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Case report

Asthma and hypercapnic respiratory failure

A 40-year-old, male non-smoker was diagnosed with asthma 6 years ago. He now presents with a 1-week history of worsening breathlessness with fever, cough, and purulent expectoration. He has had >10 emergency department visits and two admissions to hospital in the last 3 months. At each admission, he received bronchodilators and systemic steroids resulting in rapid improvement within 24 h. However, in the current presentation, the patient has no relief with corticosteroids and bronchodilators. His pulse is 140 per min, respiratory rate is 40 per min, blood pressure is 90/60 mmHg and room air oxygen saturation is 80%. Arterial blood gas (ABG) analysis shows hypercapnic respiratory failure. In view this respiratory failure, the patient is intubated and mechanical ventilation initiated. A chest radiograph is shown in figure 1. The therapy initiated includes bronchodilators, a systemic steroid, antibiotics and supportive care.

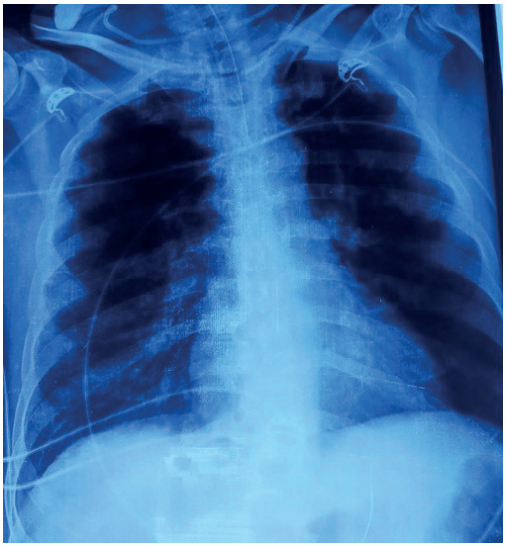

Figure 1 *Chest radiograph.*

Task 1
Which of the following factors could lead to "difficult-to-control asthma"?

a. Misdiagnosis (structural lung/cardiac disease)
b. Compliance with treatment
c. Exacerbating factors (rhinitis, sinusitis or gastro-oesophageal reflux disease)
d. Triggers (occupation or pets)
e. All the above

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@ERSpublications
Hypercapnia is an uncommon entity in asthma exacerbation. Meticulous evaluation for the underlying aetiology of hypercapnia is warranted in these patients. http://bit.ly/2sTKTk2

Answer 1
e. All the above. The abovementioned factors warrant evaluation before labelling that patient as having severe asthma. Approximately 20% of patients referred to severe asthma clinics do not have severe asthma after systematic assessment.

Patient is intubated with an 8.0-mm endotracheal tube and initiated on volume-controlled ventilation (VCV). The initial settings are tidal volume of 400 mL, inspiratory oxygen fraction of 30%, positive end expiratory pressure (PEEP) of 5 cmH_2O, inspiratory/expiratory ratio of 1/4 and respiratory rate of 12 breaths per min; the peak and plateau pressures are 20 and 15 cmH_2O, respectively. Critical care lung sonography shows the presence of lung sliding and A pattern bilaterally. Critical care echocardiography shows no regional wall motion abnormality and reduced left ventricular systolic function (45%); compression ultrasonography for deep venous thrombosis is negative. Neurological examination reveals a Glasgow Coma Scale score of E4VTM6; no cranial nerve deficit is observed. Motor system examination shows hypotonia of all limbs with diminished tendon reflexes. Muscle power is 3/5 in both upper limbs and 2/5 in both lower limbs; there is a flexor plantar reflex. No sensory deficit is present.

Laboratory testing shows mild leukocytosis with eosinophilia (total leukocyte count 12 400 per mm^3; differential leukocyte count: polymorphonuclear neutrophils 52%, lymphocytes 15%, eosinophils 30%, macrophages 3%); absolute eosinophil count 7320 cells per µL, and haemoglobin and platelets were within the normal ranges. There are no liver, renal or electrolyte imbalances. Serum procalcitonin is <0.1 $ng{\cdot}mL^{-1}$ and N-terminal pro-brain natriuretic peptide (NT-proBNP) is 180 $pg{\cdot}mL^{-1}$.

Task 2
Which of these diagnoses is most likely considering the patient's history, clinical examination, radiology and laboratory results?

a. Tropical pulmonary eosinophilia
b. Idiopathic hypereosinophilic syndrome
c. Allergic bronchopulmonary aspergillosis
d. Severe asthma
e. Eosinophilic granulomatosis with polyangiitis

Endotracheal aspirate specimens submitted for Gram staining show a few Gram-negative bacilli; culture shows no growth. Microscopic detection of acid-fast bacilli and PCR for *Mycobacterium tuberculosis* DNA are negative.

Computed tomography (CT) of the chest is shown in figure 2.

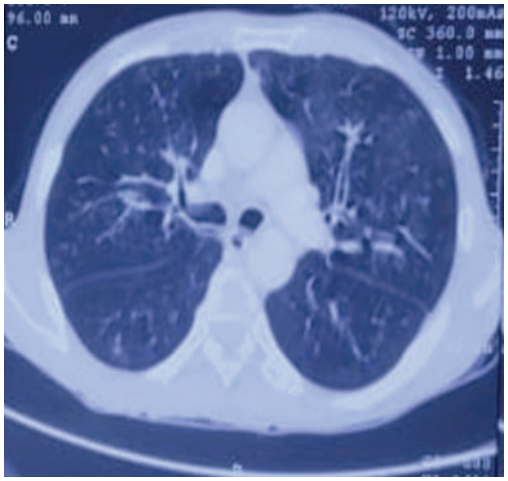

Figure 2 *CT showing diffuse centrilobular nodules.*

Answer 2
e. Eosinophilic granulomatosis with polyangiitis (EGPA). The American College of Rheumatology has established six criteria for the classification of EGPA in a patient with documented vasculitis. The presence of four or more of these criteria has a sensitivity of 85% and a specificity of 99.7% for EGPA:

- Asthma
- >10% eosinophils on differential leukocyte count
- Mononeuropathy (including multiplex) or polyneuropathy
- Migratory or transient pulmonary opacities detected radiographically
- Paranasal sinus abnormality
- Biopsy containing a blood vessel showing the accumulation of eosinophils in extravascular areas

The present case meets four criteria (asthma, eosinophilia, radiological infiltrates and polyneuropathy).

The patient becomes afebrile on the third day of antibiotics but continues to require ventilatory support. He is given a spontaneous breathing trial (SBT) with pressure support (PS) ventilation, with a PEEP of 5 cmH_2O and PS of 5 cmH_2O, generating a tidal volume of 220 mL. After 20 min of SBT, he develops tachycardia, respiratory rate 36 breaths per min and diaphoresis; oxygen saturation falls to 88% and ABG analysis shows hypercapnic respiratory failure (pH 7.34 with carbon dioxide tension 50 mmHg (6.6 kPa) and oxygen tension 60 mmHg (8.0 kPa)). His rapid shallow breathing index is 164. The patient undergoes four SBTs over 3 days, all of which fail.

On reconnecting to the ventilator post-SBT in VCV mode, the peak and plateau pressures are 21 and 16 mmHg, respectively. Maximal inspiratory pressure (MIP) is −8 cmH_2O. A bilateral diaphragmatic ultrasonographic displacement of 7 mm is noted and there are no B-lines in lung ultrasonography. NT-proBNP measured after SBT is 196 $pg{\cdot}mL^{-1}$ and ECG shows sinus tachycardia without any ischaemic changes.

Task 3
Which of the following definitions is correct regarding weaning?

a. Simple weaning: when the patient passes their first SBT
b. Difficult weaning: the patient fails their first SBT and then require up to three SBTs or 7 days to pass an SBT
c. Prolonged weaning: patients fail at least three SBTs or require >7 days to pass an SBT
d. All the above

Answer 3
d. All the above

Task 4
Based on the data from the SBTs, what may be the possible cause of failure of SBT?

a. Cardiac
b. Neuromuscular
c. Anxiety
d. Increased resistive load

Answer 4
b. Neuromuscular

The patient has neuromuscular weakness contributing to the prolonged weaning. The patient also had reduced systolic function (ejection fraction 45%). However, since post-SBT, there were no features suggestive of pulmonary oedema (absence of B-lines, and no change in ECG or NT-proBNP levels), the cardiac cause seems unlikely.

Task 5
Which of the following is not part of the Five-Factor Score (FFS) to assess vasculitis disease activity in EGPA?

a. Age >65 years
b. Cardiac insufficiency
c. Gastrointestinal involvement
d. Renal insufficiency (stabilised peak plasma creatinine >1.7 mg·dL^{-1})
e. Ear, nose and throat manifestations

Answer 5
e. Ear, nose and throat (ENT) manifestations. The presence of ENT manifestations is associated with a better prognosis in EGPA. The manifestations include serous otitis media, allergic rhinitis, nasal obstruction, recurrent sinusitis and nasal polyposis.

Since the patient has reduced left ventricular systolic function and neurological involvement, amounting to FFS 2, specific treatment of EGPA is initiated. Therapy is a combination of pulse steroid (intravenous methylprednisolone 1 g for 3 days) and *i.v.* cyclophosphamide in a dose of 15 mg·kg^{-1} followed by 60 mg prednisolone daily. The patient responds well to immunosuppressive therapy and there is clinical improvement. His muscle power recovers and his cardiac function improves. Peripheral eosinophil count starts to reduce. MIP is −48 cmH_2O and bilateral diaphragmatic ultrasonographic displacement is 22 mm. The patient passes SBT and is extubated after 14 days of mechanical ventilation.

Discussion

EGPA is an anti-neutrophil cytoplasm antibody (ANCA)-associated, multisystem, small-vessel vasculitis characterised by asthma, eosinophilia and frequent ENT involvement. It can affect any organ system, including the renal, cardiovascular and central nervous systems, and the morbidity and mortality associated with EGPA are primarily due to the extrapulmonary manifestations of the disease. Three phases of the disease characterise its natural history [1]:

- the prodromal phase of asthma and allergic rhinitis
- the eosinophilic phase with peripheral eosinophilia and eosinophilic infiltration of organs
- the vasculitis phase characterised by life-threatening systemic vasculitis with vascular and extravascular granuloma formation

Among the ANCA-associated vasculitides, EGPA has a higher incidence of peripheral nerve and central nervous system involvement than granulomatosis with polyangiitis and microscopic polyangiitis. The manifestations include peripheral neuropathy, especially mononeuritis multiplex seen in about 55–75% of cases [2]. The peroneal and sural nerves are the most commonly involved nerves, and clinically, EGPA is characterised by neuropathic pain or dysaesthesia, foot drop and muscle weakness [3], and can progress to symmetrical or asymmetrical axonal polyneuropathy if not treated adequately. Central nervous system involvement

is less common and includes cerebral infarction, subarachnoid haemorrhage, cerebral haemorrhage and neuropathy of cranial nerves. Diaphragmatic paralysis due to phrenic nerve involvement by EGPA, leading to hypercapnic respiratory failure, is sporadic but has been reported in the literature [4, 5]. EGPA can affect the nerves supplying the respiratory muscles. The inflammation of the vasa nervorum resulting in axonal ischaemia in the phrenic nerve.

Respiratory muscle weakness leading to ventilatory failure is a leading cause of difficulty in weaning from a mechanical ventilator. Motor weakness in a critically ill patient may be related to:

- pre-existing neuromuscular disorder that leads to intensive care unit (ICU) admission
- new-onset or previously undiagnosed neurological disorder
- complication of critical illness

Most of the cases of neuromuscular dysfunction are acquired during critical care unit stay and occur in >25% of patients in the ICU who are ventilated for ≥7 days [6]. Critical illness neuromuscular abnormality is the most common peripheral neuromuscular disorder encountered in the ICU setting. Evaluation of these patients includes careful, focused history and detailed neurological examination, followed by detailed electrophysiological investigations, serum creatinine kinase level, radiological neuroimaging studies, monitoring MIP and, rarely, histological examination of muscles and nerves. The electrophysiological investigation includes nerve conduction studies, needle electromyography, phrenic nerve conduction studies, diaphragm electromyography and direct muscle stimulation tests. Accordingly, precise assessment of the neuromuscular apparatus and management of any specific disorder may be a significant step towards successful weaning.

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Conflict of interest

P.K. Shamil has nothing to disclose. N. Gupta has nothing to disclose. S. Agrawal has nothing to disclose. P. Ish has nothing to disclose. S. Chakrabarti has nothing to disclose.

References

1. Guillevin L, Cohen P, Gayraud M, *et al*. Churg Strauss syndrome. Clinical study and long term follow up of 96 patients. *Medicine (Baltimore)* 1999; 78: 26–37.
2. Wolf J, Bergner R, Muttalib S, *et al*. Neurologic complications of Churg Strauss syndrome – a prospective monocentric study. *Eur J Neurol* 2010; 17: 582–588.
3. Cho H-J, Yune S, Seok JM, *et al*. Clinical characteristics and treatment response of peripheral neuropathy in the presence of eosinophilic granulomatosis with polyangiitis. *J Clin Neurology* 2017; 13: 77–83.
4. Flores-Franco RA, Castillo-Soltero J, Pacheco-Tena CF. Parálisis diafragmática en granulomatosas eosinophilia con poliangitis [Diaphragmatic paralysis in eosinophilic granulomatosis with polyangiitis]. *Rheumat Clin* 2017; 14: 61–62.
5. Sharma A, Bambery P, Bettadapura Shamanna S, *et al*. Phrenic nerve palsy in a patient of Churg Strauss syndrome and mononeuritis multiplex. *Clin Rheumatol* 2008; 27: 137–139.
6. De Jonghe B, Sharshar T, Lefaucheur JP, *et al*. Paresis acquired in the intensive care unit: a prospective multicenter study. *JAMA* 2002; 288: 2859–2867.