A hypoxic young lady in an acute confusional state

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Shareable abstract (@ERSpublications)
Patients presenting with respiratory and neurological symptoms after a breast filler injection should alert the clinician to this potential diagnosis https://bit.ly/3OodFQA

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A previously healthy 27-year-old female who was a current user of vapes presented to us with a 1-day history of progressively worsening dyspnoea associated with fever, headache, lethargy and intermittent vomiting. She does not work outside of her home, where she cares for a child. A significant history to note was that she had a bilateral filler injection to her breasts 1 day prior to the onset of her symptoms.

On physical examination she appeared confused, drowsy and lethargic with a Glasgow Coma Scale of 12 out of 15 ($E_3V_4M_5$). She was tachypnoeic with a respiratory rate of 24 breaths per min; blood pressure of 112/68 mmHg; heart rate of 115 beats per min; and saturating at 89% on room air. Chest examination revealed reduced air entry to the lower zones of lungs and her breasts were oedematous and erythematous, with no obvious palpable masses. Her muscle power was reduced at 4+/5 across all limbs. Otherwise, there was no focal neurological deficit. The remaining examination was normal.

Task 1

Describe the plain chest radiograph in figure 1.

Go to Answers >>

Arterial blood gases on room air revealed hypoxaemia with pH 7.439, oxygen tension of 65.1 mmHg, carbon dioxide tension of 28.8 mmHg, and bicarbonate of 19 mmol·L^{-1}.

Laboratory data were notable for leukocytosis (13.7×10^9 cells·L^{-1}) and a slightly low sodium level (134 mmol·L^{-1}). The complete initial laboratory investigations are listed in table 1.

Task 2

What are the possible explanations for her hypoxaemia?

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As she presented with a recent history of breast filler injections, our provisional diagnosis was breast filler-related complications. Furthermore, her symptoms started shortly after her procedure and were systemic, causing acute respiratory failure and neurological changes. EVALI was considered as a probable diagnosis due to vaping exposure, but the significant temporal relationship between breast filler injection and symptom onset made EVALI less likely as the first-choice diagnosis in this case. Both SARS-CoV-2 PCR and a rapid multiplex PCR assay for respiratory viral pathogens were negative. She was clinically stabilised after supplemental oxygen *via* a venturi mask at an inspiratory oxygen fraction (F_{IO_2}) of 0.6.

Other than her respiratory presentation, she also presented with an acute confusional state. In view of the acute presentation with raised total white cells, infectious encephalitis was one of the working diagnoses [4]. Fundoscopy did not revealed evidence of papilloedema. Her urine toxicology was negative. Cultures were

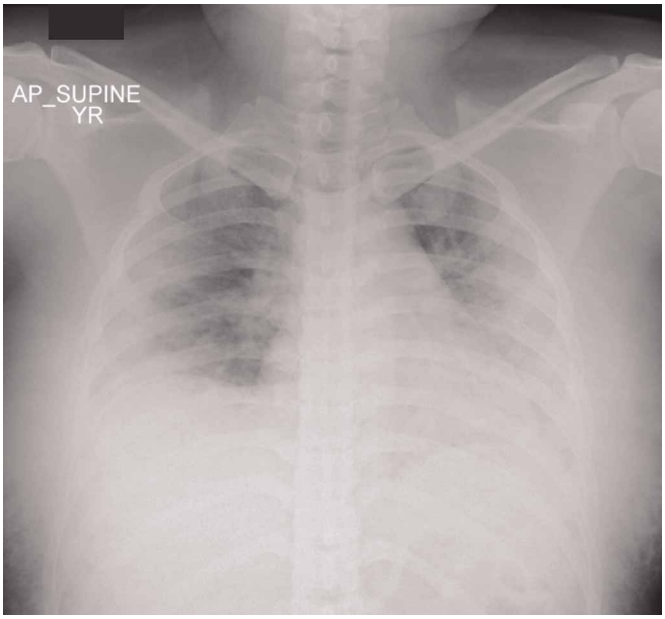

FIGURE 1 Plain chest radiograph.

taken and empirical antibiotics were started. Blood culture and sensitivity test revealed no growth after 5 days of incubation. Her serum procalcitonin was <0.02 ng·mL^{-1}. Taken together, this deems systemic bacterial infection unlikely.

Task 3

What are the next investigations to assess her acute confusional state?

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TABLE 1 Initial laboratory investigations

Parameter	Value	Normal range
Haemoglobin, g·dL^{-1}	13.8	12.0–15.0
Total white cells, ×10^9 cells·L^{-1}	13.7	4.0–10.0
Platelets, ×10^9 cells·L^{-1}	298	150–410
Sodium, mmol·L^{-1}	134	136–145
Potassium, mmol·L^{-1}	4.0	3.5–5.1
Chloride, mmol·L^{-1}	100	98–107
Urea, mmol·L^{-1}	3.8	2.5–7.2
Creatinine, µmol·L^{-1}	74	53–97
Calcium, mmol·L^{-1}	2.19	2.1–2.5
Phosphate, mmol·L^{-1}	0.87	0.74–1.52
Magnesium, mmol·L^{-1}	0.75	0.85–1.05
Total bilirubin, µmol·L^{-1}	10.3	3.4–20.5
Aspartate transaminase, U·L^{-1}	11	5–34
Alanine transaminase, U·L^{-1}	19	0–55
Alkaline phosphatase, U·L^{-1}	77	40–150
Total protein, g·L^{-1}	75	64–83
Albumin, g·L^{-1}	40	35–50
Globulin, g·L^{-1}	35	34–50
Prothrombin time	14.1	10.1–12.6
International normalised ratio	1.24	1–1.2
Partial thromboplastin time	22.4	28.2–39.8

A contrasted CT of the brain and thorax was urgently arranged. Cerebral oedema with loss of gyri and sulci with no focal space occupying lesion was seen on the neuroimaging. CT thorax revealed diffuse bilateral ground-glass opacification and consolidative changes with a predominance in the upper to middle zone with peripheral distribution, no evidence of pulmonary embolism was detected (figure 2). Diffuse subcutaneous oedema and thickening of bilateral breasts were noted with no evidence of focal collection or abscess suggestive of cellulitic changes.

Further information obtained from the unlicensed cosmetic practitioner revealed that the filler used was hyaluronic acid (HA). Unfortunately, we were unable to obtain the filler sample for official chemical testing. The erythematous and oedematous breast tissues were likely the result of a hypersensitivity reaction to HA, occurring within 24 h post-filler injection. Bacterial inoculation was less likely, as this typically occurs 3–14 days post-injection, and a CT thorax revealed no focal collection or abscess. Given the recent history of breast filler injection, her respiratory and neurological symptoms were deemed most probably due to complications from the HA filler injection. This could be attributed to either a systemic inflammatory response to HA or non-thrombotic pulmonary and cerebral embolism. Diagnostic lumbar puncture was offered to rule out infective causes but was not consented by the patient.

Task 4

What is the next most appropriate course of management?

Go to Answers >>

She was admitted to the medical high-dependency unit for subsequent management. Local therapy with warm compression was applied to bilateral breast tissue; however, regrettably, hyaluronidase was

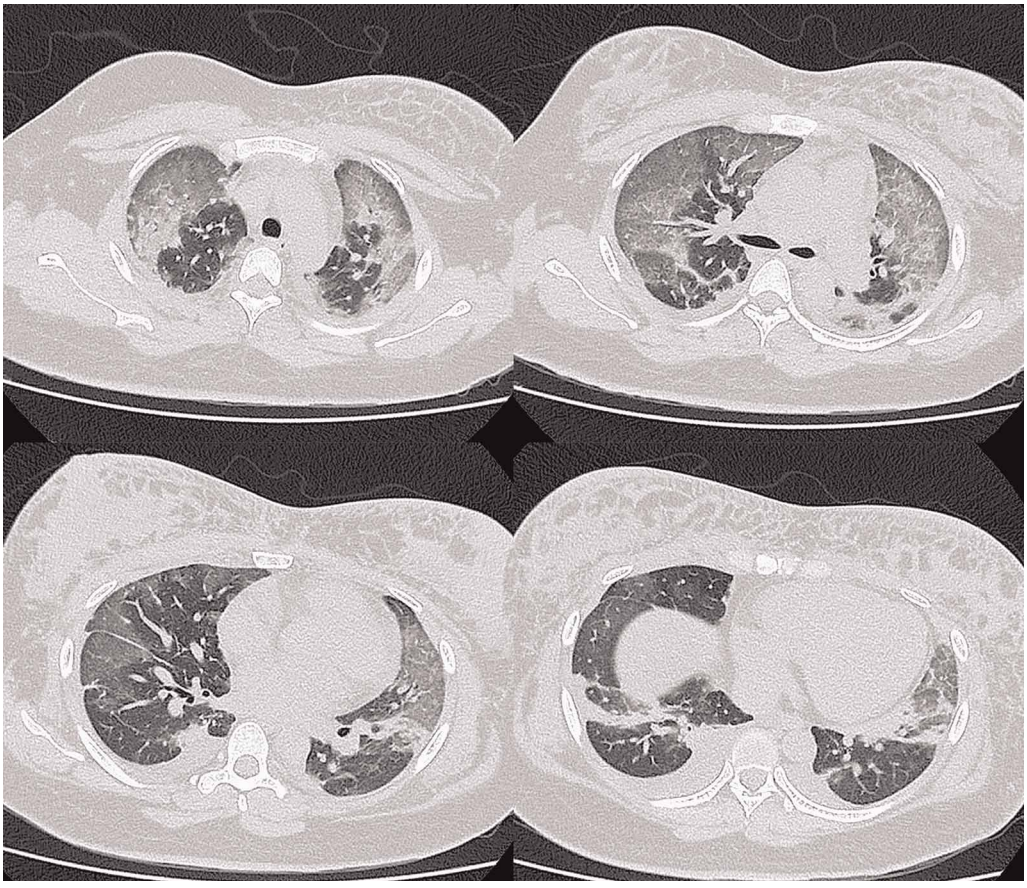

FIGURE 2 Contrast-enhanced computed tomography of the thorax revealed diffuse bilateral ground-glass opacification predominantly with upper and mid-zone distribution at the periphery. Bilateral mild pleural effusion was also noted. Breast tissue was bilaterally oedematous with thickened breast tissue.

unavailable in our centre. She received support with a venturi mask at an F_{IO_2} of 0.6, and subsequently, she was not tachypnoeic, maintaining a respiratory rate of 18 breaths per min, with oxygen saturation consistently above 95%. No further escalation of oxygen support was necessary. Suspecting a systemic inflammatory response to HA as the cause of her respiratory and neurological symptoms, we initiated intravenous hydrocortisone 100 mg three times a day for 1 week followed by a tapering course of oral prednisolone at a dose of 15 mg once daily ($0.2\ mg \cdot kg^{-1}$) over 3 weeks. Her level of consciousness improved on day 3 after commencement of treatment, and she continued to improve clinically with decreasing oxygen requirements.

An electroencephalogram (EEG) was performed during admission which revealed nonspecific generalised rhythmic delta waves suggestive of diffuse cerebral encephalopathy. Further investigations (*e.g.* magnetic resonance imaging of the brain) were not undertaken as our patient continued to improve clinically. Bronchoalveolar lavage revealed foamy histiocytes admixed with haemosiderin-laden macrophages and some lymphocytes in the background of red blood cells. Oil red O stain was negative for neutral lipid. Microbiological analysis was negative for bacteria, mycobacteria and fungi.

The patient was discharged uneventfully after 9 days of admission. 3-month follow-up revealed complete resolution of her symptoms with a normal chest radiograph (figure 3).

Discussion

Breast augmentation techniques have become a commonly performed procedure, with a range of techniques available, including implants, fillers, fat grafting and flap surgery. Among the available techniques, breast fillers have been gaining popularity due to their minimally invasive nature. Various materials have been used as fillers including paraffin, liquid silicone, polyacrylamide hydrogel, polyalkylimide gel, polymethylmethacrylate and HA. The most used synthetic filler worldwide is HA [7]. Reports on complications of filler injections, regardless of injection locations, are increasingly being reported worldwide due to the increase in their use [7–9].

Breast fillers made of different materials have been known to cause local and systemic complications. Local complications include migration of the filler material, infection, haematoma, or lumps and nodules at the injection site [10]. The most commonly known systemic complications are from silicone breast fillers, also known as silicone embolism syndrome (SES), where patients commonly present with respiratory and neurological symptoms. Respiratory-related complications post-HA injection are scarcely reported.

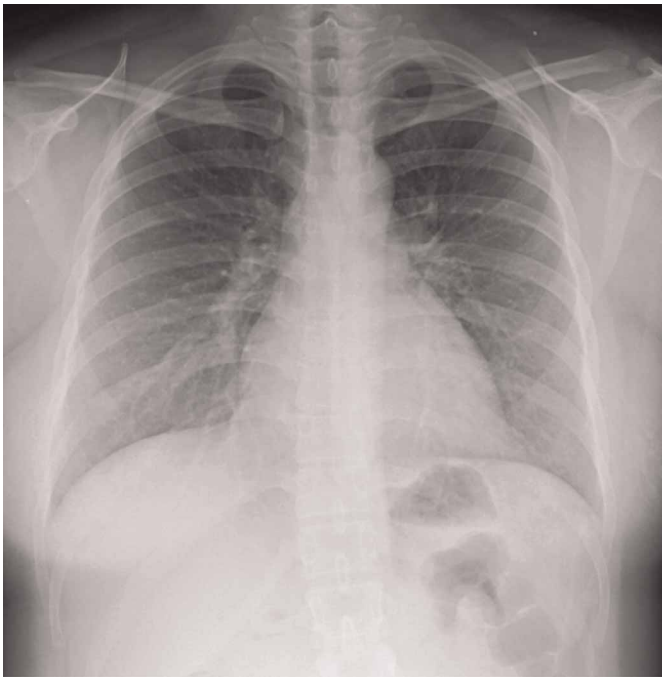

FIGURE 3 Plain chest radiograph at 3-month follow-up.

HAN *et al.* [11] reported five cases of non-thrombotic pulmonary embolism and two cases of diffuse alveolar haemorrhage post-HA injection. Although there were a few reported cases of respiratory-related complication post-HA injection in the literature, including following vaginal, facial augmentation and intra-articular injection, none were after a breast filler injection [11, 12]. To the best of our knowledge, there were no reported cases of neurological-related complications post-HA injection. We demonstrated in our report a case of HA-related pulmonary and neurological complications after a breast filler injection.

The risk of complications increases when cosmetic procedures occur outside approved healthcare facilities. In our region, the prevalence of illegal procedures performed by unlicensed beauty parlours, often promoted on social media without strict regulations, is on the rise. According to our local regulations, filler injections should be administered by registered medical practitioners in approved settings. Conducting these procedures at home or in non-approved places is against the law, carrying potential fines and/or prison sentences. Despite this, the widespread dissemination of unregulated information *via* social media and the lack of strict enforcement in our region remain significant challenges.

In our report, our patient's symptoms were probably due to a complication from her HA breast filler injection. This diagnosis was made based on the temporal relationship between her onset of symptoms and her recent history of HA breast filler injection. Similar to SES, the onset of symptoms typically starts within 24 h of the injection [7]. Respiratory symptoms for HA-related complications are generally nonspecific with acute breathlessness, cough and fever leading to acute type 1 respiratory failure [11]. Hence, accurate clinical acumen is essential in ruling out other conditions with a similar presentation, for example, inhalational injury like EVALI and viral pneumonitis, including COVID-19 pneumonia, which were all reasonably excluded in our patient. Traditionally, SES and HA pulmonary-related complications presented with two distinct clinical patterns: the first group with predominantly respiratory symptoms and the second group with respiratory and neurological symptoms [8]. This is well represented in our case as the patient presented with an acute confusional state along with acute respiratory failure. The EEG showed generalised rhythmic delta waves suggestive of diffuse cerebral encephalopathy. However, as generalised rhythmic delta activity (GRDA), previously referred to as frontal intermittent rhythmic delta activity (FIRDA), is a nonspecific finding in EEG with various possible aetiologies, including toxic, metabolic, infectious, neoplastic and epileptic entities, cautious assessment of these aetiologies is essential [13]. In our case, urine toxicology was negative and laboratory investigations were not suggestive of other metabolic causes.

The pathogenesis of filler embolism syndrome (silicone or HA) remains elusive with two main theories being postulated: mechanical obstruction and biochemical injury [7, 14–16]. The mechanical obstruction mechanism was postulated to be due to direct injection of filler materials into microvasculature leading to micro-emboli in the venous capillaries, which then eventually lodged in the pulmonary vasculature bed leading to acute respiratory failure (*i.e.* non-thrombotic pulmonary embolism). One study also demonstrated evidence of pulmonary artery and right ventricular dilatation after filler injection without evidence of thrombosis on imaging further supporting this hypothesis [17]. Other evidence that points towards the mechanical obstruction theory was the detection of micro-silicone emboli in pulmonary vessels during *post mortem* [18]. Moreover, *post mortem* brain biopsy has shown microinfarcts in the brain matter, suggesting that micro particles of silicone have travelled to the brain causing symptoms [19]. Micro-emboli may pass into the systemic circulation either *via* cardiac or intrapulmonary right-to-left shunt or directly through the pulmonary capillary bed, leading to systemic presentation. However, isolated cases where the patient presented with neurological symptoms without any pulmonary symptoms or cardiac defect, were against this theory. Thus, a biochemical or inflammatory injury pathway is suggested. The delay in developing symptoms suggests that there is an intermediate biochemical substance responsible for the pathological changes. One study showed that filler materials have caused inflammation and granulomas in multiple organs, including the cardiopulmonary, renal, hepatic and gastrointestinal organs [20]. Injected material triggers a systemic inflammatory response involving multiple organs. This mechanism can explain both the respiratory symptoms as well as the neurological symptoms particularly when the presentation does not follow an embolic stroke pattern. The exact biochemical response is uncertain but there is limited evidence indicating that filler material causes a chain of reaction in the immune system as well as the coagulation cascade [19, 21, 22].

Treatment of HA-related complications include treatment of local breast irritation. Warm compression and massage can be done to relieve local irritation. HA antagonists, such as hyaluronidase, can be injected locally to antagonise the local effect of HA [5, 6]. Local debridement and surgical extraction of breast filler is not recommended as it can further exaggerate the release of systemic mediators [14]. It is important to support the patient in terms of supplemental oxygen for the respiratory failure and to rule out other potential differential diagnoses which may mimic this condition as the presentation is nonspecific. The use

of corticosteroids has been reported in the literature to be beneficial in reducing the severity of SES and HA-related pulmonary complications. Given the suspected systemic inflammatory reaction as the potential pathogenesis, the administration of steroids may seem logical, aiming to counteract this response. However, it is essential to note that the literature on the use of corticosteroids in this situation remains scarce and unknown. Some cases were given *i.v.* methylprednisolone prior to prednisolone whereas some were given prednisolone alone. Generally, prednisolone 40 $mg \cdot day^{-1}$ was given with favourable outcomes [14, 20]. Due to the limited literature on corticosteroid use in filler-related pulmonary complications, there is no consensus on the dosage or duration of corticosteroid. Public awareness and regulation is essential regarding the potential harm of illicit use of filler injections, as well as awareness among healthcare workers to allow early recognition of this condition [14].

In conclusion, we should be more aware of HA-related complications due to the rising popularity of breast filler use in our region. Because the presentation of this condition is nonspecific, it is crucial to make an early diagnosis and provide appropriate management which will translate into a better clinical outcome.

Answer 1

The plain chest radiograph showed diffuse alveolar opacities with increased interstitial marking, predominantly in the periphery and a basal distribution. The bilateral breast shadow shows increased density and engorgement.

<< Go to Task 1

Answer 2

The causes of acute type 1 respiratory failure in a young patient include:

- Infections, for example respiratory viral infections including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1] and bacterial infection leading to pneumonia [2];
- Inhalational, for example e-cigarette or vaping use-associated lung injury (EVALI) [3]; and
- Breast filler systemic embolism.

<< Go to Task 2

Answer 3

A contrasted computed tomography (CT) of the brain to exclude acute intracranial pathology, particularly any space-occupying lesion with hydrocephalus, to allow planning of subsequent investigations, which included a lumbar puncture.

<< Go to Task 3

Answer 4

For the local complications:

- Application of warm compression (5–10 min, every 1–2 h) and massage to disburse the local HA [5]; and
- Injection of hyaluronidase (an antagonist to HA) [6].

For the systemic complications:

- Supportive treatment to treat the acute respiratory failure; and
- A corticosteroid to counteract the suspected systemic inflammatory response.

<< Go to Task 4

Conflict of interest: All authors have nothing to disclose.

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