Life-Threatening Oropharyngeal Aphagia as the Major Manifestation of Dermatomyositis

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Swallowing disturbance is a known complication of dermatomyositis, usually attributed to esophageal muscle involvement. In some patients, dysphagia for solids and liquids might be severe and even life threatening. Oropharyngeal aphagia (complete inability to swallow), if present, is usually accompanied by prominent esophageal involvement, and only rarely does it present as an isolated clinical feature. We report a case of dermatomyositis with rapidly progressive isolated oropharyngeal aphagia as an early complication and discuss the appropriate diagnostic and treatment strategies.

PATIENT DESCRIPTION

A 74 year old Caucasian woman was admitted to our department after 2 months of profound general weakness, rash, and severe dysphagia. Her past medical history included diabetes mellitus type 2, fatty liver, and hypothyroidism treated with metformin, glipizide and levothyroxine. Two months earlier she had been diagnosed with dermatomyositis, which presented with a characteristic violet photosensitive skin rash on her chest and elbows, and prominent Gottron signs. Her muscle strength was normal. She had mild elevation of creatine phosphokinase to 260 U/L (normal range 30–180 U/L), erythrocyte sedimentation rate (70 mm in the first hour) and C-reactive protein (16 mg/L, normal < 5 mg/L). Her blood count and the rest of her chemistry laboratory tests were unremarkable.

A computed tomography scan of the pharynx and larynx demonstrated a normal esophagus, multinodular goiter, and degenerative findings in the cervical spine. CT scan of the chest was normal, while abdominal CT demonstrated fatty liver and colon diverticulosis with no signs of malignancy or lymphadenopathy. Breast and gynecological examinations were normal. Gastroscopy showed dilated lower esophageal sphincter with no evidence of focal esophageal abnormality.

Treatment with prednisone 1 mg/kg (80 mg/day) was begun, leading to amelioration of the skin lesions and improved CPK levels. The patient was discharged home after a few days.

Two weeks later she was readmitted to our department with worsening of her weakness, difficulty walking, inability to swallow, and weight loss of 7 kg. Attempts to swallow solid or mashed food, water, and tablets failed and were occasionally associated with choking and regurgitation, with some of the food emerging from her nose. The patient did not report any odynophagia, nausea, vomiting, diarrhea, fever, or anorexia. On examination, skin changes compatible with dermatomyositis were noticed above her elbows and fingers, and she had periangular and palmar erythema. Chest and abdominal examination were unremarkable. Evaluation of the proximal muscles revealed weakness of 2/5 in her shoulder girdle and 3/5 in her thighs. Blood tests showed a normal blood count, CPK 256 U/L, and lactate dehydrogenase 258 U/L (normal range 60–225 U/L). The other laboratory tests, including glucose, liver enzymes, kidney functions, iron, ferritin, albumin, thyroid function, vitamin B12 and folic acid, were unremarkable. Blood tests for antinuclear antibody, rheumatoid factor, antibodies to ribonucleoprotein, topoisomerase 1, and centromere were negative. Urinalysis was normal. Electrocardiography and ECHO Doppler cardiography were normal. Electromyography showed increased spontaneous muscle activity with fibrillations, full recruitment, and low amplitude polyphasic units of short duration comparable with myositis. T1 and T2-weighted magnetic resonance imaging of the neck and pharynx with gadolinium enhancement showed C3–C4 and C5–C6 cervical disk herniation with no evidence of muscle edema or pathological enhancement.

A video fluoroscopic swallowing study illustrated normal oropharyngeal and esophageal anatomy with signs of diffuse neuromuscular disturbance of the swallowing mechanism. Movements of the larynx and the epiglottis were limited and laryngeal elevation was inadequate. A small aspiration was noted during swallowing, with evidence of residue in the valleculae and piriform fossa. Barium peristalsis in the hypopharynx was symmetrical without delay. Peristaltic movements of the esophagus were normal.

CPK = creatine phosphokinase

Treatment with intravenous methylprednisolone 75 mg/day and intramuscular methotrexate 15 mg/week was started but the patient's condition continued to deteriorate. She became very weak, needed help in all activities of daily living, and had to sleep sitting up in order not to choke on her own saliva.

Therapy was escalated to three infusions of intravenous methylprednisolone 500 mg/day, followed by IV methylprednisolone 100 mg/day and IV immunoglobulin 125 g for 5 consecutive days. As she continued to lose weight and developed hypoalbuminemia (2 g/dl, normal > 3.5 g/dl), a percutaneous endoscopic gastrostomy was inserted, allowing alimentation and oral drug delivery. The patient continued on prednisone 80 mg/day and, as her weakness and rash resolved and CPK levels normalized, tapering down of steroids became possible. During this time she continued with methotrexate injections and monthly courses of IVIG. A muscle biopsy performed more than a month after she started to take high dose corticosteroid revealed muscle fiber atrophy with no inflammation or evidence of inclusion bodies. She was transferred to a rehabilitation center and was finally discharged home 4 weeks later.

Three months later, she felt well, was able to rise from a chair, walk, and eat food with soft consistency. Her skin rash had disappeared. Repeated laboratory tests revealed normal CPK and albumin. Repeated VFSS demonstrated normal swallowing mechanism and the PEG was removed. The patient continued on prednisone 10 mg/day, oral methotrexate 15 mg/week, and IVIG 125 g every 3 months.

One year later, the patient developed a mild exacerbation manifested as an episode of skin rash and fatigue. Laboratory tests, including CPK, ESR and CRP, were unremarkable. She was treated with three IV pulses of methylprednisolone, the methotrexate dose was raised to 17.5 mg/week, and IVIG treatment was continued. There were no swallowing difficulties during that episode.

Two years after the onset of her swallowing problems, the patient was able to eat normally. There was only mild residual proximal muscle weakness on examination and she did not need help with activities of daily living. Blood tests, including CRP, CPK and albumin levels, were normal, and she was maintained on prednisone 5 mg/day, methotrexate 17.5 mg/week, and IVIG courses.

IVIG = intravenous immunoglobulins
VFSS = video fluoroscopic swallowing study
PEG = percutaneous endoscopic gastrostomy
ESR = erythrocyte sedimentation rate
CRP = C-reactive protein

COMMENT

Dermatomyositis is a chronic disease manifested by a symmetric proximal, inflammatory myopathy and a characteristic violaceous, cutaneous eruption in typical areas. In addition to involving the skeletal muscles, dermatomyositis is known to involve the respiratory muscles, the myocardium and the gastrointestinal tract.

The pharyngeal musculature is striated and thus can become inflamed and weak similar to striated muscle in other locations. It is estimated that 10–73% of patients with inflammatory myopathies suffer from dysphagia to some extent. Patients with inclusion body myositis do so more often than patients with polymyositis and dermatomyositis [1].

Dysphagia in inflammatory myopathies can result from involvement of the upper esophagus, the pharyngeal muscles, or both anatomic sites. Among 301 dermatomyositis/polymyositis patients treated with IVIG, severe dysphagia was noted in 73, all of whom had rigorous esophageal involvement [2]. Of these 73 patients, only 22 (39.8%) had dysphagia to both liquids and solids, defined as aphagia, as seen in our patient. Our case is remarkable for the fact that the patient had aphagia without involvement of the esophagus.

VFSS is a well-studied verified tool for indirect evaluation of the involvement of swallowing-related muscles [3]. In our patient we used VFSS, which revealed prolongation of the pharyngeal phase of swallowing. This finding can be confirmed by electromyography, as shown in the study by Ertekin et al. [4]. Another method for increasing the sensitivity of dysphagia evaluation, which is especially relevant for patients with esophageal involvement, is esophageal manometry [2,5]. Unfortunately, for technical reasons, manometry was not used in our patient, and barium swallow did not reveal any peristaltic abnormality.

Our patient had higher than normal CPK values, but the values were less than twice the normal limits. When approaching patients suspected of having inflammatory myopathies, we should remember that patients can be severely affected despite having only mild and even normal muscle enzymes. Expecting a correlation between limb strength and severity of the oropharyngeal dysphagia can also be misleading. As in our patient, the dissociation between the two was recently described by Kim and colleagues [3], who found no correlation between the hyolaryngeal movement and the motor power of the limb muscles.

Among factors associated with poor survival in dermatomyositis are advanced age, malignancies, delayed initiation of corticosteroid treatment, lung and myocardial involvement, and pharyngeal dysfunction. Our patient had two major risk factors, advanced age and oropharyngeal aphagia. The oropharyngeal aphagia resulted in the inability to swallow oral medication, including corticosteroids, and actually led to a significant delay of corticosteroid treatment (the third major risk factor). Marie and co-authors [2] successfully treated severe esophageal dysphagia (including 22 cases with concomitant oropharyngeal aphagia) with high dose corticosteroids and IVIG. Our patient's condition deteriorated so quickly that we decided to treat her aggressively with high dose corticosteroids and IVIG, without waiting for the results of the muscle biopsy. Early insertion of the PEG allowed a rapid switch to oral therapy and nutritional support.

In cases of dermatomyositis with a poor prognosis, early aggressive treatment may change the course of the disease. Awareness of possible oropharyngeal aphagia with or

without significant esophageal involvement (as in our case) as an early life-threatening complication of dermatomyositis is essential and may justify the switch from oral to IV medication delivery as soon as possible, in addition to prompt PEG insertion for alimentation and drug delivery.

In conclusion, aphagia may be a prominent early manifestation and a leading cause of morbidity in inflammatory myopathies. Patients suspected of having inflammatory myopathies complaining of dysphagia/aphagia should be immediately assessed by VFSS and possibly also by esophageal manometry. This evaluation should be undertaken even if the muscle enzymes are slightly elevated and muscle weakness is only minor. Patients with severe dysphagia or aphagia will probably have problems ingesting medications due to swallowing difficulties. We should be alert for this seemingly obvious problem and consider switching the oral treatment to intravenous as well as early insertion of feeding gastrostomy or an alternative alimentation route. Despite the notion that severe dysphagia or aphagia indicates a bad prognosis in patients with dermatomyositis, this condition can be reversible and, if treated early and aggressively, can change the patient's fate.

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Capsule

Autism-specific maternal autoantibodies recognize critical proteins in the developing brain

Autism spectrum disorders (ASDs) are neurodevelopmental in origin, affecting an estimated 1 in 88 children in the United States. Braunschweig and colleagues previously described ASD-specific maternal autoantibodies that recognize fetal brain antigens. Now they demonstrate that lactate dehydrogenase A and B (LDH), cypin, stress-induced phosphoprotein 1 (STIP1), collapsin response mediator proteins 1 and 2 (CRMP1, CRMP2) and Y-box-binding protein comprise the seven primary antigens of maternal autoantibody-related (MAR) autism. Exclusive reactivity to specific antigen combinations was noted in 23% of mothers of ASD children and only 1% of controls. ASD children from mothers with specific reactivity to LDH, STIP1 and CRMP1 and/or cypin (7% vs. 0% in controls, $P < 0.0002$, odds ratio 24.2, 95% confidence interval 1.45–405) had elevated stereotypical behaviors compared with ASD children from mothers lacking these antibodies. The authors describe the first panel of clinically significant biomarkers with over 99% specificity for autism risk, thereby advancing our understanding of the etiologic mechanisms and therapeutic possibilities for MAR autism.

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Eitan Israeli

Capsule

Preclinical study on cell therapy for mitigation of lethal acute radiation response by Hadassah research group is published in *PLOS ONE*

Prof. Raphael Gorodetsky and his team in the Biotechnology and Radiobiology Laboratory of the Sharett Institute of Oncology at Hadassah Hospital report a breakthrough cell-therapy study for mitigation of lethal acute radiation syndrome (ARS) by simple intramuscular injection of human placental stromal cells. This preclinical study was performed with specific composition of 3D expanded allogeneic cells (PLX-RAD) produced by Pluristem (Haifa), which were found by the researchers to be most effective for this application. The results suggest an "off the shelf" safe therapy to mitigate ARS by a simple intramuscular injection of the placental cell preparations with minimal anticipated adverse effect or complications. The immediate clinical application of this study is for scenarios of nuclear disasters, where large populations may be exposed to high doses of ionizing radiation with no accurate individual dose estimation. The treatment is practical in such events since its initiation could be delayed for at least by 1–2 days. The authors suggest that their findings may also be applied in clinical practice for bone marrow failure and pancytopenia.

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