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IM - CASE RECORD

A man with fever and bilateral limb weakness

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Case presentation

A 49-year-old Caucasian male was admitted to our Emergency Department complaining of bilateral upper and lower limb weakness, interfering with daily activities, and intermittent fever, and weight loss. Two months before presentation he had an acute respiratory illness. Both intermittent fever and nonproductive cough persisted thereafter, followed by muscle weakness and weight loss (5 kg in 2 months).

Both family and personal history were negative for cancer, endocrinopathy, hereditary muscle disorders, connective tissue diseases, and rheumatologic disorders except for Raynaud's disease, which was diagnosed 5 years before admission. The patient was an accountant, he regularly practiced non-competitive sports, and he had a pet dog but no other animals. The patient denied recent foreign travels, known contact with sick persons, smoking, high-risk sexual behavior, abuse of alcohol or illicit substances, and any recent traumas. His only medication was acetaminophen and there was no history of exposure to statins or non-drug sources of statins, as red yeast rice and dietary supplements. The chief complain was severe symmetrical muscle limb weakness and myalgia, affecting mostly the legs, with increasing difficulties in climbing upstairs, arising from chair, and getting in and out of a car. He denied diplopia, dysphagia and other gastrointestinal symptoms, shortness of breath on exertion, arthralgia, or night sweats.

Neurological examination in the Emergency Department showed symmetrical limb girdle weakness and tenderness of lower limb muscles without axial muscle involvement. Finger flexor strength was normal as well as sensory findings, reflexes, and the remainder of the neurological examination. General physical examination was unremarkable and there was no evidence of interstitial disease at lung auscultation or heart sound abnormalities. Joint examination did not detect signs of inflammatory arthritis. A thorough skin examination with particular attention to the scalp, face, eyelids, hands, fingers, did not reveal any abnormality. In particular, there were no heliotrope rash, Gottron's papules, shawl sign, mechanic hands, ulcerations, calcinosis or skin thickening of the fingers.

Routine blood tests (Table 1), including electrolytes, renal function, and thyroid hormones, were normal, but there was a marked rise in CK (19.112 UI/l, reference range 25–190), LDH (4.291 UI/l, reference range 250–450), AST (618 UI/l, reference range 8–40), ALT (553 UI/l, reference range 8–45) levels.

Dr. Bernardi, Gargiulo, Papa, Gruden (Internists) Both muscle weakness and increased CK levels suggested myopathy and electromyography (EMG), which can be useful in distinguishing myopathies from other diseases that affect the neuromuscular unit, confirmed the presence of myopathic changes. Both unintentional weight loss and fever suggested occult malignancy with paraneoplastic myopathy and the patient reported dry cough as potential localizing symptom. However, the patient did not smoke and the chest computed tomography (CT) scan was normal. Moreover, there were no gastrointestinal symptoms and the abdomen ultrasound scan was unremarkable. Other potential causes of fever of unknown origin included infections, particularly by HIV and HCV in the setting of concomitant myopathy, and systemic immune diseases given the history of Raynaud's disease and the possible overlap between myositis and rheumatic/connective tissue diseases. However, acute reactant proteins, blood and urine cultures, and test for viral, bacterial, and fungal infections (HCV, HBV, HIV, measles, mumps, herpes viruses, CMV, coxsackie, adenovirus, echovirus, enterovirus, rubella, parvovirus, borrelia salmonella, leptospira, toxoplasma, legionella, borrelia, brucella, pneumococcus, tuberculosis, aspergillus) were negative as well as

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Table 1 Laboratory data

Variable	Reference range	On presentation
Hemoglobin (g/dl)	13.5–18.0	14.6
Hematocrit (%)	40.0–52.0	42.8
White blood count (/mm^3)	4000–10,000	9540
Platelet count (/mm^3)	140,000–450,000	365,000
Sodium (mmol/l)	135–145	141
Potassium (mmol/l)	3.5–5.0	3.6
Urea nitrogen (mg/dl)	4.7–23.4	11.7
Serum creatinine (mg/dl)	0.60–1.30	0.73
Calcium (mmol/l)	1.12–1.32	1.14
Serum glucose (mg/dl)	70–109	94
Total protein (g/dl)		5.7
Albumin (g/dl)	3.6–5.2	4.0
Triglycerides (mg/dl)	50–175	144
Total cholesterol (mg/dl)	< 200	178
Total bilirubin (mg/dl)	0.2–1.0	0.6
Alanine aminotransferase (U/l)	8–45	618
Aspartate aminotransferase (U/l)	8–40	553
γ-Glutamyl transferase T (U/l)	10–50	28
Alkaline phosphatase (U/l)	53–128	52
Creatine kinase (U/l)	25–190	19,112
Lactate dehydrogenase (U/l)	250–450	4291
Prothrombin-time INR	0.85–1.25	1.02
Activated partial prothrombin time (s)	28.0–42.0	31.6
Fibrinogen (mg/dl)	200–400	533
Procalcitonin (ng/ml)	< 0.5	0.09
C-reactive protein (mg/l)	< 5	19.7
Thyroid-stimulating hormone (μU/ml)	0.270–4.200	1.970

an autoimmune screening (rheumatoid factor, antibodies to cyclic citrullinated peptides, C3, C4), except for a weakly positive ANA screening (1:320).

Dr. Cavallo Perin, Rolla (Internists) Idiopathic inflammatory myopathy (IIM) was a likely diagnosis as alternative explanations, such as traumas, medications, alcohol or substance abuse were excluded based on the patient medical history and laboratory tests did not reveal electrolytes abnormalities, endocrinopathy, or viral infection (Table 1).

There are four major categories of idiopathic inflammatory myopathies (IIM): dermatomyositis (DM), polymyositis (PM), inclusion body myositis (IBM), and immune-mediated necrotizing myopathy (IMNM) [1]. DM was unlikely because of the absence of its distinctive dermal findings (heliotrope rash, shawl sign, Grotton papules) and because DM has a predominant upper limb involvement (deltoids) and a more modest rise in CK levels. PM/DM patients with positive anti-synthetase antibodies often show subnormal muscular strength and Raynaud's phenomenon.

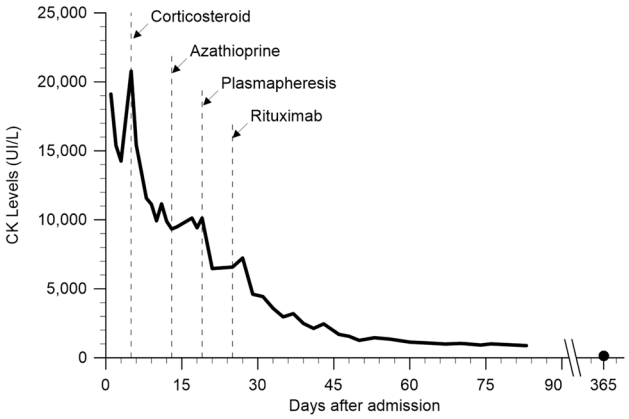

Fig. 1 Decline in creatine kinase levels from admission to 5 months after hospital discharge. The vertical arrows show the beginning of every treatment

However, the lack of mechanic hands and rheumatologic abnormalities, such as arthralgia and arthritis, made less likely this hypothesis. IBM typically affects older patients, displays finger flexor weakness and it has a more indolent onset than that observed in this patient. In our patient, the marked increased in CK values (over 100-fold) with rapidly progressing weakness of proximal muscles in the absence of skin and joints involvement was suggestive of IMNM, but differential diagnosis cannot be performed on clinical grounds alone. In addition, the hypothesis of an autoimmune rheumatic/connective tissue disease associated with myositis could not be excluded given the mild ANA positivity. However, testing for a number of myositis-associated autoantibodies (Ro, La, Sm, U1-RNP, Scl-70, PM-Scl, centromere, histone, ribosomal P, ds-DNA) was negative.

Dr. Mongini, V. Ponzalino and Bortolani (Neurologists) To establish a diagnosis, a muscle biopsy of the right quadriceps was performed. As shown in Fig. 1, histology showed a pattern of necrotizing muscle fibers with a scarce macrophage infiltrate. This supported the diagnosis of IMNM as patients with IMNM have little inflammation on muscle biopsy at variance with patients with DM, PM, and IBM, displaying inflammation either in perivascular or endomysial locations. IMNM can be classified in three distinct subtypes based upon positivity for specific autoantibodies [anti-signal recognition particle (SRP), anti-3-hydroxy-3-methylglutaryl-coenzyme-A reductase (HMGCR), autoantibody-negative IMNM]. Testing for HMGCR and other myositis-specific autoantibodies (Jo1, PL12, PL7, EJ, HMGCR, SAE1, SAE2, Mi2a-b, MDA5, TIF1 γ, NXP2) was negative. However, there was a high anti-SRP antibody title, confirming the diagnosis of anti-SRP-positive IMNM. Based on these findings, we suggested to our colleagues screening for extramuscular organ involvement (heart and lung) and first-line therapy with corticosteroids.

Dr. Papa, Bernardi, Gargiulo (Internists) In our patient both electrocardiogram and echocardiogram were normal. Respiratory function tests revealed a moderate restrictive impairment; however, diffusion capacity of the lungs for carbon monoxide was normal after correction for alveolar volume (DLCO/VA). Moreover, there was no interstitial lung disease (ILD) by high-resolution computed tomography (HRCT) scanning of the lung, suggesting a modest respiratory muscles involvement only. The patient was treated with prednisone (1 mg/kg). Fever responded to treatment, but myopathy showed only minimal improvement and CK levels declined modestly (11,157 UI/l). The steroid-sparing immunosuppressant azathioprine was thus added to therapy. After 10 days of treatment, clinical conditions worsened with progression of limb muscle weakness: the patient became bedridden and unable to lift limbs and to maintain a sitting position. Moreover, he developed incipient dysphagia and dysphonia and videofluorography confirmed oropharyngeal dysfunction.

Dr. Rolla and Mongini (Internist and Neurologist) Given the poor response to therapy and the rapid worsening of clinical conditions, we proposed to our colleagues to promptly move to second-line treatment. Both plasma exchange and administration of immunoglobulin by intravenous infusion (IVIG) are potential effective treatments in non-responders. Plasma exchange (three times in a week) was chosen in this patient because of his progressive and life-threatening symptoms. Moreover, we suggested an early switch from azathioprine to rituximab (375 mg/m^2—once a week per 4 doses and a full dose the following month).

Dr. Bernardi, Papa, Cavallo Perin (Internists). Second-line treatment resulted in a rapid and marked clinical improvement with progressive recovery of muscle strength, dysphonia and dysphagia, and CK level reduction, allowing tapering of the corticosteroid dose. Two months after the first cycle of rituximab the patient was discharged from the hospital, and he initiated physical therapy for functional rehabilitation.

Dr. Mongini and Bortolani (Neurologists) The patient attended periodic follow-up visits in our Outpatient Neuromuscular Clinic and both CK levels and CD19-positive B lymphocyte counts were periodically monitored. Five months after discharge, the patient was asymptomatic and able to return to work, neurological examination was normal, and CK levels in the normal range. Today, after three years of follow-up, the patient is asymptomatic on a low maintenance prednisone dose (10 mg OD), CK values are normal, and anti-SRP antibodies undetectable (Fig. 2).

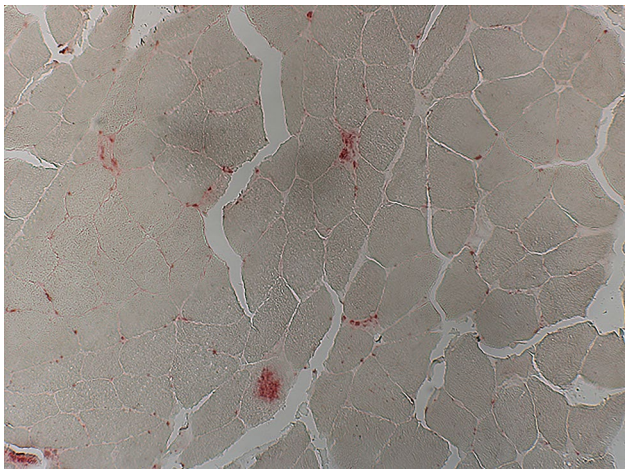

Fig. 2 A representative cross section of a muscle biopsy sample is shown. Scattered necrotic muscle fibers were visualized with an acid phosphatase reaction (red) (×10 magnification)

Discussion

Our patient had anti-SRP positive IMNM, which is a rare, but increasingly recognized clinical condition. The incidence of IIM ranges from 2.2 to 7.7 per million and IMNM accounts for ~ 20% of IIM cases [2]. Clinical features include acute or subacute severe proximal muscle weakness, significantly elevated CK levels, and prominent muscle fiber necrosis and regeneration with little or no inflammation [3]. No trigger/risk factor, such as cancer, statin use, and connective tissue diseases, was identified in our patient, though we cannot exclude the possibility that the influenza-like syndrome reported by the patient was pathogenically linked to IMNM onset. IMNM is classified in three distinct subtypes: anti-SRP positive, anti-HMGCR positive, and autoantibody-negative IMNM [4]. Patients with anti-SRP IMNM tend to be younger than those with anti-HMGCR myopathy (~40 vs. ~55 years of age) [5]. Moreover, anti-SRP myopathy often affects both proximal and distal limb muscles and the muscle damage is more severe. Cases of interstitial lung disease (ILD) have also been reported and it is thus recommended to perform pulmonary function tests, including maximum inspiratory and expiratory pressure, DLCO, and HRCT scans to distinguish reduced lung volumes due to respiratory muscle weakness from ILD [6].

Early diagnosis and treatment of IMNM can lead to significant clinical improvement; while, untreated or insufficiently treated IMNM can cause severe morbidity and mortality. In our patient, diagnosis was based on muscle biopsy results and further confirmed by the presence of serum anti-SRP antibodies. This was in line with guidelines valid at the time of patient admission in 2015. Since then the importance of autoantibodies in the diagnosis of IMNM has been increasing recognized and, according to the new European Neuromuscular Centre Criteria (ENCC), the triad of elevated CK levels, muscle weakness, and anti-SRP antibodies is now sufficient to diagnose anti-SRP IMNM and muscle biopsy is no longer required

[4]. This switch from histological to serological criteria has been favored by increasing awareness that muscle biopsy findings are less specific for IMNM than previously thought. Indeed, predominant necrosis can be found in other types of myositis and muscle inflammation has been shown in anti-SRP antibody positive patients who were clinically indistinguishable from IMNM patients [6]. Moreover, a recent unsupervised hierarchical cluster analysis of a cohort of 260 patients revealed that myositis specific autoantibodies, including anti-SRP antibodies, but not muscle biopsy findings, were crucial for classification into IIM subgroups [7].

Clinicians should be aware that nowadays serological screening for anti-SRP and anti-HMGCR antibodies is mandatory in patients with subacute (onset within a few weeks), severe proximal symmetric muscle weakness, dysphagia, and high CK level with limited extra-muscular autoimmune manifestations and absence of alternative diagnoses. Although the muscle biopsy can be avoided, if results of anti-SRP testing cannot be readily available, a muscle biopsy may still be useful to confirm an autoimmune etiology and to exclude other diagnoses. Moreover, a biopsy is required to diagnose antibody-negative IMNM. Another clinical scenario that should prompt anti-HMGCR antibody testing is when muscle symptoms and high CK levels are observed in statin-treated patients, who fail to show clear improvement after statin withdrawal [8–11].

Recent data suggest that anti-SRP antibodies may also play a role in the pathogenesis of the muscle injury [12–14]. Consistent with this, anti-SRP antibody titer correlates with IMNM activity and IMNM responds to therapies that are effective in antibody-mediated autoimmune diseases. The classification in anti-SRP positive, anti-HMGCR positive, and autoantibody-negative IMNM has also a prognostic value. Patients with HMGCR antibodies, which may also be present in subjects never exposed to statins, seem to have a milder clinical course, while those with anti-SRP myopathy show more severe muscle involvement. Furthermore, the risk of associated cancer varies according to the IMNM subtype. Specifically, autoantibody-negative IMNM has been associated with a markedly increased risk of malignancy, while anti-HMGCR myopathy shows a weak association and anti-SRP myopathy no association with cancer. Therefore, a screening for occult cancer with chest and abdomen CT, as well as age- and gender-appropriate cancer screening is only required in patients with autoantibody-negative IMNM/anti-HMGCR myopathy [15].

Skeletal muscle magnetic resonance imaging (MRI) was not performed in our patient, but is today included in the IIM diagnostic work-up. MRI can be used to select areas of active myositis for muscle biopsy and it is considered a promising tool for severity grading, differential diagnosis, and assessment of response to treatment [16, 17].

Treatment regimens for IMNMs were not evaluated prospectively and available data derive from case reports or small series of patients [18]. Nonetheless, most experts believe that patients with IMNM require both early and intense therapy to avoid long-term disability, particularly when the disease is severe and/or rapidly progressive [6]. Corticosteroids and steroid-sparing immunosuppressants, such as azathioprine or methotrexate, are standard first-line treatment. Our patient did not respond to this conventional therapy and this is in agreement with previous reports, showing that anti-SRP IMNM is often resistant to conventional treatment, particularly in young patients, regardless of the immunosuppressive agent used. On the contrary, a positive outcome was observed using plasma exchange and rituximab. Both plasma exchange and administration of IVIG have been associated with strength improvement and favorable outcome in IMNM [19]. Rituximab effectiveness in anti-SRP myopathy is increasingly recognized and according to current guidelines the drug should always be added within 6 months if other strategies are failing. There is also preliminary evidence that earlier treatment with rituximab may result in better outcome, though available data are very limited [4]. The complete and sustained remission obtained in our patient supports the argument that rituximab should not be delayed in patients with severe disease, rapid progression, not fully responding to conventional therapy. Further studies are required to establish whether rituximab should be considered a drug of first choice in anti-SRP IMNM [20].

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Author contributions SB, GG and SB wrote the manuscript, GP, CG, TM, VP, GR and PCP revised the manuscript. All the authors were directly involved in caring for the patient.

Compliance with ethical standards

Conflict of interest All author declare that they have no conflict of interest.

Statement of human and animal rights Any of the authors performed studies with human or animal participants regarding this article.

Informed consent We already required patient's informed consent prior to submission of this case report.

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