Diabetic muscle infarction in end-stage renal disease

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Abstract

Background. Diabetic muscle infarction (DMI) is an unusual disorder of type 1 and type 2 diabetic patients with advanced microvascular damage including nephropathy. Few reports describe this complication among dialysis patients.

Methods. We studied four patients with terminal renal failure due to diabetic nephropathy who developed isolated skeletal muscle infarction at our institution between January 1998 and January 2003, and reviewed 15 additional cases of DMI reported among dialysis patients (Medline database search).

Results. Analysis of available data for all 19 cases revealed the following features: mean age at symptom onset of 46.4 years; average duration of renal replacement 25.7 months (range 36 h to 72 months); male predominance (2.2:1); higher prevalence of type 2 vs type 1 diabetes (2.2:1); and more common use of haemodialysis than peritoneal dialysis (2.6:1). One patient developed symptoms after being immobilized during surgery and initiating dialysis. Thigh involvement was frequent (17/19). Fever, leucocytosis and elevated serum creatine kinase levels were noted inconsistently, but were seen commonly with early evaluation after symptom onset. Erythrocyte-sedimentation rate and C-reactive protein levels were high when checked. All 16 instances of magnetic resonance imaging (MRI) demonstrated increased T2-weighted signal from affected muscles. Seven patients were managed without muscle biopsy. Histological features included myofibre necrosis (8/12), inflammatory infiltrates (8/12) and microvasculopathy (6/12). Symptoms resolved with conservative therapy, but patients were at high risk for subsequent infarctions of other muscles (14/19).

Conclusions. DMI should be suspected in any diabetic dialysis patient who develops a painful, swollen muscle. A conservative MRI-based diagnostic approach may lead to satisfactory outcomes. The pathogenesis of the disorder is controversial, but the clinical sequence of one of our cases suggests precipitation by immobilization, direct pressure and/or haemocoagulation.

Keywords: diabetes; diabetic nephropathy; dialysis; muscle infarction

Introduction

Isolated skeletal muscle infarction is an unusual complication of diabetes mellitus that should be considered in any diabetic patient with an acutely painful, swollen muscle. Angervall and Stener [1] initially recognized the histological features of diabetic muscle infarction (DMI) in 1965 as 'tumoriform focal muscular degeneration'. Since their description, individual case accounts and small series have reported on the demographics of affected diabetics, typical clinical presentation, radiographic appearance and the spectrum of histopathological findings associated with DMI.

Despite the high prevalence of co-morbid diabetic nephropathy in 70% of patients [2], many nephrologists are inexperienced in the evaluation of DMI. The first case of DMI did not appear in the renal literature until 1998 [3]. To our knowledge, fewer than 20 cases of DMI have been reported among patients on dialysis [3–12]. Under-recognition or misdiagnosis by physicians may contribute to the relative rarity of the diagnosis [13].

We describe four cases of DMI among dialysis patients at our institution. We summarize our findings and existing reports of DMI in patients on renal replacement therapy to characterize the clinical, radiographic and pathological features of this disorder. Based on the clinical sequence in one of our cases, we propose a unique precipitant of the pathophysiological events leading to DMI.
Case reports

Case 1
A 56-year-old Caucasian woman with end-stage renal failure due to type 2 diabetes mellitus began peritoneal dialysis in March 1995. Her diabetes was also complicated by retinopathy and neuropathy, but she did not have known macrovascular disease. In January 1998, she developed painful swelling of her medial left thigh. Duplex ultrasound excluded thrombosis of the iliofemoral veins. Her pain gradually resolved, but in May 1998 she presented again with a 4 day history of severe left inner-thigh pain refractory to non-steroidal anti-inflammatory agents. She did not take aspirin prior to symptom onset.

The patient was afebrile. Her inner left thigh was firm, tender to palpation, and enlarged relative to the right thigh. Laboratory values included a white blood cell count of $15 \times 10^3/\mu l$ with 61% neutrophils and a creatinine kinase (CK) level of 1.7-fold the upper limit of normal. A non-contrast computerized tomogram (CT) revealed oedema of the left quadriceps with associated soft tissue stranding. High-signal lesions of the quadriceps muscle group excepting the rectus femoris appeared on T2-weighted magnetic resonance imaging (MRI) (Figure 1B and C). Biopsy specimens showed advanced necrosis of type I and type II muscle fibres without inflammatory infiltrates or vascular occlusions (Figure 2B). With analgesics and rest, the pain dissipated over several weeks.

Case 2
A 58-year-old Hispanic man with type 2 diabetes was evaluated in April 2000 for several months of pain and swelling of the left thigh, followed by a similar pain in the right thigh. He had advanced diabetic complications of retinopathy, neuropathy, peripheral vascular disease and end-stage kidney failure requiring haemodialysis since December 1997. He did not take aspirin on a regular basis. Initial physical findings included a low-grade fever and erythema over the anterior thighs, prompting a diagnosis of cellulitis. Symptoms persisted after 3 weeks of intravenous antibiotic administration at dialysis sessions.

Laboratory evaluation at this stage demonstrated normal white blood cell, CK and calcium levels; erythrocyte-sedimentation rate (ESR) and C-reactive protein (CRP) levels were high at 73 mm/h and 70 mg/l, respectively. Deep venous thrombosis was excluded by duplex ultrasonography. Non-contrast CT of the thighs showed bilateral quadriceps enlargement and mild oedema near the subcutaneous fat. On MRI, the enlarged quadriceps displayed hyper-intense T2-weighted signals. Excisional biopsy specimens of the left thigh muscle contained necrotic muscle mixed with areas of muscle fibre atrophy and fibrosis. The patient died of a myocardial infarction several weeks later.

Case 3
A 39-year-old Filipino man with type 2 diabetes progressed rapidly from renal insufficiency and nephrosis to the need for renal-replacement therapy. Co-morbid diabetic complications included retinopathy and neuropathy. He did not take daily aspirin. In April 2002, he underwent combined placement of a tunnelled haemodialysis catheter and a left radiocephalic arteriovenous fistula under local anaesthesia, followed post-operatively by his first haemodialysis session.

Fig. 1. (A) CT scan, Case 3. Cross-section of left calf shows oedema of the gastrocnemius and superficial fascial fluid. (B and C) MRI images, Case 1. Sagittal (B) and cross-sectional (C) views illustrate increased T2-weighted signal in left quadriceps, excepting the rectus femoris.
The treatment removed 1 kg of fluid by ultrafiltration without inducing hypotension.

The next day, the patient noted painful swelling of his posterior left calf without overlying erythema or warmth. Examination elicited exquisite tenderness of the deep tissue. Duplex ultrasonography was unremarkable. Six days after symptom onset, the patient required hospitalization for progressive calf pain that prevented weight-bearing.

On admission, the patient had a fever of 38.0°C but other vital signs were normal. White blood cell count was elevated at 16.5 x 10^3/μl with 74% neutrophils. CK level was moderately elevated at 3.6-fold the upper limit of normal, and ESR was 132 mm/h. Contrast-enhanced CT demonstrated oedema and enlargement of the lateral head of the left gastrocnemius muscle with superficial fascial fluid (Figure 1A). There was no evidence of fasciitis on surgical exploration, and tissue bed cultures were sterile. Muscle biopsy specimens contained coagulative necrosis, neutrophilic and lymphocytic infiltrates, and areas of fibroblastic proliferation (Figure 2A). After several weeks of physical therapy, symptoms improved and the patient was able to walk with a cane.

Case 4

A 31-year-old Hispanic man with terminal kidney failure due to type 1 diabetes developed painful swelling of his left thigh. Along with renal failure requiring dialysis for the prior 6 years, the patient also suffered from retinopathy and atherosclerotic cardiovascular disease. His medication regimen included aspirin 81 mg daily. His thigh pain was exacerbated by movement and intensified over 2 weeks to render him unable to walk.

Examination was notable for firm swelling of the patient’s left lateral thigh. His white blood cell count was within normal limits; CK level was not checked. Plain films and duplex ultrasonography of the thigh did not show abnormalities, but MRI detected hyperintense T2-weighted signals from the left vastus lateralis. Suspecting DMI, treating physicians deferred biopsy in favour of conservative therapy. The patient’s pain resolved and muscle function improved with analgesics and physical therapy.

Literature review

A Medline database search identified 17 cases of DMI in dialysis patients [3–12], which include 15 individual case descriptions [3,5–12]. We summarize the major clinical, radiographic and histopathological features of these and our newly reported cases in Table 1.

Results

Demographics and clinical features

We diagnosed six episodes of isolated skeletal muscle infarction among four dialysis patients at our institution between 1998 and 2003, reflecting an estimated incidence of one event per 233 patient-years of observation. Considering the collective series of DMI among dialysis patients, the mean age at the time of muscle infarction was 46.4 years. Affected patients were predominantly males and generally suffered from advanced type 2 diabetes. They required dialysis for an average of 25.7 months prior to index infarction. Haemodialysis was the active renal replacement modality in the majority of cases (13/18). Advanced diabetic microvascular complications such as neuropathy were prevalent (15/18) and peripheral macrovascular disease was noted in about half of the series (8/18).

Patients presented with abrupt or subacute onset of pain, tenderness and swelling of a localized muscle group in the lower extremities. The quadriceps group was the most common site of index infarctions (15/19); calf and buttocks infarctions each occurred in two patients [11,12; Case 3]. One half of patients with described vital signs were febrile, including five evaluated within a few days of symptom onset [12; Case 3]. There were no reports of antecedent trauma. Symptoms in one of our recently diagnosed patients began within 36 h of vascular access surgery and administration of his first haemodialysis and ultrafiltration session. Only one patient was noted to take aspirin regularly before the index infarction [Case 4]; another patient received warfarin for a confirmed deep venous thrombosis
preceding DMI in the same extremity [12]. Aspirin and pentoxyphylline were initiated after diagnosis of DMI as a strategy for recurrence prevention in one case [7]. Pain and muscle function generally improved with conservative care, but subsequent infarctions of other skeletal muscles were common (14/19 patients; 24 total events).

Laboratory and imaging studies

Peripheral white blood cell count and serum CK levels were elevated in seven of 14 and nine of 14 reported cases, respectively, to observed maximums of $26 \times 10^3/\mu l$ and 690 IU/l. Highest values were found in those evaluated early after symptom onset [12; Case 3]. ESR and CRP levels were high when checked, with ESR described as $>100$ mm/h and CRP $>100$ mg/l in most instances (6/9 and 5/7, respectively).

Doppler venous ultrasonography excluded deep venous thrombosis but did not detect changes in muscle echo-texture. CT images were abnormal in four of five instances: findings included oedema and enlargement of the infarcted muscle groups, perifascial fluid and vascular calcifications. All 16 instances of MRI demonstrated hyper-intense T2-weighted signals at the sites of infarction, as illustrated in Figure 1.

Histopathological features

Muscle biopsy specimens from the cases at our institution illustrate a temporal progression from subacute to chronic injury. Histological examination of the affected gastrocnemius in Case 3, taken 6 days after symptom onset, found features of subacute infarction with extensive coagulative necrosis and neutrophilic infiltration (Figure 2A). The tissue also

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**Table 1. Characteristics of dialysis patients with DMI**

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Case Literature: 15 cases a</th>
<th>Total b</th>
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</thead>
<tbody>
<tr>
<td>Age (years), mean (range)</td>
<td>56 58 39 31 46.5 (31–63)</td>
<td>46.4</td>
</tr>
<tr>
<td>Gender (male:female)</td>
<td>F M M M 10:5</td>
<td>13:6</td>
</tr>
<tr>
<td>Diabetes mellitus (type 1:2)</td>
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<td>5:10</td>
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<tr>
<td>Comorbidities</td>
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<td>15/18</td>
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<tr>
<td>Peripheral vascular disease</td>
<td>– + – – 7/14</td>
<td>8/18</td>
</tr>
<tr>
<td>Months on dialysis (mean)</td>
<td>34 26 36 h 72 22</td>
<td>25.7</td>
</tr>
<tr>
<td>Muscle (index event)</td>
<td>Thigh + + – + 14/15</td>
<td>17/19</td>
</tr>
<tr>
<td>Quadriceps</td>
<td>+ + – + 12/14</td>
<td>15/19</td>
</tr>
<tr>
<td>Vastus lateralis</td>
<td>+ + – + 8/13</td>
<td>11/17</td>
</tr>
<tr>
<td>Vastus medialis</td>
<td>+ + – – 5/13</td>
<td>7/17</td>
</tr>
<tr>
<td>Vastus intermedius</td>
<td>+ + – – 2/13</td>
<td>4/17</td>
</tr>
<tr>
<td>Rectus femoris</td>
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<td>4/13</td>
</tr>
<tr>
<td>Hamstring</td>
<td>– – – – 1/13</td>
<td>1/17</td>
</tr>
<tr>
<td>Calf</td>
<td>– – + –</td>
<td>1/13</td>
</tr>
<tr>
<td>Gastrocnemius</td>
<td>– – + –</td>
<td>1/13</td>
</tr>
<tr>
<td>Soleus</td>
<td>– – – –</td>
<td>1/13</td>
</tr>
<tr>
<td>Buttocks</td>
<td>– – – –</td>
<td>2/13</td>
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<tr>
<td>Clinical features</td>
<td>Fever – + + + 5/10</td>
<td>7/14</td>
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<tr>
<td>Recurrence</td>
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<td>14/19</td>
</tr>
<tr>
<td>Laboratory studies</td>
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<td>7/14</td>
</tr>
<tr>
<td>CK elevation</td>
<td>+ + – + n/a a</td>
<td>7/11</td>
</tr>
<tr>
<td>ESR elevation</td>
<td>n/a + + n/a</td>
<td>7/7</td>
</tr>
<tr>
<td>CRP elevation</td>
<td>n/a + n/a n/a</td>
<td>6/6</td>
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<tr>
<td>Imaging studies</td>
<td>CT scan: muscle oedema n/a + + n/a 2/3</td>
<td>4/5</td>
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<tr>
<td>MRI: hyper-intense T2 signal</td>
<td>+ n/a n/a + 14/14</td>
<td>16/16</td>
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<td>Histological features</td>
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<td>8/12</td>
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<tr>
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<td>– + + n/a</td>
<td>7/9</td>
</tr>
<tr>
<td>Microvasculopathy</td>
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</tr>
<tr>
<td>Fibrosis</td>
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<td>4/9</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>– – + n/a</td>
<td>3/9</td>
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aExpressed as proportions of positive findings per cases with available data.
bHD, haemodialysis; PD, peritoneal dialysis.
cn/a, information not available.
contained microvasculopathy in the form of small vessel and endothelial swelling, and a single fibrin thrombus. Patient 1 underwent biopsy several weeks after pain began. Her specimens showed advanced muscle fibre necrosis, atrophy and areas of fibre regeneration (Figure 2B). Fibrosis and scar replaced affected muscle fibres in the sample taken from Case 2 1 month after pain onset.

Compiled biopsy features from the series summarize histopathological findings over varied times in the disease course. Muscle fibre necrosis and inflammatory infiltrates were the most common abnormalities, each reported in eight of 12 pathological descriptions. Microvasculopathy, fibrosis and frank haemorrhages ranked next in frequency based on six, five and three respective observations. Microvascular abnormalities included endothelial swelling, luminal narrowing, fibrinoid occlusion and intramural calcifications.

**Discussion**

Isolated skeletal muscle infarction is a rare disorder of diabetic patients with advanced end-organ damage. Extension of dialysis eligibility to diabetic patients with a high burden of microvascular comorbidities places many people with DMI-risk factors under the primary care of nephrologists. The aim of this review is to familiarize nephrologists with the clinical, radiographic and pathological features of DMI, and to integrate a novel putative precipitant with existing theories of pathogenesis.

DMI is characterized by localized muscle tenderness, swelling and painful restriction of movement in patients with diabetic microvascular complications. There is a strong predilection for involvement of the lower extremity, particularly the thigh [2,7,8,13]; rare upper extremity infarctions are reported in non-dialysis patients [7]. The predominance of haemodialysis over peritoneal dialysis in DMI patients with terminal renal failure may reflect the relative modality use in reporting centres or a causal role of haemodialysis in triggering the cycle of muscle infarction.

The differential diagnosis of DMI includes superficial and deep venous thromboses, pyomyositis, myositis ossificans, traumatic muscle rupture, muscle haemorrhage, fasciitis, osteomyelitis, abscess and soft tissue neoplasm [2,13]. Laboratory findings in DMI are neither sensitive nor specific. Ultrasonography excludes deep venous thrombosis but is otherwise not diagnostically useful. CT scanning may localize lesions to the muscle compartment but does not differentiate causes of muscle swelling [14,15].

MRI is the most useful tool in the evaluation of DMI, because it detects characteristic changes with high sensitivity [5,14–17]. Hyper-intense T2-weighted muscle signals, a reflection of increased tissue water, appeared with every reported use of MRI in the evaluation of DMI among dialysis patients. Localization of the signal within a single muscle or muscle group and adjacent subfascial fluid further narrows diagnostic considerations. On T1-weighted images, infarcted muscles may appear iso- or hypo-intense relative to normal muscle; increased T1-weighted muscle signals indicate post-infarction haemorrhage [17]. Typical MRI findings may obviate the need for biopsy in appropriate clinical contexts, particularly in recurrences [13,18,19]. A conservative MRI-based approach led to satisfactory outcomes in seven dialysis patients with DMI. Muscle biopsy may clarify the diagnosis when clinical findings support several aetiologies. Histopathological changes in DMI vary with timing of biopsy acquisition from acute coagulative necrosis with inflammatory infiltrates to myofibre atrophy and fibrosis [4,6–11,13].

Several theories on the pathogenesis of DMI have emerged since recognition of the disorder, but the aetiology remains controversial. Banker and Chester [20] proposed two explanations based on biopsy and post-mortem findings. Ulcerative abdominal aortic plaques in an early case prompted the hypothesis that atheroembolism leads to infarction and necrosis. Later findings of extensive arterial occlusive disease without evidence of embolic sources in four patients supported arteriosclerosis obliterans as the primary event [4]. The authors further speculated that hypoperfusion and resultant anoxia produces a mild compartment syndrome that worsens ischaemia. The theory of primary macrovascular occlusion is bolstered by arteriographic evidence of atherosclerosis in medium and large vessels supplying the involved muscles in DMI [20]. However, advanced atherosclerosis is not universal [21].

Microvascular rather than macrovascular disease may predispose to DMI. Conversion of the normal rich collateral circulation of muscle to an end-vessel circulatory pattern renders it particularly vulnerable to injury [22]. In this compromised setting, tissue oedema and swelling may promote intra-compartmental ischaemia sufficient to cause myonecrosis. Based on findings of muscle hyperaemia by Tc-sestamibi scanning in an affected patient, Silberstein et al. [10] recently proposed a model of hypoxia–reperfusion injury in which initial ischaemia causes inflammation and hyperaemia. Oxygen-free radicals generated during reperfusion may cause both direct myotoxicity and indirect injury via vascular leak and worsened oedema.

Other authors propose that acquired hypercoagulability and associated endothelial damage lead to some cases of DMI, speculating that nephrosis-related anti-thrombin III deficiency, hyperhomocysteinaemia, or other factors predispose diabetics with renal failure to arteriolar thromboses. Supporting evidence includes abnormalities of coagulation and fibrinolytic pathways seen by Bjørnsklov et al. [23] in patients with DMI, and detection of prothrombotic antiphospholipid antibodies in two cases [24]. To date, there are no prospective studies on the impact of anticoagulation or anti-platelet agents on DMI recurrence. Aspirin and warfarin use were uncommonly reported among dialysis patients with DMI.

Case 3 in our series provides a unique example of close temporal association between DMI and potential precipitating events: vascular access surgery, with
requisite immobilization and compression of the affected posterior calf during supine positioning, and initiation of hemodialysis. We hypothesize that the combination of intra-operative lower extremity stasis and compression, followed by increased blood viscosity due to ultrafiltration, incited micro-thromboembolism in this patient with diffuse microangiopathy. Awareness among nephrologists of the typical features of DMI will likely increase recognition and appropriate management of this disorder. Proper evaluation includes prompt MRI, as detection of a localized hyper-intense T2-weighted signal may avert the need for muscle biopsy. Clearer understanding of pathogenesis may lead to preventative strategies in vulnerable patients. Further study of the cause and prevention of this disorder is needed.

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