily missed when a patient has been on the offending medication for a prolonged period. It is important to recognize drug toxicity as the etiology of eosinophilic pneumonia to allow for the prompt removal of the causative agent, which can result in clinical cure.

Conflicts of interest

RAG and LS have no conflicts of interests. The authors alone are responsible for the content and writing of this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2019.100922.

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