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Case Report

A case of anti-HMGCR myopathy in a patient with breast cancer and anti-Th/To antibodies

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Abstract

Statins competitively inhibit the activity of HMGCR (3-hydroxy-3-methylglutaryl coenzyme A reductase), which is a key enzyme in cholesterol synthesis. These are effective drugs for the management of cardiovascular disease and are generally well tolerated but several side effects have been reported. Muscular adverse symptoms are various and, rarely, statin exposure may lead to authentic immune-mediated necrotizing myopathy (IMNM), namely anti-HMGCR myopathy. However, cases of IMNM associated with cancer have been described. We discuss herein a case of IMNM in a patient with breast cancer previously exposed to statins and with the presence of anti-Th/To antibodies without clinical correlation.

INTRODUCTION

Immune-mediated necrotizing myopathy (IMNM) is a rare and severe condition and makes part of the idiopathic inflammatory myopathies (IIM) spectrum as well as dermatomyositis, polymyositis and inclusion body myositis [1]. It is defined by the association of proximal bilateral and symmetrical muscle weakness, hyperCKemia and specific histopathological findings such as necrosis and regeneration of muscle fibers with a preponderance of macrophage cells [1].

The European Neuromuscular Center recently developed classification criteria for IMNM distinguishing three sub-types: anti-3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) myopathy, anti-SRP myopathy and antibody-negative myopathy [2]. Anti-HMGCR myopathy was first described in patients with statin exposure who developed persisting myopathy despite drug withdrawal and required immunosuppressive treatment [3]. The physiopathology is still unknown but has a genetic basis. Treatment based on expert consensus involves discontinuation of statins and use of immunosuppressive agents but the functional prognosis remains poor. We report a case of anti-HMGCR myopathy in a patient with medical history of breast cancer previously exposed to statins. During diagnosis work-up, we detected the presence of seric anti-HMGCR but also anti-Th/To antibodies without any feature of systemic sclerosis (SSc) despite their high specificity. History of breast cancer had also to be considered in the work-up given the existence of genuine paraneoplastic myositis, but this potential link was not retained.

CASE REPORT

A 71-year-old woman presented to the rheumatology department with a month's history of symmetric proximal muscle weakness of the lower limbs leading to difficulties in climbing stairs and getting up from a low sitting position. At the interrogatory, the patient did not describe any other systemic complaint. She had no prior history of trauma. The patient had medical history of hypercholesterolemia previously treated with atorvastatin (gradually increased up to 40 mg within 1 year) for 5 years and discontinued by the end of 2017 (Fig. 1). She is also currently in remission from a stage T4N0M0 ductal breast cancer (Scarff-Bloom-Richardson III), diagnosed by the end of 2014 and treated by surgery, chemotherapy (Epirubicin, Cyclophosphamide and Paclitaxel), immunotherapy (Trastuzumab) and radiotherapy. Physical examination demonstrated a symmetric reduction of strength in both upper legs (scored at 4 on 5) along with a slight amyotrophy of the left one. Gowers's sign was positive. Neuromuscular examination did not reveal fasciculation or reflexes abnormality. Skin and chest examinations were unremarkable. Blood laboratory exams revealed an elevated serum creatine kinase (CK) up to 40 times the normal range along with hepatic cytolysis (GOT GPT), dyslipidemia (LDL and triglycerides) and elevated level of lactate dehydrogenase. There was no biological inflammatory syndrome. Renal function was normal. Screening of anti-nuclear factors was positive with a nucleolar pattern and further work-up demonstrated anti-Th/To antibodies (directed against the Th/To complex) at high-titer. Myositis-specific antibody panel and

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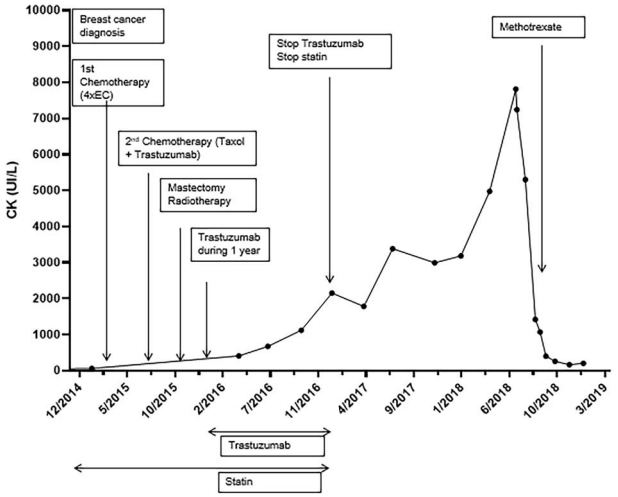

Figure 1. CK kinetics in relation to treatment.

specific antibodies for autoimmune hepato-biliary diseases were negative. Microbiological investigations including blood serologic viral assays for HIV, HCV, HBV and EBV were negative. Electroneuromyography (ENMG) highlighted myotonic and pseudo-myotonic discharges at rest in several muscles (right psoas and left vastus medialis and lateralis) without myogenic activity. Right quadriceps femoris muscle biopsy was therefore carried out and indicative of myopathic process suggested by the presence of necrotic cells along with degeneration and regeneration of muscle fibers without inflammation or endomysial fibrosis (Fig. 2). MRI was not performed because the patient was claustrophobic. The diagnosis remained unclear at this time, and proposed etiologies were paraneoplastic, autoimmune disease or adverse reaction to treatment. Despite the presence of anti-Th/To antibodies, which were present in further controls, the patient did not show any clinical features of SSc. Kinetics analysis of the hyperCKemia appeared to coincide with the initiation of Trastuzumab (Fig. 1). Given that myositis in a cancer patient is highly suggestive of paraneoplastic syndrome, a PET scan was performed and showed diffuse hypermetabolic captation of striated skeletal muscle consistent with myositis (Fig. 3). There was no argument in favor of a recurrence of neoplasia, making the diagnosis of paraneoplastic myositis thus unlikely. According to biological, radiological and histological findings along with the previous history of statin exposure, anti-HMGR antibody was sought and specific semi-quantitative assay for the search of anti-HMGCR antibodies returned positive. Diagnosis of anti-HMGCR myopathy was therefore suggested and treatment with corticoids, methotrexate and intensive physiotherapy has been initiated. After a few weeks, the patient reported a favorable clinical course and markedly improved muscle strength with physical and functional improvement. Concomitantly, the biology showed a clear decrease in CK reaching normal values. After over 4 years of follow-up, the patient is in prolonged remission and has also not experienced a cancer recurrence.

DISCUSSION

Statins are one of the most prescribed drugs in the world and generally well tolerated. Most adverse effects are linked to direct drug toxicity. Approximately 20% of patients undergo statin muscle-related adverse effects [4] but the development of necrotizing myopathy remains unfrequent.

Anti-HMGCR myopathy was first described in patients with statin exposure who developed persisting myopathy despite drug withdrawal and required immunosuppressive treatment [3].

This myopathy generally affects adults previously exposed to statin use although it has been also described in statin-naive patients. The proportion of statin-exposed patients developing anti-HMGCR myopathy differs between ethnic groups. For example, the Chinese population appears to be less exposed to statins compared with western cohorts [5]. A richer diet in alternative sources of statins (oyster mushroom, red yeast rice, ...) could be an explanation for this phenomenon leading to anti-HMGCR myopathy in susceptible patients [6]. Anti-HMCGR myopathy involves specific antibodies that also target HMGCR allowing consideration of the statin usage in the physiopathology of the disease and highlighting this immuno-mediated nature [7]. Cause of this myopathy is currently unknown but immunogenetic background may be part of the pathogenesis. The presence of HLADRB1*11:01 has been identified in the majority of patients and strongly predisposes to the development of anti-HMGCR myopathy in adults [1]. Patients present typically subacute symmetric proximal weakness and significant increase in CK levels. Dysphagia and muscle involvement are less described than in anti-SRP myopathy [1]. Patients with long disease duration and significant muscle atrophy can present lower CK levels over time and in this case, distinction from Limb-Girdle Muscular Dystrophy (LGMD) may thus be tricky [1]. We do not retain this diagnosis in our patient. Extra-muscular manifestations are infrequent but skin, cardiac and lung involvement were also described [1, 8]. In cases of myositis, possibility of an infectious cause should be discussed. In our patient, given the prolonged duration of symptoms, a notable and sustained elevation of CK levels (up to 40 times the normal range), prior exposure to statins, presence of anti-HGMCR antibodies and histological findings, the diagnosis of IIM, specifically anti-HMGCR myopathy, was logically retained. It is important to note that although infectious myositis should be considered in case of acute myositis with symptoms related to infection, an alternative cause, typically immune-related, should be investigated when muscular symptoms and signs persist despite the resolution of the infection. Furthermore, we identified in our patient seric anti-Th/To antibodies that are specific to limited cutaneous systemic sclerosis (lcSSc) and may be detected in 2–5% of lcSSc [9]. Those antibodies are directed against nucleolar antigens (as anti-U3 RNP, anti-PM/Scl) and show nucleolar staining in indirect immunofluorescence, as detected in our case. Anti-Th/To antibodies are particularly associated with the development of myositis, interstitial lung disease and pulmonary hypertension [10]. Further investigation identified a second antibody (anti-HMGCR) more consistent with the current symptoms. Even though the patient carried anti-Th/To antibodies, there were no clinical features of lcSSc. Although presence of the latter antibody has been reported in other autoimmune diseases [11], SSc auto-antibodies (such as anti-Th/To) are remarkably monospecific, and their existence probably precedes the onset of SSc symptoms by several months to years [12]. The presence of SSc specific antibodies is one of the earliest observable features of the disease [13], with 95% of SSc patients carrying those at initial presentation. As stated above, cases of myositis linked to anti-Th/To are described but this association is not usual [14]. We did not find any large series of such cases in the literature. Conversely, authentic co-occurrence of anti-HMCGR with other rheumatic diseases has been reported. Nevertheless, given the high specificity of these antibodies, diagnosis of IMNM based on presence of anti-HMGCR is almost always made if the clinical

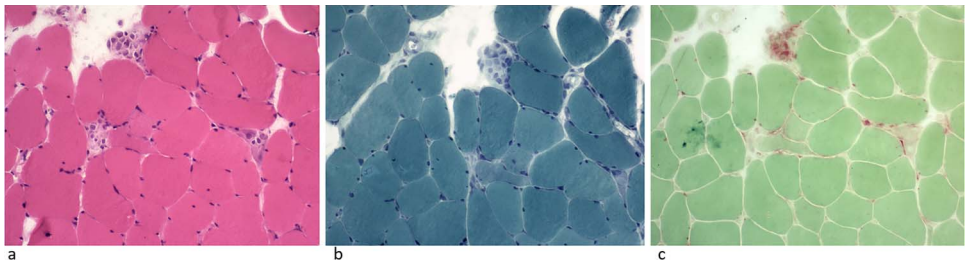

Figure 2. Right quadriceps femoris muscle histology. Frozen sections of the quadriceps muscle biopsy. In addition to moderate variation in fiber size, necrotic fibers are seen and highlighted with acid phosphatase stain. Those fibers are surrounded by macrophages. No lymphocytic infiltrate was observed. (**a**) Harris HE stain (×200); (**b**) Modified Gomori trichrome stain (×200); (**c**) Acid phosphatase stain (×200).

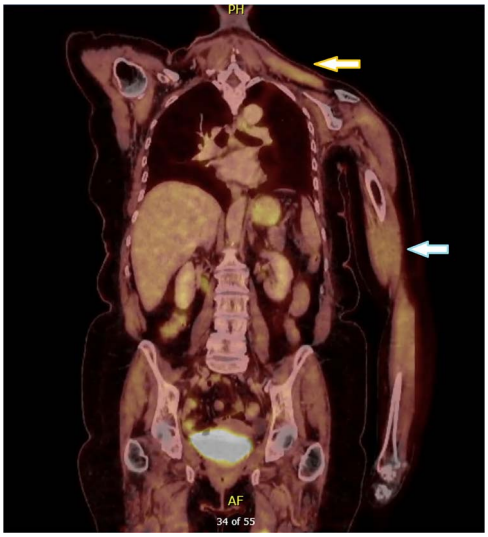

Figure 3. Coronal view of PET-CT. Coronal view of PET-CT showing diffuse muscular hypermetabolism of the striated skeletal musculature, in particular in the trapezius and left upper limb.

context refers to. Their presence is a clue in patients with muscle weakness, hyperCKemia or necrotizing myopathy pattern on histology [2]. Consequently, presence of anti-Th/To antibodies appears to be a hazard conjunction and imposes therefore a close follow-up even if the patient does not currently show any stigma of SSc. Several studies focused on the relationship between cancer and IMNM. Allenbach *et al.* reported in their observational study that malignancy occurs more frequently in HMGCR myopathy and seronegative IMNM compared with anti-SRP patients without predominance of specific cancer [15] but this observation was not obtained in other studies [16, 17]. The relationship between cancer and IMNM and their subtypes is still unclear, and further studies are needed to precise this potential link. Our patient had a history of cancer in remission, and there was no clinical or PET-CT evidence of recurrence. One study was able to demonstrate that the use of PET scan may be just as sensitive to detect cancer in polymyositis and dermatopolymyositis patients compared with the combination of all of the other tests but further studies are required to determine if this is the case in IMNM [18]. Given the chronology of the events, association with IMNM and the use of Trastuzumab had to be ruled out but there seems to be no data in the literature linking a potential non-specific immunosuppressive effect of Trastuzumab with the development of IMNM. Although the presence of hyperCKemia associated with muscle weakness is sufficient to establish the diagnosis of IMNM in patients with anti-HMGCR or anti-SRP antibodies [2], other assessments may help to make the diagnosis. ENMG can be useful in the diagnosis of IMNM by confirming the presence of a myopathic pattern and also helps to exclude other differential diagnoses of muscle weakness [19]. MRI can also provide valuable diagnostic help as it can show extension and severity of the disease [19] but shows lower diagnostic performance in IMNM than in other types of IIM such as dermatomyositis [20]. This examination could not be performed because our patient is claustrophobic. We performed a biopsy of the right quadriceps femoris showing myopathic process suggested by the presence of necrotic cells along with degeneration and regeneration of muscular fibers features without inflammation or endomysial fibrosis. According to the literature, the histological features generally found in IMNM include necrosis and regeneration of muscle fibers sometimes associated with slight macrophagic inflammatory infiltrate without endomysial lymphocytic infiltration [1]. Muscle biopsy is sometimes not required to make the diagnosis but remains useful in case of suspected IIM or in antibody-negative IMNM [2, 19]. In case of anti-HMGCR myopathy in patients with previous exposition to statin, the first treatment step is to discontinue the latter [1]. Clinical improvement may be therefore noticed but most patients will require immunosuppressive therapy. Since no randomized blinded controlled trials have been published, the choice of treatment is based on expert consensus and observational studies and involves corticosteroids in combination with a corticosteroid-sparing agent proposed as methotrexate [2]. Steroid-free induction strategies are effective in anti-HMGCR myopathy when managed before muscle weakness occurs [1]. An important proportion of treated IMNM patients will present persistent muscle weakness; IMNM represents the group of IIM with the poorest prognosis [21].

CONCLUSIONS

Anti-HMGCR myopathy is a rare but severe complication of statin exposure in genetically predisposed patients. The presence of both muscle weakness and hyperCKemia should raise suspicion of myositis, and a thorough evaluation of medical history (such as statin exposure) should be conducted. Diagnosis is based on a combination of clinical, biological and/or histological findings, and treatment is defined by statin discontinuation and immunosuppressive therapy with a better prognosis in case of early management. Co-occurrence of other inflammatory rheumatism with anti-HMGCR myopathy appears to be more of a hazard conjunction than a real association. Moreover, the link between anti-HMGCR myopathy and cancer remains unclear to this day, and further studies are required to target this potential association.

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AUTHOR CONTRIBUTIONS

Mohammad Yassine Chérif: Conceptualization, data curation, formal Analysis.

Sophie Lecomte: Obtaining and commenting on histological sections.

Marjolaine Weynand, Ioannis Raftakis, Elena Dragan, Carole Nagant, Sophie Lecomte, Valérie Badot: data curation

All the data provided in the system corresponds to the data in your manuscript file.

Patient's written consent was obtained before drafting the report.The data that support the findings of this study are available from the corresponding author, M.Y. Chérif, upon request.

CONFLICTS OF INTEREST STATEMENT

None declared.

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