CASE REPORT

Bronchiolitis obliterans organising pneumonia associated with anticonvulsant hypersensitivity syndrome induced by lamotrigine

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Accepted 28 December 2015

SUMMARY

A 14-year-old girl who was known to have a seizure disorder and on lamotrigine treatment was admitted to the hospital, with a history of rash, fever and cough. Her condition deteriorated with clinical features suggestive of anticonvulsant hypersensitivity syndrome (ACHS) complicated with bronchiolitis obliterans organising pneumonia (BOOP). Her chest CT showed multifocal parenchymal opacities and lung biopsy was typical for BOOP. Initially, the lamotrigine was discontinued since the onset of the rash, then she was treated for pneumonia with antibiotics, which may have delayed the diagnosis. Eventually, BOOP was considered and she was treated with a high dose of corticosteroid. She improved clinically and her repeated chest CT showed a marked resolution of the lesions. This case illustrates the possible occurrence of BOOP as a complication of ACHS secondary to lamotrigine treatment.

BACKGROUND

A rare lung condition, bronchiolitis obliterans organising pneumonia (BOOP) is characterised by an inflammatory process simultaneously involving both the terminal bronchioles and alveoli. BOOP can be secondary to infections, various drugs and other medical conditions. Discontinuing the offending drug and implementing supportive care are both keys in managing BOOP, as it can be fatal. However, in many cases, the underlying cause of BOOP is unknown.

On the other hand, anticonvulsant medications are widely used in paediatrics, for different seizure disorders. Anticonvulsant hypersensitivity syndrome (ACHS) is characterised by symptoms of fever, rash and internal organ involvement. It is also a rare, but life-threatening adverse event of anticonvulsant use.¹ Lung involvement in ACHS has been described in different case reports to be associated with acute respiratory distress syndrome, pneumonitis, respiratory failure and bronchiolitis obliterans in Stevens-Johnson syndrome (SJS).²

By writing this case report, we hope to increase physicians' awareness for early detection of ACHS and the possible lung involvement in the form of BOOP without the evidence of SJS, to prevent the delay in the diagnosis and treatment, which can lead to an adverse outcome.

CASE PRESENTATION

A 14-year-old girl, known to have a partial seizure disorder, began treatment on lamotrigine after failure of other antiepileptic medications

(carbamazepine and oxcarbazepine) to achieve the desired control of her disease. Nine weeks after starting the medication, while she was travelling to Jamaica, she developed a maculopapular skin rash and the family was instructed to discontinue the use of lamotrigine. A few days later, on her first presentation, she had fever, which was thought to be due to otitis media, and was started on amoxicillin-clavulanic acid. However, she only had three doses of the antibiotic, then it was discontinued by the family, as she did not improve. Following that, she went back to Canada, and presented to the emergency department, with decreased appetite, a tactile fever, rigour, chills and a mild cough. She had no significant respiratory distress. The rest of the systemic review was otherwise unremarkable and she had no sick contact.

This time, she was admitted to the hospital for further investigation. Her initial vitals were normal for her age. Her physical examination revealed bilateral decreased air entry. She had no rash, no mouth ulcers and no lymphadenopathy. Her cardiovascular, abdominal and neurological examinations were within normal limits.

Her temperature continued to spike and she deteriorated in respiratory status, with worsening neutropaenia, anaemia and inflammatory markers. She was taken to the operating room for a bronchoscopy, left bronchioalveolar lavage (BAL), thoracoscopic lung biopsy and a bone marrow aspiration, to exclude any infectious or malignant aetiologies for her symptoms.

INVESTIGATIONS

In terms of the patient's initial investigations, her complete blood cell count revealed haemoglobin of 95 g/L (120–166 g/L), which further decreased over the course of her admission to 64 g/L; a white cell count of 8.4 (4–11 × 10⁹/L), which decreased to 2.6, with platelets low at 136 (150–400 × 10⁹/L), and eosinophils elevated at 1.5 (0.0–0.7 × 10⁹/L).

Serum sodium, potassium, urea and creatinine were within normal range and chloride was low at 85 (98–110 mmol/L).

Her inflammatory markers were elevated, including C reactive protein of 490 (0.0–8.8 mg/L), erythrocyte sedimentation rate of 62.4 (0.0–20 mm/h) and ferritin of 4140 (13–375 µg/L). Her coagulation profile showed elevated International Normalised Ratio of 1.7 (0.9–1.1), partial thromboplastin time of 39.9 (25–35 s) and D-dimer of 2.76 (<0.46 mg/L fibrinogen equivalent units).

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To cite: Ghandourah H, Bhandal S, Brundler M-A, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-207182

Initial chest X-ray showed bilateral patchy opacities on the right middle and lower zones as well as on the lingual lobe of the left lung (figure 1).

As the patient started to require more oxygen, we obtained a chest CT, which revealed multifocal patchy areas of airspace disease with ground glass haziness on both lower lobes, with mediastinal lymphadenopathy (figure 2A, B).

Bronchoscopy showed diffuse lung disease with pulmonary haemorrhage. The patient's BAL was sent for cytology and was negative, supportive of neither an infectious process, nor systemic lupus erythematosus (SLE), nor sarcoidosis. Specifically, there was no lymphocytosis and no abnormal CD4/CD8 ratio expected in sarcoidosis. Also, the cellular activity was measured by means of cytofluorometry, and chemiluminescence did not support an SLE diagnosis. A Gram stain and acid-fast bacilli were negative. Also, the BAL analysis did not indicate any viral, bacterial, atypical or fungal aetiologies. The BAL bacterial and fungal cultures, including for *Pneumocystis jiroveci*, remained negative.

The lung biopsy showed BOOP characterised by loose fibroblast plugs within alveoli and focally within bronchioles (figure 3A, B). There was no eosinophilic vasculitis seen on lung biopsy, ruling out Churg-Strauss syndrome.

Bone marrow biopsy showed a hypocellular marrow with left shift and immature neutrophils. Also, erythroid hypoplasia was noticed.

The infectious work up also included blood and urine cultures, which were negative. A blood smear for malaria was negative. A nasopharyngeal swab for viruses, bacteria and mycoplasma PCR were negative. Serology for dengue fever, cytomegalovirus, Epstein-Barr virus, hepatitis A, parvovirus, HIV, *Francisella tularensis*, brucella, coccidioidomycosis, histoplasmosis and toxoplasmosis were all negative.

Rheumatology work up was negative for antinuclear antibodies, perinuclear antineutrophil cytoplasmic antibodies, cytoplasmic antineutrophil cytoplasmic antibodies and double stranded-DNA. C3 and C4 were elevated at 1.7 (0.6–1.6 g/L) and 0.47 (0.1–0.4 g/L), respectively.

Though the patient had a skin biopsy, it was an insufficient sample hence inconclusive.

Figure 1 Chest X-ray showing bilateral patchy opacities on the right middle and lower zones as well as on the lingual of the left lung.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis in this case is wide and includes multiple potential causes. The history of recent travel to Jamaica and the respiratory symptoms guided our initial focus toward infectious causes such as bacterial pneumonia, tuberculosis and fungal infections. However, all the patient's infectious work, up as mentioned above, was negative.

The patient in this case received amoxicillin-clavulanic acid while in Jamaica, which might have confused the clinical picture. Noteworthy, she had fever and skin rash prior to the start of the incomplete antibiotic treatment. That made the possibility of penicillin-related rash and serum sickness less likely.

Rheumatological causes such as SLE, sarcoidosis and Churg-Strauss syndrome were considered as well, however, the blood work and lung biopsy were not suggestive.

Another differential diagnosis that was investigated in this case was malignancy, such as leukaemia or lymphoma. For that reason, a bone marrow biopsy and aspiration were carried out to exclude these diagnoses.

Finally, the presence of fever, rash and multiple organ involvement with hypereosinophilia in the absence of evidence of other pathology led us to believe this clinical picture was most likely due to ACHS. The interesting finding of BOOP was confirmed

Figure 2 (A) CT scan showing multifocal parenchymal opacities. (B) Axial CT image shows multifocal patchy areas of airspace disease with a ground glass-haziness appearance on both lower lobes.

Figure 3 (A) A wedge biopsy of the lingula shows patchy organising pneumonia with loose fibroblast proliferations obliterating small airways (A) (H&E, ×10 original magnification). (B) Obliterative bronchiolitis with intraluminal fibrous proliferation is illustrated (H&E, ×20 original magnification).

on the lung biopsy, which has not been reported before in ACHS triggered by lamotrigine treatment.

TREATMENT

The patient was treated with intravenous ceftriaxone and oral azithromycin for infectious pneumonia. She started to have

Figure 4 CT scan showing complete resolution of the multifocal parenchymal opacities.

Table 1 Causes of bronchiolitis obliterans with organising pneumonia³

Idiopathic bronchiolitis obliterans with organising pneumonia	Drugs:
Postinfection	Antibiotics;
Bacterial infection:	Sulfasalazine,
<i>Mycoplasma pneumoniae</i>	Cephalosporin
<i>Staphylococcus aureus</i>	Sulfamethoxypyridazine
<i>Streptococcus pneumoniae</i>	Amphotericin
<i>Chlamydia pneumoniae</i>	Acebutolol
<i>Pseudomonas aeruginosa</i>	Sotalol
<i>Legionella pneumophila</i>	Amiodarone
<i>Nocardia asteroides</i>	Bleomycin
<i>Coxiella burnetii</i>	Busulphan
<i>Serratia marcescens</i>	Methotrexate
Viral infection:	Carbamazepine
Herpes virus	Cocaine
Influenza virus,	Gold salts
Parainfluenza virus	Interferon α
HIV	Phenytoin
	Tacrolimus
	Ticlopidine
	Vinabarbital-aprobarbital
Connective tissue/immunological disease:	Miscellaneous:
lupus erythematosus	Inflammatory bowel disease
rheumatoid arthritis	Cancer (solid and
Sjögren's syndrome	haematological)
polymyositis/dermatomyositis	Myelodysplastic syndrome
Behçet disease	
Polymyalgia rheumatic	
Ankylosing spondylitis	
Sweet syndrome	
Essential mixed cryoglobulinaemia	
Common variable immunodeficiency syndrome	
Organ transplantation:	
Lung, renal, bone marrow transplant	
Environmental:	
Radiotherapy	
Textile printing dye	
House fire	

respiratory distress and needed oxygen to maintain her saturation.

Her antibiotics were discontinued and she was started on pulse methylprednisolone. Her clinical status started to improve gradually and her fever disappeared. Lung CT was repeated after 2 weeks and showed some improvement (figure 4). The patient was discharged home with a plan of tapering down oral prednisone.

OUTCOME AND FOLLOW-UP

The patient was seen in the respiratory clinic 4 weeks after discharge and remained well with normal lung function on spirometry.

DISCUSSION

BOOP is a distinct clinicopathological entity with clinical, imaging and prognostic features. It is characterised by the presence of organising fibroblastic tissue in the bronchiolar lumen, alveolar ducts and alveoli. It is also associated with a variable degree of interstitial and airspace infiltration by mononuclear cells and foamy macrophages. Several causes of BOOP have been recorded (table 1) but most cases are idiopathic.³

On the other hand, ACHS is characterised by fever, rash and internal organ involvement. It is a rare, but potentially life-threatening adverse event that occurs following exposure to an anticonvulsant, most commonly to aromatic anticonvulsants

(phenytoin, phenobarbitone, primidone, carbamazepine) or lamotrigine.^{1–4} ACHS has been reported in the literature to occur as a result of lamotrigine treatment.^{5–7}

ACHS had been described as a concomitant sequel to atypical pneumonia.⁸ In ACHS, the lungs can be affected in different ways including by acute respiratory distress syndrome, pneumonia, respiratory failure and bronchiolitis obliterans specifically with SJS.^{1–2}

This case indicates the occurrence of organising pneumonia in ACHS even without SJS.

Learning points

- ▶ Anticonvulsant hypersensitivity syndrome (ACHS) is characterised by the triad of fever, rash and internal organ involvement.
- ▶ Physicians should be proactive in eliciting the symptoms of ACHS in patients on anticonvulsant medications.
- ▶ Early detection and elimination of the anticonvulsant agent with supportive treatment can decrease the morbidity and mortality associated with ACHS.
- ▶ Lung involvement in ACHS can present in different forms including bronchiolitis obliterans with organising pneumonia and should be carefully investigated to exclude the possibility of infections, malignancies or rheumatological diseases.

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Acknowledgements Many thanks to Mona Bechervaise (secretary assistant) for editing the report.

Contributors HG was responsible for preparing the case and organising the discussion. M-AB was responsible for preparing the pathology slides and the description. SB was responsible for preparing the images and the description.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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