

# Respiratory Failure in a Rare Case of Juvenile Dermatomyositis – Systemic Scleroderma Overlap Syndrome

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## BACKGROUND

Juvenile dermatomyositis (JDM) is one of the pediatric systemic connective tissue disorders, consisting of an idiopathic inflammatory myopathy, affecting primarily skin and muscle, representing approximately 85% of cases in this group. A significant source of morbidity is the occurrence of overlap characteristics with other connective tissue disorders, including systemic sclerosis (SSc). Overlap JDM/SSc syndrome is rare in children, with only a few reported cases. The diagnosis is often challenging, presence of anti-PM/Scl antibodies playing a pivotal role. Although SSc/JDM overlap syndrome has less frequent visceral involvement, pulmonary dysfunction may occur. The respiratory function evaluation using overnight cardiorespiratory polygraphy may reveal important alveolar hypoventilation with impact on therapeutic approach. Non-invasive ventilation may be indicated to potentiate medical treatment. In the acute phase, non-invasive ventilation is a life-saving therapeutic option until the maximum efficiency of drug treatment is reached. In the case of a complex respiratory pathology, associating elements of nocturnal alveolar hypoventilation specific to neuromuscular disease, with that of chronic interstitial lung disease, the evaluation of respiratory sleep disorders should be considered, sometimes requiring home nocturnal non-invasive ventilatory support.

We present the case of a 15-year-old girl who was admitted to our clinic with a history of high fever, productive cough and severe dyspnea. Detailed anamnesis revealed that the patient accused one-year history of proximal muscle weakness of the lower limbs, with functional limitations, weight loss, dysphonia, swallowing difficulties and dyspnea at minimal efforts. Following the physical examination, laboratory and imaging investigations were all suggestive for an inflammatory myopathy. Anti-PM/Scl antibodies were positive, confirming the diagnosis of a severe form of JDM/SSc overlap syndrome, with minimal cutaneous changes, significant muscle involvement and respiratory distress. Complex therapy using antimicrobial agents, steroid pulse therapy, immunosuppressive agents, non-invasive ventilation,

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Article received on the 16<sup>th</sup> of September 2020 and accepted for publication on the 22<sup>nd</sup> of September 2020

*oxygen supplementation and physiotherapy was started, with significant status improvement. However, pulmonary function tests maintained severe restrictive aspect and nocturnal cardio-pulmonary polygraphy revealed residual pulmonary failure with important nocturnal alveolar hypoventilation. Nocturnal non-invasive ventilation was continued at home, along with medical treatment. Her disease was clinically well controlled, immunosuppressive therapy was decreased and interruption of ventilatory support was possible at six months after the diagnosis.*

**Keywords:** dermatomyositis-systemic sclerosis overlap, child, pulmonary dysfunction, overnight cardiorespiratory monitoring, non-invasive ventilation.

## INTRODUCTION

Juvenile dermatomyositis (JDM) is one of the systemic connective tissue disorders that affect children, representing approximately 85% of cases in this group. The reported annual incidence ranges from two to four cases per one million children, with girls being affected more often than boys. It consists of an idiopathic inflammatory myopathy, affecting primarily skin and muscle. Despite treatment improvements, it is still associated with significant mortality and morbidity. An important source of considerable morbidity is the occurrence of overlap characteristics with other connective tissue disorders, including systemic sclerosis (SSc), rheumatoid arthritis, Sjogren's syndrome and systemic lupus erythematosus (1, 2). Overlap JDM/SSc syndrome is rare in children, with only a few cases been reported. The diagnosis is often challenging. Although it is a rare disease in children, the presentation appears similar to adults, except for the visceral involvement. In patients with unusual clinical features, an unusual clinical course or those with scleroderma overlap features, testing myositis-specific antibodies is useful. Usually, the initial characteristic presentation in pediatric patients is JDM (3).

Juvenile dermatomyositis is diagnosed using clinical, laboratory and microscopic methods. In 2017, the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) developed revised the classification and diagnostic criteria for adult and juvenile inflammatory myopathies, including variables related to muscle weakness, skin manifestations, laboratory findings and other clinical manifestations. Muscle biopsies are infrequently performed in children (4).

The occurrence of overlap features with other systemic connective tissue disorder creates difficulties in diagnosis. JDM/SSc overlap presents with facial skin changes, Raynaud's phenomenon,

sclerodactyly and may progress to associate other SSc features. However, during the disease, at some periods, symptoms of scleroderma or dermatomyositis are prevalent, variously pronounced in individual cases. Cutaneous changes of both SSc and JDM develop within the first year of the disease. The JDM/SSc overlap differs from systemic scleroderma by the absence of digital pits and ulcer, acrololysis and contractures of the fingers. Some sclerodermoid features of the face are common. Exceptionally, the onset can be sudden, with fever, myalgia, Raynaud's phenomenon. Muscle involvement can be insidious. Myositis is clinically indistinguishable from primary JDM. It is proximal, symmetric, causing function limitations, such as frequent falls, difficulty in climbing stairs, washing, feeding themselves. The muscle and cutaneous signs of JDM are usually transient. Visceral involvement is often mild than in adults (5). Laboratory findings are supportive of the diagnosis: elevated levels of muscle enzymes, presence of autoantibodies, elevated serum and urine myoglobin. The presence of anti-PM/Scl antibodies has a key role in confirming the diagnosis (3). Magnetic resonance imaging (MRI) of skeletal muscles is helpful for detecting areas of muscle inflammation. Electrophysiologic abnormalities on electromyography (EMG) and muscle biopsy are invasive diagnostic procedures that are reserved for cases in which other investigations are inconclusive (13).

Although SSc/JDM overlap syndrome in children has less frequent visceral involvement than adults, pulmonary dysfunction may occur. Respiratory muscle weakness, affecting inspiratory, expiratory and upper airway muscles, can cause insufficient ventilation, ineffective cough, nocturnal hypoventilation, along with bulbar dysfunction. Impairment of both upper airway muscles and upper esophagus induces difficulty swallowing, tracheal aspiration or food reflux into the nasopharynx, dysarthria, nasal voice, weak mastication

tion, abnormal secretion clearance and protruding tongue (1, 6). These perturbations, along with decreased accessory respiratory muscle activity, may produce upper airway obstruction during inspiration and exacerbate hypoventilation, especially during nocturnal sleep. An ineffective cough may be associated and the risk of aspiration, secretion retention, pneumonia and respiratory failure is very high (6). Although pulmonary manifestations are much less common in children than adults, interstitial lung disease (ILD) may occur. The pulmonary pathology is mostly extrapolated from adults because 30% to 50% of adults with dermatomyositis have ILD, whereas the pulmonary expression in JDM/SSc or JDM is extremely rare in children (7). The diagnosis of ILD in patients with known JDM can usually be established based on the clinical presentation, imaging studies and pulmonary function tests. The most common findings on chest radiography are diffuse reticular and nodular opacities. High-resolution computed tomography (HRCT) is preferred and typical changes include patchy ground-glass opacification, basilar consolidation, honeycombing and septal thickening. Pulmonary function tests demonstrate a restrictive pattern, with decreased lung volumes and diminished diffusing capacity. Bronchoalveolar lavage or even lung biopsy may be indicated (1, 7).

The respiratory function evaluation using overnight cardiorespiratory polygraph or even polysomnography may reveal important alveolar hypoventilation with impact on therapeutic approach. In addition to medical therapeutic measures, non-invasive ventilatory support may be indicated to control nocturnal alveolar hypoventilation and other nocturnal respiratory disorders, diurnal respiratory failure and to potentiate the medical treatment, inclusive the treatment of acute respiratory infections (8). □

### CASE REPORT

A previously apparent healthy 15-years-old girl was admitted to our clinic with a history of productive cough and high fever, lasting for eight days, progressive worsening despite symptomatic treatment given by her general physician. To a more detailed anamnesis, we found out that the patient accused one-year history of the lower limbs' proximal muscle weakness, with functional limitations, such as difficulty getting into or out of

motor vehicles and climbing stairs. Later, she noticed the progressive association of voice changes – nasal voice, dysphonia, swallowing difficulties for liquids or solids, reflux of food into the nasopharynx, dyspnea at minimal efforts, involuntary weight loss (8 kg through the last six months) and accentuated proximal motor deficit. The antenatal, natal and postnatal histories were insignificant. There was no family history of any neurological disease.

Physical examination upon presentation revealed an underweight patient, with a poor general condition, inexpressive mimic, stretch marks in the lower limbs, without other cutaneous suggestive elements, apparent normal osteoarticular system, but with severe proximal muscle weakness and fatigability to minimal efforts. Respiratory rate was 30 per minute and oxygen saturation was 90% in room air. Decreased breath sounds in the lower right lung field, bilateral crackles and rhonchi were evident on pulmonary auscultation. Intercostal and subcostal retractions, along with abdominal paradox breathing movement and ineffective productive cough were also noticed. She was tachycardic, with rhythmic cardiac sounds and normal blood pressure. Neurological examination revealed normal sensorium. Assessment of cranial nerves showed normal oculomotricity, inexpressive facies with bilateral facial weakness (cannot whistle), absence of palatine reflex, lateral atrophy and fasciculations of the tongue, dysarthria and nasal voice. She accused difficulties in swallowing solids and liquids. The muscle strengths of neck flexors and all, upper and lower, extremities were decreased at the proximal level. The deep tendon reflexes were hyperactive in all extremities. Babinski's and Gower's signs were present. An otolaryngology examination confirmed the velopalatine paralysis. A nasopharyngeal endoscopy was also performed, with normal anatomic structures in this area.

Laboratory investigations revealed normal complete blood count, positive inflammatory tests (erythrocyte sedimentation rate 60 mm/h, C-reactive protein level 140 mg/dL), elevated creatine kinase (CK), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) levels (320 U/L, 50 U/L, 72 U/L and 502 U/L, respectively). Troponin T level was also highly elevated (974 ng/dL), with no electrocardiography or echocardiography abnormalities. Arterial blood gas analysis was normal. The chest radiograph showed a heterogeneous opacity in

the right lower pulmonary lobe and an atelectatic band at this level, with diaphragm traction. Pulmonary functional testing could not be performed because of poor status.

Firstly, we presumed the diagnosis of right inferior lobar pneumonia with respiratory failure, central and peripheral motor neuron syndrome. We started medical treatment with broad-spectrum antibiotics (Ceftriaxone, Vancomycin), bronchodilator agents, respiratory nursing and oxygen therapy, with clinical, biological and radiological improvement. However, bulbar dysfunction and muscle weakness persisted, with minimal alleviation.

In order to evaluate muscle weakness, electromyography was performed, with inconclusive results, suggestive for neurogenic abnormalities rather than myogenic lesions. Considering the patient presenting symptoms of both central and peripheral motor neuron syndromes associated with bulbar dysfunction and elevated levels of muscle enzymes, with a non-specific electromyography aspect, further investigations were required. Magnetic resonance imaging (MRI) of the brain with entire spine screening was normal, eliminating the possibility of cerebral or medullary lesions (tumor, malformation, hemorrhage) and demyelinating or degenerative disease at this level. Myasthenia gravis was excluded by the physical examination (absence of circadian variation of muscle weakness, absence of palpebral ptosis), along with electromyography aspect, elevated muscle enzymes and negative anti-acetylcholine receptor antibodies. Paraneoplastic involvement was taken into discussion, with no evidence of tumors on chest radiography and abdominal ultrasound and a normal level of alpha-fetoprotein level. Different forms of progressive bulbar palsy have been also considered. In order to exclude Fazio Londe disease, plasma riboflavin levels and acylcarnitine levels were performed, with normal values. Absence of sensorineural hearing loss eliminated hereditary motor neuropathy type I. Slowly progressing reduction of muscle strength, with prevailing expression at girdle level, respiratory difficulties, orthopnea, gradual bodyweight loss, swallowing difficulties, elevated CK levels, were highly suggestive for late-onset Pompe disease, so that the activity of alpha glucosidase was tested, being within its reference range; thus, there was no indication of Pompe disease. Screening for autoimmune illness was also performed, but only anti-

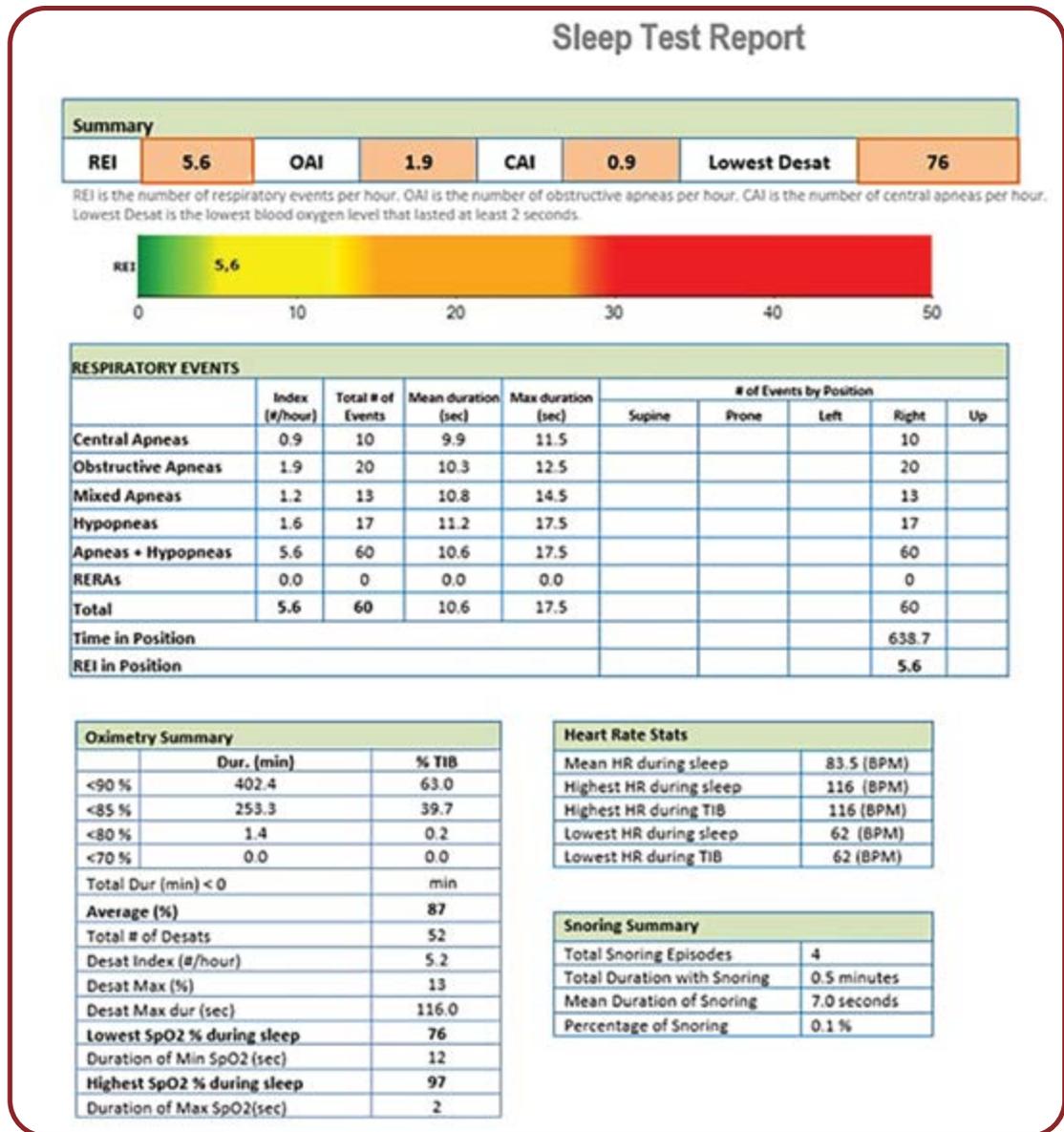
nuclear and anti dsDNA antibodies results were early available, showing normal levels.

Despite initial complex medical treatment and respiratory nursing, the patient's clinic and paraclinical course was undulating, with sudden deterioration on 14th day of hospitalization, with an altered general condition, persistent hyperpyrexia, severe respiratory distress, bulbar paralysis and inability to perform antigravitational movements. Laboratory tests showed leukocytosis, neutrophilia, positive inflammatory markers, persistently elevated muscle enzymes and mild mixed acidosis. Chest radiography revealed large opacity with air bronchogram occupying the inferior left lobe, suggestive for pneumonia, associated with pleural effusion in the left lower lung, confirmed by thoracic ultrasonography.

A neurologic reassessment was done, and a new electromyography was performed, revealing myogenic abnormalities. Muscle biopsy could not be effectuated. Reevaluation of the case was imposed. Anamnestic data, consisting of insidious, symmetrical, proximal muscle weakness for one year, swallowing and phonation disorder and important weight loss, along with physical exam, serum elevated muscle enzymes and EMG aspect, were all suggestive for an inflammatory myopathy. Cutaneous characteristics were minimal, but we considered all clinical and paraclinical features suggestive for JDM. Nailfold capillaroscopy demonstrated a lower density of capillaries, typical cutaneous changes for JDM. Immunologic screening autoantibodies panel for myositis performed as a part of the initial diagnostic workup, but with late available results (one day after clinical deterioration), showed positive anti-PM/Scl 100 and anti-PM/SCL 75 antibodies, so that the diagnosis of JDM with scleroderma overlap syndrome was sustained. Intravenous pulsed methylprednisolone was commenced, with significant improvement of clinical status, in the first 24 hours, constituting another argument for systemic inflammatory disease diagnosis.

In order to assess the proper therapeutic plan, we asked for an immunologic evaluation (at "Alfred Rusescu" Institute for Mother and Child), confirming the diagnosis of a severe form of JDM/SSc overlap syndrome, with minimal cutaneous changes and important muscle involvement. In addition to steroids, we started weekly Methotrexate.

To clarify the extend of lung damage, HRCT was performed, revealing focal consolidations



**FIGURE 1.** Thoracic HRCT – focal consolidations, micronodules, septal thickening and patchy ground glass opacities

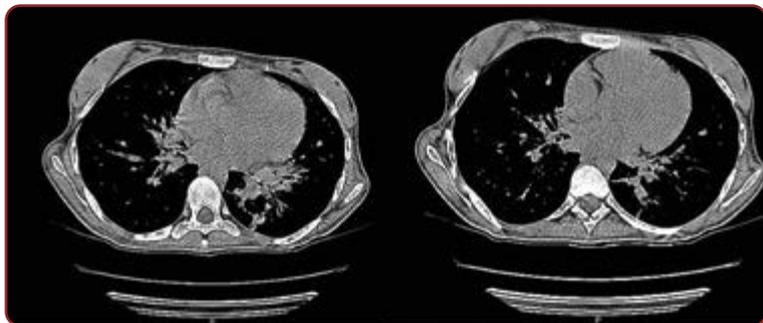
with air bronchogram in the basal segment of the lower lobe of the left lung and in the medium lobe of the right lung, with interstitial peribronchial changes: micronodules, septal thickening and patchy ground-glass opacities (Figure 1).

Pulmonary function tests were used to assess the severity of respiratory impairment. They demonstrated the persistence of a restrictive pattern (low forced vital capacity – 21% of predicted, low total lung capacity – 52% of predicted) and diminished alveolo-capillary diffusing capacity, taking into consideration difficult examination because of tachypnea, respiratory muscle weakness and low pulmonary volumes. The arterial blood gas

analysis showed a pattern of hypoxic-hypercapnic respiratory failure.

As a result of severe respiratory distress, with mixt respiratory failure and ineffective cough, we considered it necessary to initiate continuous non-invasive ventilation along with oxygen therapy, respiratory nursing and medical treatment. We opted for bilevel positive airway pressure support, with back up rate, associated with oxygen therapy, using a standard nasal mask, with an important improvement of the respiratory function.

After three weeks of complex therapy using antimicrobial agents associated with steroids pulsed therapy, immunosuppressive therapy,



**FIGURE 2.** Overnight cardio-pulmonary monitoring test – nocturnal alveolar hypoventilation

non-invasive ventilation and physiotherapy, the patient status was alleviated, with significant improvement of muscle force, reducing respiratory distress with no need for oxygen therapy and progressive weaning of diurnal non-invasive ventilation, improvement on respiratory clearance, amelioration of swallowing and phonation. The patient regained mobility and could maintain orthostatic position and walk for short distances. The level of muscle enzymes and blood gases normalized and serum inflammatory markers became negative. Repeated chest X-ray showed a regression of focal infiltrations and pleural effusion.

However, pulmonary function tests maintained severe restrictive aspect. As interstitial lung disease with pulmonary fibrosis may develop secondary to systemic connective disorders (dermatomyositis and scleroderma), and considering the respiratory muscle weakness, we performed nocturnal cardio-pulmonary polygraphy in order to evaluate the possibility of residual sleep-related breathing disorder. We revealed the persistence of nocturnal alveolar hypoventilation, with hypercapnia and hypoxemia (oxygen saturation < 90% in room air for 63 percent of sleep time) (Figure 2). However, diurnal oxygen saturation was normal. We decided to continue nocturnal non-invasive ventilation at home, along with medical treatment. We scheduled a close follow-up, keeping in touch with the immunology department too. The subsequent evolution was favorable. Her disease was clinically well controlled, and her immunosuppressive therapy was decreased. The pulmonary function was also improved, with alveolar hypoventilation resolution on repeated nocturnal cardiorespiratory monitoring polygraphy, so that the interruption of ventilatory support was permitted at six months after the diagnosis. □

## DISCUSSIONS

Overlap syndromes of JDM/SSc are rare and have primarily been described in adults. In children, only few cases have been described. We reported the case of a young girl who presented an overlap syndrome of dermatomyositis and scleroderma, with positive anti-PM/Scl 100 and anti-PM/Scl 75 antibodies, highlighting the complex mechanism of pulmonary complications as a result of systemic connective tissue disorder.

The main characteristics of JDM are symmetrical, proximal muscle weakness and chronic inflammation of the skin. The diagnosis is suggested by the clinical features and confirmed through laboratory and microscopic methods. In our patient, the diagnosis was difficult to establish following a clinical examination dominated by muscle weakness, with minimal cutaneous changes. Her initial biological evaluation showed elevated muscle enzymes, positive inflammatory tests, negative antinuclear antibodies and anti-dsDNA antibodies. Electromyography, an invasive test used to distinguish muscle weakness caused by muscle denervation from that caused by inflammatory myopathy, may be falsely negative in some patients, as in our case, making the diagnosis more difficult. We could not perform a muscle biopsy because of her severe pulmonary status. The presence of anti-PM/Scl antibodies had a key role in confirming the diagnosis of JDM/SSc overlap syndrome.

Although JDM/SSc overlap syndrome has less frequent visceral involvement, pulmonary dysfunction may occur. The extent of lung involvement in patients with dermatomyositis may develop secondary to infection, aspiration pneumonia, reflux, interstitial lung disorder or respiratory muscle weakness. The decreased strength of respiratory muscles induces inadequate ventilation, causing tidal volume to decrease. To maintain a good tidal volume, patients use accessory inspiratory muscles and increase respiratory frequency. When the increase of respiratory rate becomes insufficient to maintain alveolar ventilation, hypercapnia develops. Inadequate ventilation and low tidal volumes induce atelectasis, and right to left pulmonary shunt develops, producing hypoxemia that accompanies insufficient ventilation. Impairment of upper airway muscles and upper esophagus creates bulbar dysfunction, including difficulty in swallowing, tracheal aspira-

tion or food reflux into the upper airway tract. In our patient, the clinical picture was dominated by respiratory symptoms and muscle disorders. Pulmonary infection developed secondary to respiratory muscle severe weakness, and the pleural effusion probably secondary to infection rather than rheumatologic disorder. The progression of respiratory complications to acute respiratory failure, persistent with medical and supportive measures, required a non-invasive ventilatory treatment.

Interstitial lung disease can occur, although it is less common in children with JDM/SSc overlap syndrome. During the acute illness, our patient could not undergo pulmonary function testing. On recovery, she presented a persistent restrictive pattern on repeated pulmonary functional tests, with low alveolo-capillary diffusing capacity and rare patchy ground-glass opacification on HRCT examination. Also, nocturnal cardio-pulmonary polygraphy showed persistence of alveolar hypoventilation and hypoxemia in the complex context of severe muscle and pulmonary dysfunction within the systemic inflammatory disorder. Home nocturnal non-invasive ventilation was continued and closely follow-up was scheduled. Supportive management of respiratory muscle weakness, including ventilatory support, along with medical therapy, provided symptomatic relief and improved the quality of life. □

### CONCLUSIONS

We illustrated a rare case of JDM/SSc overlap syndrome with important visceral involve-

ment in a young girl presenting severe respiratory distress. This condition is a rare entity in childhood and adolescence. Only a few cases have been reported so far. It is associated with features of SSc and dermatomyositis. Muscle weakness and severe respiratory illness dominated the disease course, requiring ventilation support. We highlighted the key involvement of anti-PM/Scl antibodies in establishing the diagnosis. Also, the case illustrates the reversibility of muscle weakness in severe JDM/SSc overlap syndrome and shows that active management, including non-invasive ventilation and treatment of chest infections, are essential in-patient boarding. The importance of nocturnal cardio-pulmonary polygraphy in the diagnosis of sleep-related breathing disorder is sustained. In the presence of a multisystemic pathology with severe neuromuscular and respiratory impairment, association with nocturnal hypoventilation and hypoxemia should be considered and specific tests (eg, nocturnal cardiopulmonary monitoring test) should be proceed in a time of clinical stability. Nocturnal non-invasive ventilation is an important therapeutic solution in this type of pathology. Once the resolution of neuromuscular and pulmonary dysfunction is realized, withdrawal from nocturnal ventilatory support is possible. □

*Conflicts of interest: none declared.*

*Financial support: none declared.*

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