Case Reports in Gastroenterology

Case Rep Gastroenterol 2016;10:525–530

DOI: 10.1159/000448882
Published online: October 6, 2016

Single Case

Paraneoplastic Necrotizing Autoimmune Myopathy in a Patient Undergoing Laparoscopic Pancreatoduodenectomy for Distal Cholangiocarcinoma

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Keywords
Paraneoplastic necrotizing autoimmune myopathy · Cholangiocarcinoma · Laparoscopic pancreatoduodenectomy

Abstract
A 73-year-old male presented with jaundice and severe muscle weakness. He was diagnosed with distal cholangiocarcinoma and paraneoplastic necrotizing autoimmune myopathy (NAM). Treatment of NAM consisted of dexamethasone pulse therapy, prednisone, and single-dose intravenous immunoglobulin. The distal cholangiocarcinoma was resected through a total laparoscopic pancreatoduodenectomy. After hospital discharge, muscle strength initially increased postoperatively; however, pneumonia resulted in the deterioration of his general condition and death 5 months after the diagnosis of paraneoplastic NAM.

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DOI: 10.1159/000448882

Introduction

Dermatomyositis and polymyositis are idiopathic inflammatory myopathies (IIMs), which can be associated with malignancy. Since 2003, necrotizing autoimmune myopathy (NAM) is recognized as part of the IIMs. This subtype can be associated with connective tissue disorders, viral infections, medications (in particular statins) [1, 2], and malignancy. The latter, however, has been reported in much lower numbers of around 50 cases worldwide [1, 3–8]. Types of cancer associated with NAM are among others: gastrointestinal tumors, small cell lung cancer, breast cancer, and prostatic adenocarcinoma [3]. Usually, NAM presents with subacute progressive symmetrical weakness of the proximal muscles [2, 5]. Because the number of cases is limited, types of predominantly associated malignancies are uncertain, and pathogenesis is mostly unknown [8]. On that account, it is important to report cases of paraneoplastic NAM to learn if this subtype, like polymyositis and dermatomyositis, is associated with a distinct group of cancer types. To our knowledge, this is the first report of paraneoplastic NAM associated with cholangiocarcinoma.

Case Report

A 73-year-old male presented to a community hospital with jaundice, which was caused by a 2-cm mass in the pancreas with obstruction of the common bile duct and pancreatic duct without signs of metastases. An endoprosthesis was placed endoscopically in the bile duct, and brush cytology was obtained, which revealed adenocarcinoma. A few weeks after initial presentation, the patient developed severe progressive muscle weakness of his legs and, to a lesser extent, of his arms, without pain, loss of sensation, or skin abnormalities. Within a few weeks, he was confined to a wheelchair and not able to stand or walk. The patient was referred to our tertiary center. His medical history revealed diabetes mellitus type 2 and a spontaneous subdural hematoma that was surgically drained. Family history revealed breast and colon carcinoma in both parents.

Investigations

Laboratory investigation revealed a creatinine kinase level of 12,570 U/l (reference range <170 U/l), aspartate aminotransferase 594 U/l (reference range <35 U/l), alanine aminotransferase 523 U/l (reference range <45 U/l), lactate dehydrogenase 648 U/l (reference range <250 U/l), and C-reactive protein 11 mg/l (reference range <5 mg/l). Magnetic resonance imaging showed diffuse edema in upper as well as in lower leg muscles, suggestive of an inflammatory process. Muscle biopsy revealed numerous necrotic fibers infiltrated by macrophages and only a few lymphocytes compatible with NAM. Furthermore, regenerating fibers were seen along with membrane attack complex (complement C5b9) positive fibers and a single major histocompatibility complex class I (MHV-I) positive non-necrotic muscle fiber (fig. 1) [8]. Skin histology revealed no abnormalities.

Differential Diagnosis

Acquired subacute proximal muscle weakness with a highly elevated serum creatine kinase activity should raise high suspicion on an inflammatory myopathy [5]. Furthermore, toxic or drug-induced myopathies should be considered. The latter could be excluded on the basis of the clinical history. Because of the absence of skin abnormalities, dermatomyositis could be excluded. Magnetic resonance imaging was suggestive of an inflammatory process,

and muscle biopsy confirmed the diagnosis of NAM. Cooccurrence of NAM with cholangiocarcinoma strongly suggests a paraneoplastic cause.

Treatment

Medical treatment of the NAM started preoperatively at the time of diagnosis and consisted of high-dose dexamethasone therapy, 40 mg per day during 4 days every 4 weeks, prednisone 20 mg per day in the intervening days, and a single dose of intravenous immunoglobulin of 2 g/kg body weight divided over 2 days. Treatment of the underlying cancer is also important to decrease symptoms [3]. A total laparoscopic pancreatoduodenectomy (Whipple procedure) was performed. Pathologic examination revealed a R0 resected pT3N0M0 distal cholangiocarcinoma (UICC, 7th edition, 2009) originating from the common bile duct. No adjuvant chemotherapy was given because of the muscle weakness and poor performance status. Improvement in NAM symptoms has been reported during cancer remission, and recurrence of symptoms accompanied with relapse of cancer has also been described [9–11]. In almost every reported case, treatment consisted of corticosteroids; in some cases, supplementary medication was started when symptoms were not improving, and, in other cases, prednisone was supplemented from the beginning of medical treatment [3–6]. Dexamethasone pulse therapy has proven to generate the same effect as high-dose prednisone by Vlekkert et al. [12] but causes fewer side effects. Intravenous immunoglobulin seems to be efficient in some cases reported by Sampson et al. [5] and Bronner et al. [6]. In one case, symptoms did not improve on high-dose prednisone treatment alone; however, muscle strength increased with addition of intravenous immunoglobulin [5, 6]. In a single case report, the chemotherapeutic agent cetuximab was associated with improvement of myopathic symptoms while malignancy was progressive [11]. Treatment with azathioprine has also been reported, resulting in moderate improvement of symptoms [5]. Despite the promising results from these treatments, response to treatment in NAM remains diverse, ranging from complete response to fast progressive disease [3, 5, 6, 11]. If treatment is (partially) successful, the time that has elapsed between the initiation of treatment and rehabilitation until being able to walk varies from weeks to months [4, 11].

Outcome and Follow-Up

The patient was discharged from the hospital to a rehabilitation center 10 days after laparoscopic pancreatoduodenectomy. Surgery was complicated by a pancreatic fistula, which was treated with a percutaneous drain that could be removed 4 weeks postoperatively. Muscular strength slowly increased postoperatively, and the patient was able to walk a few steps 4 weeks after the operation. Pneumonia, presenting 6 weeks after surgery, which was initially treated by antibiotics in the outpatient clinic, deteriorated his general condition confining him to a wheelchair again. After 6 more weeks, he was admitted for a week to the intensive care unit suffering from pneumosepsis. Despite maximized supportive care including enteral tube feeding at the surgical ward and later at the rehabilitation center, no signs of recovery were seen in the next few weeks. Therefore, the patient and his family advised to discontinue all medical treatment leading to his death 4 months after the operation and 5 months after the diagnosis of NAM.

Discussion

In this case report, we present the first cholangiocarcinoma-associated NAM. Our patient showed fast progression of muscle weakness preoperatively. After laparoscopic pancreatoduodenectomy and medical treatment consisting of dexamethasone pulse therapy, daily prednisone, and intravenous immunoglobulin, muscle strength increased slowly in the first weeks. However, during the following months, his condition declined until he died 4 months after surgery.

Gastrointestinal cancers have been reported in association with NAM including one case of gallbladder cancer [3]. Spielmann et al. [7] reported a case of NAM in a patient with pancreatic carcinoma; however, this myopathy was caused by gemcitabine treatment with muscle symptoms presenting 6 months after pancreatoduodenectomy and vanished completely after gemcitabine discontinuation without additional medical treatment. Heffner et al. [13] reported a case with malignancy-related muscle necrosis in a patient with pancreatic cancer. In this case, however, the muscle necrosis, only involving the right gastrocnemius muscle and accompanied by thrombotic material in arterioles, had an embolic origin instead of an immune-mediated mechanism (gemcitabine was considered to be the causative agent). Because reported cases of paraneoplastic NAM are scarce, little is known about the pathogenesis. Cellular immunity has been suggested as the cause for paraneoplastic polymyositis and dermatomyositis by the presence of MHC-I; however, in NAM, MHC-I is not or only slightly expressed on non-necrotic muscle fibers, like in our patient, where MHC-I expression was found on only few non-necrotic muscle fibers (fig. 1), suggesting more of a humoral mechanism than cellular. MHC-I expression on necrotic muscle fibers can be explained by a non-specific response to tissue injury [5]. In nonparaneoplastic NAM, multiple antibodies (Ab), such as SSA Ab, Jo-1 Ab, PL-12 Ab, and PL-7 Ab, are associated with connective tissue disease, and HMG-CoA with statin-caused NAM [14, 15]. In paraneoplastic NAM, it is, like with other IIMs, very likely that the immune process is driven by autoantibodies. However, they have not been proven yet. Future research should confirm this process.

Medical treatment is mostly based on more frequently arising IIMs. Prednisone treatment is the first choice on an empiric basis [16]. Second-line treatment consists of azathioprine (although there is inadequate evidence to be recommended by a Cochrane review), intravenous immunoglobulin (possibly effective based on a class II study), and cyclosporine (limited in usage because of the cost and potential side effects) [17]. Especially, an understanding of the pathogenesis has to be increased to make the treatment more specific and treatment outcomes more consistent. In the case of muscle weakness in a patient with malignancy, NAM, but also IIMs in general, should be considered. Treatment of the cancer as well as the myopathy should be started early to limit the intensity and duration of symptoms, decreasing dependency on others, and increasing quality of life.

Statement of Ethics

The authors state that the patient's family has given consent for this publication.

Disclosure Statement

There are no conflicts of interest.

References

1 Liang C, Needham M: Necrotizing autoimmune myopathy. Curr Opin Rhematol 2011;23:612–619.
2 Van der Meulen MF, Bronner IM, Hoogendijk JE, Burger H, van Venrooij WJ, Voskuyl AE, Dinant HJ, Linssen WH, Wokke JH, de Visser M: Polymyositis: an overdiagnosed entity. Neurology 2003;61:316–321.
3 Levin MI, Mozaffar T, Al-Lozi MT, Pestronk A: Paraneoplastic necrotizing myopathy: clinical and pathological features. Neurology 1998;50:764–767.
4 Wegener S, Bremer J, Komminoth P, Jung HH, Weller M: Paraneoplastic necrotizing myopathy with a mild inflammatory component: a case report and review of the literature. Case Rep Oncol 2010;3:88–92.
5 Bronner IM, Hoogendijk JE, Wintzen AR, van der Meulen MF, Linssen WH, Wokke JH, de Visser M: Necrotising myopathy, an unusual presentation of a steroid-responsive myopathy. J Neurol 2003;250:480–485.
6 Sampson JB, Smith SM, Smith AG, Singleton JR, Chin S, Pestronk A, Flanigan KM: Paraneoplastic myopathy: response to intravenous immunoglobulin. Neuromuscul Disord 2007;17:404–408.
7 Spielmann L, Messer L, Moreau P, Etienne E, Meyer C, Sibilia J, Gottenberg JE, Geny B, Lannes B, Meyer A: Gemcitabine-induced myopathy. Semin Arthritis Rheum 2014;43:784–791.
8 Stenzel W, Goebel HH, Aronica E: Review: immune-mediated necrotizing myopathies, a heterogeneous group of diseases with specific myopathological features. Neuropathol Appl Neurobiol 2012;38:632–646.
9 Silvestre J, Santos L, Batalha V, Del Rio A, Lima C, Carvalho A, Martins A, Miranda H, Cabral F, Felix A, Aleixo A: Paraneoplastic necrotizing myopathy in a woman with breast cancer: a case report. J Med Case Rep 2009;3:95.
10 Vu HJ, Pham D, Makary R, Nguyen T, Shuja S: Paraneoplastic necrotizing myopathy presenting as severe muscle weakness in a patient with small-cell lung cancer: successful response to chemoradiation therapy. Clin Adv Hematol Oncol 2011;9:557–560.
11 Galani E, Bonakis A, Christodoulou C, Klouvas G, Drougou A, Skarlos D: Can cetuximab affect paraneoplastic myopathy? J Neurooncol 2009;93:437–438.
12 Van de Vlekkert J, Hoogendijk JE, de Haan RJ, Algra A, van der Tweel I, van der Pol WL, Uijtendaal EV, de Visser M: Oral dexamethasone pulse therapy versus daily prednisolone in sub-acute onset myositis, a randomised clinical trial. Neuromuscul Disord 2010;20:382–389.
13 Heffner RR: Myopathy of embolic origin in patients with carcinoma. Neurology 1971;21:840–846.
14 Kao AH, Lacomis D, Lucas M, Fertig N, Oddis CV: Anti-signal recognition particle autoantibody in patients with and patients without idiopathic inflammatory myopathy. Arthritis Rheum 2004;50:209–215.
15 Christopher-Stine L, Casciola-Rosen LA, Hong G, Chung T, Corse AM, Mammen AL: A novel autoantibody recognizing 200- and 100-kd proteins is associated with an immune-mediated necrotizing myopathy. Arthritis Rheum 2010;62:2757–2766.
16 Dalakas MC, Hohlfeld R: Polymyositis and dermatomyositis. Lancet 2003;362:971–982.
17 Van der Kooi AJ, de Visser M: Idiopathic inflammatory myopathies. Handb Clin Neurol 2014;119:495–512.

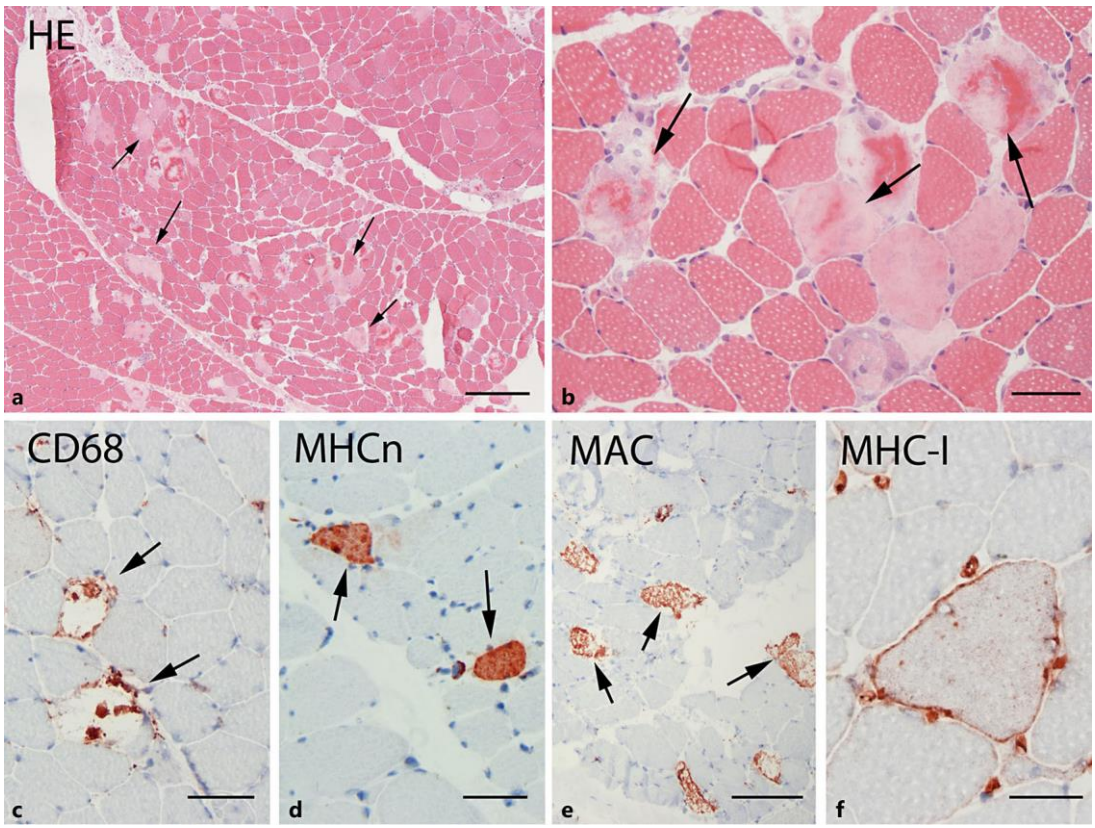

Fig. 1. Muscle biopsy. **a**, **b** Many necrotic fibers (arrows) are shown. HE. **c** Macrophages in necrotic muscle fibers (arrows). **d** Positivity in regenerating fibers (arrows). MHCn = Myosin heavy chain neonatal. **e** Fibers positive for membrane attack complex (MAC, complement C5b9; arrows). **f** Sarcolemmal upregulation of MHC-I in one non-necrotic fiber. Scale bars: 300 μm (**a**), 80 μm (**b–d**), 160 μm (**e**), and 40 μm (**f**).