EUROPEAN RESPIRATORY journal

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Research letter

Diffuse alveolar haemorrhage secondary to e-cigarette “vaping” associated lung injury (EVALI) in a young European consumer

Thomas Villeneuve, Grégoire Prevot, Aurélie Le Borgne, Magali Colombat, Samia Collot, Stephanie Ruiz, Thomas Lanot, Laurent Brouchet, Audrey Rabeau, Elise Noel-Savina, Alain Didier

Please cite this article as: Villeneuve T, Prevot G, Le Borgne A, *et al*. Diffuse alveolar haemorrhage secondary to e-cigarette “vaping” associated lung injury (EVALI) in a young European consumer. *Eur Respir J* 2020; in press (https://doi.org/10.1183/13993003.00143-2020).

This manuscript has recently been accepted for publication in the *European Respiratory Journal*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJ online.

Title: Diffuse alveolar haemorrhage secondary to e-cigarette "vaping" associated lung injury (EVALI) in a young European consumer.

Authors: Thomas VILLENEUVE[1], Grégoire PREVOT[1], Aurélie LE BORGNE[1], Magali COLOMBAT[2], Samia COLLOT[3], Stephanie RUIZ[4], Thomas LANOT[5], Laurent BROUCHET[6], Audrey RABEAU[1], Elise NOEL-SAVINA[1], Alain DIDIER[1]

[1] Service de Pneumologie, Hôpital Larrey, Université Paul Sabatier, CHU Toulouse, France.

[2] Service d'Anatomo-Pathologie, Institut Universitaire du Cancer, CHU Toulouse, France.

[3] Service de Radiologie, Hôpital Rangueil et Larrey, Université Paul Sabatier, CHU Toulouse, France.

4 Service de Réanimation polyvalente adultes, Hôpital Rangueil, Université Paul Sabatier, CHU Toulouse, France.

[5] Laboratoire de Pharmacocinétique et toxicologie, Institut Fédératif de Biologie, Université Paul Sabatier, CHU Toulouse, France.

[6] Service de Chirurgie thoracique, Hôpital Larrey, Université Paul Sabatier, CHU Toulouse, France.

Correspondence: Thomas Villeneuve. Hôpital Larrey, CHU Toulouse. Chemin de Pouvourville, 31059 Toulouse Cedex, France. e-mail: villeneuve.t@chu-toulouse.fr

Words: 1997 (<1200); Number of references: 13 (<15), Figures and Tables: 1; no abstact; no online supplement

We report the case of a 28-year-old woman admitted with acute respiratory failure. The patient had no personal or familial medical history involving respiratory disease as asthma, thrombotic events or bleeding. She was a heavy smoker (15 cigarettes per day for the past five years) and "vaped" electronic-cigarettes (e-cigarettes) one month prior to the incident. She consumed 10 ml of e-liquid bottle with nicotine salt (12 mg/ml) in two days. No cannabidiol (CBD) or tetrahydrocannabinol (THC) was detected. No other home-made components were added. The patient did not take any regular medicines or contraceptives. No consumption of cannabis, cocaine or any other drugs was reported (confirmed with negative urinary drug test). She had not travelled outside of France. She was referred to the Emergency Department (ED) for tachypnea (respiratory rate 22-25/min), desaturation at 80% in the context of dyspnea evolving for 15 days. No cough, haemoptysis or extra-thoracic manifestations were reported. Her temperature was 36.8°C, pulse 98 beat per minute, blood pressure 123/79 mm Hg. Heart sounds were regular but crackles were audible on thoracic auscultation. An alveolar and interstitial syndrome was observed on chest radiography (data not shown). Ceftriaxone and spiramycin was initiated in ED and oxygen therapy was started at 12L/min. Serum creatinine was 52 µmol/l and complete blood cell count highlighted an anaemia of 5.4 g/dl. Leucocyte count was $10.6x10^9$/L, C-reactive protein levels 60.3 mg/dL and procalcitonin was normal (<0.1 ng/ml). Platelet count, liver enzymes and haemostasis parameters were inconspicuous. No proteinuria or haematuria was detected. Antinuclear (ANAs), anti-neutrophil cytoplasmic (ANCAs) and anti-glomerular basement membrane (GBM) antibodies were all negative. Complement levels were normal. *Dot-myositis* and antiphospholipid antibodies were negative. Pneumococcal and legionella antigenurias were negative. Blood cultures did not identify any bacteria. Serological results for HIV, *Chlamydiae pneumoniae*, *psitacci* and *Mycoplasma pneumoniae* were negative. Computed tomography (CT) scan showed no proximal pulmonary embolism but identified a diffuse alveolar condensation with ground glass opacities (GGO) (figure 1A). No pleuropericardial effusion was observed. Echocardiography found normal left and right ventricular function. A rapid respiratory deterioration occurred. The patient was finally intubated and ventilated with lung protective ventilation strategy at day 1. A bronchoalveolar lavage (BAL) was performed at day 2. An alveolitis with 850 000 red cells/mm^3 and 4 000/mm^3 white blood cells consisting of 48% neutrophils, 2% eosinophils, 3% lymphocytes, and 47%

macrophages and mono-histiocytic cells was observed. BAL fluid revealed an alveolar haemorrhage with 95% of siderophages and a Golde score of 196. No cytological image of CMV-like virus was noted and *Pneumocystis jirovecii* staining was negative. Cultures of aspirated secretions were negative. Treatments administered are summarised in figure 1D. Because of a PaO2/FiO_2 ratio at 70, a pulmonary compliance reduced at 8 ml/cm H2O and a failure of the prone position, a veno-venous extracorporeal membrane oxygenation (VV-ECMO) was implanted. Several prone position sessions under VV-ECMO were necessary to improve compliance. A surgical lung biopsy (SLB) was performed at day 3. The architecture of the lung parenchyma was preserved and pneumocyte vacuolization were seen. Red blood cells, siderophages (identified with Perls staining), and neutrophils, were observed in alveoli (figure 1B). No oedema, hyaline membranes, granuloma was described. No interstitial deposits and no deposits in elastic limiting vessels were identified. Immunofluorescence (IgA, IgG, IgM, C3, C1q, Kappa, Lambda) was negative. We confirmed a diagnosis of diffuse alveolar haemorrhage (DAH). After SLB, bolus of corticosteroids (10 mg/kg) was performed over three days. Lung exchanges improved gradually under corticosteroids (1 mg/kg). At day 10, a ventilator-associated pneumonia occurred. Tracheal aspiration identified *Pseudomonas aeruginosa* and piperacillin-tazobactam was started (during 14 days). VV-ECMO was explanted at day 18. Despite ECMO withdrawal, the situation remained severe and an immunosuppressant drug was discussed due to (i) a life-threatening disease requiring ventilation (ii) the recurrence of DAH (visualised at day 21 by bronchial fibroscopy with a Golde score of 222) (iii) no etiological feature found on SLB. The patient was treated with rituximab (*375* mg/m^2) at day 22 and 29. Sedation was stopped at day 31, ventilation was weaned at day 37 and oxygen at day 50. Opacities and GGO subsequently became less marked on CT imaging (figure 1C). The aetiology was investigated in more detail. An intensive exposure to e-cigarette purchased from specialised store and initiated one month ago was reported. The reference product used was sent to the local poison control centre for investigation. The e-liquid sample were analysed by *gas chromatography coupled* to *mass spectrometry* (*GC*–MS) and detected glycerol, nicotine, propane-1,2-diol, ethyl maltol and ethyl lactate which was consistent with the manufacturer's disclosed composition data (which we obtained by contacting the particular e-liquid brand). A progressive weaning of corticosteroids was performed over a period of four

months. At the one-year follow-up and after complete cessation of tobacco and vaping, the patient showed no pulmonary symptoms and no recurrence of DAH. Diagnostic criteria proposed by the US Centre for Disease Control (CDC) and Prevention for e-cigarette or vaping product use–associated lung injury (EVALI) include: use of an e-cigarette (vaping) in the 90 days before symptom onset, pulmonary infiltrate or GGO on chest CT and absence of pulmonary infection or alternative diagnoses. The majority (80%) of e-liquids purchased via the Internet contain CBD or THC [1]. In Europe, e-liquids containing CBD or THC are prohibited for sale but can still be sourced from the internet. Very few cases of EVALI have been reported in Europe and no biopsy was performed [2]. To date, case reports indicate a variety of presentations including lipoid pneumonia [3], hypersensitivity pneumonitis [4], acute eosinophilic pneumonia [5,6], organising pneumonia [7], DAH [8] and giant cell interstitial pneumonia [9]. A clinical practice algorithm for the evaluation and management of EVALI has been proposed [10]. BAL is essential to eliminate any potential pulmonary infection on initial workup. In the *Layden and al.* series, fourteen BAL specimens were reported [1]. BAL most commonly detected neutrophilia (median value 65%) and often identified the presence of lipid laden macrophages by Oil Red O staining or Sudan staining, but the latter is not an essential criterion for the diagnosis of EVALI [11]. No histologic findings were specific [12]. *Butt et al.* describe patterns of diffuse alveolar damage, acute fibrinous pneumonitis and organising pneumonia [12]. Our particular case satisfies the clinical, radiological criteria of confirmed EVALI according to CDC guidelines. BAL fluid and histopathological findings showed DAH without any specific signs of secondary involvement. Recent reports suggest that vitamin E acetate may be implicated in EVALI [13]. In our case, no cannabis derivatives were identified and the implications of other toxic substances may be discussed, underscoring the importance of knowing whether patients have been exposed to e-cigarettes. Currently, approximately 2/3 vaping patients require management in the intensive care unit [10]. A clinical improvement documented with use of systemic glucocorticoids is often described [1]. In our case, rituximab injections were done but benefit is uncertain and not recommended in EVALI guidelines. Previously, only *Agustin M, Et al.*, published a case with a pattern of DAH induced by vaping [8]. We report the first case of a European DAH-EVALI not involving cannabis derivatives as confirmed by SLB and

requiring intensive care treatment with mechanical ventilation and VV-ECMO. Toxicity of e-cigarettes requires further investigations.

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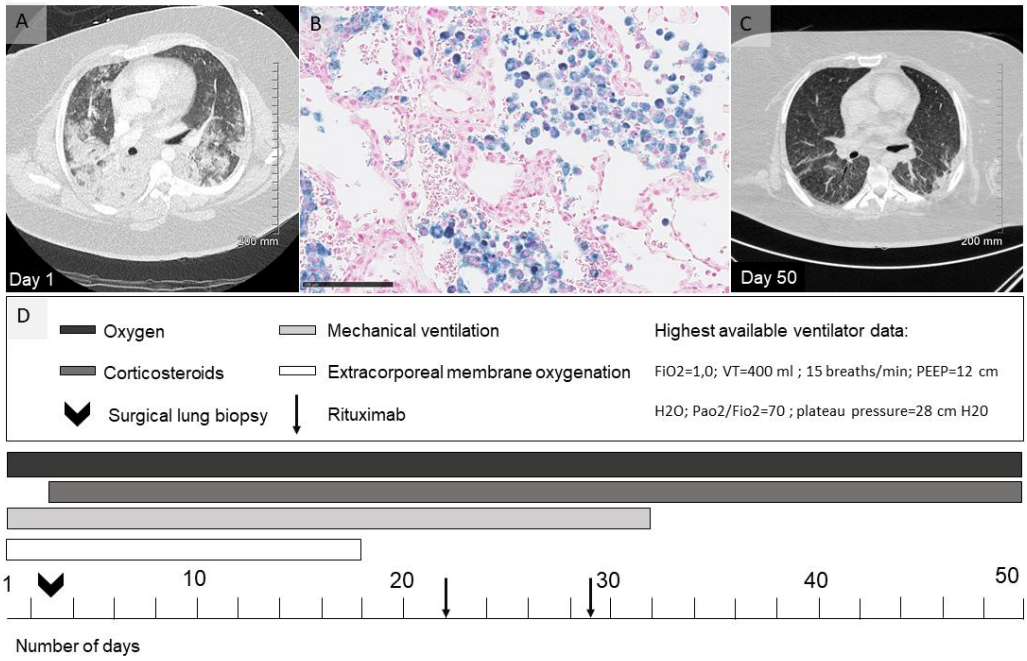

(Panel A) Initial axial CT scan showed no proximal pulmonary embolism but bilateral GGO and consolidation with peri-bronchovascular and lobar distribution. (Panel B) Surgical lung biopsy: Perls staining detected siderophages, compatible with a pattern of diffuse alveolar haemorrhage. (Panel C) Axial CT scan at day 50 revealed less GGO and consolidation. (Panel D) Treatments administered in the intensive care unit.