An unexpected cause of muscle pain in diabetes

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Abstract

Diabetic muscle infarction is a rare condition which may present to a rheumatologist. It was first reported in 1965. Two illustrative cases are described here and the mechanisms of pathogenesis discussed. Analysis of the published data, results of the muscle biopsies, and a technetium-99m sestamibi scan suggest that the condition, which occurs against a background of diabetic microangiopathy, can be triggered by an ischaemic event and causes extensive muscle necrosis through hypoxia-reperfusion injury and compartment syndrome.

Diabetic muscle infarction is a rare cause of acute severe muscle pain in patients with diabetes mellitus. The differential diagnosis includes focal or systemic myositis, localised abscess, haematoma, deep venous thrombosis, osteomyelitis, and a muscle tumour (sarcoma or lymphoma). We describe two illustrative patients and discuss the investigations and possible pathogenesis of this condition.

Case 1

A 46 year old West Indian woman with a 14 year history of type II diabetes mellitus complicated by diabetic nephropathy and proliferative retinopathy presented to a local hospital with a painful swollen left leg after an insulin injection into the left femoral canal area. Deep venous thrombosis was excluded by Doppler ultrasound, and a computed tomography (CT) scan showed swelling of the left vastus medialis muscle. The erythrocyte sedimentation rate (ESR) was raised at 130 mm/1st h, antineutrophil cytoplasmic antibodies (ANCA), antinuclear antibodies (ANA), and rheumatoid factor were negative. Muscle biopsy showed chronic inflammation. She received treatment with steroids and antituberculous drugs, but did not improve. Six weeks later she was transferred to this hospital for further assessment.

Clinically she was afebrile and markedly overloaded with fluid. There was swelling and tenderness of the left vastus medialis compartment and proximal weakness of the left leg. Investigations showed no neutrophilia, creatine kinase (CK) 202 IU/l (reference range 0–170 IU/l), ESR 97 mm/1st h, and albumin 16 g/l. A renal biopsy confirmed diabetic nephropathy. She was given intravenous albumin and diuretics. Although no specific treatment for the swelling of the leg was prescribed, the symptoms gradually improved. She did, however, develop contractures in the thigh muscles requiring physiotherapy. At the time of discharge she could walk with a stick.

She presented again five months later with a one week history of painful swelling of the opposite thigh. On this occasion, there were no precipitating factors. The medial compartment of the right thigh was markedly swollen. There was no neutrophilia or CK rise. A CT scan showed generalised swelling of the anterior and medial groups of muscle and connective tissue from the pelvis distally.

The patient underwent surgical debridement of the mass. The sartorius muscle was necrotic and was excised. Swollen but viable muscles in the adductor and quadriceps compartments were noted. Histological examination showed widespread necrosis. The vessels had luminal stenosis and calcification consistent with long-standing diabetes.

In view of the worsening renal failure, peritoneal dialysis was started. She remained well for the next four years, but her condition later deteriorated and she died from a complication of peritoneal dialysis.

Case 2

A 55 year old Afro-Caribbean man with a 24 year history of type II diabetes complicated by peripheral neuropathy, proliferative retinopathy, and nephropathy requiring continuous ambulatory peritoneal dialysis (CAPD), presented to his local hospital with a tender swelling on his left upper lateral thigh. Serial blood cultures, cryoglobulins, dsDNA, and ANCA were all negative. A biopsy showed lumenal thrombosis and organisation, and infiltration by neutrophils. The arteries showed generalised swelling of the anterior and medial groups of muscle and connective tissue from the pelvis distally. The patient was given fusidic acid and clindamycin and gradually improved.

Two months later he re-presented with painful well defined swelling in the left thigh. C reactive protein (CRP) on admission was 60 mg/l (reference range 0–10 mg/l) and rose to 105 mg/l one week later. He was given intravenous flucloxacillin and ciprofloxacin for four weeks, but failed to improve and the entire mass was excised. Histological findings were...
similar to the previous biopsy, but arteriolar fibrinoid necrosis was more marked.

Ten months later the patient was admitted with pain and swelling of the opposite thigh, which had developed over a few weeks. On examination he had a large discrete swelling on the lateral aspect of the right thigh which was warm and exquisitely tender. He had a mild neutrophilia, markedly raised CRP of 132 mg/l, but normal CK. A plain x-ray examination of the right hip was normal, apart from widespread vascular calcification. Doppler ultrasound showed no evidence of a deep vein thrombosis. A magnetic resonance imaging (MRI) scan of the thighs showed an area of increased signal density in the right vastus lateralis muscle consistent with oedema of the muscle (fig 1). He was treated with intravenous antibiotics and analgesia. His symptoms gradually improved, he no longer required opiates, and could walk with a stick. A technetium (Tc) labelled bone scan performed two weeks after discharge showed increased blood flow to the affected area of the muscle with slightly increased tracer uptake in the soft tissues and normal uptake in the skeletal system.

The patient was readmitted a month later with worsening pain in the right thigh. Serial CK measurements remained normal. He was given a small dose of steroids and his condition improved. A \(^{99m}\)Tc-sestamibi scan showed increased vascularity at the lesion in the right thigh, seen on the bone scan, and the presence of living muscle (fig 2).

Over the next three months he was admitted several times with infection of the fascial spaces of the hand and CAPD peritonitis; he died from the complications of diabetes.

**Discussion**

Diabetic muscle infarction is a rare complication of diabetes, which should be suspected in any diabetic subject with atypical severe muscular pain. It was first described in 1965 by Angerall and Stener as a “tumoriform focal muscular degeneration” and since then has been reported in a total of 86 patients. Sixty five patients had type I diabetes, 19 patients had type II diabetes, and in two patients the type was not specified. The male/female ratio was almost equal (44/42), with an age range of 19–81 years. Most patients had longstanding diabetes and extensive end-organ damage due to microvascular disease.

The condition presents as an atraumatic swelling of the limb, commonly the thigh. The onset of pain is usually gradual, but can be sudden. The swelling is exquisitely tender. It resolves within a few weeks, but frequently recurs. The white cell count and the level of CK are normal or slightly raised. Muscle biopsy typically shows large confluent areas of muscle necrosis and oedema. The best imaging results are with \(T_2\) weighted MRI scans, which have a fairly characteristic, but non-specific appearance showing the absence of a discrete mass and increased signal within the affected muscle.

The differential diagnosis includes a muscle tumour (sarcoma or lymphoma), localised abscess, haematoma, focal or systemic myositis, deep venous thrombosis, and osteomyelitis. The management should include bed rest, analgesia, tight metabolic control, and physiotherapy.

Various mechanisms of pathogenesis have been proposed. Earlier reports focused on diabetic microangiopathy, atheromatosis, and embolisation of atheromatous material from ulcerated aortic plaques as the causes of muscle infarction. In the presence of diabetic microvascular disease, a thromboembolic event is more likely to lead to infarction because of impaired collateral circulation. However, later reports showed that only a minority of cases had a vascular occlusion which would correspond to the extent of muscle necrosis. The above concept was therefore modified, suggesting that an initial ischaemic event itself does...
not cause infarction but leads to it by produc-
ing muscle oedema which increases the pres-
sure within a fascial compartment and causes
further ischaemia.\(^4\)

We suggest that hypoxia-reperfusion injury may have an important role in the pathogenesis of diabetic muscle infarction. The likely sequence of events leading to muscle necrosis is as follows. Compartment syndrome, precipi-
tated by a small thrombotic/embolic event or intraneural carotid injection, produces is-
chaemic muscle damage. This leads to a potent inflammatory response, hyperaemia, and reper-
fusion with generation of reactive oxygen species causing further muscle damage, both
directly and through worsening of the com-
partment syndrome due to muscle oedema. Thus there is a “vicious circle” which eventu-
ally results in extensive muscle necrosis. It is of note that a Tc labelled bone scan in case 2
confirmed the presence of hyperaemia, which was consistent with the findings of other inves-
tigators.\(^5\) Although a “1Tc-sestamibi scan showed the presence of a living muscle at the
site of the injury, it is possible that the “vicious circle” was disrupted and the images were
taken before significant muscle necrosis had occurred. Interestingly, Jawed et al have shown
that cyclical hypoxia-reperfusion injury is responsible for synovial damage in chronic inflammatory diseases as they are charac-
terised by a rise in the intra-articular pressure above the capillary perfusion pressure.\(^6\)

The clinical features of our two patients closely resemble those of previously reported cases. Both of them had longstanding diabetes with retinopathy, neuropathy, and nephropathy requiring CAPD. They both presented with tender recurrent swelling of the muscles of the affected limbs improved with supportive treat-
ment, though steroids may have contributed to the recovery in the second patient. The
diagnosis was confirmed by a muscle biopsy, except for the last recurrence of the disease in
the second patient, where the procedure was not performed in view of the similar clinical
presentation and characteristic MRI findings.\(^7\)

Diabetic muscle infarction is a rare condition that has become more frequently recognised in
the past few years. It should be suspected in a patient with a longstanding diabetes who presents with a painful swollen limb. MRI is the best imaging modality, but early core-needle- or open muscle biopsy at first presentation is essential to establish the diagnosis.

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