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Myopathy in Post-Radiation Cervico-Scapular Syndrome

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Introduction

Post-radiation myelopathy and brachial plexopathy have been well established in the literature.[1,3-5] In recent years there have been several reports of myopathy in association with radiation therapy (RT) for Hodgkin's disease. Cervical paraspinal and shoulder girdle muscles are within the radiation portal for Hodgkin's disease, and most patients with radiation-induced myopathy exhibit weakness and atrophy of these muscles, sparing distal muscles and cranial nerves. Onset of these symptoms typically occurs from two to thirty years after radiation.[3,10]

We present a patient with unusual features both on clinical exam and pathologic studies. Muscle biopsies revealed nemaline rod myopathy along with inflammatory changes, as well as the presence of myofiber necrosis suggestive of necrotizing myopathy in and outside the radiation portal, suggesting that perhaps not only muscles that are directly radiated are damaged.

Case Report

A 47-year old right-handed man presented for evaluation of neck and shoulder weakness two years after receiving chemotherapy and radiation therapy for Hodgkin's lymphoma, stage IA. Radiation was given to bilateral neck muscles, supraclavicular fossa and left preauricular area. The dose of radiation was 3060 cGy in 17 fractions. He reported loss of muscle bulk of the neck as well as the shoulders that began 18 months prior to consultation. He also complained of restriction of movement most likely as a result of weakness. In addition to weakness, the patient described pain and stiffness in the above areas that did not respond to over-the-counter non-steroidal anti-inflammatory drugs (NSAIDS). He denied any weakness in the lower extremities. He denied sensory complaints. There were no complaints of dysphagia, diplopia, dyspnea or chewing difficulties.

Initial clinical examination revealed reduced strength of neck flexors to 3/5 but intact neck extensors. Weakness of sternocleidomastoid, trapezius, supraspinatus and infraspinatus muscles was also noted. There was evidence of atrophy of bilateral trapezius, supraspinatus and infraspinatus muscles. No fasciculations were seen. The rest of the muscles had

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Table 1

NERVE CONDUCTIONS

Stimulate	(Record)	AMPLITUDE (milli/micro) volts			VELOCITY meters/sec.			DISTAL LATENCY milliseconds			F-WAVE LATENCY milliseconds	
		right	left	normal	right	left	normal	right	left	normal	right	left
Median, motor	(Abductor pollicis br)	5.9	-	(>4.0)	57	-	(>48)	4.2	-	(<4.5)	27.7	-
Median, sensory	(Index)	20	-	(>15)	62	-	(>56)	3.5	-	(<3.6)		-
Ulnar, motor	(Abductor digiti mini)	10.9	-	(>6.0)	57	-	(>51)	2.7	-	(<3.6)	28.2	-
Ulnar, sensory	(Fifth)	25	-	(>10)	65	-	(>54)	2.8	-	(<3.1)		-

VOLUNTARY MOTOR UNIT POTENTIALS

MUSCLE	INSERT. ACTIVITY	SPONTANEOUS Fib.	Fasc.	MUP NORMAL	RECRUITMENT Act	Reduced	Rapid	DURATION LONG	SHORT	AMPLITUDE HIGH	LOW	PHASES %	TURNS
R. Biceps brachii	Increased	++	0				++		++		++	25%	++
	Comment: Some areas of 3+ fibrillation												
R. Deltoid	Normal	0	0						+/-				
R. First dorsal interosseous	Normal	0	0				+		+				
R. Triceps brachii	Increased	+	0				+		+/-				
R. Gluteus medius	Increased	+	0				++		++		+	25%	++
R. Tibialis anterior	Normal	0	0	Normal									
R. Vastus lateralis	Increased	+/-	0						++				+
R. Vastus medialis	Increased	+	0						+		+		
R. Cervical paraspinals	Increased	++	0						+++		+++		
	Comment: Very little muscle												

normal bulk and strength. Reflexes were 2+ throughout without pathologic reflexes. Other features of the neurological exam including mental status, the rest of the cranial nerves, reflexes and sensory exam were unremarkable.

Laboratory investigations were remarkable for elevated CPK of 400 U/L (normal 26-174 U/L) and aldolase of 26.5 U/L (normal 1.5-8.1 U/L). An MRI of the cervical spine did not reveal any spinal cord or nerve root abnormalities. Nerve-conduction studies (NCS) and electromyography (EMG) (Table 1) showed active myopathic potentials with active denervation in selected proximal muscles, as well as positive waves and fibrillations in the muscles outside the radiation port. No evidence of sensorimotor peripheral neuropathy was found, and there was no evidence of decremental response to repetitive nerve stimulation. Biopsy of the left trapezius muscle showed nemaline rods (Figure 1). Immunohistochemical analysis for dystrophin (DYS1, DYS2, DYS3), alpha-sarcoglycan, beta-sarcoglycan, delta-sarcoglycan, gamma-sarcoglycan, laminin-alpha-2 (merosin) and spectrin all showed normal patterns of staining. The stain for dysferlin showed the presence of dysferlin in the sarcolemma and increased cytoplasmic dysferlin, compatible with a myopathic pro-

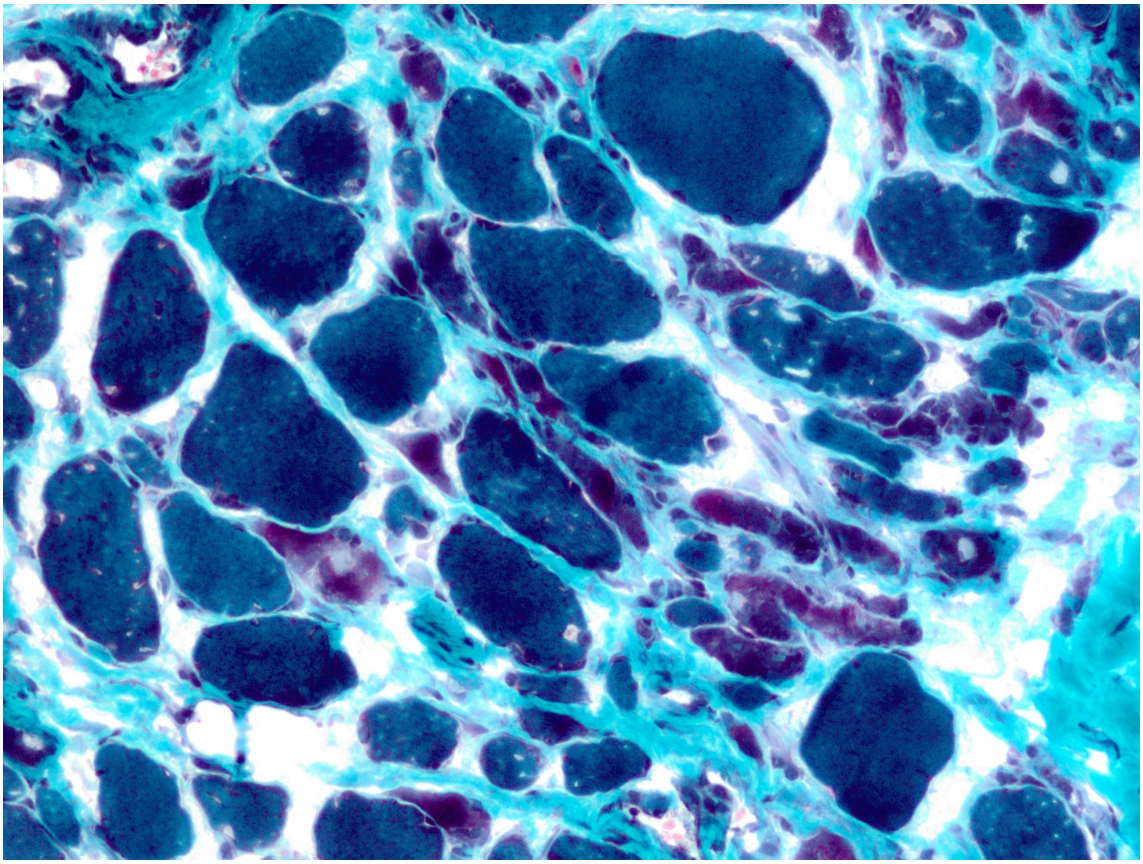

Figure 1: This section of left trapezius muscle exhibits numerous mostly angulated atrophic myofibers that are randomly distributed throughout the field. Some of the atrophic myofibers stain red; in the microscope this material has a granular appearance consistent with nemaline rods. The myofibers are separated by moderate endomysial fibrosis. Cryostat section, Gomori trichrome, original magnification 200x.

cess. There was no pathological evidence of a neurogenic process. Given the fact that electrodiagnostic studies revealed elements of both neurogenic and myopathic pathophysiology, the precise character of injury was not clear; however, we believed the active denervation seen on NCS/EMG studies to be myopathic in nature. The patient was diagnosed with a non-inflammatory myopathy with probable nemaline rods. The patient was treated with a course of intravenous immune globulin (IVIG) but without significant response.

The patient returned for follow-up 16 months after the initial biopsy, at which time his symptoms had progressed to involve bilateral biceps, deltoids and extensor neck muscles. Muscle biopsy was repeated, this time from the left biceps brachii muscle, showing chronic myopathy with myofiber necrosis and mild inflammation with some evidence of denervation.

Additional laboratory studies included limb girdle myotonic dystrophies, all of which were negative; acetylcholine receptor binding antibody, CRMP-5-IgG (collapsin response-

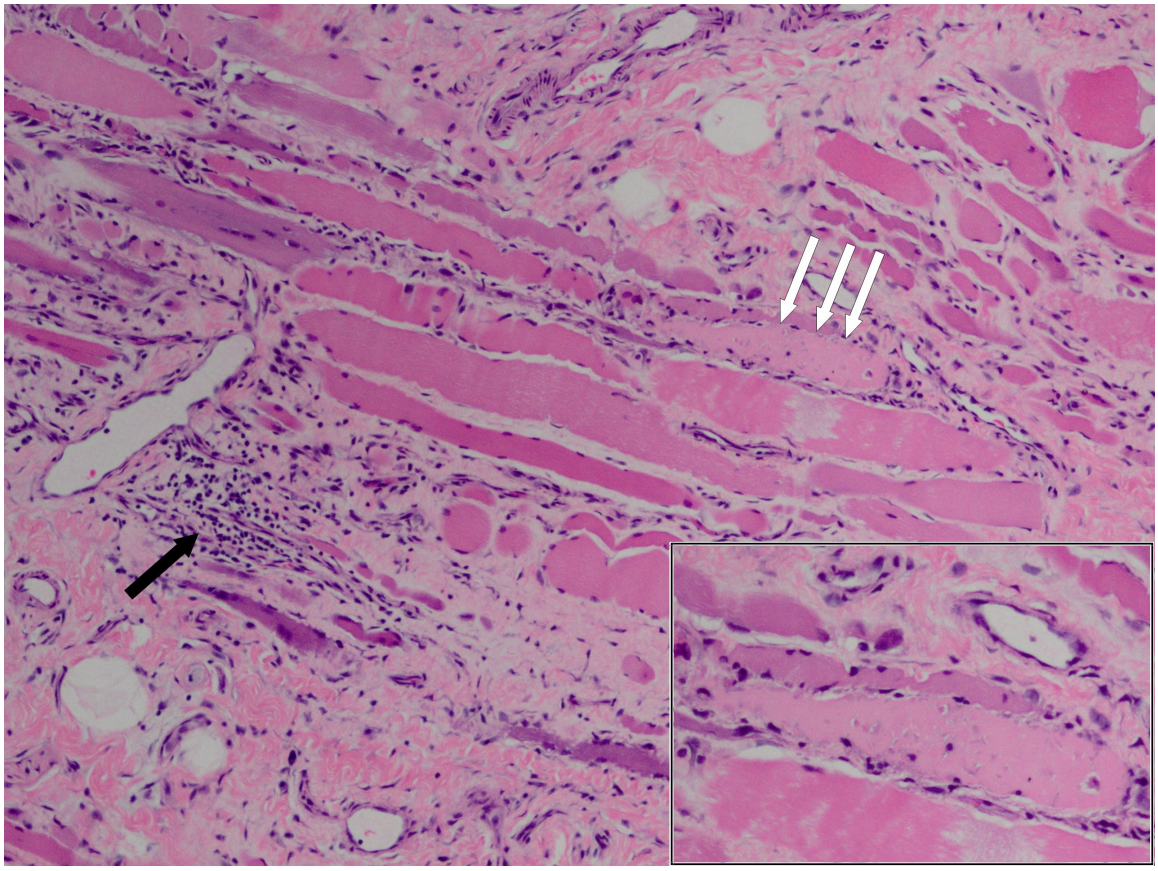

Figure 2: This low power view of a paraffin section of the left biceps brachii muscle demonstrates moderately severe myofiber atrophy and loss of muscle mass with replacement by fibrous connective tissue. A necrotic myofiber, identified by the three white arrows, is seen at higher power in the inset in the lower right quadrant of the image. A few regenerating myofibers, characterized by the relatively blue color of their sarcoplasm, are present in this field. The area indicated by the black arrow contains a mild lymphocytic inflammatory infiltrate. Hematoxylin and eosin, original magnification 100x.

mediator protein) western blot, striated muscle antibody, N-type calcium channel antibody, P/Q type calcium channel antibody, GAD 65 (glutamic acid decarboxylase) antibody, and neuronal voltage-gated potassium channel antibody were all negative. ANA cascade antigens were negative. Lactic acid and pyruvic acid were negative. Repeat CPK was 3486 U/L. Myeloperoxidase antibody, proteinase antibody, thyroid stimulating hormone, serum protein electrophoresis and immunofixation, ACE (angiotensin converting enzyme) level, and rheumatoid factor were normal. HIV (Human Immunodeficiency Virus) antibody was non-reactive. PET (Positron emission tomography) scan was also done looking for malignancy but was negative.

The patient's weakness worsened in the neck extensors/flexors now to 1/5, biceps 3/5, but normal distal strength and persistent normal strength in the lower extremities. A third muscle biopsy was performed from the left triceps, which revealed acute and chronic necrotizing myopathy.

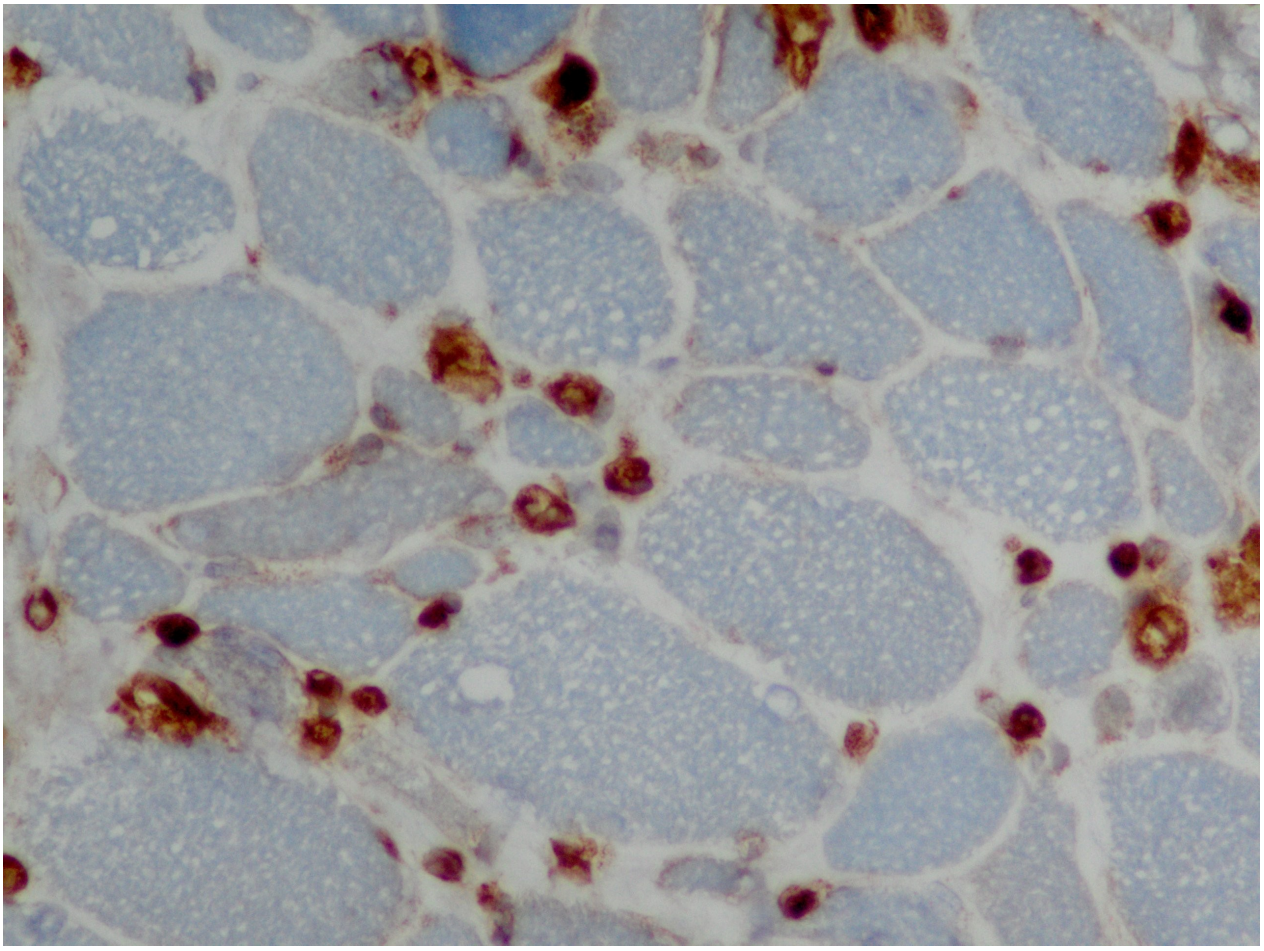

Figure 3: This immunohistochemistry preparation for Human Leukocyte Antigen Class ABC (or Major Histocompatibility Complex Class I antigen) demonstrates no expression on myofiber surfaces. This provides compelling evidence that this is not an inflammatory myopathy, but that the inflammation in this case, which is mild, is reactive to the degenerative process. The blood vessels demonstrate labeling, which is manifested as brown staining of their walls; this is a normal finding and serves as an internal positive control in contrast to the negative myofibers. The clear vacuoles in the sarcoplasm of the myofibers represent mild ice crystal artifact. Cryostat section, original magnification 400x.

The patient was started on a course of treatment that included prednisone and IVIG every 7 weeks. After his first course of IVIG there was minimal improvement in strength.

Pathology

Section from biceps brachii (Figures 2 and 3) had mild, focal, mostly lymphoid endomysial inflammation. A single mitotic figure was present. There were occasional necrotic myofibers and a small number of regenerating fibers randomly distributed throughout the biopsy. Internal nuclei were increased in number. The myofibers did not contain inclusions or vacuoles. Occasional whorled fibers were noted. The biopsy was remarkable for the presence of moderately severe at-

rophy, consisting of an admixture of both rounded and angulated atrophic myofibers randomly distributed throughout the sample. The atrophic myofibers were of both types. Some of the angulated ones stained intensely with the NADH stain. The fiber-typing stains demonstrated some fibers of indeterminate type. The trichrome stain demonstrated a few fibers with excessive red staining. The PAS stain was normal and there was no evidence of abnormally stored material. The fat stain demonstrated excessive lipid content in a moderate number of myofibers. There was moderate endomysial fibrosis.

Discussion

It has been well established that radiation causes relatively little or no direct damage to mature muscle fibers.[2] Thus, the mechanism of damage to mature muscle fibers undergoing radiation is likely multifactorial and not only from direct radiation damage itself.[8] Several reports[1,3] describe patients with myopathy within radiated muscles following mantle radiation for Hodgkin's lymphoma. However, myopathy in muscles outside of the radiation portal is rarely reported in the literature. We suspect that there is a common pathogenesis in muscles both within and outside the treatment portal.

The most typical histopathological changes due to post-radiation myopathy are nemaline rods. However, prior case reports have also shown other changes that were seen on biopsies, such as variation in muscle fiber size, disorganized architecture, nuclear variations and infiltration by adipocytes. This heterogeneity of pathological features seen in Hodgkin's lymphoma patients could represent different stages of the disease or different pathogenic processes. Findings of active denervation on NCS/EMG studies suggest that either neurogenic or myopathic processes may be involved, or perhaps even both. However, in our case report the NCS/EMG findings together with the histopathologic findings (particularly of necrosis and reactive inflammation) point to an aggressive necrotizing myopathy. Additionally, it has been hypothesized that radiation induces vascular changes and results in increase of collagen content and proliferation of fibrous tissue in vessels, eventually leading to denervation of muscle cells.[7] The patient presented here had three muscle biopsies, with the first one revealing findings of nemaline rods, but the next two showing evidence of necrotic fibers, indicating progressive damage to the radiated and non-radiated muscles, the character of which is not entirely clear. To our knowledge, necrotic fibers have not been reported in prior cases of radiation induced myopathy, even several years after completion of RT, again implicating a progressive nature of the cervico-scapular syndrome that our patient seems to have.

There are several possibilities to explain our patient's myopathy: radiation-induced myopathy; inflammatory myopathy, possibly paraneoplastic given the history of Hodgkin's lymphoma; or late-onset nemaline rod myopathy. It is not clear if nemaline rod myopathy may arise as a radiation therapy-related disorder as Portlock et al. have suggested[1] or if nemaline rods are in fact not a specific finding for a single type of myopathy.

Portlock et al.[1] described the synchronous impact of chemotherapy and irradiation. However, there has also been a case of nemaline rod myopathy reported by Zamecnik[9] after radiation treatment without chemotherapy for laryngeal squamous cell carcinoma. Interestingly, Kimura et al.[6] reported nemaline bodies in muscle after chemotherapy treatment alone of pharyngeal cancer. Kimura suggested that an alteration of myotu-

Table 2

Conditions that present with "dropped head syndrome"
Isolated neck extensor myopathy
Post-radiation therapy myopathy
Nemaline myopathy
Inflammatory myopathies: polymyositis, dermatomyositis, inclusion body myositis
Mysthenia gravis
Amyotrophic lateral sclerosis
Chronic inflammatory demyelinating polyneuropathy
Carnitine deficiency
Facioscapulohumeral dystrophy
Congenital myopathy
Myotonic dystrophy
Hyperparathyroidism

bules and small nerves by infiltrating neoplastic cells may cause a reactive inflammatory process. Alternatively, malignancy-associated myopathy could be paraneoplastic, that is, without any relation to any kind of therapy.[9] Although our work-up did not reveal any evidence of paraneoplastic syndrome, we cannot exclude this possibility entirely. Isolated neck extensor myopathy may also be considered in someone receiving radiation to the same areas as our patient; however, since the weakness progressed to involve other muscles of upper extremities and since the pathology was much more aggressive than is typically found, it is not consistent with this diagnosis.

Evidence of necrotic fibers as was found on our biopsy would be suggestive of additional processes with a more aggressive course. Therefore, while the precise mechanism is not yet certain, it is imperative to be aware of myopathy as a possible complication of radiation therapy and to keep in mind that the pathophysiology of post-RT cervico-scapular syndrome is unclear. It is likely to be both neurogenic (from injury to motor fibers in nerve roots and plexus) and myopathic (from direct damage to vascular tissue in muscle) in nature, and may present with various phenotypes. Hence, if at all possible the field of radiation should be limited. This entity is a diagnosis of exclusion and one must still look for other neuromuscular etiologies of dropped head syndrome (Table 2).

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