Received: 2 March 2022 | Accepted: 6 April 2022

DOI: 10.1002/rcr2.952

CASE REPORT

Respirology Case Reports OPEN ACCESS APSR WILEY

Post-ictal diffuse alveolar haemorrhage: clinical profile based on case reports

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Associate Editor: Coenraad F. Koegelenberg

Abstract

Diffuse alveolar haemorrhage (DAH) after a generalized tonic–clonic seizure is a rarely described illness likely involving physical disruption of alveolar–capillary interface similar to the mechanism of neurogenic pulmonary oedema. Based on our review of the English literature, only 11 cases have been reported to date. Recognition of this sparsely reported entity is important for optimal management, including avoidance of medications that have been implicated in causing DAH. Current experience with two additional patients with post-ictal DAH extends the reported experience to 13 and summarizes what is, to our knowledge, the entire experience of such patients reported in the English literature. This case report highlights the key aspects of clinical presentation, radiological and pathological findings, clinical course and management implications with the goal of enhancing awareness of this condition by respiratory clinicians.

KEYWORDS
diffuse alveolar haemorrhage, Muller manoeuvre, negative-pressure pulmonary oedema, post-ictal haemoptysis

INTRODUCTION

Diffuse alveolar haemorrhage (DAH) following a seizure (post-ictal DAH) is a recognized but sparsely reported entity. Our recent experience with two patients whose post-ictal DAH resulted in respiratory failure prompted us to summarize the reported experience with post-ictal DAH to enhance respiratory clinicians' recognition and understanding of this distinctive clinical problem.

CASE REPORT

Case 1

A 24-year-old male with a history of epilepsy, developmental delay, sickle cell trait and alpha thalassemia minor presented to the emergency room after having a generalized tonic–clonic seizure with haemoptysis. He had experienced prior episodes of haemoptysis and diffuse infiltrates, always following a seizure, one of which prompted a bronchoalveolar lavage and transbronchial lung biopsy at an outside hospital. No evidence of infection or malignancy was found on analysis of the lavage fluid, and the transbronchial biopsy showed fragments of lung parenchyma 'without significant pathological findings'.

Laboratory evaluation showed a normal platelet count (207,000/μl) and normal prothrombin time and partial thromboplastin time. Anti-nuclear antibody, anti-neutrophil cytoplasmic antibody and anti-glomerular basement membrane antibody were negative. Anti-epileptic medications included levetiracetam, clonazepam, perampanel and zonisamide, but neither valproate nor carbamazepine. Concern for airway protection prompted intubation in the emergency room and he was admitted to the medical intensive care unit (ICU), where bronchoscopy confirmed the diagnosis of DAH with progressive bloody return in serial lavages. A computed tomography (CT) scan of his chest showed diffuse bilateral infiltrates (Figure 1A). Echocardiogram on the first day of admission was completely normal. After intubation, his oxygenation improved promptly, with reduction of fraction of inspired oxygen (FiO_2) from 1.0 to 0.3 and

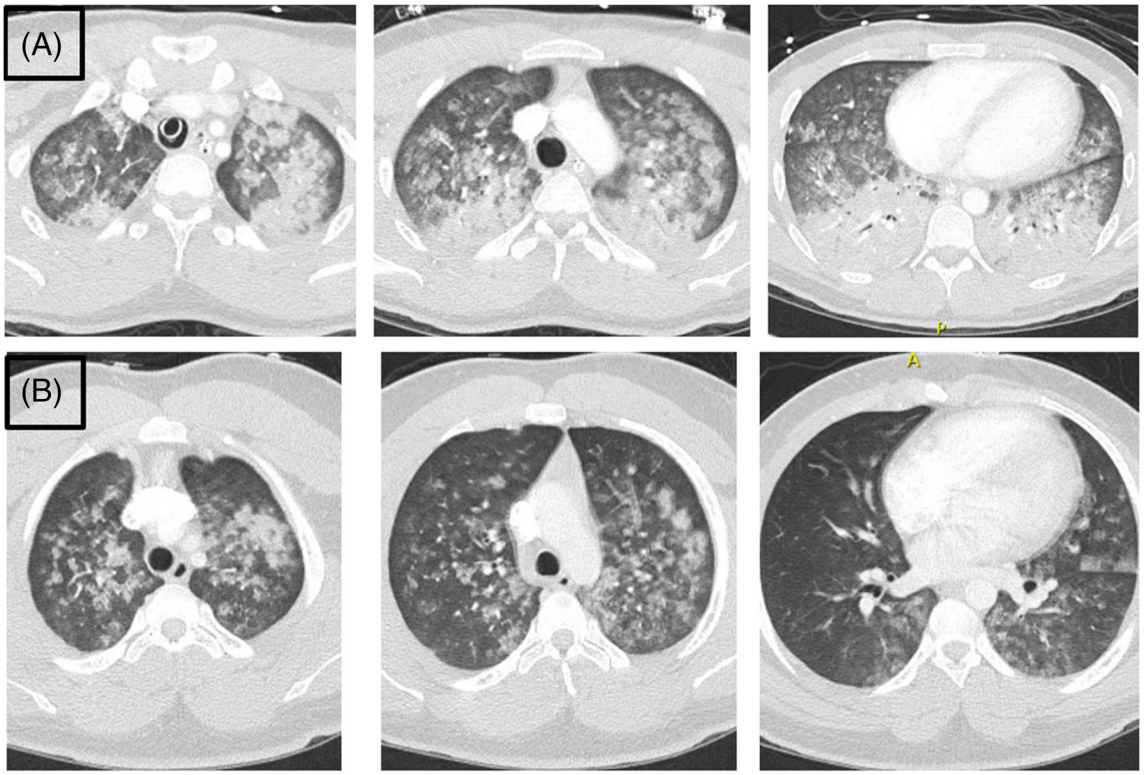

FIGURE 1 Chest computed tomography images (with intravenous contrast) showing diffuse bilateral infiltrates due to diffuse alveolar haemorrhage (A: Patient 1, B: Patient 2)

positive end-expiratory pressure from 10 to 5 cm H_2O within the first 12 h. Pending receipt of the outside pathology report and the serologies sent on admission, initial management included administration of 1 g of methylprednisolone daily for three consecutive days and anti-epileptic medications. On Day 3, the patient was extubated to nasal cannula (3 L/min) and oxygenated well on room air by Day 4.

Case 2

An 18-year-old male with no significant past medical history presented to the emergency room with haemoptysis immediately following a first-time generalized tonic–clonic seizure. He took no chronic medications and had never previously taken valproate or carbamazepine. His pulse oximetry oxygen saturation was 85% on room air for which he required oxygen supplementation through nasal cannula (4 L/min).

Laboratory evaluation showed a normal platelet count (336,000/μl) and normal prothrombin time and partial thromboplastin time. CT scan of his chest showed bilateral diffuse opacities with slight prominence in the upper lobes (Figure 1B). He underwent bronchoscopy on hospital Day 2 which confirmed DAH with progressive bloody return on serial lavages. Echocardiogram on the second day was completely normal. He was started on levetiracetam for the seizure and received two doses of antibiotics (ceftriaxone and azithromycin) for possible community-acquired pneumonia; antibiotics were discontinued promptly as suspicion of infection declined. No organisms were found in samples from the bronchoalveolar lavage and a vasculitis work-up was also negative (Table 1, Patient 2). Within 48 h following admission, the patient no longer required supplemental oxygen, with oxygen saturation above 95% on room air. On Day 4, his chest x-ray showed complete resolution of the initial bilateral opacities (Figure 2).

DISCUSSION

Search of PubMed using search terms ‘diffuse alveolar haemorrhage’, ‘seizure’ and ‘post-ictal’ and of papers cited in the available reports yielded reports of 11 patients with post-ictal DAH (Table 1)[1–5]; the current patients (Patient 1 and Patient 2, Table 1) were included as 12th and 13th patients to the reported experience. The mean age of the 13 patients was 27.5 years (range 18–41) and seven were female. All patients had generalized tonic–clonic seizures before experiencing DAH; in several patients (including the current Patient 1), DAH recurred following multiple seizure episodes. One patient expired after experiencing anoxic encephalopathy.[5] All others experienced rapid resolution of infiltrates and rapid restoration of normal oxygenation; patent 1 was liberated from mechanical

TABLE 1 Summary of reported experience with post-ictal diffuse alveolar haemorrhage

Patient (reference)	Year	Age	Gender	Medical history	Use of prior anti-epileptic medications	Timing of onset of haemoptysis	Key physical examination findings	PO_2 (mmHg)/ saturation (%)	Haemoglobin (g/dl)	Autoimmune laboratory values	Infectious work-up results	Treatment offered	Timing of radiographic resolution
1 (Patient 1)	2021	24	M	Epilepsy, developmental delay, sickle cell trait, alpha thalassemia minor	Keppra, Perampanel, Zonegran, Klonopin	Immediately after GTC seizure	Diffuse bilateral crackles	131/100 (ventilator FiO_2 80%, PEEP 8)	13.7	ANCA− ANA− AGBM−	Negative (BAL)	AED and pulse steroid (1 g methylprednisolone × 3 days)	No follow-up imaging but extubated within 72 h
2 (Patient 2)	2021	18	M	No past medical history	None	Immediately after GTC seizure	Bilateral rhonchi	−/94 (4 L NC)	14.6	ANCA− ANA− AGBM−	Negative (BAL)	AED and two doses of antibiotics	4 days
3[1a] (a–f episodes)	1975	38	F	Epilepsy	Diphenylhydantoin, phenobarbital	Immediately after GTC seizure	Diffuse bilateral crackles	a. − b. − c. − d. 46/− (RA) e. 112/− (NC) f. 38/− (RA)	—	—	—	a. AED, ABX b. AED, ABX c. AED, ABX d. AED, ABX e. AED f. AED	a. 1 week b. 5 days c. 36 h d. 2 days e. 2 days f. 52 h
4[1]	1975	29	M	Epilepsy	Diphenylhydantoin	Immediately after GTC seizure	Diffuse bilateral crackles	60/− (RA)	—	—	—	Anti-epileptic	72 h
5[2]	1988	21	M	None	None	Immediately after GTC seizure	Diffuse rales	57/88 (RA)	14.3	ANA−	Negative (BAL)	AED	72 h
6[3]	2002	38	F	Epilepsy	Non-compliant	Immediately after GTC seizure	Coarse crackles	38/76 (RA)	11.5	ANCA− ANA−	Negative (BAL)	AED and empiric ABX	72 h
7[4]	2011	35	M	History of tuberculous meningitis, epilepsy	Non-compliant with AEDs	Immediately after GTC seizure	—	—	14.5	ANCA− ANA− AGBM−	Negative (BAL)	AED and pulse steroid (1 g methylprednisolone × 3 days)	12 days
8[5]	2000	19	M	Epilepsy	No carbamazepine or valproate use	Immediately after GTC seizure	Diffuse crackles	80/− (RA)	14.1	ANCA− ANA− AGBM−	Negative (BAL)	AED and supportive care	24–48 h
9[5]	2007	41	F	Thyroidectomy	No carbamazepine or valproate use	Immediately after GTC seizure	Crackles at left base	59/− (RA)	10.7	ANCA- ANA- AGBM-	Negative (BAL)	AED and supportive care	24–48 h
10[5]	2009	21	F	Obesity, epilepsy	No carbamazepine or valproate use	Immediately after GTC seizure	Diffuse crackles L > R	156/− (15 L)	10.3	ANCA− ANA−	Negative (BAL)	AED and supportive care	24–48 h

(Continues)

TABLE 1 (Continued)

Patient (reference)	Year	Age	Gender	Medical history	Use of prior anti-epileptic medications	Timing of onset of haemoptysis	Key physical examination findings	PO_2 (mmHg)/ saturation (%)	Haemoglobin (g/dl)	Autoimmune laboratory values	Infectious work-up results	Treatment offered	Timing of radiographic resolution
11[5]	2012	24	F	Obesity, epilepsy	No carbamazepine or valproate use	Immediately after GTC seizure	Bilateral crackles	216/– (15 L)	11.6	ANCA– ANA–	Negative (BAL)	AED and supportive care	24–48 h
12[5]	2012	24	F	Obesity, epilepsy	No carbamazepine or valproate use	Immediately after GTC seizure	Bibasilar crackles R > L	71/– (2 L)	9.3	—	Negative (BAL)	AED and supportive care	24–48 h
13[5]	2013	26	F	Obesity, epilepsy	Valproate level undetected	Immediately after GTC seizure	Diffuse bilateral crackles	ECMO	10.8	—	Negative (BAL)	AED and supportive care	Expired from anoxic encephalopathy

Abbreviations: ABX, antibiotics; AED, anti-epileptic drug; AGBM, anti-glomerular basement membrane antibody; ANA, anti-nuclear antibody; ANCA, anti-neutrophil cytoplasmic antibodies; BAL, bronchoalveolar lavage; ECMO, extracorporeal membrane oxygenation; FiO_2, fraction of inspired oxygen; GTC, generalized tonic–clonic; NC, nasal cannula; PEEP, positive end-expiratory pressure; RA, room air.

[a]Patient 3 had six episodes of haemoptysis immediately following GTC seizure.

ventilation within 3 days. While serologic work-up for other causes of DAH (e.g., glomerulonephritis with polyangiitis, Goodpasture's syndrome) were uniformly negative when reported, our first patient is unique in having undergone transbronchial biopsy (during a prior hospitalization at another hospital). The absence of any parenchymal pathological abnormalities on that biopsy militates against alternative explanations and favours traumatic rupture of the alveolar–capillary interface as the cause of DAH in this setting, presumably precipitated by the negative pressure of inspiring against a closed glottis (i.e., a Muller manoeuvre) during a tonic–clonic seizure.

The acute onset of respiratory failure and diffuse bilateral infiltrates following a seizure invokes three main aetiologies: aspiration pneumonitis, negative-pressure pulmonary oedema (e.g., produced by the prolonged Muller manoeuvre prompted by the seizure) and post-ictal DAH.[5] The progressively bloody bronchoscopic lavage in our patient establishes diagnosis of DAH as the cause of our patient's infiltrates. The lack of pathological abnormalities on prior transbronchial biopsy along with negative serologies, low suspicion of vasculitis; and rapid resolution discounts alternate explanations of DAH.

Post-ictal DAH is an uncommon cause of DAH. In the largest antecedent available series, Contou et al. described post-ictal DAH in six of 149 (4%) patients admitted to their ICU over a 35-year interval.[5]

In contrast to the pathogenesis of negative-pressure pulmonary oedema and neurogenic pulmonary oedema (which may involve both hydrostatic and/or permeability abnormalities that allow fluid leakage into the alveoli[2]), DAH likely involves physical disruption of the alveolar–capillary interface. Negative intrathoracic pressure during a Muller manoeuvre can exceed −100 cm H_2O,[6] thereby expanding the pulmonary capillary bed and potentially disrupting the alveolar–capillary interface.

The importance of excluding alternative causes of DAH in this setting relates to avoiding treatments that are indicated with other aetiologies of DAH (e.g., steroids, other immunosuppressive medications, plasmapheresis) but not indicated in post-ictal DAH, where treatment focuses on minimizing the seizure burden and avoiding anticonvulsants (e.g., valproic acid, carbamazepine) that have been implicated in causing alveolar haemorrhage.[7–9] Rapid radiographic resolution and improvement of oxygenation, often with only supportive care, characterize post-ictal DAH and support a non-immunological mechanism of bleeding.

DAH precipitated by a grand mal seizure is an uncommon and sparsely reported entity; the current cases present, to our knowledge, only the 12th and 13th reported cases in the English literature. Our experience highlights the importance of respiratory clinicians' recognizing this entity in order to avoid therapies that are not indicated and focusing attention on seizure avoidance as well as avoiding anticonvulsants (e.g., valproic acid, carbamazepine) that have also been implicated in causing DAH.

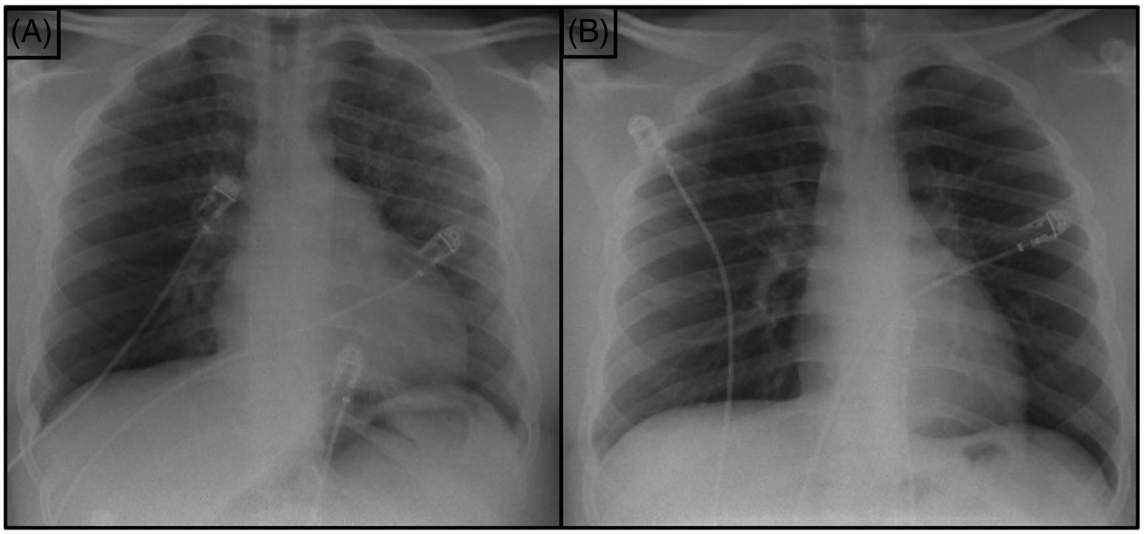

FIGURE 2 Rapid resolution of chest x-ray finding in Case 2 (A: Day 1, B: Day 4)

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTION

James Stoller made substantial contributions to the conception and design of the work. James Stoller also contributed on critical revision and comments for the final manuscript and approved the final version of the paper including references. Jee Young You made substantial contributions to drafting the work with searching and collecting data and made significant intellectual contribution to the work described in the paper. Jee Young You is the main contributor to the figures, figure legends and table.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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REFERENCES

1. Greene R, Platt R, Matz R. Postictal pulmonary edema. N Y State J Med. 1975;75(8):1257–61.
2. Pacht ER. Postictal pulmonary edema and hemoptysis. J Natl Med Assoc. 1988;80(3):337–9. 342.
3. Ryu JS, Cho JH, Kwak SM, Lee HL, Lee IK. Massive hemoptysis after generalized tonic clonic seizure requiring mechanical ventilation. Yonsei Med J. 2002;43(4):543–6.
4. Azuma M, Ito I, Matsumoto R, Hirai T, Mishima M. Pulmonary hemorrhage induced by epileptic seizure. Heart Lung. 2012;41(3):290–3.
5. Contou D, Voiriot G, Djibre M, Labbe V, Fartoukh M, Parrot A. Clinical features of patients with diffuse alveolar hemorrhage due to negative-pressure pulmonary edema. Lung. 2017;195(4):477–87.
6. Pathak V, Rendon IS, Ciubotaru RL. Recurrent negative pressure pulmonary edema. Clin Med Res. 2011;9(2):88–91.
7. Inzirillo F, Giorgetta C, Ravalli E, Pona CD. Diffuse alveolar hemorrhage due to valproic acid: case report and review of the literature. Lung India. 2015;32(2):175–7.
8. Wilschut FA, Cobben NA, Thunnissen FB, Lamers RJ, Wouters EF, Drent M. Recurrent respiratory distress associated with carbamazepine overdose. Eur Respir J. 1997;10(9):2163–5.
9. Sleiman C, Raffy O, Roue C, Mal H. Fatal pulmonary hemorrhage during high-dose valproate monotherapy. Chest. 2000;117(2):613.

How to cite this article: You JY, Stoller J. Post-ictal diffuse alveolar haemorrhage: clinical profile based on case reports. Respirology Case Reports. 2022;10: e0952. https://doi.org/10.1002/rcr2.952