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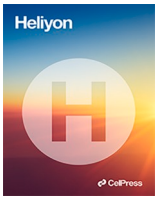

Weaning difficulty after severe pneumonia in adult-onset mitochondrial myopathy with A3243G mutation in the mitochondrial tRNA gene: A case report

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ABSTRACT

Background: Mitochondrial myopathy is a group of diseases caused by abnormal mitochondrial structure or function. The mitochondrial myopathy impacts muscles of the whole body and exhibits variable symptoms. Respiratory muscle deficits deteriorate pulmonary function in patients with severe pneumonia.

Case presentation: We report the case of a male patient with severe pneumonia-induced respiratory failure. He was abnormally dependent invasive ventilator-assisted ventilation after his condition had improved. Then we found abnormal ventilator waveform and a decline in muscle strength of him. Mitochondrial myopathy was ultimately confirmed by muscle pathological biopsy and body fluid genetic testing. Vitamin B complex, coenzyme Q10, Neprinol AFD, L-arginine, and MITOTONIC were used to improve mitochondrial function and muscle metabolism. After treatment, discomfort associated with chest tightness, fatigue, cough, and sputum disappeared, and the patient was discharged.

Conclusion: This case presented an uncommon cause of difficult weaning and extubation—acute onset of mitochondrial myopathy. Muscle biopsy and genetic testing of body fluid are essential for diagnosing mitochondrial myopathy. The A3243G mutation in the MT-TL1 gene of mitochondrial DNA contributes to pathogenesis of this case.

1. Introduction

Mechanical ventilation provides respiratory support for severe cases, such as acute respiratory failure caused by severe pneumonia. As respiratory failure improves, patients should be weaned from ventilation as soon as possible. However, a small number of patients have difficulty in weaning or experience delayed weaning for various reasons and even develop ventilator dependence, resulting in mechanical ventilation complications [1].

Mitochondrial myopathy is a group of diseases caused by abnormal mitochondrial structure or function and primarily affects

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skeletal muscles, causing muscle weakness and fatigue [2]. Involvement of respiratory muscles is often accompanied by respiratory failure. In cases of co-existing severe pneumonia and neuromuscular disease, diagnosis and treatment become quite difficult. Here, we report a case of difficult weaning following acute respiratory failure caused by severe pneumonia. The patient was ultimately diagnosed with adult-onset mitochondrial myopathy based on muscle biopsy. To provide additional clinical references, we also summarize the clinical, pathological, and molecular characteristics of mitochondrial myopathy based on published literature.

2. Case presentation

A 50-year-old male patient was admitted to our hospital on 22 June 2021 due to cough and chest tightness for more than 1 month, which had worsened in the previous 3 days. According to family members, the patient presented with a cough and moderate white sputum following a cold episode one month prior to admission. He simultaneously had chest tightness, shortness of breath, and general fatigue, which significantly worsened with minimal physical activity. Oral capsules of amoxicillin and Qingkailing were administered but not effective. On June 19th, he developed large amounts of sputum with increasing chest tightness and fatigue. The patient was immediately transferred to the emergency department of a nearby municipal hospital. Although standard treatment was administered, he developed increasing shortness of breath and became confused on June 22th. Arterial blood gas (ABG) analysis showed pH of 7.40, SaO_2 of 88 %, PaO_2 of 56 mmHg, and $PaCO_2$ of 80 mmHg, with 2L/min oxygen flow by nasal cannula. Thus, the patient underwent tracheal intubation and ventilator assistance, and then was transferred to our respiratory intensive care unit (RICU).

The patient looked thin and short. His body temperature was 36.8 °C, pulse rate 95/min, respiratory rate 18/min, and blood pressure 116/83 mmHg, a few moist rales could be heard in the bilateral lungs. The muscle strength of his limbs was MRC (UK Medical Research Council) grade IV. Other physical examination parameters were unremarkable.

The results of laboratory tests revealed a white blood cell count of 12.62×10^9/L (3.5–9.5), neutrophil percentage 88 % (40%–75 %), C-reactive protein 22.43 mg/L (0–8), procalcitonin 0.38 ng/mL, creatine-kinase 284.0 U/L (40–200), creatine kinase-MB isoenzyme 26.7 U/L (0–24), and lactate dehydrogenase 436.1 U/L. Next-generation sequencing of bronchoalveolar lavage fluid showed the presence of *Streptococcus pneumoniae*. Chest computed tomography (CT) (Fig. 1A, B, 1C, 1D) showed multiple areas of abnormally increased density in both lungs, and the right upper lobe bronchus was stretched and dilated. Results of rest tests were normal, including myositis antibodies, coagulation function, NT-proBNP, urinary routine, stool routine, TORCH pathogens, T-SPOT, neostigmine test, electrocardiogram, brain magnetic resonance imaging, echocardiography, and abdominal ultrasound.

After invasive ventilator-assisted ventilation and anti-infection and symptomatic supportive treatment for two days in our hospital, the patient regained consciousness and the infection index had dropped as well. ABG analysis (40 % oxygen) showed a pH of 7.42, SaO_2 of 95 %, PaO_2 of 172 mmHg, and $PaCO_2$ of 45 mmHg. Then the patient underwent spontaneous-breathing trial—ventilator only provides additional oxygen (40 %). However, he complained dyspnea and sleepiness following a 4-h spontaneous-breathing trial, and ABG analysis showed the $PaCO_2$ had increased to 65 mmHg. Invasive mechanical ventilation was applied again, and the patient's ventilator waveform showed a abrupt collapse of the expiratory airway (Fig. 2).

Then we acquired more information of the patient and his relatives: the patient was thinner and weaker than his peers since childhood. His mother was short in stature, but his father and children were reportedly healthy. He denied histories of surgery, central nervous system dysfunction, tumor, diabetes mellitus or a family history of neuromuscular disease.

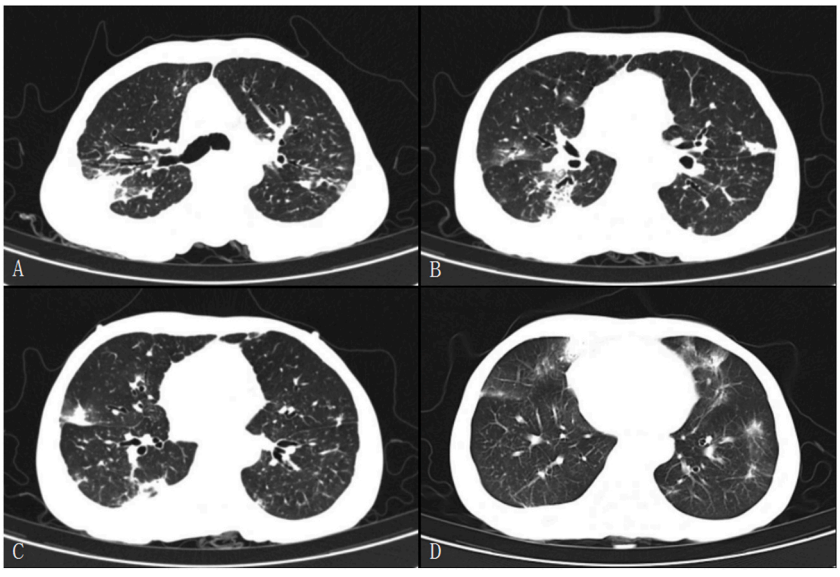

Fig. 1A. B, 1C, 1D. Chest CT showed multiple areas of abnormally increased density in both lungs, and the right upper lobe bronchus was stretched and dilated.

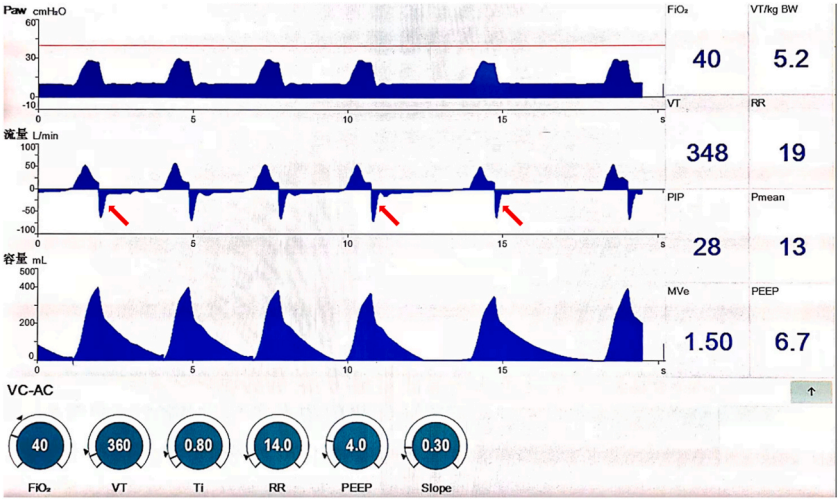

Fig. 2. The ventilator waveform indicated that the airway was suddenly restricted.

Thus, we assessed if the patient had generalized muscle weakness, including respiratory muscle that ultimately led to respiratory failure. A muscle specimen was taken at his left bicep by the biopsy. Pathology of the skeletal muscle biopsy, conducted on the July 4th, showed pathological changes including atrophy, ragged red fibers, and ragged blue fibers. These changes are consistent with the characteristic pathological features of mitochondrial disease, as depicted in Fig. 3A, B, 3C, and 3D. Furthermore, the full mitochondrial gene sequencing of the urine sample conducted on July 26th indicated an abnormality at the mitochondrial chrM-3243 site (out of a total of 16,569 sites): variant gene, MT-TL1; variant region, tRNA; variant information, A3243G chrM-3243 utr-5; the deep variants sequence ratio was 3632.0/31007 (0.90). Genetic testing also revealed that his mother had identical mutations. Neither his father nor his offspring exhibited any mutations (Fig. 4A, B, 4C).

The diagnosis of mitochondrial myopathy was confirmed based on the results of muscle biopsy analysis and genetic testing. The patient was treated with vitamin B complex (1 tablet tid p.o.), L-arginine (1000mg bid po) and coenzyme Q10 (5 mg qd i.v.gtt),

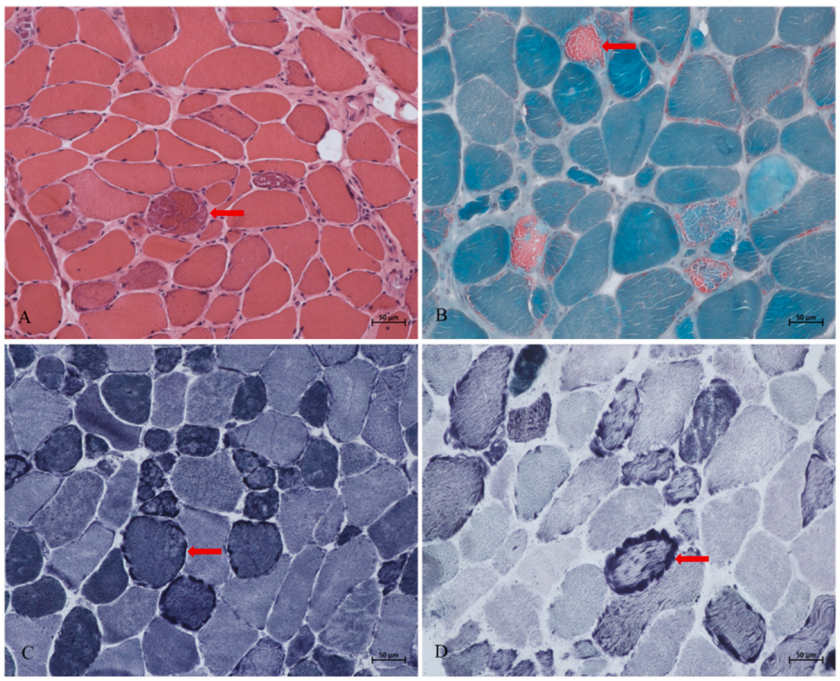

Fig. 3A. B, 3C, 3D. Biopsy results of the patient's left biceps muscle. A: HE staining showed that the muscle had varying numbers of broken muscle fibers, with basophilic granules deposited within. B: MGT staining showed typical and atypical broken ragged red fibers (RRFs). C: NADH staining showed intense staining under the broken muscle fiber membrane. D: SDH staining showed markedly dark-stained broken muscle fibers and ragged blue fibers (RBFs).

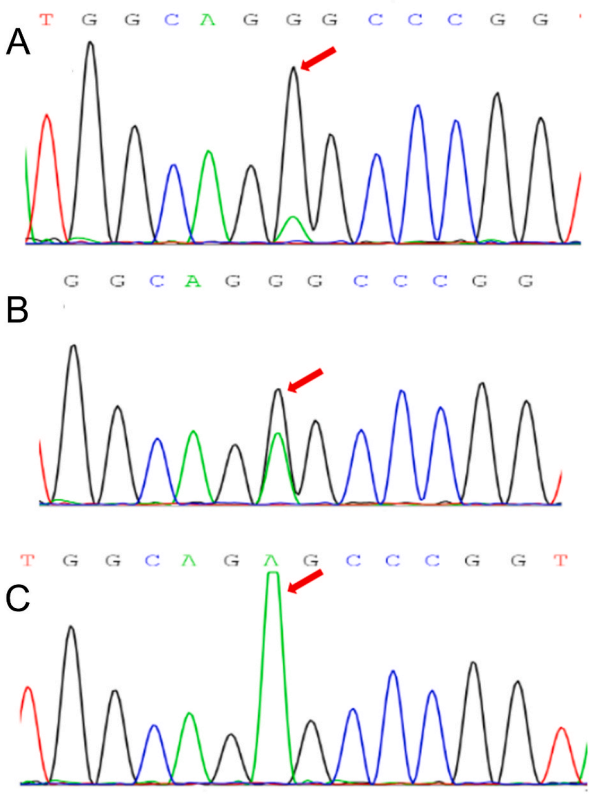

Fig. 4A. B, 4C. Mitochondrial DNA mutation map. A: The patient harbored an m.3243A > G heterozygous mutation, with a mutation ratio of 90 %. B: The patient's mother also harbored the same point mutation. C: The patient's father did not harbor the point mutation.

Neprinol AFD (2 capsules bid p.o.) and MITO-TONIC (1 spoonful bid p.o.) were added after diagnosis of mitochondrial myopathy. By combining of anti-infection, anti-asthmatic medications and nutritional supplement, the tracheal intubation was removed on June 27th, but he still required assistance from a non-invasive ventilator. Subsequent chest CT scan (Fig. 5A and B) showed substantial reduction in the size of the lesion. The patient was discharged on July 27th. The patient used a non-invasive ventilator during nighttime and took drugs above for a month, with monthly telephone follow-up. Until August 5, 2022, he suffered mild bacterial pneumonia again in the fourth month and reported that he could take care of himself in daily life.

3. Discussion

Weaning in mechanically ventilated patients poses a daily challenge for many intensive care physicians, and weaning failure is associated with increased case fatality rate [1,3]. Difficult weaning from ventilators is caused by a range of underlying diseases or complications, including disorders of respiratory muscle, airway, central nervous system, cardiac function, and metabolism [4,5]. Furthermore, prolonged use of ventilator causes disuse atrophy of the diaphragm and ventilator-related pneumonia to increase the risk of weaning failure [6]. Therefore, comprehensive management strategies facilitate to wean early and smoothly in patients with severe pneumonia or respiratory failure, including active antimicrobial therapy, strengthening airway secretion drainage, maintaining

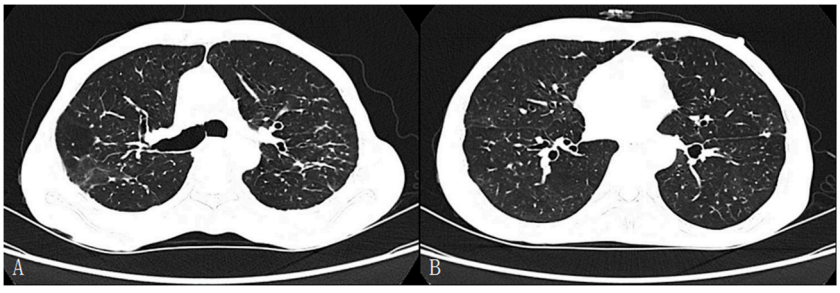

Fig. 5A. B. Follow-up chest CT showed abnormally increased density in the lungs and well-absorbed lesion.

electrolyte and acid-base balance and reasonable nutritional support.

In this case, the patient did not have cardiac failure or brain injury. Although the present patient had severe community-acquired pneumonia and respiratory failure, he underwent a brief duration of mechanical ventilation, and there was no prior history of high-dose glucocorticoids, sedatives, neuromuscular blockers. Although myalgia was absent, we suspected the presence of neuromuscular illness involving the respiratory muscles due to reduced muscle strength and an abrupt collapse of the expiratory waveform. The results of muscle biopsy and laboratory tests excluded Guillain-Barre syndrome, myasthenia gravis and other neuromuscular diseases that cause myasthenia.

It is noteworthy that critical illness polyneuropathy (CIP) is the major form of ICU-acquired myasthenia, which is induced by sepsis, systemic inflammatory response syndrome, and multiple organ dysfunction syndrome [7]. Clinical manifestations includes paresthesia, weakened or absent tendon reflexes, muscle atrophy, respiratory muscle weakness, and even quadriplegia that are not consistent with primary disease [6]. Tests, such as the electromyogram, muscle enzymes, myositis antibodies, and biopsy, in combination with medical history can assist in diagnosis. The patient in this case did not exhibit any predispositions or usual clinical signs listed earlier for CIP. Therefore, CIP could be disregarded.

Although abnormal mitochondrial structure or function can affect all tissues and organs of the body, the brain and muscles are primarily affected. Shibasaki [8] was the first to report one case of adult-onset mitochondrial myopathy in Japan in 1973, which first manifested as decreased muscle strength in the limbs. A review of the literature to date revealed twelve cases of mitochondrial myopathy with acute respiratory failure as the primary manifestation [9–19]. Among these cases, three patients experienced acute onset, respiratory failure was the only clinical manifestation, but they displayed other symptoms prior to the start of respiratory failure, which are different from this case.

As cells divide, the mutated mitochondrial DNA (mtDNA) is randomly distributed to progeny cells, resulting in varying proportion of mutant mtDNA in different tissues and organs in the same individual. In addition, different tissues and organs have different thresholds. When the percentage of mutant mtDNA exceeds the threshold of a particular tissue or organ, corresponding clinical symptoms will appear, which is why different patients have different clinical features [20].

The A3243G variations are most common mutation in mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome, and multi-organ dysfunction, which exhibits characteristics of maternal inheritance [21]. The A3243G mutation in the gene encoding mitochondrial tRNA leads to a reduction in mitochondrial protein synthesis. This mutation affects the subunits of the mitochondrial electron transport chain complex, resulting in a decrease in mitochondrial energy output and mitochondrial injury. Thus, it is potential strategy to improve mitochondrial stability, decrease oxidative stress damage and enhance adenosine triphosphate synthesis [22–24]. In cases of isolated mitochondrial myopathy with respiratory failure as the primary manifestation, significant relief has been reported with coenzyme Q10 supplementation, with good prognosis [19]. This patient was supplemented with coenzyme Q10 and so on during hospitalization and after discharge. Therefore, timely diagnose and treatment of mitochondrial myopathy is crucial for patients with isolated mitochondrial myopathy.

However, the diagnose of this case had some limitations. First, ultrasound was not used to assess diaphragm mobility. It could directly present severe muscle disability in this case which caused CO_2 retention and weaning difficulty. Second, the electromyography should be obtained but the patient refused this test.

4. Conclusion

Based on the diagnosis and treatment of this case, mitochondrial myopathy can emerge with acute respiratory failure as primary symptom and cause difficulty of weaning and extubation. The A3243G mutation in the MT-TL1 gene of mtDNA is an important molecular factor in the pathogenesis of this disease, and infection played a crucial role in the sudden beginning of the condition.

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Consent for publication

This article does not contain any data that would reveal the participant's identity. The patient provided informed consent for publication of the case.

Ethics declaration

This study was approved by the ethics committee of The First Affiliated Hospital of Nanchang University (2022-4-005).

Data availability statement

All data analyzed during this study are included in this manuscript.

CRediT authorship contribution statement

Xiong Peng: Writing – original draft. **Li-xiu Ma:** Writing – original draft, Conceptualization. **Ce Xiao:** Writing – review & editing, Data curation. **Zhi-zhe Zhang:** Writing – review & editing, Data curation. **Min Zhu:** Writing – review & editing, Data curation. **Dao-jun Hong:** Resources, Data curation. **Yi-an Zhan:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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