

# Paraneoplastic Necrotizing Myopathy with a Mild Inflammatory Component: A Case Report and Review of the Literature

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## Key Words

Necrotizing myopathy · Inflammatory myopathy · Paraneoplastic syndromes

## Abstract

Inflammatory myopathies such as dermatomyositis and polymyositis are well-recognized paraneoplastic syndromes. Little is known, however, about necrotizing myopathies in association with cancer. We here describe a case of paraneoplastic necrotizing myopathy with a mild inflammatory infiltrate in a patient with adenocarcinoma. After the rapid development of a severe, disabling muscle weakness, the patient experienced near complete recovery within 4 months under oral prednisone treatment. In the context of the presented case, we will review current knowledge about paraneoplastic necrotizing myopathies.

## Introduction

In contrast to inflammatory myopathies, paraneoplastic necrotizing myopathy is a very rare clinical entity [1]. Symptoms can mimic polymyositis or dermatomyositis with symmetrical, predominantly proximal muscle weakness of acute or subacute onset [1, 2]. Necrotizing myopathy has been associated with gastrointestinal tumors, small cell lung cancer, and breast cancer, among others [3]. Here we report a case of paraneoplastic necrotizing myopathy with a mild inflammatory component and near complete recovery.

## Case Description

A 75-year-old woman developed muscle weakness first affecting the proximal muscles of her legs, then of her arms. During the initial workup, elevated liver enzymes were noticed, and an abdominal CT scan revealed a peripancreatic tumor mass.

Whipple resection disclosed a 7-cm, well-demarcated encapsulated peripancreatic carcinoma in lymphatic tissue most probably representing a lymph node metastasis of a solid adenocarcinoma ([fig. 1](#)). Resection borders as well as 17 regional lymph nodes were free of tumor. The tumor tissue exhibited cytokeratin immunoreactivity (CK7, CK5/6, CK19 but not CK20) and a weak positivity for WT1. All other immunohistochemical markers (trypsin, beta-HCG, inhibin, p63, cdx-2, TTF1, melan A, estrogenreceptor, BerEP4, HepPar1 and synaptophysin) were negative. Based on the conventional histology and immunohistochemical results, no clear diagnosis concerning a possible primary tumor could be made. Intraoperatively, no other abnormalities were noted.

Within 8 weeks, the patient was wheelchair-bound. The respiratory muscles were also affected. The forced expiratory volume declined to 1.5 l. The profound proximal symmetrical tetraparesis with areflexia was not associated with sensory symptoms or pain. The integument was intact; in particular, no rash was noted. Electromyography of proximal muscles exhibited sustained spontaneous activity, consistent with myopathy.

The search for a primary tumor including fluorodeoxyglucose positron emission tomography, MRI of brain and spinal cord, CT of chest, gastroscopy, colonoscopy, gynecological and urological exam, thyroid gland ultrasound and liver biopsy was negative. Pathological laboratory results on admission to our department included creatine kinase (CK) 6,794 U/l (<67), lactic acid dehydrogenase (LDH) 3,460 U/l (normal range: 240–420), aspartate aminotransferase (AST) 626 U/l (10–35), alanine aminotransferase (ALT) 905 U/l (10–35), and gamma-glutamyl transferase (GGT) 71 U/l (35–104). Levels of tumor markers CA125, CA15-3, CA19-9, CA72-4 and carcinoembryonic antigen were unremarkable. Cerebrospinal fluid analysis was normal. Immunological parameters, including anti-signal recognition particle antibodies and anti-CNS antibodies (anti-Yo, -Ri, -Hu, -amphiphysin, -CV2, -Ta/Ma2, -Ma, -recoverin) were negative, as were serological tests for hepatitis and HIV.

A biopsy of the quadriceps vastus lateralis muscle showed extensive muscle fibre necrosis, regenerating fibres and only mild endomysial lymphocytic infiltrates, mainly localized close to necrotic muscle fibres. Lymphocytes did not invade intact muscle fibres. Membrane attack complex (C5b-9), which is typically present on endomysial capillaries in dermatomyositis, was detected on necrotic fibres but not on endomysial capillaries. In addition to the endomysial expression of major histocompatibility complex class I (MHC-I), in this biopsy, it was present in necrotic and regenerating, but only on a subset of intact mature muscle fibres ([fig. 2](#)). An extensive mainly acute necrotizing myopathy with mild inflammatory infiltrates was diagnosed. In the clinical context, a paraneoplastic origin was assumed.

A brief course of methylprednisolone at 1 g/d for 3 days was administered and the patient was referred to neurorehabilitation where oral prednisone (1 mg/kg body weight) was continued, in addition to physiotherapy. She recovered substantially, being able to walk without assistance 4 months later. A year later, the clinical condition was stable and most laboratory abnormalities (LDH 562 U/l, AST 66 U/l, ALT 64 U/l, CK 248 U/l) had resolved, except GGT (204 U/l).

## Discussion

In patients with cancer, symptoms not directly evoked by the tumor spread are usually referred to as paraneoplastic. Such syndromes may even precede the identification of the tumor. Classical paraneoplastic syndromes affecting the muscle are inflammatory myopathies, such as dermatomyositis, which has been shown to be associated with malignancy in 15% of cases [4]. First described by Smith in 1969, myopathies with little or no inflammatory infiltrate but extensive muscle fibre necrosis have also been associated with malignancies [5]. There are, however, no systematic studies assessing the overall risk of cancer in patients with this condition. In 1 case series, 3 out of 8 patients had cancer preceding the myopathy or following it within 3 years of diagnosis [6].

Histopathological findings in paraneoplastic necrotizing myopathies have been reported to be heterogeneous, with a picture ranging from sparse, segmental necrotic lesions to massive necrosis [5, 7]. In 4 cases with paraneoplastic necrotizing myopathy described by Levin et al., an average of 50% of muscle fibres were necrotic (8–100%), while only 2 of 16 cases with inflammatory paraneoplastic myopathy had a fraction of necrotic fibres higher than 3% [1]. The pathognomonic hallmark of a necrotizing myopathy in contrast to an inflammatory one, however, are sparse inflammatory cells confined to damaged, necrotic muscle fibres, while normal-appearing fibres are spared. Furthermore, MHC-I, which is physiologically expressed on endomysial capillaries, is also detected on necrotic muscle fibres. It is typically upregulated on almost every muscle fibre in polymyositis. In a series of 8 cases with necrotizing myopathy, T-lymphocytes and macrophages were found in the vicinity of necrotic fibres, while B lymphocytes were absent in most cases [6]. MHC-I immunoreactivity was detected on 10% of nonnecrotic muscle fibres in 6 out of the 8 cases. The pattern of necrosis in muscle specimens was not uniform between and within subjects and judged as focal in 4, scattered in 5, and diffuse in 3 cases.

In the case presented here, about 10% of muscle fibres were necrotic. Macrophages and T-lymphocytes were detected in the endomysium of the affected muscle biopsy, mainly localized close to necrotic muscle fibres. Although the number of lymphocytic cells was rather large (see fig. 2), the extent of necrosis and immunohistochemistry characteristics (MHC-I expression) strongly argued against polymyositis.

Neurological paraneoplastic syndromes seem to be triggered by the response to ‘onconeural antigens’ that are expressed only in the tumor cell and in the nervous system, thereby inducing an immune response to both tumor and antigen-expressing neural structures. Knowledge about mechanisms causing paraneoplastic syndromes affecting the muscle is scant. In inflammatory paraneoplastic myopathies, T cell-mediated immune responses as well as humoral factors seem to be involved [3]. The small number of inflammatory cells in muscle specimens of patients with necrotizing myopathy raises the possibility of a toxic molecule mediating the syndrome, but the response to steroids or immunoglobulins is more compatible with an immune-mediated process [6]. The mechanism of a putative therapeutic response to the epidermal growth factor receptor antibody, cetuximab, remains obscure [2, 8].

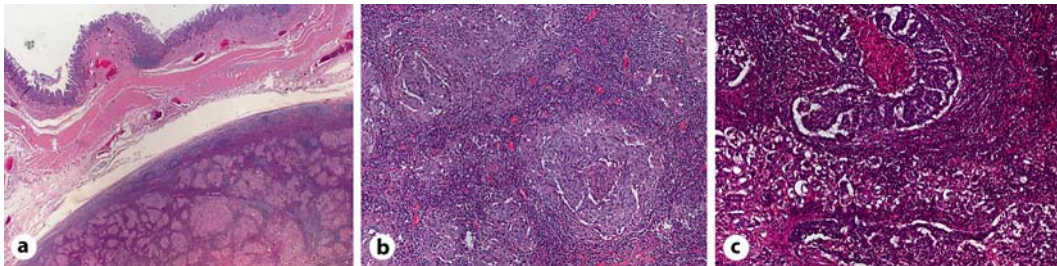
One striking feature of paraneoplastic necrotizing myopathy is the wide range of reported outcomes, from fast progression with no remission to complete recovery [1, 2, 6, 8]. The severity of the condition does not always parallel tumor progression [2]. However, since the pathophysiology of the disease is still poorly understood, treatment of the underlying cancer seems to be the mainstay of therapy. In our case, where the underlying malignancy was not unambiguously identified, complete recovery was spontaneous or occurred with oral prednisone treatment only. Additional treatment with steroids (i.v. and/or orally), intravenous immunoglobulins, or other immune modulators may be of benefit to some patients.

Clearly, more studies on the pathophysiology and treatment of paraneoplastic necrotizing myopathy are warranted, as the condition is severe and outcome differs dramatically among patients, which complicates treatment decisions. Muscle pathology findings in this case support the view that paraneoplastic inflammatory and necrotizing myopathies might resemble a continuum of a condition caused by similar pathogenetic mechanisms, but manifested with varying degrees of necrosis and inflammation, rather than 2 separate entities.

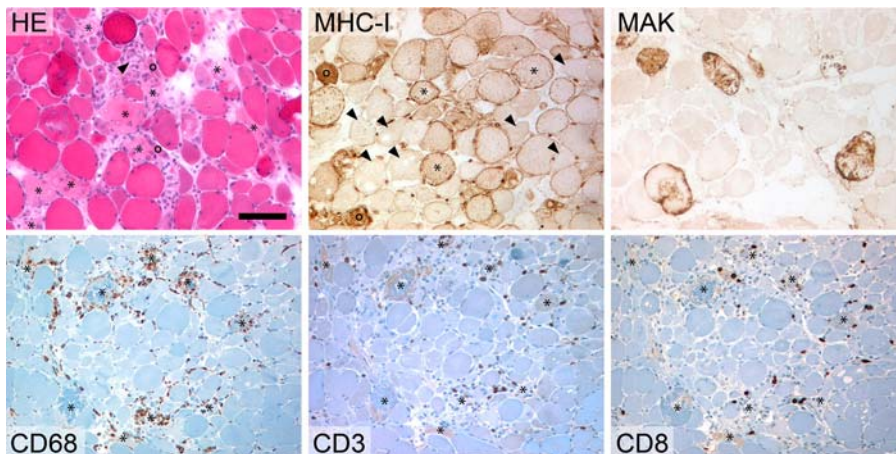
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**Fig. 1.** Whipple resection specimen with a 7-cm encapsulated peripancreatic tumor. **a** Overview of the tumor tissue (lower right corner) which is well demarcated and embedded in lymphatic tissue (probably lymph node). **b** Closer view of the tumor tissue with central necrosis and solid tumor growth. **c** In higher magnification some areas exhibit diffuse tumor growth and occasional papillary projections.



**Fig. 2.** A biopsy of the m. vastus lateralis showed an extensive acute necrotizing myopathy with mild inflammatory infiltrates. HE: On the haematoxylin and eosin staining (HE), numerous necrotic muscle fibres were seen (black asterisks) beside basophilic regenerating fibres (examples are marked by black circles). Some necrotic fibres were undergoing myophagocytosis (black arrowhead). MHC-I: MHC-I was detected in an even distribution on necrotic fibres (black circles) and on the sarcolemma of some muscle fibres (black asterisks). Many fibres, however, lacked expression of MHC-I. MAK: Membrane attack complex was deposited in necrotic fibres (brown staining) but was not detectable on endomysial capillaries. In immunohistochemistry on the consecutive sections, numerous CD68 positive macrophages were present in the endomysium, mainly in the vicinity of and within necrotic fibres (black asterisks). Considerably fewer CD3-positive T lymphocytes, mainly CD8-positive ones, were present in the endomysium, mainly in the vicinity of necrotic fibres (black asterisks). They did not invade intact muscle fibres. Scale bar: 100 µm.



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