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CASE BASED REVIEWS

Pulmonary sarcoidosis and immune-mediated necrotizing myopathy: an uncommon coincidence

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ABSTRACT

Introduction: Immune-mediated necrotizing myopathy (IMNM) is characterized by acute or subacute, severe proximal muscle weakness and myofiber necrosis with minimal inflammatory cell infiltrate observed on muscle biopsy. On the other hand, sarcoidosis is characterized by the presence of non-caseating granulomas that can develop in several organs.

Case report: We present the unique case of a 49-year-old woman, with no previous medical history, who had a rare concomitant occurrence of IMNM and pulmonary sarcoidosis. This condition was successfully treated with a combination of corticosteroids and rituximab along with rehabilitation program.

Discussion: This association has been reported in only two previous case reports. This highlights the importance of further research on the connection between sarcoidosis and other forms of inflammatory myopathies.

Keywords: Rituximab; Pulmonary sarcoidosis; Corticosteroids; Immune-mediated necrotizing myopathy; Myositis and muscle disease.

Immune-mediated necrotizing myopathy (IMNM) is a type of immune-mediated myopathy characterized by acute or subacute, severe proximal muscle weakness, myofiber necrosis with minimal inflammatory cell infiltrate on muscle biopsy, and infrequent extra-muscular involvement[1,2]. Among inflammatory myopathies, IMNM comprises up to 10% of cases and is associated with specific antibodies, such as anti-signal recognition particle (anti-SRP) and anti-3-hydroxy-3-methylglutaryl coenzyme A reductase (anti-HMGCR)[3,4].

Sarcoidosis is a multisystemic inflammatory disease of unknown etiology characterized by the presence of non-caseating granulomas that can develop in several organs[5]. While the lungs and intrathoracic lymph nodes are the primary targets, skeletal muscle involvement occurs in 50% to 80% of individuals, often asymptomatic[6].

In this case report, we present a unique case of a concomitant IMNM and pulmonary sarcoidosis.

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CASE REPORT

A 49-year-old woman, with no previous medical history and a non-smoker, presented to the Rheumatology Department with severe proximal muscle weakness, initially involving the lower limbs with subsequent progression to the upper limbs, over the last 2 months. In addition to muscle weakness, she complained of myalgias, Raynaud's phenomenon, anorexia and unintentional weight loss of 4 kg (6.5% of corporal body weight) in the same 2 month-period. The patient denied having fever, skin lesions, dysphagia, arthralgia or complaints related to respiratory, cardiovascular, genitourinary, gastrointestinal or neurological systems. There were no recent infections or introduction of new drugs. No family history of neuromuscular disease was reported. Physical examination revealed significant proximal upper and lower extremity muscle weakness (shoulder abduction 4/5, elbow flexion 4/5, hip flexion 3/5, knee flexion 3/5, foot dorsiflexion 4/5 bilaterally, according to the Medical Research Council, MRC, scale) and she was unable to rise from a seated position without help. Deep tendon reflexes, sensation and coordination were intact. Heart and lung auscultation and abdominal examination didn't reveal abnormalities. No cutaneous manifestations were found in physical examination.

The laboratory workup revealed elevated levels of creatine kinase (CK, 15894 U/L), myoglobin (3490.4 ng/mL), aldolase (145.8 U/L), aspartate transaminase (AST, 513 U/L), and alanine transaminase (ALT, 360 U/L). The complete blood count (hemoglobin 12.6 g/

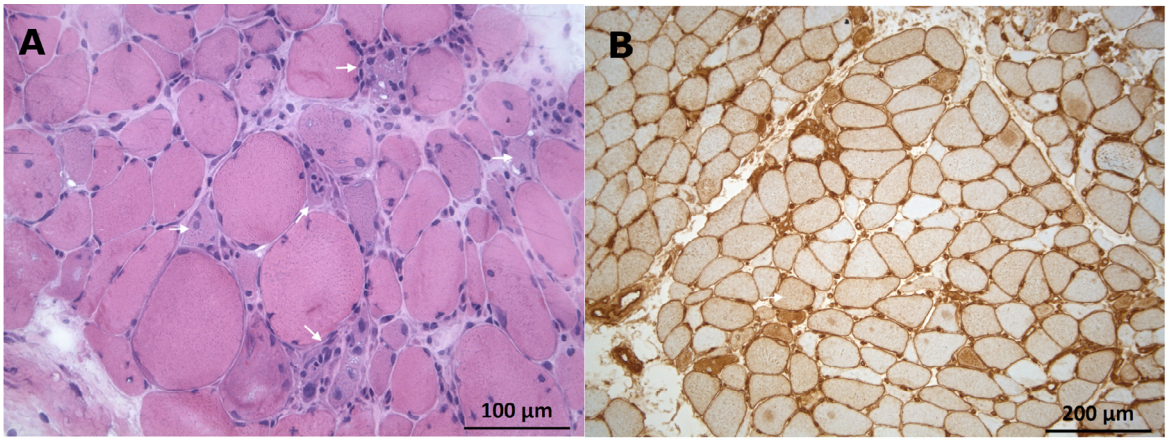

Figure 1. Histological and immunohistochemical analysis of the muscle biopsy. (a) Hematoxylin and eosin staining reveals numerous necrotic fibers, myophagocytosis, basophilic fibers, various atrophied fibers with nuclear internalizations and an absence of inflammatory infiltrates. No non-caseating granulomas were found (b) In the immunohistochemical analysis, a diffuse upregulation of MHC-I in the sarcoplasm is evident in numerous fibers, but it is more pronounced in the most severely affected fibers.

dL, leucocytes 8.12x10^9/L, platelets 302x10^9/L), inflammatory markers (C-reactive protein 2.7 mg/L, erythrocyte sedimentation rate 24 mm/hour), renal function (creatinine 0.45 mg/dL, urea 30 mg/dL), thyroid function (TSH 2.43 mUI/mL, T4 0.92 ng/dL), calcium (4.7 mEq/L), phosphorus (4.5 mg/dL) magnesium (1.65 mEq/L) and potassium (4.4 mEq/L) values were all within the normal range. The angiotensin-converting enzyme (ECA) level was slightly increased (74, N <70) and vitamin D was low (21 ng/mL). Results for myositis specific and associated autoantibodies showed positive anti-SRP, while the rest of autoimmune workup was negative (including antinuclear antibodies, anti-double stranded DNA, anti-extractable nuclear antigens and rheumatoid factor). Serologic tests for herpes simplex, Epstein-Barr virus, cytomegalovirus, varicella-zoster virus, toxoplasmosis, human immunodeficiency virus and hepatitis B and C virus were negative.

Electromyography (EMG) revealed abnormal spontaneous muscle activity and a diffuse myopathic pattern characterized by small, short polyphasic motor unit potentials, with more pronounced involvement of the proximal muscles. Magnetic resonance imaging (MRI) of the upper and lower limbs showed extensive *edema*, primarily affecting biceps, triceps, gluteus, quadriceps, hamstrings and paraspinal muscles. A muscle biopsy of vastus lateralis muscle showed profound myopathic features with numerous necrotic fibers, minimal inflammatory cellular infiltrates, and a diffuse overexpression of major histocompatibility complex (MHC) class I products. No non-caseating granulomas were found (Figure 1).

A diagnosis of immune-mediated necrotizing myopathy (IMNM) was established. Due to the known association between inflammatory myopathies and malignancy, an investigation was conducted. Mammography, thyroid ultrasound, upper endoscopy and colonoscopy were normal. Computed tomography (CT) of the chest, abdomen, and pelvis was normal, except for prominent mediastinal and bilateral hilar lymphadenopathy (Figure 2a). To further assess the lymphadenopathy, the patient underwent an endobronchial ultrasound-*guided* transbronchial needle aspiration. The biopsy results showed non-necrotizing epithelioid cell granulomas with no evidence of malignancy. Additionally, all stains and cultures from the biopsy were negative. An increased CD4/CD8 ratio (superior to 3.5) was observed. Consequently, a diagnosis of stage I pulmonary sarcoidosis was made[7].

The patient started intravenous (IV) methylprednisolone pulse (1 g daily for 3 days), followed by a 1 mg/kg daily of oral prednisolone and IV immunoglobulin (0.4 g/kg/day) for 5 days. Additionally, prophylaxis for *Pneumocystis jiroveci* (sulfamethoxazole-trimethoprim 800/160 mg 3 times per week) was initiated. Calcium (1250 mg daily) and vitamin D (calcifediol 0.266 mg monthly) supplementations were started and continued during the first months of high-intermediate doses of corticosteroids. Over time, both clinical and laboratory improvements were observed. CK levels decreased to 1552 U/L and myoglobin to 340 ng/mL. After 25 days, the patient was discharged with a tapered dose of steroids and a rehabilitation program was prescribed.

After discharge, rituximab 500 mg IV on days 1 and 15, with subsequent administrations scheduled every 6 months, was started. At the 12-month follow-up, a significant improvement in muscle strength was evident (shoulder abduction 5/5, elbow flexion 5/5, right hip flexion 4/5, left hip flexion 5/5, knee flexion 5/5

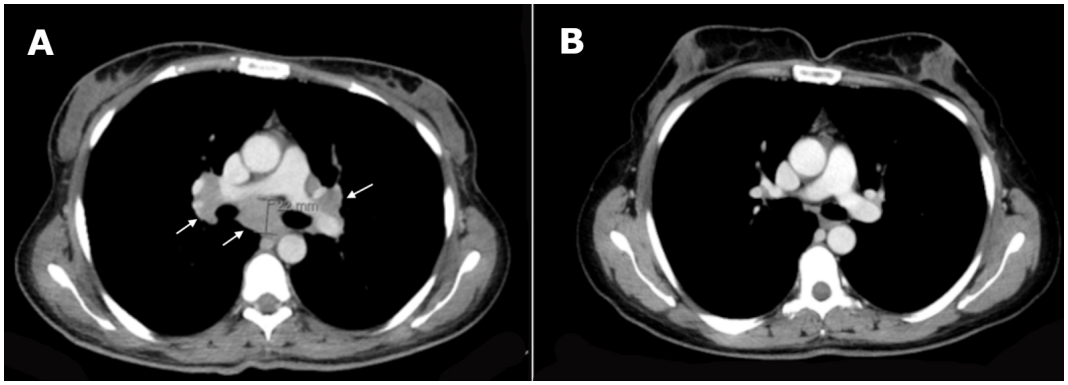

Figure 2. (A) Computed tomography of the chest shows prominent mediastinal and bilateral hilar lymphadenopathy, with the larger lymph node measuring 22 mm. (B) Computed tomography of the chest 12 months after the diagnosis shows complete resolution of the mediastinal and bilateral hilar lymphadenopathy.

and foot dorsiflexion 5/5 bilaterally, according to the MRC scale). A normalization of muscle enzymes (CK 65 U/L, aldolase 2.8 U/L, myoglobin 120 ng/mL) was also observed. Pulmonary function tests revealed normal results, and positron emission tomography for sarcoidosis staging indicated no evidence of extra-pulmonary sarcoidosis involvement. Furthermore, a chest CT scan revealed complete resolution of the previously observed lymphadenopathies (Figure 2b).

DISCUSSION

IMNM is a group of rare acquired immune-mediated myopathies classified into three subtypes based on the presence of specific auto-antibodies: anti-SRP, anti-HMGCR and seronegative IMNM[1]. Clinically, SRP-IMNM is characterized by acute or subacute, severe, and symmetrical proximal weakness. Along with muscle weakness, myalgia, dyspnea, dysphagia, and muscle atrophy can occur[4,8,9]. However, involvement of distal leg, bulbar and axial muscles is uncommon in SRP-IMNM[9]. Compared to HMGCR-IMNM, muscle weakness appears to be more severe in SRP-IMNM[4,8]. Elevated levels of CK, often exceeding 1000 IU/L, are prominent in SRP-IMNM and are positively correlated with myofiber necrosis[8-10]. Extramuscular manifestations are rare, but interstitial lung disease and myocardial involvement can be seen in SRP-IMNM[11].

Our patient presented with classic symptoms and histological features highly suggestive of SRP-IMNM, namely widespread fibre necrosis, minimal inflammatory cellular infiltrates, and upregulated MHC-1 on the sarcolemma[12]. Exclusion of other potential causes of necrotizing myopathy, such as connective tissue disorder, viral infections or malignancy, was performed. Other inflammatory myopathies were excluded considering factors such as the absence of skin lesions, the lack of specific histologic findings in muscle biopsy like perifascicular atrophy and significant endomysial or perimysial mononuclear infiltrate and the absence of suggestive autoantibodies.

The concomitant diagnosis of pulmonary sarcoidosis was established based on the presence of asymptomatic bilateral hilar lymphadenopathy in conjunction with the exclusion of other potential causes of granulomatous inflammation. This manifestation is a common finding in patients with sarcoidosis and is indicative of stage I of pulmonary sarcoidosis. Symptomatic muscle involvement in sarcoidosis is uncommon and mostly due to sarcoid myopathy[6]. However, the absence of histological findings suggestive of sarcoid myopathy, along with the presence of a specific antibody for IMNM and suggestive histology, makes the diagnosis of sarcoid myopathy unlikely. To the best of our knowledge, the coexistence of IMNM and sarcoidosis has been reported in only two previous case reports[13,14]. While there have been rare reports of an association between inclusion body myositis and sarcoidosis, the association with IMNM is extremely uncommon[15,16].

The other two cases also presented with progressive and painful weakness, accompanied by anti-SRP positivity. In one case, the CK level was lower than ours (2962 U/L), while the other had similar values (13 649 U/L). In terms of sarcoidosis, one patient had bilateral hilar lymphadenopathy, while the other exhibited more prominent ganglionar involvement, with extra-thoracic lymphadenopathy affecting cervical, axillary and inguinal nodes, along with pulmonary nodules. Regarding treatment, one patient was treated with prednisolone, methotrexate and immunoglobulins IV, resulting in an improvement in muscle strength and a reduction in the size of lymphadenopathy. The other patient was treated with prednisolone, immunoglobulins, and subsequent-

ly, mycophenolate mofetil. This patient fully recovered her muscle strength (*grade 5/5 in MRC scale*) and CK levels reduced to 962 U/L. Our patient was initially treated with prednisolone and immunoglobulins. However, due to incomplete resolution and the concomitant diagnosis of pulmonary sarcoidosis, we decided to introduce a low-dose of rituximab, which led to the achievement of remission for both diseases.

In conclusion, this case describes a unique association between IMNM and sarcoidosis, which was successfully treated with rituximab. This highlights the importance of further research into the connection between sarcoidosis and other forms of inflammatory myopathies.

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