MRI in Inflammatory Myopathies and Autoimmune-Mediated Myositis

Umesh A. Badrising, Hermien E. Kan, and Jan JGM Verschuuren

Contents

Abstract

In this chapter, dermatomyositis, polymyositis, inclusion body myositis, and the necrotizing myopathies are discussed in detail with regard to their clinical features, laboratory and histopathological findings, mimics and the imaging findings with magnetic resonance imaging, computed tomography, and ultrasound. With the focus on magnetic resonance imaging, its discriminating role between disorders during the diagnostic work-up, the evaluation of the extent and activity of the disease, and the gathering of information on fat replacement of muscles are considered. Furthermore, its use to locate the best site for a muscle biopsy to enhance the diagnostic yield of a histopathologically confirmed diagnosis and its use during the follow-up of patients in assessing the therapeutic effect of immunosuppressive and immunomodulating therapies and to detect signs of relapse are outlined.

Abbreviations

ATP	Adenosine triphosphate
CK	Creatine kinase
CT	Computed tomography
DM	Dermatomyositis
DWI	Diffusion weighted imaging
EMG	Electromyography
HIV	Human immunodeficiency virus
HLTV-I	Human T cell lymphotropic virus
HMGCR	3-hydroxy-3-methylglutaryl-coenzyme A reductase
IBM	Inclusion body myositis
IIM	Idiopathic inflammatory myopathies
JDM	Juvenile dermatomyositis
MAC	Membrane attack complex
MDA5	Melanoma differentiation matrix protein
MHC	Major histocompatibility complex

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MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
MSA	Myositis specific antibody
MUAP	Muscle unit action potential
NM	Necrotizing myopathy
NXP-2	Nuclear matrix protein
PCr	Phosphocreatinine
PET	Positron emission tomography
Pi	Inorganic phosphate
PM	Polymyositis
SRP	Single recognition particle
STIR	Short tau inversion recovery

1 Key Points

1. MRI is useful to enhance the diagnostic yield of a muscle biopsy in inflammatory myopathies.
2. The key feature of inclusion body myositis is fatty infiltration, while edema is central in dermatomyositis, polymyositis, and necrotizing myopathy.
3. Whole body (STIR) MRI is best informative with regard to activity and extent of the disease and to detect the best location for a muscle biopsy.
4. MRI can be used to evaluate the effect of immunosuppressive treatment and relapses during follow-up.

2 Introduction

The inflammatory myopathies can be subdivided into infectious and non-infectious myopathies. Among the latter are the idiopathic inflammatory myopathies (IIM) comprising dermatomyositis (DM), polymyositis (PM), inclusion body myositis (IBM), and autoimmune necrotizing myopathy (NM). DM, PM, and NM are often associated with connective tissue disorders, and are then regarded as a part of an overlap syndrome. All IIM are rare sporadic disorders and their annual incidence is estimated at 1–9 per 100.000 inhabitants (Smoyer-Tomic et al. 2012; Furst et al. 2012; Lindberg et al. 1994). The infectious inflammatory myopathies comprise infections with viruses, bacteria, fungi, and parasites. The prevalence of these infections is related to geographical, cultural, dietary and hygienic differences, and food inspection regulations of governments.

This chapter will primarily focus on the non-infectious inflammatory myopathies as magnetic resonance imaging (MRI) is becoming a frequently used imaging modality in these disorders. Those infectious inflammatory myopathies in which imaging is of high importance or those that are of cardinal importance in the differential diagnosis will be addressed as well.

3 Idiopathic Inflammatory Myopathies

3.1 Clinical Presentation

Dermatomyositis has a female predominance (female–male ratio 2:1) and a peak incidence between 30 and 50 years of age. DM presents with an insidious onset (weeks to months) of progressive symmetrical limb muscle weakness, which is predominantly proximal, and neck flexor weakness. In some cases, muscle pain may be present, in particular exercise-induced pain.

Patients may show characteristic skin features such as a purplish discoloration of the eyelids (heliotrope rash) often associated with periorbital edema or a erythematous or violet-colored symmetrical rash over the extensor surfaces of the metacarpophalangeal and interphalangeal joints, elbows, knees, and medial malleoli (Gottron's sign). This rash may evolve into scaly lichenoid papular eruptions (Gottron's papules), but these papules may also be located on the volar side, and then referred to as inverse Gottron's papules. Another characteristic skin abnormality is the erythematous rash on sun-exposed areas such as the face, neck, anterior chest, and upper back ("V-sign" and "shawl-sign"). The nail beds may have dilated capillary loops with periungual hyperemia, and there can be skin ulcerations, livedo reticularis, alopecia, and lipodystrophy. In DM patients with the antisynthetase syndrome (arthritis, Raynaud's phenomenon, and interstitial lung disease) thickened and cracked skin (mechanics' hands) on the volar and dorsal parts of the hands can be present. Skin abnormalities usually precede or appear simultaneously with muscle weakness. The degree of muscle and skin involvement is part of a spectrum with amyopathic DM (also called DM sine myositis), patients with skin features of DM but without clinical evidence of weakness on one side and adermatopathic DM with isolated myositis at the other end. About 20 % of patients with amyopathic DM develop muscle weakness within 5 years during follow-up.

Proximal muscle weakness results into difficulty using the hands above the head and inability to get up from a deep chair or to climb stairs. This pattern of weakness is frequently seen in other myopathies as well. Dysphagia and to a lesser degree dysarthria may occur. In rare cases, cardiomyositis and interstitial lung fibrosis may be features.

DM may present in concurrence of a connective tissue disease. DM is associated with a higher risk of cancer, especially that of adenocarcinoma of the lung, colon and rectum, and of breast and ovarian cancer. The first years after developing DM are associated with the highest odds of a concurrent malignancy, but cancer may also precede DM. Risk factors for cancer include older age, male sex, dysphagia, and cancer associated myositis specific antibodies

(MSA). Therefore, screening for cancer is recommended after diagnosis, but a validated algorithm is lacking so far. This encompasses a thorough medical history and physical examination, including inspection of the skin for melanoma, breast palpation and rectal examination, laboratory testing, computed tomography (CT), scanning of chest and abdomen, colonoscopy in patients above 50 years, and mammography with pelvic ultrasound in women and ultrasound of testis in men under the age of 50. Repeat screening is recommended during 3 years at least annually (Titulaer et al. 2011). Different approaches have also been suggested, such as a yearly positron emission tomography (PET)/CT scan (Selva-O'Callaghan et al. 2010b).

Patients with DM have a mortality risk >10 % to die from disease related causes such as cancer, pulmonary complications, lethal adverse events of drugs used and cardiac complications, especially in the first years after onset.

Juvenile DM (JDM) is the only idiopathic inflammatory myopathy in non-adults. Subcutaneous calcinosis, joint contractures and multisystem involvement are common in JDM in contrast to the adult form. Necrotizing vasculitis of the bowel may cause perforation due to ischemia and necrosis. Nailfold capillary density is diminished in JDM and inversely correlated to disease activity of the muscle and skin.

Polymyositis is considered to be an overdiagnosed, but still a distinct, clinical entity (van der Meulen et al. 2003; Fernandez et al. 2013; Hoogendijk et al. 2004). Some physicians still use the Bohan and Peter criteria to diagnose PM (Bohan and Peter 1975), which do not discriminate inclusion body myositis or DM without a rash as separate disorders from PM, or use PM as an exclusionary diagnosis in patients who do not have a rash or other likely neuromuscular disorder. PM is more common in women and occurs in adults after the age of 20 years. As in DM, symmetric proximal muscle weakness of the limbs progresses subacutely in weeks to months. Muscle pain and tenderness, fever, non-destructive arthritis, mild facial weakness, neck flexor weakness, and dysphagia may accompany limb muscle weakness. PM patients are considered to have a higher chance of an emerging malignancy, but due to ill-defined inclusion criteria in the literature, this remains debatable. PM can be present in conjunction with a connective tissue disorder.

Inclusion body myositis is considered to be the most frequent myopathy after the age of 50 years. There is a male predominance (male–female ratio 2:1) and weakness is usually slowly progressive with mostly asymmetric weakness of distal or proximal muscles, mostly coexistent, with a preference for weakness of the forearm flexors, quadriceps muscles and pharyngeal muscles (Badrising et al. 2000; Needham et al. 2008). This leads to complaints of diminished grip strength, difficulty with rising from low chairs or walking stairs, falls due to buckling of the knees, and dysphagia. Weakness usually commences after the age of 40 and progresses with ventrally located muscles being affected more than dorsally located muscles and shoulder and hip abductors remaining least affected (Badrising et al. 2005). Mean muscle strength decline is estimated at 3.5–5.4 % per year (Badrising et al. 2002; Cox et al. 2011a; Cortese et al. 2013). Myalgia is not a feature of the disease. End-stage disease is accompanied by major disabilities leading to confinement to a wheel chair or bed, recurrent aspiration and cachexia. Life expectancy is not affected by the disorder on group level, but end of life measures are not uncommon at end-stage disease (Cox et al. 2011b; Benveniste et al. 2011).

IBM is associated with autoimmune disorders (Badrising et al. 2004; Koffman et al. 1998). There is no increased risk for malignancy (Cox et al. 2011a).

Autoimmune necrotizing myopathy has a subacute progressive onset of proximal muscle weakness and lacks a rash. Weakness is usually severe within 6 months (Medical Research Counsel scale $\leq$ 3) and can include dysphagia and respiratory failure. Myalgia is common. Data with regard to sex preponderance in prevalence are inconsistent, but in a large cohort of 64 patients a male predominance was found. It can occur after the age of 20, but the mean age of onset is around 57 years (Ellis et al. 2012). NM is associated with cancer preceding or following the myopathy (Bronner et al. 2003). Although the frequency of associated cancer is not clear, screening is advised as in DM. There is also an association with connective tissue disorders, statin-triggered autoimmunity, and viral infections such as acquired immunodeficiency syndrome and hepatitis C (Liang and Needham 2011). Statin-induced autoimmune NM may occur up to 10 years after initiation of a statin and can advance many months after discontinuation of a statin (Grable-Esposito et al. 2010).

3.2 Laboratory Findings

In DM patients, serum creatine kinase (CK) is elevated up to 50 times the upper limit of normal, but can be normal in <10 % of patients, regardless of its presentation within the clinical spectrum. The most common MSA in DM patients is the Jo-1 (histidyl t-RNA synthetase) antibody, associated with the antisynthetase syndrome. Less common anti-synthetase antibodies are anti-PL-7, anti-PL12, anti-EJ, anti-OJ, and anti-KS, occurring only in 1–3 % of patients. Usually no more than one antibody is found in a patient. Suspicion of interstitial lung disease, a major cause of morbidity and mortality, which is part of the antisynthetase syndrome, warrants pulmonary consultation, chest imaging,

and pulmonary function testing. Anti-P155/140 antibody is associated with an increased risk of a malignancy in adult DM and with severe cutaneous juvenile DM. Anti-MJ directed toward the nuclear matrix protein (NXP-2) is associated with cancer in adult DM patients and is the most common MSA in juvenile DM. Anti-CADM-140 directed against the melanoma differentiation associated gene 5 (MDA5) is associated with DM with only mild inflammation in the muscle biopsy and clinically amyopathic DM. Highly specific for DM and suggestive of an encouraging outcome are anti-Mi-2 antibodies, which are more infrequent in Caucasians, and occur in 15–30 % of DM patients.

Electromyography (EMG) shows a myopathic pattern with low amplitude, short duration polyphasic motor unit action potentials (MUAPs) with spontaneous muscle fiber activity (fibrillations, positive sharp waves, and complex repetitive discharges) and early recruitment. In chronic patients, MUAPs become longer in duration.

In PM, serum CK is 5–50 times the upper limit of normal and correlates well with treatment response (decrease) or relapse (increase). Several anti-synthetase antibodies have been described in PM, but precise frequencies remain obscure as a result of differences in disease definition. In the "pure" PM form MSA are perhaps rare. They probably represent the presence of an overlap syndrome.

EMG findings in PM are similar to those of DM patients.

In IBM, serum CK levels may be normal or elevated up to 12 times the upper limit of normal. Recently, two study groups independently described an autoantibody targeted against cytosolic 5'-nucleotidase 1A (Mup44) present in 25–40 (33) % of IBM sera and it is only rarely found in other neuromuscular disorders and is absent in normal sera (Pluk et al. 2012; Salajegheh et al. 2011). In up to 30 % of patients, EMG shows a mild sensory neuropathy on nerve conduction studies. Needle EMG shows the pattern of a myopathy but can be confusing as some patients may show a mixed myopathic-neuropathic pattern with high amplitude MUAPs overshadowing the small ones leading to a wrong conclusion of a motor neuron disorder.

In NM, serum CK is more than 10-fold elevated. NM with rapidly progressive and severe weakness and an onset during fall has been related to anti signal-recognition particle (SRP) antibodies. This type of NM is regularly steroid-resistant (Miller et al. 2002; Fernandez et al. 2013). An Australian study detected no anti-SRP autoantibodies in stored serum of a retrospective NM series and casted doubt on the previous association (Ellis et al. 2012). In progressive statin-associated autoimmune myopathy antibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) can be found and used to discriminate from self-limited statin induced myopathy with improvement after discontinuation of the statin (Mammen et al. 2011). EMG shows small amplitude, short duration, polyphasic motor unit potentials with sometimes fibrillations, and positive sharp waves and complex repetitive discharges. Electrical myotonia is prominent according to some but has not been formally studied, and has been described in cases with self-limited statin induced myopathy (Dimachkie and Barohn 2012).

3.3 Histopathology and Pathogenesis

DM is considered to be a complement-mediated microangiopathy. The first histopathologic manifestation consists of the perivascular deposition of immune complexes of membrane attack complex (MAC) i.e. the C5b-9 of complement. Due to destruction of capillaries and ischemia muscle biopsies may show atrophic, degenerating, and regenerating myofibers often with a perifascicular distribution. Inflammatory infiltrates consist of B cells, macrophages and plasmacytoid dendritic cells and have a perimysial or perivascular location. They present a presumed antigen to naïve CD4 + T-lymphocytes. MAC deposition helps to discriminate DM from other myopathies. Invasion of non-necrotic fibers is not a feature of DM.

PM muscle biopsies are considered to signify a cell-mediated cytotoxic immune response against the muscle fiber. Besides atrophic, hypertrophic, necrotic, and regenerating fibers focal mononuclear infiltrates with a predominantly endomysial location and consisting of mainly CD8 + cytotoxic T cells that surround and invade non-necrotic fibers that express major histocompatibility complex (MHC) class I molecules on their sarcolemma are present. It is assumed that MHC-1 antigens express an undetermined peptide that acts as an autoantigen (Arahata and Engel 1986, 1988).

IBM muscle biopsies show the same features as in PM and therefore PM muscle biopsy features are not considered distinctive. Thirty-seven percent of patients with histopathological PM have the clinical features and clinical course of IBM patients (Chahin and Engel 2008). Apart from the inflammation the muscle biopsy in IBM shows degenerative changes such as "rimmed vacuoles," which are seen in fresh frozen muscle biopsy specimens stained with hematoxylin-eosin or Gomori trichrome. These vacuoles contain amorphous material. With electron microscopy tubulofilaments with a 15–21 nm diameter can be observed near rimmed vacuoles or the nucleus. Degenerative proteins such as hyperphophorylated tau and β-amyloid accumulate near these tubulofilamentous structures. The precise connection between the degenerative and inflammatory changes remains elusive.

NM is characterized by widespread necrosis, surrounded by macrophages, and regeneration of muscle fibers, which contradicts in abundance to the lack of inflammation and absence or minimal MHC-I staining of non-necrotic fibers.

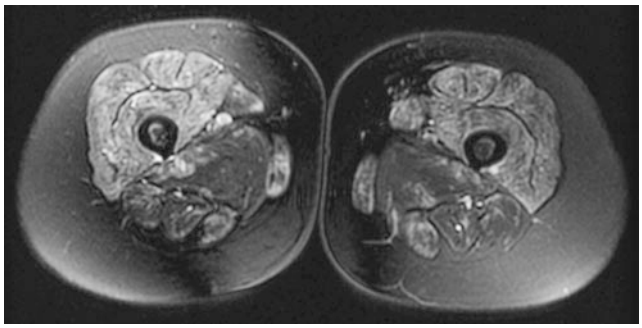

Fig. 1 Axial spectral presaturation with inversion recovery image of the thigh with more or less symmetric hyperintensities of mainly the anterior compartment in DM. Fat suppression is not uniform over the leg

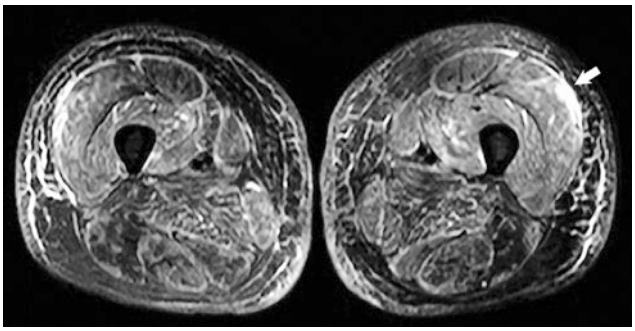

Fig. 2 Axial STIR images of the thigh in a different patient with DM with hyperintensities of mainly the anterior compartment and fascia with chemical shift artifact between skin and subcutis (*arrow*)

4 Imaging in Idiopathic Inflammatory Myopathies

4.1 Magnetic Resonance Imaging in Idiopathic Inflammatory Myopathies

MRI in inflammatory myopathies is usually directed at assessment of muscle anatomy and fatty infiltration on T1-weighted images, and assessment of muscle edema as a sign of inflammation on fluid-sensitive sequences consisting of fat-suppressed T2-weighted images or short tau inversion recovery (STIR) images (Fig. 1). MRI is used as a noninvasive diagnostic tool but also as a longitudinal follow-up tool for therapeutic monitoring and outcome, and has the advantage that previous images of the same patient obtained in a similar scanner can mostly be reliably compared. A second important reason to perform MRI in IMM is to guide muscle biopsies. Blind muscle biopsies may be false-negative in 10–45 % of myositis patients (Bohan et al. 1977; Schweitzer and Fort 1995).

Thigh muscles that are affected on MRI in DM/PM patients show a significantly higher number of inflammatory cells in muscle tissue after a muscle biopsy compared to non-affected MRI muscles of the same patients, thus perhaps indicating an increase in the yield of a histological diagnosis after MRI-guided biopsy (Tomasova Studynkova et al. 2007).

The cost effectiveness of MRI in suspected PM is evaluated in a small study of 25 patients through comparing false-negative biopsies in patients with biopsies based upon MRI results versus untargeted biopsies. False-negative results are reported in one of 14 patients after MRI-guidance biopsies and in 5 of 11 without MRI guidance. MRI prior to biopsy has been associated with a medical costs reduction from 20,000 USD to 14,000 USD, which the authors presented as cost-effective. These costs are outdated and cannot be used at present as patients were admitted for many days, which was included in the price as were other ancillary investigations (Schweitzer and Fort 1995; Fleckenstein 1996). A 1994 study in the Washington DC area found that the cost of performing and interpreting an MRI ranged from 680 to 1030 USD whereas the costs for performing a muscle biopsy and interpretation ranged from 1520–2400 USD. The authors concluded that MRI might be more cost-effective than repeat biopsy (Adams et al. 1995). So far consensus is lacking on this subject.

In IIM, STIR sequences are preferred over fat-saturated T2-weighted sequences due to their more uniform fat suppression (Fig. 2). Administration of gadolinium appears to have no advantages compared to T2-weighted images (Reimers et al. 1994) or in comparison to STIR and fat suppressed T2 images (Dion et al. 2002). MRI protocols in IIM commonly contain axial slices of several muscle groups aimed at the highest probability of finding diagnostically helpful features. The upper legs are preferentially studied, because they are often affected, and are an easy target for a muscle biopsy.

Increasingly, whole-body MRI becomes available to clinicians (see also MRI in Muscle Dystrophies and Primary Myopathies of this book). It has the advantage to detect areas of muscle inflammation in clinically unsuspected muscles, which may even be easily accessible for a muscle biopsy (Cantwell et al. 2005). Furthermore, it gives an overall picture of the anatomic distribution and size of lesions, and expands our knowledge about disease variability as muscles such as the intercostal muscles have now observed to be also affected by the disease process and inflammation can be visualized in cases of suspected amyopathic DM (Fig. 3). Whole-body STIR MRI can be done in 15–30 min, depending on respiratory triggering and the number of coronal slices needed on each level (O'Connell et al. 2002). Whole body T1-weighted MRI can be done even faster.

The hyperintensity observed on STIR or fat-suppressed T2-weighted images, is often regarded as muscle edema, an unspecific sign. It can be subtle, focal, diffuse, inhomogeneous, and with ill demarcated margins and be the result of

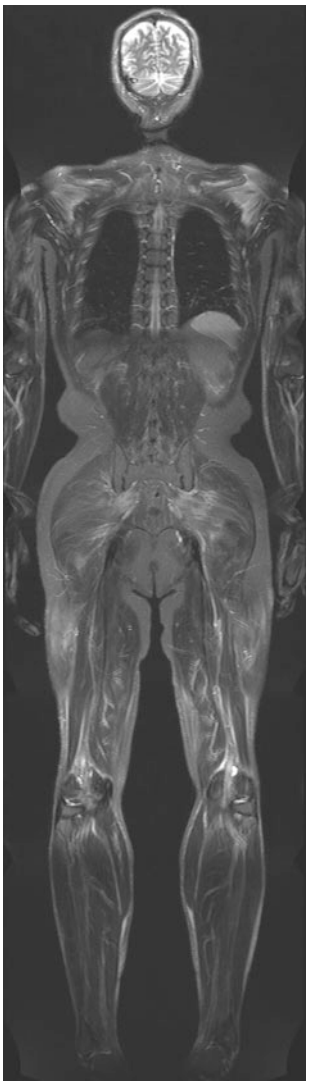

Fig. 3 Coronal STIR MR whole body image of a 56-year-old patient with DM. Symmetrical edema-like changes are present within the shoulder girdle and the thighs, as well as the gluteal muscles (image courtesy of Prof. Dr. M.-A. Weber, Heidelberg)

muscle injury, inflammation, interstitial fluid overload or (sub)acute denervation. Apart from inflammatory myopathies, muscle edema is also observed, diffuse or focal, in muscular dystrophies such as Duchenne's muscular dystrophy, fascioscapulohumeral dystrophy and myotonic dystrophy, metabolic myopathies, toxic myopathies, infectious myopathies, congenital myopathies such as minicore disease, muscle channelopathies such as hypokalemic periodic paralysis, rhabdomyolysis, sports injuries, after acute exercise, but also in neurogenic lesions, including neuropathies such as hereditary motor and sensory neuropathies and spinal muscular atrophy. Apart from metabolic myopathies these increased T2 signal intensities are usually infrequent, relative and unspecific (Schedel et al. 1992, 1995).

In a small series of DM and PM patients, MRI has been shown to have a sensitivity of 100 %, a specificity of 88 %, a positive predictive value of 77 %, and a negative predictive value of 100 %, as compared to histopathological diagnosis (Weber et al. 2006). Another larger study reported a sensitivity of 80 % (Reimers et al. 1994). So far, only studies in 0.5–1.5 T MRI have been published on the subject of IIM.

4.2 Muscle Involvement Patterns in IIM on MRI

The number of studies looking at MRI abnormalities in DM is limited. Focal or diffuse areas with high signal intensity on fat-suppressed T2-weighted images are the most common findings. These areas suggest edema or inflammation and are preferentially located in proximal muscles and tend to be more or less symmetrical. In unusual cases, however, a unilateral distribution can be seen (Reimers et al. 1994). Within these high signal intensity areas, signal intensities may fluctuate. There is a preference for involvement of the four heads of the quadriceps muscles and the dorsiflexors of the lower legs. Least affected muscles are the pectineus, obturatorius, thigh adductors, biceps femoris caput brevis, gracilis, soleus and caput laterale of the gastrocnemius (Reimers et al. 1994). There can be diffuse or focal subcutaneous edema, and edema may show a myofascial pattern in some muscles (Cantwell et al. 2005; O'Connell et al. 2002; Schulze et al. 2009; Yoshida et al. 2010).

In PM studies, the problem of uncertainty with regard to the correct diagnosis at inclusion reappears. Reported MRI studies may be hampered by unjustly including IBM patients or DM patients without a rash and consequently the results of these PM studies are less reliable. In those studies where IBM patients have been excluded inflammation is a more prominent feature than fatty infiltration (Cantwell et al. 2005; Dion et al. 2002; Reimers et al. 1994). Patients may have inflammation as a sole manifestation, thus in the absence of fatty infiltration. Both, however, are located preferentially in proximal limb muscles with a more or less symmetrical distribution. Most studies focused on abnormalities in the legs. Muscles with high signal intensity on fat-suppressed T2-weighed images are most frequently the vasti of the quadriceps, the anterior tibial and the caput laterale of the gastrocnemius. Fatty infiltration is preferentially observed in the hamstrings, vastus muscles of the quadriceps, and the gastrocnemius.

Least affected muscles by inflammation are the gracilis, peroneal, extensor digitorum, posterior tibial, flexor digitorum, and flexor hallucis longus muscles. Comparatively spared from fatty infiltration are the rectus femoris, gracilis, posterior tibial, and soleus muscles (Reimers et al. 1994). During treatment, inflammatory changes on MRI resolve but without a clear clinical correlation.

The MRI hallmarks of IBM are inflammation, fatty infiltration and (asymmetric) atrophy, with fatty infiltration

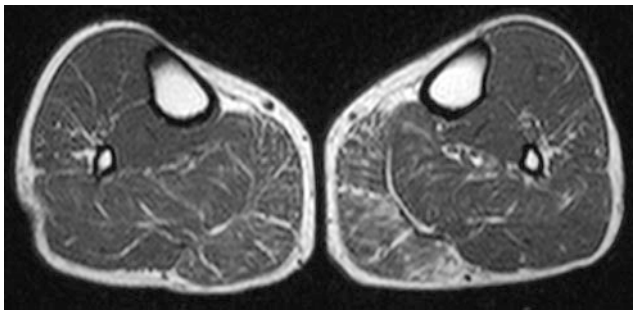

Fig. 4 Axial T1-weighted images of the lower legs showing the beginning of preferential and asymmetric fatty infiltration of the medial gastrocnemius muscle, most pronounced on the left side, in inclusion body myositis

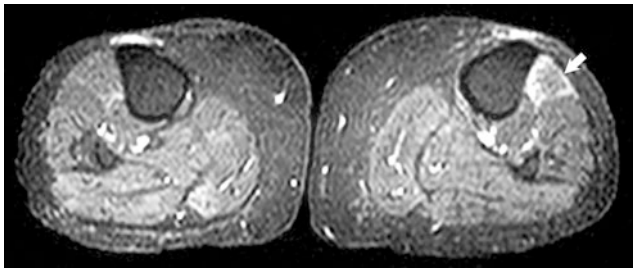

Fig. 5 Axial STIR images through the lower legs showing hyperintensity in the left anterior tibial muscle (*arrow*) in inclusion body myositis

as the most noticeable feature (Fig. 4). Inflammation is erratically present, most often in a patchy focal nature (Fig. 5). It is repeatedly found in the extensor carpi ulnaris, soleus and gastrocnemius muscles.

Fatty infiltration is more prominent in the legs than in the arms, and the lower legs have less muscle bulk left compared to the upper legs. The upper arms are more affected than the shoulder girdle muscles and in the forearm the deep finger flexors appear to be the most vulnerable to fatty infiltration. In the upper legs, the ventral muscles are more affected than the dorsal muscles and adductors, with sparing of the rectus femoris muscle (Phillips et al. 2001). In the lower legs, the medial part of the gastrocnemius muscle appears to be the most susceptible for fatty infiltration, and the lateral head is often spared (Cox et al. 2011a).

Asymmetry of muscle bulk usually follows the clinical pattern of muscle weakness distribution and that of fatty infiltration of muscle groups. Disease duration, the degree of muscle weakness, and functional disability scores correlate well with the level of fatty infiltration in IBM. Fatty infiltration is more usual and apparent in IBM than in PM. Inflammation is less obvious in IBM than in PM and does not relate to the level of weakness.

MRI in NM (Fig. 6) has hardly been reported and shows edema of the thigh muscles (100 %), muscle atrophy (75 %), fatty replacement (67 %), and fascial edema (25 %) in a selection of 16 patients with auto-immune associated necrotizing myopathy (Christopher-Stine et al. 2010).

4.3 Other Magnetic Resonance Imaging Techniques in IIM

Phosphorous magnetic resonance spectroscopy (MRS), ^{31}P MRS, is used to assess energy metabolism in muscle. With this technique, high energy phosphate metabolites phosphocreatinine (PCr), adenosine triphosphate (ATP), and inorganic phosphate (Pi) can be assessed as well as tissue pH (see also chap 8 of this book). In the quadriceps muscles of DM patients, elevated levels of the ratio of Pi/PCr are observed, which is attributed to lower levels of PCr. During exercise, PCr levels drop further compared to controls and the recovery of PCr after exercise is slower in these patients. In addition, the level of phosphorylated sugars is increased compared to control subjects (Park et al. 1990). These changes all indicate disturbed energy metabolism, both at rest and during exercise, and show problems with oxidative ATP production. Interestingly, these abnormalities are also found in mitochondrial dysfunction. The problems in DM are not thought to be due to impaired mitochondrial function, but are due to reduced oxygen supply by the vessels. Also in PM, problems with oxidative ATP production are found, which is in contrast to IBM, where PCr recovery after exercise is normal. In IBM, lower levels of PCr and increased levels of Pi are observed (Argov et al. 1998; Lodi et al. 1998; Cea et al. 2002).

Diffusion-weighted imaging (DWI) enables quantification of the apparent diffusion coefficient, a measure of random motion of water. Using sophisticated models, diffusion of water within the muscle fibers and in the capillary bed can be separated. Using this technique, skeletal muscles of DM and PM patients that appear normal on T1 and T2 weighted images also show no differences in diffusive properties compared to healthy muscles. Muscles with inflammation showed increased diffusion values, which agree with an increase in the amount of fluid in these muscles. In contrast, muscles with fat infiltration show decreased diffusion values, in agreement with a reduction in water content. Interestingly, modeling of the diffusion signal indicates that there is a reduced perfusion volume in muscles with inflammation, which could be due to a reduced capillary bed (Qi et al. 2008).

Magnetic resonance elastography is a method to measure muscle stiffness based upon the propagation of shear waves. A decrease of muscle stiffness is found in patients with PM/DM/JDM (McCullough et al. 2011). Wave attenuation, a viscoelastic parameter, is significantly different in healthy

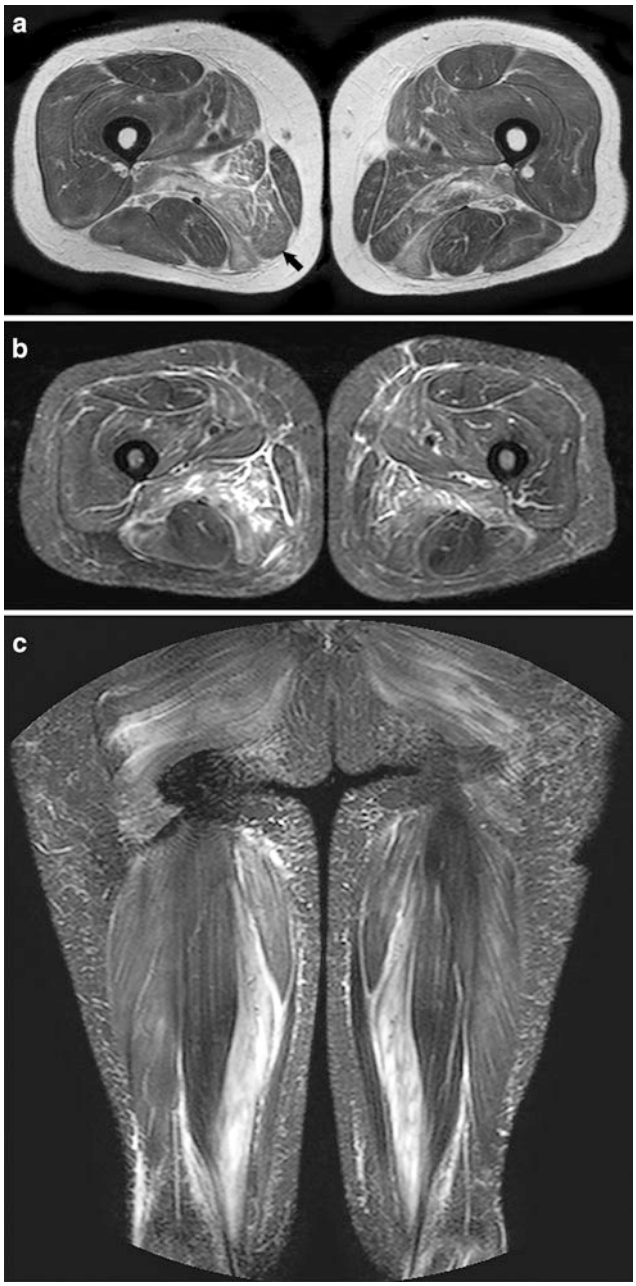

Fig. 6 **a** Axial T2-weighted images (without fat suppression) of the thigh in a patient with necrotizing myopathy with hyperintensities of preferentially the dorsomedial compartment (*arrow*) and fascia **b** Axial STIR images of the thigh of the same patient as in Fig. 5a **c** Coronal STIR images of the same patient as in Fig. 6a

muscles compared to muscle of patients with DM/PM (Domire et al. 2009).

Quantitative and semi-quantitative assessment with MRI has been done by measuring the T2 relaxation time as well as by visual or automated assessment of signal intensity values on fat saturated T2-weighted or STIR images. An increased T2 relaxation time gives rise to increased signal intensity on STIR or fat-suppressed T2-weighted images, but can also be quantitatively and semi-quantitatively assessed to enable a more objective and accurate measure of muscle edema. While this has significant advantages in terms of therapy follow-up or disease monitoring, in severely atrophied and fat infiltrated muscles it is impossible to measure the T2 relaxation time accurately. In the acute phase of DM and PM, semi-quantitative visual analysis of signal intensity correlates well with global disease activity and muscle disease activity (Tomasova Studynkova et al. 2007).

In response to treatment, MRI intensity parameters on STIR and T2-weighted fat-suppressed images improve (Reimers et al. 1994; Fujino et al. 1991). This improvement precedes improvement of muscle biopsy features in a second biopsy (Tomasova Studynkova et al. 2007). Another method based upon pixel intensity values is the myositis index, which uses a histogram of intensity values obtained from STIR images. This method appears to be equally sensitive to changes on MRI in PM, DM, and one patient with IBM as visual analysis (Bartlett et al. 1999).

Whether swift improvement of MRI abnormalities is predictive of a favorable outcome remains to be studied. In JDM, T2 values were measured and compared to inactive JDM. The T2 relaxation time is significantly increased in active JDM and correlates with muscle strength (Maillard et al. 2004).

In IBM, the increased T2 relaxation time of the quadriceps and hamstring muscles is related to the level of muscle weakness (Phillips et al. 2001). In adults, fat-corrected muscle T2 maps may become a useful marker of disease activity (Yao and Gai 2012).

4.4 Other Imaging Modalities Used in IIM

Computed tomography scanning in the inflammatory myopathies can be useful in muscle imaging in IBM, but is less informative in PM and least in DM and NM. CT has a good spatial resolution, but lacks the contrast resolution of MRI to distinguish smaller muscles from each other. In IBM, CT is able to detect fatty infiltration, muscle atrophy, and asymmetry, but inflammation is missed as is the case in the other types of immune-mediated myopathies. Although CT scanning is widely available, faster, less sensitive to motion artifacts and cheaper, it has the disadvantage of ionizing radiation exposure and is less informative compared to MRI, especially in detecting edema-like muscular changes. Therefore, MRI is the preferred imaging modality unless contraindications exist, such as certain metal implants like pacemakers and cochlear implants or claustrophobia, making it impossible to use. CT is superior in detecting muscle calcifications.

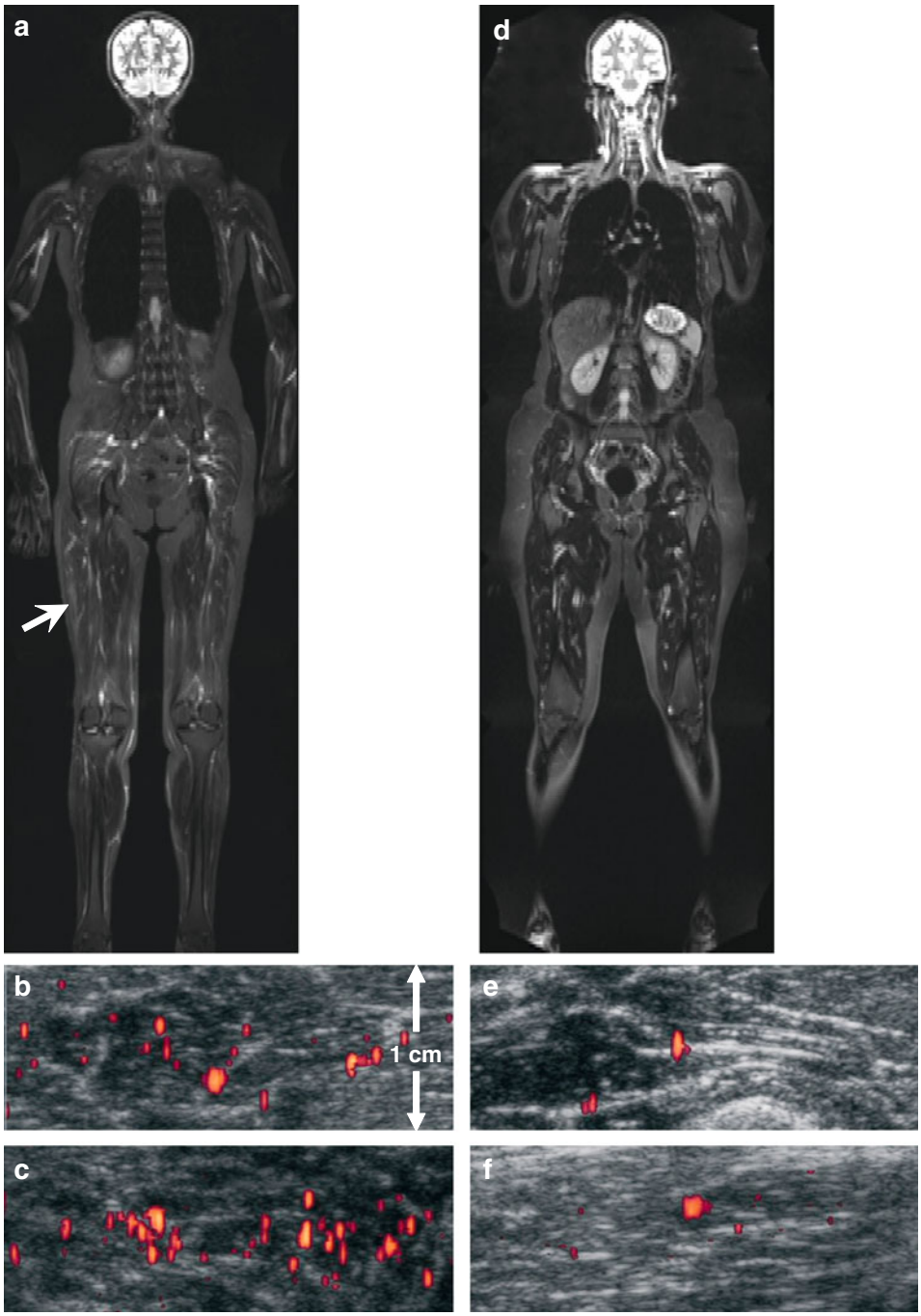

Fig. 7 **a**–**c** 64-year old woman with DM. **d**–**f** 36-year old woman with final diagnosis of collagenosis and exclusion of myositis on histologic analysis. **a** and **d** Whole-body MR imaging using a fat-suppressed T2-weighted short tau inversion recovery sequence. Transverse images of power Doppler sonography (7 MHz) after bolus injection of 10 mL Levovist in 1.5 cm depth (focus area) showing initial increase **b**, **e** and maximum plateau **c**, **f**) of microbubbles' replenishment. In DM, a focal area of moderate signal enhancement in the right vastus lateralis muscle is visible (*arrow* in **a**), whereas in the other patient, muscles are free of pathological signal alterations **d**. The corresponding contrast-enhanced power Doppler signals clearly visualize the higher concentration of microbubbles in muscle tissue of the woman with myositis **b**, **c** due to the higher muscle perfusion. Reprinted from Weber et al. (2006) J Neurol 253: 1625–1632 with permission from Springer

Muscle ultrasonography can be used to detect inflammation in muscles and has, in particular, been described in PM and DM patients. Affected muscles show increased echogenicity and the fasciae and septa become obscured and the normal architecture changes. Contrast-enhanced intermittent power Doppler ultrasound in PM and DM showed significant higher blood flow velocities, blood volume, and blood flow compared to patients without myositis, with blood flow being the best measure for DM and PM with a sensitivity of 73 %, a specificity of 91 %, a positive predictive value of 80 %, and a negative predictive value of 88 % (Weber et al. 2006) (Fig. 7). Ultrasound is compared with MRI often readily available, not distressing, and easy to do without contraindications and cheap. Reproducibility may vary between sonographers. Ultrasound can be used for muscle biopsy guidance as well to reduce the false-negative rate. MRI, however, gives a more global scope on involvement because more muscles and even deeply located muscles are investigated at once than with ultrasound. Calcifications can also be

detected by ultrasound as bright echogenic foci with acoustic shadowing.

Scintygraphy has been used to assess myositis using technetium (Tc 99 m), gallium (Ga 67), and indium (In111) altumomab pentetate-labeled antimyosin antibodies. Uptake of antimyosin antibody in the legs correlates with myositis activity based on CK levels (Lofberg et al. 1998). Scintigraphy lacks the ability to distinguish between lesions in different muscle groups and does not reflect atrophy or fatty infiltration compared to MRI.

Swallowing video-fluoroscopy is the method of first choice to objectively assess dysphagia. Dysphagia is common in the idiopathic inflammatory myopathies. Obstruction due to cricopharyngeal dysfunction, vallecular and piriform sinus residues, pharyngeal weakness, diverticula and aspiration can be visualized.

18F-fluorodeoxyglucose-PET/CT has limited value in detecting active inflammation in PM and DM patients because of its low sensitivity; the diagnostic yield is lower than that of EMG, MRI, and muscle biopsy (Owada et al. 2012). However, it is useful in the detection of malignancies and one study group advocates that it is equally sensitive to conventional screening with CT scanning of the chest and abdomen, mammography, gynecological screening, ultrasonography, and tumor marker analysis (Selva-O'Callaghan et al. 2010a). However, cost and accessibility have to be weighed against personal convenience and distress of these investigations.

5 Other Idiopathic Inflammatory Myopathies

Granulomatous myositis can occur in isolated form, as part of sarcoidosis or secondary to a disorder associated with skeletal muscle granuloma such as inflammatory bowel disease, thymoma, myasthenia gravis, and lymphoma. It can be asymptomatic or present as a subacute or chronic myositis. The acute form presents with proximal muscle weakness, whereas the chronic form can evolve into a clinical picture that is indistinguishable from IBM (Le Roux et al. 2007; Larue et al. 2011). On MRI of the thigh, preferential affliction by fatty replacement in the adductors and semimembranosus muscles, with relative sparing of the rectus femoris and semitendinosus muscles has been described in chronic cases (Reimers et al. 1994), but given the small numbers of patients investigated is it still uncertain whether MRI may be helpful in discriminating between IBM and isolated granulomatous myositis.

Eosinophilic polymyositis occurs as part of the hypereosinophilic syndrome with an idiopathic rise of eosinophils causing infiltration and clinical signs and symptoms of the involved organs. There is slow onset of muscle aching with weakness of proximal muscles. There can be skin changes, Raynaud phenomenon, and small hemorrhages of the nail beds. Serum CK is elevated and the muscle biopsy shows predominantly eosinophilic infiltration, scattered necrosis, and regeneration of muscle fibers. MRI data are scarce, but suggest a diffuse and irregular hyperintensity of muscle on STIR images (Hundt et al. 1999; Layzer et al. 1977).

6 Therapy in Idiopathic Inflammatory Myopathies

The first line of treatment in DM and PM is administration of corticosteroids, based on empirical data, in order to improve muscle strength. High dose prednisolone is given during 6–8 weeks and then tapered off during a year. Pulsed oral dexamethasone compared with daily oral prednisolone is equally effective, but the latter has more side effects but a longer median time to relapse (van der Meulen et al. 2000). A second immunosuppressive agent (azathioprine, methotrexate, cyclophosphamide, cyclosporine A) is added in case of relapse, ineffective treatment, failure to lower the prednisolone dose in time, or in order to minimize side effects. Sometimes intravenous immunoglobulin is used. Treatment of a concurrent neoplasm can result in improvement or fading of clinical symptoms.

In IBM, none of the immunosuppressive or immunomodulating therapies tested have shown long-term benefit, neither improvement, nor stabilization of the disorder. Intravenous immunoglobulin may temporarily improve dysphagia.

Chronic obstructive dysphagia in the IIM can be treated with a cricopharyngeal myotomy. Botulinum toxin injections have been reported to be effective as well. Sometimes a percutaneous gastrostomy is needed to prevent cachexia and orally administered fluid or food aspiration.

7 Infectious Inflammatory Myopathies

The infectious inflammatory myopathies can be split up into viral, parasitic, fungal, and bacterial myopathies. Apart from infectious myositis via the direct infection of skeletal muscle, microorganisms may also cause myositis past immune mechanisms. Bacterial myositis ordinarily presents with focal infection of the muscle, whereas viruses and parasites present with a more diffuse clinical picture of widespread myalgia or multifocal muscle involvement.

Acute viral myositis is a disorder following a short illness, usually accompanied by fever, associated with a viral infection. The most common symptom is myalgia, but muscle tenderness and swelling, weakness, and a moderately

elevated serum CK can accompany this disorder. Benign acute childhood myositis begins within a week after developing symptoms like malaise, fever, sore throat, headache, nausea or rhinorrhea, and usually starts with pain of the calves, gait difficulties, and sometimes leading to refusal to walk. It most commonly resolves within a week (Middleton et al. 1970; Rubin et al. 2010). It is related to an Influenza virus infection but has also been described after adenovirus, parainfluenza virus, respiratory syncytial virus, and herpes simplex virus infections. Muscle biopsies of the gastrocnemius muscle may show necrosis and mononuclear inflammatory infiltrates depending on the time between the biopsy and initial symptoms. Influenza virus myositis in adults is uncommon, but when present, weakness and tenderness are more diffuse compared to children.

Overall, acute viral myositis in adults is rarely described in large series, but has been associated in small series and case reports with many viruses, such as Epstein-Barr virus, echovirus, cytomegalovirus, human immunodeficiency virus (HIV) type I, adenovirus, herpes simplex virus, hepatitis B and C, dengue virus, and parainfluenza virus.

Subacute viral myositis, resembling adult-onset PM, typically occurs in retrovirus-related viral infections, such as HIV and human T-cell lymphotropic virus type I (HLTV-I). HIV polymyositis starts with proximal symmetric weakness of the legs, which extends to the proximal arm muscles, with or without muscle wasting. Serum CK is elevated 10–15 times the upper limit of normal. Muscle biopsy shows perivascular, perimysial or endomysial, predominantly mononuclear, infiltrates surrounding and invading non-necrotic muscle fibers, with necrosis and degeneration (Johnson et al. 2003). Muscle MRI shows hyperintensity on T2-weighted sequences and isointensity on T1-weighted images (Restrepo et al. 2004). HLTV-I polymyositis occurs in regions where HLTV-I is endemic such as in the Caribbean region (especially Jamaica and Haiti).

The most common parasitic infections of muscle are trichinosis, toxoplasmosis, and cysticercosis. Trichinosis, caused by the nematode *Trichinella spiralis*, is characterized by a period of nausea, anorexia, diarrhea, and abdominal pain followed by fever, muscle pain, and tenderness of particularly proximal muscles and muscle weakness. There can be skin involvement resembling that of DM. The infection is transferred through inadequately cooked meat of pork, bear, and walrus. The diagnosis can be confirmed by serum antibodies against Trichinella or by identification of *Trichinella* larvae in the muscle biopsy. Toxoplasmosis, caused by *Toxoplasma gondii*, can mimic polymyositis and DM, usually in immune-compromised hosts. The myositis can appear to be present alone with fever and lymphadenopathy or may be accompanied by other features such as pneumonia, hepatitis, uveitis, meningoencephalitis, hepatosplenomegaly, hepatitis, or chorioretinitis. The diagnosis can be established by serological tests, but can also be established by isolation of *T. gondii* from blood or demonstration of cysts or trophozoites in the muscle biopsy or other histological specimens. Muscle biopsy shows inflammation with lymphocytes, histiocytes, and giant cells in the perimysium and endomysium. Transmission of the infection usually occurs through ingestion of ill cooked meat and through contact with feces of cats. Cysticercosis is caused by *Taenia solium* and transmitted through ingestion of *T. solium* eggs excreted in the feces of human carriers of the tapeworm. Infestation of the muscle is often asymptomatic and accidentally discovered on radiographs of muscles with calcified cysts with a "puffed rice" presence. In rare cases, it may present as a pseudohypertrophic myopathy with symmetric enlargement and tenderness of muscles, in particular of the calf muscles. Muscle MRI, CT, and ultrasound investigations may all show cysts, however MRI is superior in detecting cysts and CT is superior in visualizing calcifications The scolex is best seen with ultrasound (Jankharia et al. 2005). Ultrasound reveals an intramuscular anechoic area with an eccentric echogenic intraregional focus suggestive of scolex. MRI shows oval cysts with hypointense signal on T1 and hyperintense signal on T2-weighted images. There is perilesional contrast enhancement, suggestive of edema, and the lesions are oriented along the muscle fiber direction (Tripathy et al. 2012). The diagnosis is confirmed by serological or histological testing. American trypanosomiasis, also called Chagas disease, may present with a PM/DM syndrome in the beginning of the disease. Diagnosis is made by demonstrating *T. cruzi* in the blood or in tissue. Transmission occurs through a bite from an infected vector, the *reduviid* bug, or through blood transmission. A travel history to an endemic region or eosinophilia in blood should give rise to the suspicion of a parasitic infection. Other parasites giving cause to myositis or myalgia are *Sarcocystis spp.*, *Entamoeba histolytica*, *Echinococcus spp.*, *Toxocara canis*, *Microsporidia spp.*, *Schistosoma spp.*, *Spirometra mansonoides*, *Plasmodium falciparum*, and *Onchocerca volvulus*.

Fungal myositis is especially seen in the immune-compromised host. The most common infections are with *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Aspergillus spp.*, *Coccidiodes spp.*, *Pneumocystis jiroveci*, *Fusarium spp.*, and *Candida spp.*, *Candida spp.* gives rise to multiple diffuse microabscesses, which can be localized with ultrasound, CT, and MRI imaging for the purpose of muscle biopsy for diagnostic confirmation.

Bacterial muscular infections can be related to infection through extensio per continuitatem by nearby open wounds or penetrating trauma or through hematogenous spread. The etiology of the infection is related to the type of bacteria involved. In hematogenous dissemination, *Stafylococcus*

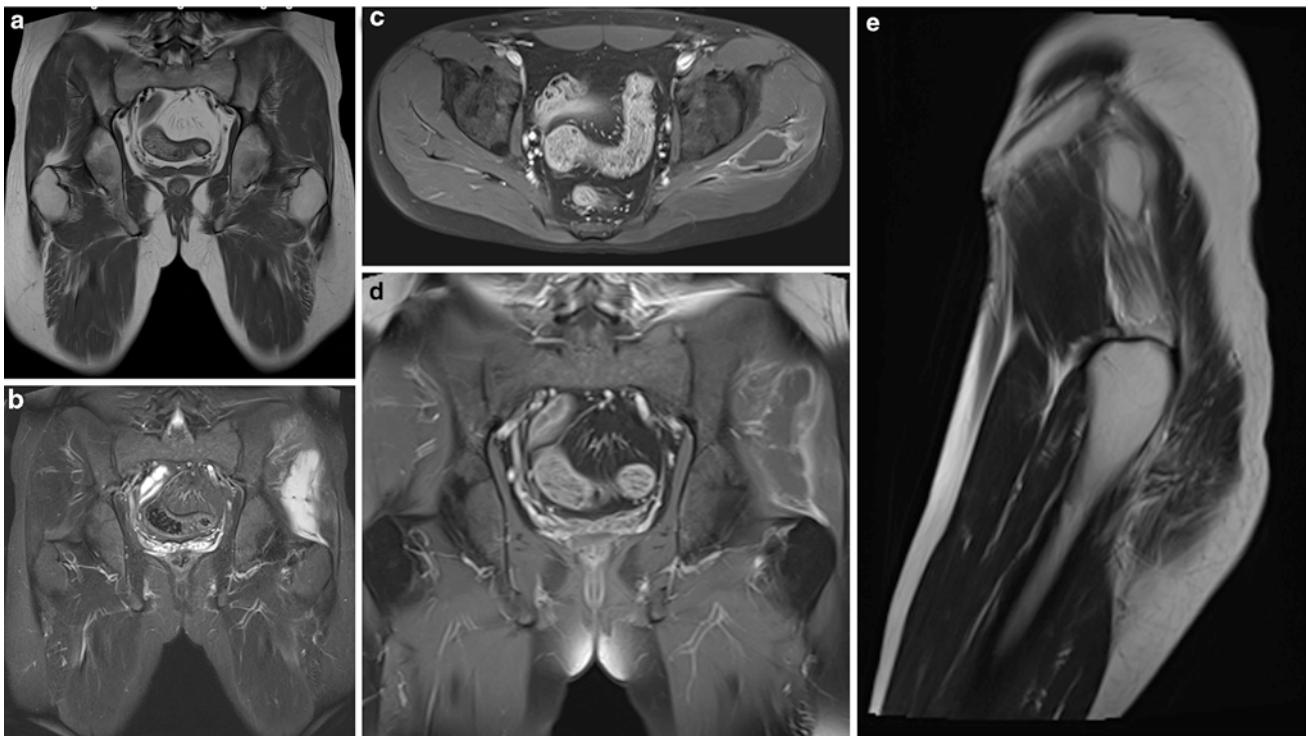

Fig. 8 A 23-year-old woman with muscle abscess formation in the left gluteal muscles. MRI images (coronal T1-weighted (**a**) and STIR images (**b**), axial (**c**) and coronal (**d**) fat-saturated contrast-enhanced T1-weighted images and sagittal T2-weighted (**e**) image) show a hyperintense area on STIR and T2-weighted images with a gadolinium enhanced rim on T1-weighted images (images courtesy of Prof. Dr. M.-A. Weber, Heidelberg)

aureus is the most common causative organism resulting in pyomyositis, or when located in the psoas muscle usually referred to as psoas abscess. Pyomyositis is increasingly diagnosed due to the increase of immune-compromised hosts as a result of more prevalent immune-deficiencies and greater use of chemotherapy and immunomodulating therapies. It usually develops gradually with local swelling, slight pain, and undulating temperatures during one or a few weeks followed by more obvious fever and muscle aching. This may be followed by sepsis. Pyomyositis is usually restricted to one muscle group, but can be more diffuse in a minority of patients. It can present in any muscle group. There is, however, a preference for the lower extremities, in particular the glutei and quadriceps muscles. The diagnosis can be made through imaging and aspiration of fluid from the abscess. CT scanning shows muscle enlargement and hypodense areas in the muscle with fluid collections in the center and with enhancement of the rim after administration of intravenous contrast fluid (Gordon et al. 1995). MRI images show hypointense areas with a gadolinium-enhanced rim on T1-weighted images (Fig. 8). More diffuse heterogeneous or homogeneous intermediate signal intensity on T1-weighted images and high signal intensity on T2 weighted images can be seen in muscle infection without an apparent fluid collection. Frequently, there is spread of infection to subcutaneous tissue, deep fascia, and bone marrow, all seen as low signal intensity on T1 and high signal intensity on T2-weighted images (Soler et al. 2000). CT scanning with contrast appears to be equally effective in detecting abscesses as Gadolinium-enhanced MRI (Gordon et al. 1995). Fat-suppressed T2-weigthed images appear to be as good as, but probably better than Gadolinium-enhanced T1-weighted images in detecting inflammatory changes in muscle (Miller et al. 1997). Diffuse bacterial infection of muscle without abscess formation, is rare in comparison to pyomyositis and psoas abscess. Many types of bacteria have been associated with acute bacterial myositis, such as for example *S. aureus* and group A and B streptococci, *Legionella* and *Borrelia burgdorferi*.

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