

Case Report

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Juvenile antisynthetase syndrome successfully treated by rituximab**Forough Emami¹; Reza Shiari^{1*}; Mohammad Samami²; Sara Shiari³; Yalda Nilipour⁴; Khosro Rahmani¹; Azadeh Zeinab Mirzaee³; Vadood Javadi Parvaneh¹; Niloofar Shashaani¹; Reza Sinaei^{5,6}**¹Shahid Beheshti University of Medical Sciences, Department of Pediatric Rheumatology, Tehran, Iran.²Dental Science Research Center, Department of Oral and Maxillofacial Medicine, Guilan University of Medical Sciences, Rasht, Iran.³Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Pediatric Respiratory Diseases Research Center (PRDRC), Masih Daneshvari Hospital, Tehran, Iran.⁴Pediatric Pathology Research Center, Research Institute for Children's Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran.⁵Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Pediatric Respiratory Diseases Research Center (PRDRC), Masih Daneshvari Hospital, Tehran, Iran.⁶Department of Pediatrics, School of Medicine, Kerman University of Medical Sciences, Kerman, Iran.***Corresponding Author: Reza Shiari**

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Abstract**Background:** The Antisynthetase Syndrome (ASS) is a rare autoimmune disease considered as a subset of idiopathic inflammatory myopathies. This syndrome is associated with antisynthetase antibodies and clinical manifestations such as Raynaud's phenomenon, mechanic's hands and interstitial lung disease.**Case presentation:** Here in we reported a 16 years old Afghani girl who was diagnosed as having ASS. Rare diseases such as ASS should be suspected in idiopathic inflammatory myopathy patients who are resistant to standard medical regimens.**Conclusion:** In such cases, the use of Rituximab is strongly recommended. To the best of our knowledge is the first report of juvenile ASS in Middle East.**Keywords:** Antisynthetase syndrome; Myopathy; Rituximab; Auto-immune disease.**Abbreviations:** ASS: Antisynthetase Syndrome; IIM: Idiopathic Inflammatory Myopathies; ILD: Interstitial Lung Disease; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; CPK: Creatine Phosphokinase; LD: Lactate Dehydrogenase; ANA: Antinuclear Antibody; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; EMG: Electromyography; NCV: Nerve Conduction Velocity; HRCT: High Resolution Computed Tomography; IVIG: Intravenous Immunoglobulin; JDM: Juvenile Dermatomyositis; PM: Polymyositis; DM: Dermatomyositis; MTX: Methotrexate.

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Introduction

Myopathies are classified into two main categories: inflammatory and non-inflammatory [1,2]. The Antisynthetase Syndrome (ASS) is a rare autoimmune connective tissue disease defines as a subset of Idiopathic Inflammatory Myopathies (IIM) associated with antisynthetase antibodies and various clinical manifestations such as Raynaud's phenomenon, mechanic's hands and Interstitial Lung Disease (ILD) [3,4]. Here in we reported a 16-year-old Afghan female with 3 months history of muscle weakness but no previous history of systemic disease who was finally diagnosed as antisynthetase syndrome. To the best of our knowledge this is the first report of juvenile ASS from Middle East.

Case report

A 16-year-old Afghani girl with no record of any systemic disease, presented with a 3 months history of muscle weakness especially in proximal upper and lower extremities, positive gower sign and fatigue. Furthermore, she had a 1 month history of Raynaud's phenomenon, erythema of extensor surfaces of hands, bilateral hand and foot swelling, periorbital edema, skin photosensitivity and diffuses labial swelling. Dyspnea on exertion and dysphagia were occurred later. In more evaluation, nail fold Telangiectasias was detected.

Initially, baseline studies were done. laboratory studies revealed elevated aspartate Aminotransferase (AST) of 252 U/L, Alanine Aminotransferase (ALT) of 162 U/L, Creatine Phospho-Kinase (CPK) of 5773 IU/L, *Lactate Dehydrogenize* (LDH) of 1772 U/L, negative ANA(1:40), C-Reactive Protein (CRP) of 2 mg/L, *Erythrocyte Sedimentation Rate* (ESR) of 68 mm/h. Electromyography (EMG) and Nerve Conduction Velocity (NCV) tests concluded that was consistent with an irritative generalized symmetric myopathic disorder with evidence of active denervation.

Imaging studies were accomplished including High Resolution Computed Tomography (HRCT) of chest, echocardiography and barium swallowing test. HRCT showed multifocal sub-pleural ground-glass lesions. The *COVID-19* real time-PCR and antibodies were negative. Echocardiogram revealed mild pulmonary hypertension with borderline pulmonary arterial pressure.

A muscle biopsy and auto-antibodies measurements were performed. Although, treatment was started with single dose of Intravenous Immunoglobulin (IVIG) at 2 g/kg and followed by intravenous injection of methylprednisolone, one gram daily for 5 days based on initial diagnosis of Juvenile Dermatomyositis (JDM). However, her muscle weakness and exertional dyspnea did not improve significantly. The results of other auto-antibodies including: Anti JO-1, Anti M2, Anti dsDNA, Anti SS/A, Anti SS/B, Anti RNP, Anti Scl-70, Anti PM-100; all were negative. Muscle biopsy revealed some perifascicular necrotic fibers with some perimysial fragmentation but no inflammation, compatible with histological diagnosis of ASS (Figure 1).

Following the ASS diagnosis, treatment with Rituximab at 375 mg/m²/week for 4 weeks was initiated. 2 months after starting the drug, the patient's clinical signs and symptoms such as muscle weakness, exertional dyspnea, skin and nail manifestations, and dysphagi all relieved dramatically. Muscle enzymes and inflammatory markers were normalized. Amusingly, her

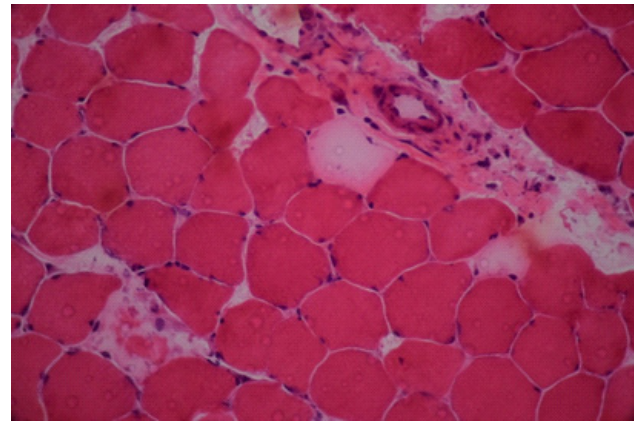


Figure 1: Muscle biopsy. Perifascicular necrotic fibers with perimysial fragmentations, but no inflammation was detected (Haematoxylin and Eosin x400).

ground-glass lesions of chest HRCT disappeared after 4 months. There were no signs or symptoms of the disease flare-up after one-year follow-up.

Discussion

ASS is a chronic connective tissue disease of unknown cause. Three sub-groups of IIMs include: 1) sporadic inclusion-body myositis; 2) polymyositis (PM); and 3) dermatomyositis (DM). ASS is a sub-class of PM/DM [5]. This chronic disease was first described by Marguerie et al. in 1990 [6]. The pathogenesis of this disease is explained by the presence of myositis-specific autoantibodies against aminoacyl tRNA synthetase, which may occur due to genetic predisposition, viral agents or medications. The most common autoantibody is anti-JO-1 antibody which is present in 80% of ASS patients [2,7]. However, in our patient, the results of myositis-specific autoantibodies (Anti JO-1, Anti M2) and myositis-associated autoantibodies (Anti SS/A, Anti SS/B, Anti RNP, Anti Scl-70, Anti PM-100) all were negative.

Considering the rarity and delay in diagnosing of ASS, there is little data about its incidence and prevalence in the literature. The annual incidence of IIM and ASS in the general population has been reported approximately 2 and 0.6 per 100,000 individuals, respectively [8,9]. The disease primarily affects adults aged 22-74 years with an average age of about 50 years [5,8,10,11]. It develops in children extremely rare, with annual incidence of 2.5-4 cases per million and a peak incidence of 5-10 years old [12]. The females are more affected than men (2-3 ratio), and there is a predominance of caucasians [5,8,10-12]. Our case is a 17-year-old girl who, to the best of our knowledge, is the first report of juvenile ASS from the Middle East.

Clinical manifestations of the disease can include fever, fatigue, ILD, inflammatory myopathy, non-erosive arthritis; arthralgia, skin manifestations such as mechanic's hands, Raynaud's phenomenon and oral manifestations such as dry mouth and ulcers [7,10].

Our patient had fatigue, muscle weakness, Raynaud's phenomenon, hand erythema, bilateral swelling and arthralgia of the hands and feet, orofacial edema, photosensitivity, exertional dyspnea and dysphagia. Inflammatory myopathy was confirmed by performing EMG-NCV.

The patient also had borderline PAP and ILD, which was diagnostic on the chest HRCT as ground-glass opacities [10]. It is commonly seen in the adults and has been reported rarely in children [13]. ILD overall prevalence has been reported to be 60%-100% according to various studies, since it occurs in up to 30% of patients as an initial presentation [5,14,15]. It is considered the most important prognostic factor (predicting morbidity and mortality) [16,17] which manifests as exertional dyspnea and dry cough. ILD may cause pulmonary hypertension, however, pulmonary hypertension development without ILD has also been reported [5,14]. Anti-JO-1 antibodies have been reported as the most important predictor of ILD in patients with ASS and is detectable in 60-70% of ASS patients with ILD [5,18].

Because of low prevalence of ASS and lack of adequate randomized clinical trials, the treatment of these patients is challenging. However, treatment of this kind of IIM is typically based on the severity of ILD or myositis [14,19]. The most common recommended initial medication is systemic corticosteroids (prednisone or methylprednisolone). Depending on the severity of the disease, a steroid sparing agent such as azathioprine can be added which decreases the rates of relapses and improves survival [14,18]. Other immunomodulating agents such as IVIG, Methotrexate (MTX), cyclophosphamide and cyclosporine have also been mentioned as effective medications in various studies. IVIG is used to treat myositis in IIM, but is not effective in cases of ILD [15,20]. Recently, there has been a growing tendency to use of Rituximab in the treatment of ASS specifically for patients with refractory ILD and/or myositis [19]. According to studies, this drug can cause significant improvement in clinical symptoms and imaging, especially in patients with duration of less than one year [14,15,20]. In current reported case, the patient was initially treated with IVIG and intravenous methylprednisolone pulse which did not relieve symptoms. In the second line, the patient was treated with Rituximab and showed dramatic improvement in symptoms after 2 months. HRCT imaging manifestations of the ILD disappeared entirely within 4 months, during which no evidence of infection was found. Maintenance treatment was continued with oral prednisolone tapering and subcutaneous MTX. There is no evidence of muscle weakness, ILD or any relapsing symptoms during the 9 months follow-up.

Conclusion

Rare diseases such as antisynthetase syndrome must be suspected in idiopathic inflammatory myopathy patients who are resistant to standard treatment. In such cases, the use of Rituximab is strongly recommended.

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