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Case report

Phenytoin induced Steven–Johnson syndrome and bronchiolitis obliterans – case report and review of literature

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ABSTRACT

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are both rare but serious idiosyncratic drug reactions characterized by diffuse muco-epidermoid injury and high mortality. Keratinocytes in both skin and mucous membranes (including eyes, mouth and genitalia) are injured resulting in a diffuse maculopapular rash, blistering lesions and epithelial detachment with minimal force (Nikolsky's sign). SJS is typically diagnosed when less than 10% of the skin surface is involved and the term TEN is used in cases with more than 30% involvement. Respiratory involvement in SJS-TEN is common with 30–50% of cases demonstrating respiratory epithelial sloughing with severe short and long term complications. Patients who survive SJS-TEN are often left with impaired respiratory function and bronchiolitis obliterans. Cases of bronchiolitis obliterans with SJS/TEN have been very rarely reported. We report a case of phenytoin induced SJS/TEN followed by severe bronchiolitis obliterans in an adult patient. The presentation, pathophysiology and management of SJS/TEN related bronchiolitis obliterans is also reviewed.

1. Case

A 67 year old nonsmoking Caucasian male was evaluated for hypertension and a history of partial seizures. He had no prior history of chronic obstructive pulmonary disease or asthma. His family history was positive for GTP cyclohydrolase 1 gene mutation in his sister and niece, which is an autosomal dominant condition with childhood-onset dystonia.

In 2003, he was started on phenytoin for his partial seizures. He had previously had an anaphylactic reaction to carbamazepine. Three weeks after starting phenytoin, he broke out in a generalized body rash involving both skin and mucous membranes. A diagnosis of Steven–Johnson syndrome (SJS) was made and patient was hospitalized for a week. During the hospitalization he developed pneumonia and a staphylococcal skin infection for which he was treated with antibiotics. His valproic acid dose needed to be reduced due to a mild increase in liver enzymes and development of a tremor.

Soon after hospital discharge, he noticed significant shortness of breath and inability to perform even basic activities of daily living. He did not have any other symptoms of respiratory disease such as cough, fever, hemoptysis or subsequent respiratory infections. His dyspnea failed to improve over time and he remained markedly impaired in his overall functioning. Chest radiographs done over the years showed bilateral apical scarring with fibrosis and volume loss in upper lung fields (Fig. 1). Pulmonary function testing performed in 2014 (11 years after the episode of SJS) showed very severe obstruction with marked air trapping. His FEV1 was 1.02 L (25% predicted), FVC was 2.80 L (52% predicted) and TLC (total lung capacity) was 7.80 L (103% predicted). His residual volume was markedly elevated at 4.88 L (222% predicted) with a RV/TLC ratio of 62.5%. No bronchodilator response was noted. His diffusing capacity was surprisingly normal (77% predicted) confirming an airway-centric obstructive process rather than a defect in pulmonary gas-exchange. His resting and exercise oxygen concentrations were also within normal limits. He was prescribed an albuterol inhaler but was non-compliant. A chest CT scan showed findings compatible with a diffuse airway centric-process affecting the large and small airways (Fig. 2). The chest CT scan showed marked air trapping with areas of mosaic attenuation along with diffuse thickening of visible airway walls. In addition, there were areas of peri-bronchial linear scarring noted in the upper lung fields and

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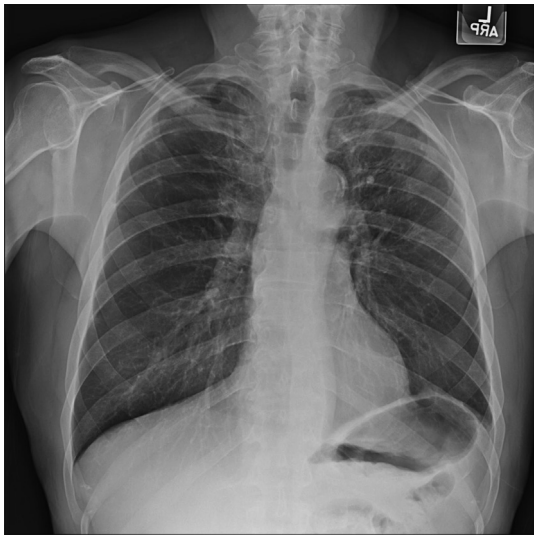

Fig. 1. Chest X-ray.

compatible with a diagnosis of constrictive bronchiolitis/bronchiolitis obliterans secondary to the episode of SJS-TEN that had occurred 11 years earlier. Repeat pulmonary function testing obtained 1 year later in 2015 showed stable lung function.

2. Discussion

Both Stevens – Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are typically medication induced and are characterized by widespread epidermal necrosis and mucous membrane involvement. Mortality rates are generally below 5% for SJS but approaches 30–50% or higher in patients with TEN with higher mortality rates seen in older patients [1]. The cardinal manifestation of SJS-TEN is a febrile illness along with headache, cough, malaise, rhinorrhea occurring along with prodromal 'target' type skin lesions that later develop into a diffuse erythematous rash involving both skin and mucous membranes [2]. As the disease evolves, the epidermis undergoes necrosis in broad sheets and classically detaches from the underlying dermis with even minimal effort (Nikolsky sign). Mucous membrane involvement is reported to occur in 90%–100% of cases and can involve virtually all areas of

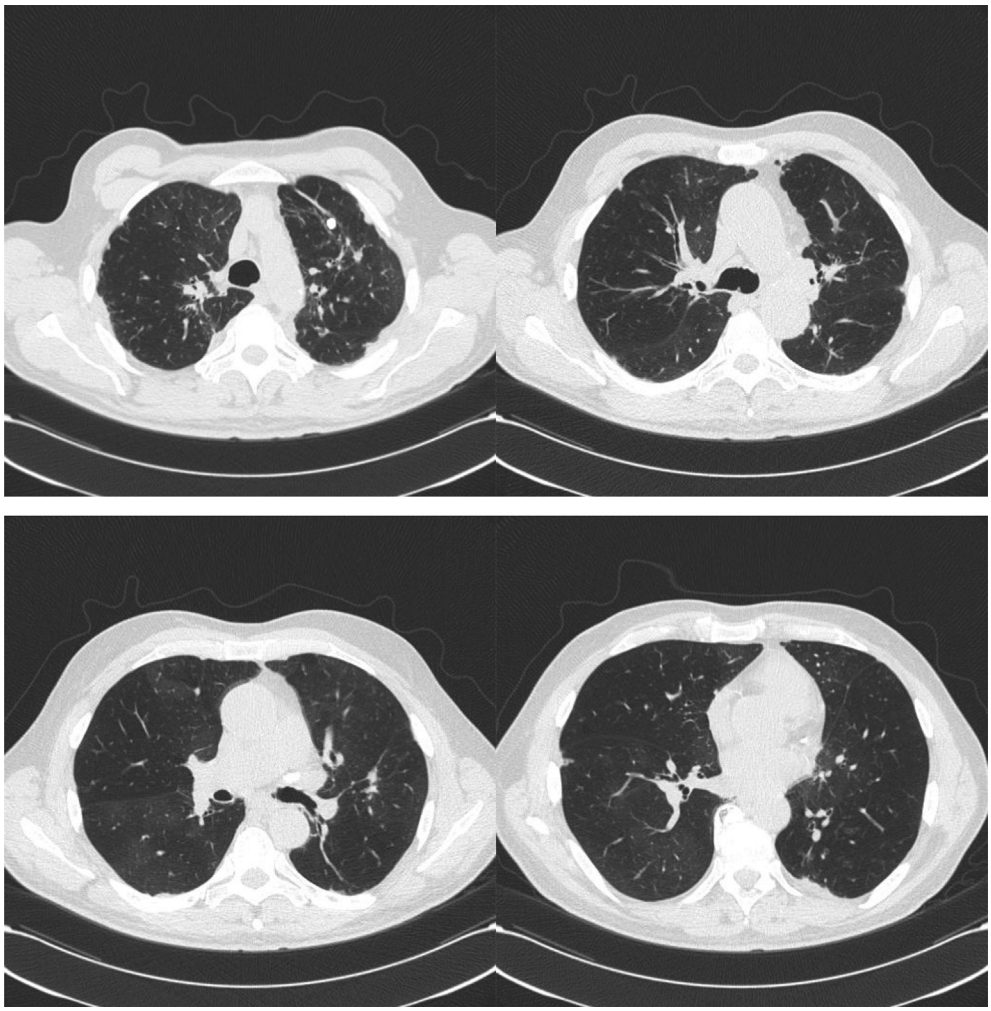

Fig. 2. Chest CT scan.

marked stenosis at the origin of the bronchi to the lingula. Given the lack of other plausible explanations, all these findings were

the body including the mouth, nose, genitalia, eyes and visceral organs. Visceral involvement is common and seen in over 2/3rd of

patients. Manifestations include sloughing of the gastrointestinal mucosa, diffuse tracheal and bronchial inflammation with mucosal injury and sloughing, glomerulonephritis and hepatitis [1–4].

The pathogenesis of SJS-TEN induced constrictive bronchiolitis/bronchiolitis obliterans (BO) is not completely clear, but likely reflects severe bronchial epithelial injury and subsequent scarring in a process akin to that seen in other mucous membranes. Damage to the bronchiolar epithelium due to immune complex deposition in SJS-TEN may initiate necrosis and subsequent exudation of fibrin and inflammatory cells into the airways [5]. Obliteration of bronchiolar lumens can then develop due to formation of fibrous granulation tissue. BO is a clinical diagnosis and pathologic confirmation is not mandatory for diagnosis. Lung involvement in SJS-TEN appears to be quite common with both early and delayed presentations. Onset of BO has been reported to occur from 5 days to 10 months after the development of SJS [5–8]. In a prospective study of 41 SJS-TEN patients by Lebargy and colleagues, bronchial epithelial involvement was noted in 27% of cases [5]. Bronchoscopy findings were consistent with epithelial sloughing in the proximal airways. In the autopsied lungs of patients with BO after SJS-TEN, Sugino and colleagues noted extensive occlusion of bronchi at the 4th and 5th generation bronchi and beyond [7]. These occlusive lesions were sporadically and intermittently located from the small bronchi all the way to the membranous bronchioles. Common pulmonary manifestations included dyspnea, bronchial hypersecretion, hypoxemia, atelectasis, pulmonary edema, need for mechanical ventilation and superimposed bacterial pneumonias.

The risk for SJS-TEN appears to be the highest in the first few weeks ($\leq$8 weeks) after initiation of the culprit medication as was the case in our patient. Treatment of SJS-TEN should begin with the prompt withdrawal of the culprit drug. A multidisciplinary approach is necessary to manage the diffuse skin, ocular, mucous membrane and visceral organ involvement. Respiratory involvement is treated with airway humidification, bronchodilators and chest physiotherapy. Around 25% of TEN cases may require mechanical ventilation with poor outcomes and high mortality rates in patients with severe respiratory tract involvement. Severe cases of SJS-TEN are best treated in burn centers with studies showing that prompt referral to a burn center is associated with improved survival [2]. No randomized controlled studies exist for intravenous immunoglobulins, systemic corticosteroids, cyclosporine, cyclophosphamide, plasmapheresis, hemodialysis and other therapies that are sporadically used in SJS-TEN.

3. Conclusion

In conclusion, we present a rare case of severe bronchiolitis obliterans following phenytoin induced SJS-TENS. This case serves to highlight the severe and long term respiratory impairment that can occur in the setting of SJS-TEN induced bronchiolitis obliterans. Unfortunately, effective therapies for the treatment of SJS-TEN do not exist and supportive therapies with prompt discontinuation of the offending agent remain the standard of care.

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Disclosure

None for all authors.

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