

Diabetic Muscle Infarction

An underdiagnosed complication of long-standing diabetes

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OBJECTIVE — To systematically review all the reported cases of diabetic muscle infarction (DMI) and its pathogenesis, clinical features, prognostic implications, and management.

RESEARCH DESIGN AND METHODS — We searched databases (MEDLINE and EMBASE) from their inception to August 2001 and reviewed bibliographies in reports retrieved. Data were extracted in a standardized form.

RESULTS — A total of 47 references were retrieved; 115 patients and 166 episodes were included. DMI was more frequent in women (61.5%, mean age at presentation 42.6 years). Of the cases, 59% had type 1 diabetes; the mean duration of disease was 14.3 years, and multiple diabetic end-organ complications were noted. DMI affects the lower limbs with abrupt onset of pain and local swelling. Diagnosis is made by biopsy, but the characteristic features in magnetic resonance imaging are very typical. Treatment includes bed rest and administration of analgesics, but recurrence is common.

CONCLUSIONS — DMI is a very uncommon complication of long-standing diabetes; presentation is well characterized and management is simple.

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Spontaneous aseptic diabetic muscle infarction (DMI) is a rare complication of diabetes. It has been reported as aseptic myonecrosis, ischemic myonecrosis, and tumoriform focal muscular degeneration. Clinical presentation is uniform, with acute onset of painful swelling of the affected muscle and, occasionally, a palpable mass. The differential diagnosis is extensive and DMI is frequently misdiagnosed clinically. The illness is certainly diagnosed by histological biopsy analysis, although the results of T2-weighted magnetic resonance imaging (MRI) may be sufficient to enable other clinical entities to be excluded, thus avoiding inappropriate diagnosis and treatment (1). Although DMI was first reported in 1965 by Angervall and Stener (2) and seems to be a well-characterized complication of diabetes, only a few cases have been published.

The goal of this systematic review was

to identify the clinical features, pathogenesis, diagnostic aspects, therapeutic management, and prognosis of DMI.

RESEARCH DESIGN AND METHODS

Questions asked

Our review was designed to answer various questions about DMI regarding clinical features, pathogenesis, diagnosis, microscopic and macroscopic appearance, prognosis, and therapeutic aspects.

Identification and retrieval of primary studies

We searched MEDLINE (OVID Technologies and PubMed), EMBASE (OVID Technologies) using the heading “diabetic muscle infarction” and all synonyms and related terms. Databases were searched from their inception to August 2001.

Study selection and data extraction

Data were systematically extracted from all retrieved reports. Proportions were used in descriptive analysis, and the denominator corresponded to the number of cases in which the investigated characteristic was described.

RESULTS

Search results

After searching the electronic databases, we identified 47 reference sources (1–47) that included 115 patients with 166 episodes of DMI. The most frequent report was one case by reference, but two large series were retrieved, including 21 and 14 patients, respectively. In most articles, the cases were exhaustively described, but in those two large series, a lot of summary data were reported.

Data synthesis

The baseline characteristics of the DMI are shown in Table 1. In summary, DMI was more frequent in diabetic women (61.53%) and the mean age at presentation was 42.63 years (range 19–81 years). A total of 68 patients (59.1%) had type 1 diabetes and 27 patients (23.8%) had type 2 diabetes; reference to type of diabetes was not made in the remaining 20 patients (17.1%). The mean duration of diabetes, from initial diagnosis to the first episode of DMI, was 14.35 years; values ranged from 0 (diabetes not diagnosed) to 50 years. Patients with DMI usually had multiple typical end-organ diabetic complications. Vascular complications of diabetes were reported in most patients, largely in the form of nephropathy (74 of 104 patients reported, 71.1%), retinopathy (56 of 99 patients reported, 56.6%), and neuropathy (54 of 99 patients reported, 54.5%). Other complications reported peripheral arteriopathy in seven patients (7 of 92 reported, 6%), hypertension in eight patients, gastroenteropathy in four patients, and antiphospholipid antibodies in two patients.

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Abbreviations: CK, creatine kinase; DMI, diabetic muscle infarction; MRI, magnetic resonance imaging.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—Clinical features of patients with DMI

Number of patients	Number of episodes	Episodes/patient	Age (range) (years)	Sex (male/female)	Diabetes type	Duration of diabetes (range) (years)	Complications (n/reported)
115	166	1.44	42.63 (19–81)	61/54 (38.47%)/(61.53%)	Type 1: 68 (59.1%) Type 2: 27 (23.8%) Not indicated 20 (17.1%)	14.35 (0–50)	Nephropathy: 74/104 (71.1%) Retinopathy: 56/99 (56.6%) Neuropathy: 54/99 (54.5%)
Muscle involved	Weeks from onset (range)	Clinical features	CK level	Leucocytosis	ESR increased		
Thigh: 139 (83.7%)	3.98	Pain: 133 (80.12%)	High: 27/56 (48.2%)	7.01 (8%)	28 (52.8%)		
Calf: 32 (19.28%)	(1 day to 40 weeks)	Swelling: 126 (75.9%)	Normal: 29/56 (52.7%)				
Both: 4 (2.41%)		Mass: 56 (33.73%)	Not reported: 110				
Bilateral: 14 (8.43%)		Fever: 3 (10.71%)					
Biopsies	Treatment	Weeks until resolution (range)	Recurrences				
Fine-needle: 39	Bed rest: 32 (19.28%)	4	Same muscle: 10 (8.69%)				
Open: 29	Analgesics: 48 (28.92%)	(2–17)	Another muscle: 45 (39.13%)				
Total: 95	Physical therapy: 23 (13.86%)						
Type not reported: 27	Not indicated: 36 (21.69%)						

Clinical features

Typical clinical presentation of DMI included abrupt onset of pain in the affected muscle (133 of 166 episodes, 80% of cases), accompanied by local swelling (126 of 166 episodes, 75.9%), with subsequent partial resolution and appearance of a palpable painful mass (56 of 166 episodes, 33.7%). Fever was present in 3 of 28 episodes (10.71%) and was not present in 25 of 28 episodes (89.29%); body temperature was not indicated for the remaining 138 of 166 episodes (83.1%).

DMI most frequently affected the thigh (139 of 166 episodes, 83.7%), and the quadriceps was the most commonly affected muscle; calf involvement was reported in 32 cases (19.28%). Bilateral affection was reported in 14 cases (8.4%). The muscles more frequently affected were the vastus lateralis (40 cases of 166 episodes, 24%) and the vastus medialis (37 cases of 166 episodes, 22%). Only one case report of DMI in a muscle of the upper limb (forearm) was reported (34).

No specific marker was noted in laboratory findings. Increased plasma levels of muscle enzymes were infrequent: creatine kinase (CK) levels were elevated in 27 patients (48.2%), normal in 29 patients (52.7%), and not reported in 110 cases (66.2% of 166 episodes). Lack of correlation between muscle involvement and increased CK levels may have been a result of the delay in requesting medical

advice after onset of symptoms (3,23), a reported delay of ~4 weeks (range 1 day to 40 weeks). On the other hand, leukocytosis was reported in 7 of 88 patients reported (8%; not reported in 78 episodes) and elevated erythrocyte sedimentation rate was reported in 28 of 53 patients (52.8%; not reported in 113 episodes).

Pathogenesis

The pathogenesis of DMI remains to be wholly clarified. The most likely hypothesis is that muscle infarction is caused by vascular disease such as arteriosclerosis and diabetic microangiopathy (6). Chester and Banker (25) suggest an atheroembolic phenomenon as the initial event, but in their review of six cases, no source of embolic material could be found. Instead, they observed severe distal peripheral vascular disease in the muscles of two patients, suggesting that the underlying process was arteriosclerosis obliterans. Moreover, they proposed that the initial ischemia could cause tissue swelling that, through a pressure effect, might compromise blood flow. However, some authors have shown an alteration in the coagulation-fibrinolysis system, in the form of hypercoagulability, with increased factor VII activity, impaired response of tissue plasminogen activator to venous occlusion, and increased plasma levels of both plasminogen activator inhibitor and throm-

bomodulin (15). The hypothesis about an alteration in the coagulation-fibrinolysis system as the cause of DMI is supported in a recent paper by Palmer and Greco (45), who described two patients with DMI and antiphospholipid syndrome. Although it is difficult to assess the relative contribution of microvascular complications of diabetes versus antiphospholipid antibodies to the DMI, the experiences of Palmer and Greco further support the assertion by Gargiulo et al. (48) that indicates the antiphospholipid antibodies as contributing factors in the progression of diabetes complications, acting as a link between the immunological and hemostatic systems in the pathogenesis of diabetic microangiopathy. Additional evidence between both systems is supported by Galtier-Dereure et al. (49), who found a high prevalence of antiphospholipid antibodies in type 1 and type 2 diabetic patients with end-organ complications but no difference between control and uncomplicated diabetic subjects. By contrast, only Umpiérrez et al. (3) found vasculitic phenomenon, characterized by fibrinoid necrosis, in patients with DMI.

Diagnosis

DMI may be diagnosed by means of a combination of clinical presentation and radiological imaging. The most valuable diagnostic technique is MRI; axial images are the best plane for diagnosis, although

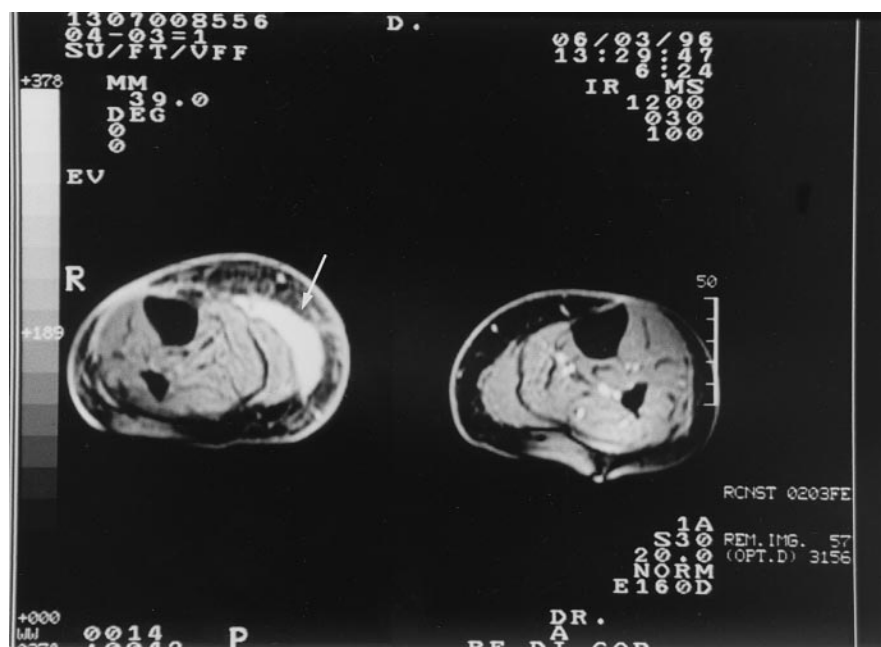


Figure 1—T2-weighted MRI scan: increased density of the lesion in the right internal gastrocnemius, corresponding to focal muscle infarction (arrow) (47).

coronal and sagittal images may be useful to document the extent of involvement (3). Moreover, this technique enables the exclusion of other conditions that frequently require differential diagnosis, such as deep venous thrombosis, pyomyositis, and primary or secondary muscle tumors. The characteristic feature of DMI in MRI is an increased signal from the affected muscle area (intramuscular and perimuscular tissues) in T2-weighted, inversion-recovery, and gadolinium-enhanced images and isointense or hypointense areas on T1-weighted images, secondary to increased water content from edema and inflammatory changes that accompany the infarction (4) (Fig. 1). Other features are a diffuse enlargement with ill-defined borders secondary to loss of the normal fatty intramuscular septa (more easily shown in T1-weighted images) and tiny foci of hyperintense signal consistent with foci of hemorrhage (4). After intravenously administered gadolinium, the areas of MR contrast enhancement have higher signal intensity than unaffected skeletal muscle, similar to those of the T2-weighted and inversion-recovery sequences, and small focal areas of rim enhancement that correspond to areas of high signal intensity on T2-weighted images (that represent infarction or necrosis within the areas of ischemic muscle) (4). However, in one

case report, an atypical feature was found: a hyperintensity of the affected muscle on T1-weighted images, probably caused by hemorrhage within the infarcted muscle (43). Images obtained by MRI are not specific for DMI, because some inflammatory or autoimmune myopathies may prompt similar changes (3).

Other radiographic techniques may help to exclude other illnesses more than make the correct diagnosis of DMI. Standard radiographic films are rarely helpful, except to exclude bony abnormalities or soft-tissue calcifications (19). Sonographic findings in DMI include a well-margined, hypoechoic, intramuscular lesion with the following additional features: internal linear echogenic structures coursing through the lesion, an absence of internal motion or swirling of fluid transducer pressure, and a lack of a predominantly anechoic area. These findings may help differentiate DMI from a necrotic mass or abscess, although a direct sonographic comparison of these entities has not been made (38). Computed tomography examination shows diffuse muscular enlargement with diminished attenuation of the affected muscle (24 Hounsfield units; 1,000 scale), increased attenuation of the subcutaneous fat, and thickening of subcutaneous fascial planes and of the skin (33). On gallium scintigraphy, areas of DMI show no increase in uptake, dif-

ferentiating these areas from tumor or inflammation. Bone scintigraphy, however, shows increased blood flow and isotope accumulation at the site of muscle infarction but not in the skeleton (14,16).

Needle electromyography of the muscle affected of DMI shows fibrillation potentials and positive sharp waves and small motor unit potentials with early recruitment in some areas and reduced interference pattern. Some areas of the muscles, however, can be electrically silent, both at rest and after voluntary contraction, thus indicating replacement of muscle fibers by fibrous tissue (14,40).

In the systematic review, we found that the diagnosis of DMI was confirmed by biopsy in 95 cases (57.2%): 39 fine-needle biopsies, 29 open biopsies, and 27 biopsies of unreported type. Currently, because of the potential complications of excisional and incisional biopsy in DMI and the possibility of diagnosing the condition using MRI, and with a good prognosis, physicians tend to eschew all invasive diagnostic methods. Biopsy should be reserved for cases in which the clinical presentation is atypical or the diagnosis uncertain or when appropriate treatment fails to elicit improvement (25).

Grossly, DMI presents as a nonhemorrhagic, pale, whitish muscle. Light microscopy shows large areas of muscle necrosis and edema, phagocytosis of necrotic muscle fibers, and appearance of granular tissue and collagen (Figs. 2 and 3). Findings at later stages include replacement of necrotic muscle fibers by fibrous tissue, myofiber regeneration, and mononuclear cell infiltration (37). There is only one report of vasculitis and small-vessel angiopathy in patients with DMI (3), the latter indeed being one factor that differentiates DMI from the small-vessel vasculitis typically found in elderly patients with type 2 diabetes.

Differential diagnosis of DMI was most frequently required with regard to deep venous thrombosis and pyomyositis, although soft-tissue abscess, necrotizing fasciitis, dermatomyositis, proliferative myositis, focal myositis, nodular myositis, primary lymphoma of the muscle, diabetic amyotrophy, osteomyelitis, exertional muscle rupture, and ruptured Baker's cyst. The clinical course, the MRI images, and obviously, the histologic specimen can confirm the correct diagnosis (4,22,25).

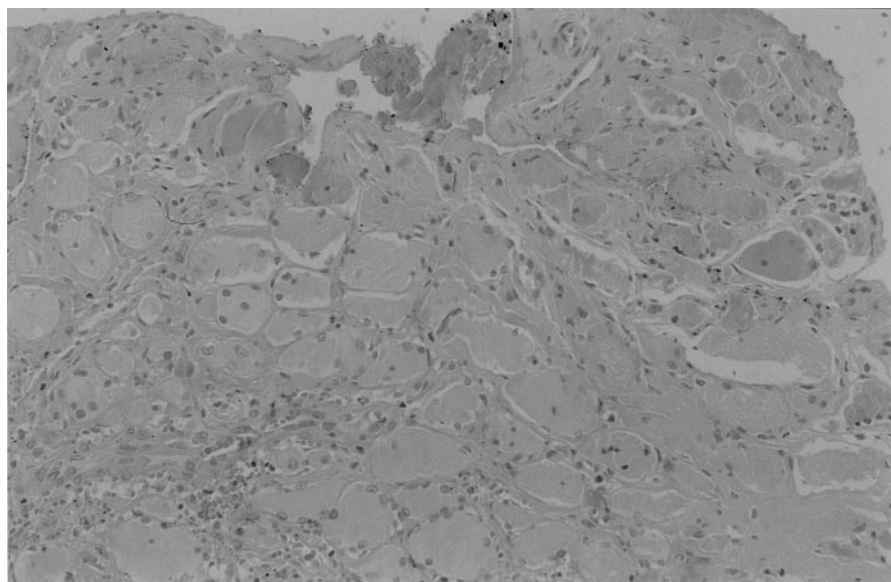


Figure 2—Necrotic muscle fibers and extravasation of blood (hematoxylin-eosin stain, $\times 40$) (47).

Management and prognosis

In the review, DMI was managed with bed rest (32 cases of 166 episodes, 19.28%) and analgesics (48 cases of 166 episodes, 28.9%), although resolution of the illness has been complication-free in most cases and treatment was generally symptomatic. Careful metabolic control of diabetes is usually recommended, although perhaps, because the rare nature of the condition hinders the drawing of valid conclusions, this control has not been

shown to influence results in a current episode. It may be of value in limiting a possible recurrence of the illness. Other therapeutic measures include nonsteroidal anti-inflammatory drugs, glucocorticoids, aspirin, and pentoxifylline; some of these are useful in diabetic vasculitis and potentially valid in DMI. Bjornskov et al. (15) administered anticoagulant agents to two patients with hypercoagulability; no recurrence or complications were observed in these patients. Similarly,

Palmer and Greco (45) treated one of their two patients with antiphospholipid antibodies with corticosteroid and anticoagulant agents (which were contraindicated in the second patient because of concerns of retinal hemorrhages), but recurrences of the DMI occurred. Other authors have not reported blood-flow alterations and, thus, have not recommended anticoagulant treatment. Some authors recommend avoidance of physical therapy (reported in 23 cases, 13.86%) because recovery is prolonged (25), but other authors have not observed this in their patients (23).

The short-term prognosis of DMI is good, although recurrence has been reported in a total of 55 cases (47.82%): 10 cases (8.69%) involving the originally affected muscle and 45 cases (39.13%) involving another muscle. Generally speaking, patient prognosis is poor, given that patients usually have end-organ microvascular complications when DMI is diagnosed.

CONCLUSIONS— DMI is a very rare complication of diabetes, with atherothrombotic or coagulopathic cause, presenting clinically with pain, swelling, and occasionally, a palpable mass, with normal or elevated plasma CK levels. Increased signal intensity in T2-weighted MRI images is common, and the condition usually resolves spontaneously or after immobilization and administration of analgesics. Muscle biopsy is only indicated in cases of atypical presentation or progression of the condition.

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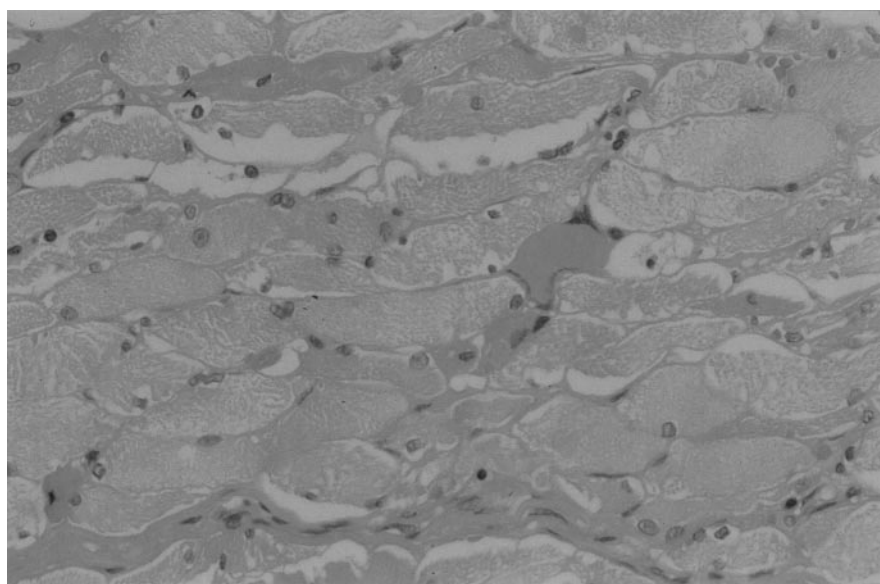


Figure 3—Muscle fibers showing signs of regeneration (nucleolus present) (hematoxylin-eosin stain, $\times 400$) (47).

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