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Pipestem capillaries in necrotizing myopathy revisited

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Abstract

Pipestem-capillaries in necrotizing myopathy, have been reported as a feature of a distinct type of myopathy. Here, we analyze four muscle biopsy specimens from patients exhibiting endomysial fibrosis associated with pipestem capillaries using histological and electronmicroscopic techniques. However, only one case displayed all of the originally described features, including necrotic fibres, capillary thickening and lack of a significant lymphocytic inflammation, while one case exhibited striking capillary pathology with minimal necrosis and absence of inflammation, and the other two cases were accompanied by additional pathological features. These data support the existence of a microangiopathy with pipestem capillaries as a characteristic and distinct histopathological pattern, and indicate that it occurs in the context of a variety of muscular disorders broader than initially suspected. Furthermore, we show that the pipestem-capillary associated decrease in fibre size is at least in part a result of hypoxic changes.

Keywords: Myopathy; Pipestem capillaries; Microangiopathy; Hypoxic damage

1. Introduction

Necrotizing myopathy with "pipestem" capillaries has been described as a myopathy distinct from dermatomyositis, polymyositis or unspecific/necrotizing inflammatory myopathies in six patients so far [1–4]. In these cases, pathology was characterised by a marked thickening of capillaries with deposition of the C5b9 membrane attack complex (MAC), associated with muscle fibre necrosis. Ultrastructurally, capillaries showed thickening of the walls consisting of amorphous material different from amyloid, and lacking undulating tubules [1,2]. Strikingly, these extensive pathologic changes were not accompanied by inflammatory infiltrates. In all patients reported so far, these changes were associated with extramuscular pathology, including malignant disease, vasculitis as well as fibrosing alveolitis [1,2]. One recently reported case featured capillary thickening with MAC-deposition in a peripheral nerve sample also, however, the latter sample also featured vasculitic changes, which were absent in the muscle [3]. A recent report describes seven cases of non-necrotizing autoimmune myopathies with pipestem-type capillaries, MAC deposition was not a consistent finding and all seven cases did not develop any symptoms of systemic disease [5].

Here, we describe four cases of myopathy with pipestem capillaries and MAC deposition clearly distinct from the above cited inflammatory myopathies. In line with the previous reports mentioned above [1–4], all patients exhibited accompanying diseases. However, in two cases, biopsies additionally showed conspicuous inflammation. Pipestem pathology was furthermore associated with increased fibre size variation and clusters of atrophic fibres, and with smaller muscle fibres showing an increased expression of

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HIF-1α, indicating an etiopathogenetic link to hypoxia. Based on the pathological features observed, we propose a sequence of events, probably driving disease development and progression.

2. Materials and methods

Muscle specimens were obtained by open biopsy. Enzyme histochemistry and immunohistochemistry of frozen sections were performed as described before [6]. Ultrastructural studies using glutaraldehyde-fixed tissue were performed according to standard protocols. For immunohistochemistry, 7 μm thick cryostat sections were prepared for demonstration of CD3, CD8, CD20, CD45/leucocyte common antigen (LCA), utrophin, laminin α2, collagen VI, CD68, histocompatibility complex (MHC)-class I, MHC-class II, HIF-1α, VEGF-R, IgM, IgG and IgA. For immunohistochemistry we used the *i*view-Ventana ABC kit (Ventana, Tucson, Arizona, USA) with appropriate biotinylated secondary antibodies and DAB-visualisation of the peroxidase reaction product on a Benchmark XT immunostainer (Ventana). For anti-IgG, -IgM and -IgA as well as anti-HIF-1α stainings, control muscle tissue without apparent pathological changes was employed as indicated.

3. Results

3.1. Case 1

A 40-year-old woman developed myalgia, accompanied by elevated creatine kinase (CK) levels exceeding 4000 U/l (normal <180 U/l). She had been treated in an intensive care unit due to pulmonary hypertension of unknown origin shortly before. CK decreased after steroids were administered, but the patient developed skin necrosis of her acra prompting a muscle biopsy to exclude vasculitis.

Muscle biopsy showed marked pathology, comparable to published cases of necrotizing myopathy with "pipestem" capillaries with increased fibre size variation, and small groups of atrophic fibres, (Fig. 1A). The most striking feature was thickened capillaries, displaying a pipestem-like morphology on transverse sections (Fig. 1A, B). Paucicellular infiltration but no frank vasculitis of vessels was observed. Additionally, scattered necrotic fibres were noted as well as, to a lesser extent, basophilic regenerating fibres. The capillary pathology could be highlighted by using antibodies against laminin α5 (Fig. 1C, in comparison with a control biopsy). Ultrastructurally, capillaries showed deposition of an amorphous, non-fibrillary material corresponding to changes in "pipestem"-pathology described before [1–4]. The majority of "pipestem"-capillaries showed marked deposition of MAC, however, in some areas no deposits were seen despite marked thickening of the vessel walls (Fig. 1D). There was only a slight increase in transsarcolemmal MHC class I expression without any focal or perimysial increase (Fig 1E). As described previously, also in this case, only few scattered lymphocytes were observed (CD45-staining, Fig. 1F).

3.2. Case 2

An 82-year-old woman was diagnosed with panarteriitis nodosa with predominant axonal manifestation of her polyneuropathy, associated with respiratory dysfunction. Additionally, she exhibited weight loss and elevated blood pressure. Axonal sensorimotor polyneuropathy of unknown origin was diagnosed clinically and confirmed electrophysiologically, with nerve biopsy revealing vasculitic changes, confirming the diagnosis. She additionally underwent muscle biopsy to evaluate a potential involvement of her skeletal muscles.

The biopsy showed a variegated picture, with some areas displaying marked atrophy of muscle fibres with surrounding inflammatory infiltrates (Fig. 2A, left side). Adjacent areas stained with laminin α5 antibodies (Fig. 2C) revealed thickened capillaries in both, inflamed and non-inflamed areas. MAC-deposition was noted in the capillary walls (Fig. 2D), and MHC class I molecules were up-regulated in areas displaying inflammation as well as in non-inflamed areas (Fig. 2E). Furthermore, CD68-positive macrophages were detected around necrotic fibres within the inflamed areas (Fig. 2F). Lymphocytic infiltrates (CD45-staining, Fig. 2G) additionally consisted of CD8-positive cytotoxic T-cells (CD8-staining, data not shown). CD20-positive B-cells were not observed in significant numbers (data not shown). In contrast to nerve biopsy, vasculitis was not a feature of this muscle biopsy. Ultrastructurally all capillaries displayed "pipestem morphology" with diffuse, homogenous thickening of basal lamina (Fig. 3A–C). In contrast to basal lamina changes described in the context of diabetes [7], no differences in density regarding the innermost and outermost portion of basal lamina were noted. About 20% of capillaries displayed extensive thickening of basal lamina (Fig. 3B), while in a small subset, additional corpuscular elements such as mitochondria could be discerned (Fig. 3C). No fibrillary elements suggestive of amyloid were found.

3.3. Case 3

A 50-year-old woman suffered from acute pancreatitis. Additionally, erythema nodosum of both legs was noted. ANA titers were slightly elevated (1:80). During the course of therapy with steroids, an indurated area was noted within the left gastrocnemius muscle, and this area was biopsied.

Histologically, the muscle tissue displayed marked fibrosis with an increase in fibre size variation with a sparse inflammatory infiltrate (Fig. 4A). Already recognisable in HE-stains and, in particular, after staining with antibodies against laminin α5, capillaries featured "pipestem" morphology (Fig. 4A–C), which was confirmed by ultrastruc-