A Case of Nemaline Myopathy With Associated Dilated Cardiomyopathy and Respiratory Failure

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Summary

Nemaline myopathy is a representative form of congenital myopathy, and is characterized by nemaline bodies in muscle fibers. Here we report a 47-year-old man with congenital nemaline myopathy complicated with dilated cardiomyopathy-related heart failure, and restrictive respiratory failure. The complication of dilated cardiomyopathy in nemaline myopathy has rarely been reported. In this case, nemaline bodies were detected in the cardiac muscle fibers, demonstrating the presence of underlying disease-related myocardial degeneration. The patient responded to the combination of conventional therapy for heart failure including β-blocker and noninvasive continuous positive-pressure ventilation for respiratory failure. His general condition has been stable during a 10-month follow up period.  

Key words: Nemaline myopathy, Dilated cardiomyopathy, Respiratory failure, Heart failure, Noninvasive positive pressure ventilation

CASE REPORT

The patient was a 47-year-old man. His medical history, other than spontaneous pneumothorax at 26 years of age, was not contributory. During childhood, his gait was slightly delayed, and movement disorder such as an inability to stand up from a squatting position was noted. However, no subsequent examinations were performed, and he was not definitively diagnosed as having a neuromuscular disease. During adolescence, he had shown mild weakness on exercise, although there had been no problems in daily life. He did participate in a 10 km long distance running race while in high school. After graduating from high school, he worked as a cosmetician until his admission. He married and had a son at the age of 37. At the age of 46, 10 months before his admission, he complained of persistent fatigue. He needed a handrail when going up and down stairs, and could not lift up any heavy baggage. He tired easily when standing and edema of the lower limbs was observed one month before he visited our hospital. Dyspnea occurred two weeks later and then he developed nocturnal dyspnea. The patient was examined by the department of internal medicine of our hospital, and was hospitalized with a diagnosis of heart failure.

Even though the patient exhibited an orthopneic position, his pulse and blood pressure were maintained at 62/minute and 102/68 mmHg, respectively. His height and body weight were 164 cm and 50 kg, respectively. His jugular vein was dilated. Auscultation revealed Ipp accentuation, but no cardiac murmur was found. Respiratory sounds were reduced and difficult to hear. Bilateral pretibial pitting edema was noted. The neurologic findings included an elongated face and a high arched palate. Pectus excavatum and muscular atrophy involving the limbs and trunk were noted. Neither scoliosis nor articular contracture was observed. Muscle strength was systemically and symmetrically reduced so he was unable to stand up from the squat-down position. The deep tendon reflex was diffusely and symmetrically reduced. The patient was negative for Babinski’s reflex.

Chest X-ray films showed pulmonary congestion, and bilateral retention of pleural effusion (Figure 1A). The cardiothoracic ratio (CTR) was 66%. Electrocardiography revealed a sinus rhythm, with a heart rate of 80/minute. Right axis deviation,
Elevated.

In the plasma brain natriuretic peptide concentration and a mild increase in liver transaminase concentration (Table). Creatine phosphokinase and cardiac troponin T levels were not elevated.

The elevation of LV filling pressure.

The peak pressure gradient across the tricuspid valve was 26.4 mmHg. E/e’ was elevated up to 18, suggesting the presence of right sided heart failure that may be attributed to the respiratory failure or left sided heart failure. Ejection fraction was calculated using the modified Simpson rule.

Echocardiogram on admission. Echocardiogram on admission revealed slight left ventricular dilatation and substantially and diffusely decreased left ventricular contraction. Dilatation of the right ventricle, mild mitral regurgitation, and mild tricuspid regurgitation were also noted. E/e’ was elevated to 18. These findings suggest the presence of systolic left ventricular dysfunction and elevated left ventricular filling pressure with functional mitral regurgitation. Right ventricular dilatation suggests the presence of right sided heart failure that may be attributed to the respiratory failure or left sided heart failure. Electrocardiograph revealed sinus rhythm, with a heart rate of 80/minute. Right axis deviation, complete right bundle branch block, and negative T waves involving the V3 to V6 areas were observed.

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On the basis of these clinical findings, the patient was diagnosed as having heart failure with reduced systolic function. A continuous intravenous infusion of carperitide at a dose of 0.025 μg/kg/minute was initiated, and spironolactone and furosemide were orally administered. The symptoms were gradually relieved until he was able to walk and assume the supine position. Carperitide was administered for 7 days, and switched to candesartan cilexetil at a dose of 2 mg/day. After the heart failure was controlled and his body weight decreased by approximately 10 kg, carvedilol was introduced at an initial dose of 1.25 mg/day. A transient decrease in blood pressure and an increase in pleural effusion were observed. Therefore, the dose of carvedilol was transiently decreased while elevating the dose of a diuretic, following which it was gradually titrated (Figure 3).

Later on, oxygen desaturation occurred frequently, despite a clinical improvement in the heart failure. Therefore, blood gas analysis was performed, and it showed an arterial partial pressure of carbon dioxide (PaCO₂) of 124.4 mmHg, suggesting marked hypercapnia. Respiratory function tests were performed. The vital capacity was reduced to 58.8% (VC) probably due to muscular atrophy-related chronic weakness of the respiratory muscles and thoracic deformity-associated restrictive disturbance. After providing information about treatment options such as a respirator and tracheotomy to the patient and his family, we introduced assisted respiration by noninvasive, continuous positive-pressure ventilation (NIPPV). Respiratory status was improved when the inspiratory positive airway pressure (IPAP) and expiratory positive air way pressure (EPAP) were established as 14 and 4 cmH₂O, respectively.

In addition to the introduction of NIPPV to prevent respiratory failure, we consulted a neurologist and considered the presence of congenital neuromuscular disease, as an underlying disease, based on his facial/physical characteristics.

Electromyography revealed a nontypical, myogenic change. To differentiate from congenital myopathy, muscle biopsy of the rectus femoris was performed. Gomori’s trichrome staining showed that there was marked variation in fiber size with many fibers containing nemaline bodies predominantly in atrophic fibers (Figure 4A). They were largely aggregated at the subsarcolemmal space. ATPase staining revealed type 1 fiber predominance and atrophy commonly seen in congenital nemaline myopathy (Figure 4B). These findings and the physical characteristics including an elongated face, high arched

**Table. Laboratory Data on Admission**

<table>
<thead>
<tr>
<th>Test</th>
<th>Unit</th>
<th>Value</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>/μL</td>
<td>6690 (3300-9400)</td>
<td></td>
</tr>
<tr>
<td>RBC</td>
<td>/μL</td>
<td>461x10⁶ (365-490)</td>
<td></td>
</tr>
<tr>
<td>Pt</td>
<td>/μL</td>
<td>15.1x10⁹ (18-39)</td>
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</tr>
<tr>
<td>Na</td>
<td>/mequiv/L</td>
<td>139 (138-144)</td>
<td></td>
</tr>
<tr>
<td>K</td>
<td>/mequiv/L</td>
<td>4.9 (3.7-5.0)</td>
<td></td>
</tr>
<tr>
<td>BUN</td>
<td>/mg/dL</td>
<td>15.2 (8-20)</td>
<td>2.8-5.8 mg/dL</td>
</tr>
<tr>
<td>Cr</td>
<td>/mg/dL</td>
<td>0.52 (0.48-0.82)</td>
<td>(&lt;0.2) mg/dL</td>
</tr>
<tr>
<td>AST</td>
<td>/IU/L</td>
<td>44 (14-32)</td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td>/IU/L</td>
<td>51 (9-25)</td>
<td></td>
</tr>
<tr>
<td>ALP</td>
<td>/IU/L</td>
<td>610.5 (20-28)</td>
<td></td>
</tr>
<tr>
<td>γ-GTP</td>
<td>/IU/L</td>
<td>39 (125-225)</td>
<td></td>
</tr>
<tr>
<td>LDH</td>
<td>/IU/L</td>
<td>214 (112-334)</td>
<td></td>
</tr>
<tr>
<td>CPK</td>
<td>/IU/L</td>
<td>108 (39-163)</td>
<td></td>
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<tr>
<td>UA</td>
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<tr>
<td>BNP</td>
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<td>610.5 (20-28)</td>
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<tr>
<td>CRP</td>
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<td>ALP</td>
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<td>108 (39-163)</td>
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<td>ALT</td>
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<td>51 (9-25)</td>
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</tr>
<tr>
<td>AST</td>
<td>/IU/L</td>
<td>44 (14-32)</td>
<td></td>
</tr>
</tbody>
</table>

WBC indicates white blood cells; RBC, red blood cells; Pt, platelets; BUN, blood urea nitrogen; Cr, creatinine; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; CPK, Creatine phosphokinase; UA, uric acid; CRP, C-reactive protein; and BNP, brain natriuretic peptide.

**Figure 1.** Chest radiograph (A) and electrocardiogram (B) on admission. Chest radiograph showed cardiomegaly, bilateral pulmonary congestion, and pleural effusion. Electrocardiograph revealed sinus rhythm, with a heart rate of 80/minute. Right axis deviation, complete right bundle branch block, and negative T waves involving the V3 to V6 areas were observed.

**Figure 2.** Echocardiogram on admission. Echocardiogram on admission revealed slight left ventricular dilatation and substantially and diffusely decreased left ventricular contraction. Dilatation of the right ventricle, mild mitral regurgitation, and mild tricuspid regurgitation were also noted. E/e’ was elevated to 18. These findings suggest the presence of systolic left ventricular dysfunction and elevated left ventricular filling pressure with functional mitral regurgitation. Right ventricular dilatation suggests the presence of right sided heart failure that may be attributed to the respiratory failure or left sided heart failure. Ejection fraction was calculated using the modified Simpson rule.
A CASE OF NEMALINE CARDIOMYOPATHY

Nemaline myopathy, which was first described in 1963, is the most frequently occurring among various types of congenital myopathy. It is characterized by the presence of rod-shaped structures (nemaline body) in muscle fibers and is classified into 6 types: (1) severe congenital form; (2) intermediate congenital form; (3) typical form; (4) mild, childhood-, or juvenile-onset form; (5) adult-onset form; and (6) other forms, including cardiomyopathy and ophthalmoplegia. In our patient, the type of nemaline myopathy was classified as (3) typical form based on the clinical course.

To make a definitive diagnosis, nemaline bodies and muscle-fiber abnormalities, characteristic of this disorder, must be demonstrated by muscle biopsy. As nemaline bodies may be detected in the presence of other disorders such as HIV-associated myopathy, physical/biopsy findings should be comprehensively evaluated. On modified Gomori’s trichrome staining, purple rod-like nemaline bodies are detected in muscle cells. On ATPase staining, type-1 fiber predominance and atrophy are observed. Concerning muscle fiber abnormalities, it was reported that all findings are not always detected. However, in the present case, almost all of the above findings were observed, therefore, the condition was thought to be pathologically typical.

To date, six different genes associated with nemaline myopathy have been identified: alfa-tropomyosin (TPM3), nebulin (NEB), alfa-actin (ACTA1), beta-tropomyosin (TPM2), Troponin T1(TNNT1), and cofilin 2(CFL2). The genes for nebulin (NEB) and alfa-actin (ACTA1) were reported to be involved in the gene mutation in some autosomal-recessive and sporadic cases of nemaline myopathy. We could not evaluate the gene mutation of this case, but if we could have, the mutations of ACTA1 and NEB should have been evaluated.

In our case, respiratory failure was detected. In patients
with congenital myopathy, respiratory failure is emphasized as a fatal complication. Previous studies have indicated that, in some patients with the typical form of nemaline myopathy, severe respiratory failure suddenly occurred without other clinical symptoms.1-3 This was possibly because the respiratory muscles were more readily affected than other skeletal muscles, and because of the poor respiratory response to inhaled carbon dioxide attributed to impairment of the central nervous respiratory chemoreceptors.14,15 In the present case, heart failure symptoms masked the respiratory failure symptoms, and respiratory failure was not detected immediately after the admission. The present case suggests that it is necessary to actively suspect the presence of respiratory failure in the differential diagnosis of myopathy. Furthermore, severe respiratory failure in the presence of neuromuscular disease was associated with acute airway infection in many patients.16 Therefore, in the future, the risk of pneumonia-related rapid deterioration must be considered even when symptoms are stable in this case.

We have presented concomitant dilated cardiomyopathy and its treatment course in our patient. It is known that nemaline myopathy may be complicated by heart disease, as reported for other types of myopathy. However, according to a study of 143 patients with various types of nemaline myopathy, cardiovascular complications were observed in only 2 patients:3-5 the incidence rate was very low. Therefore, this matter must be analyzed based on individual case reports. Concomitant heart disorders include hypertrophic cardiomyopathy,15-18 dilated cardiomyopathy,19-21 pulmonary hypertension,22 and ventricular septal defect.17 According to some reports of nemaline myopathy patients with dilated cardiomyopathy-like conditions, nemaline bodies were also detected in the cardiac muscle,4,15,16 but not in all patients.5 In our patient, electron microscopy showed nemaline bodies in the cardiac muscle fibers (Figure 4C), demonstrating the presence of nemaline myopathy-related myocardial degeneration. According to individual case reports, nemaline myopathy with dilated cardiomyopathy ultimately led to a fatal outcome in most patients. However, in our patient, heart failure symptoms subsided, and the serum BNP level was normalized; the course has been favorable thus far. In the treatment of dilated cardiomyopathy, it has been reported that combination therapy with β-blocker and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker improved the quality of life (QOL) and prognosis.19,20 In our case, the combination of carvedilol and candesartan cilexetil may also have contributed to the relief of heart failure. The influence of type-II respiratory failure (hypcapnea and hypoxia) can be attributed to the restrictive respiratory disorder on cardiac function and the effects of NIPPV on this situation have to be considered. A recent study involving chronic heart failure patients with sleep apnea syndrome suggested that the hypoxemia-related activation of the sympathetic nervous system results in cardiac over loading.19,20 In our case, restrictive respiratory disorder-related hypoxemia had been present. Furthermore, monitoring with a pulse oximeter at night showed transient, repeated, marked SpO2 reduction. The correction of such findings by NIPPV may have favorably influenced the heart. Another study indicated that in chronic heart failure patients, NIPPV decreased the heart rate via a reduction of systemic vascular resistance and improvement in the left ventricular EF/cardiac index, lead to stabilization of the status of heart failure.21 Thus, the correction of restrictive respiratory failure by NIPPV may have reduced heart failure severity, achieving a better general condition.

In the literature, there are no case reports that depicted the treatment course for these two fatal complications in the presence of the typical form of nemaline myopathy and no studies have reviewed the treatment for nemaline cardiomyopathy, nor its effects in detail. Therefore, the present case contributes meaningful suggestions for the treatment of nemaline cardiomyopathy.

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**References**


