Endomysial lymphocytic infiltrates are considered to be a key histological feature of IIM with some muscular dystrophies [2]. The late onset presentation of the dysferlinopathies and the clinical presentation of these disorders can be potentially toxic immunosuppressive drugs as highlighted in our recent routine molecular evaluation. Further, DNA testing confirmed the diagnosis of Becker muscular dystrophy (BMD). The prevalence of the idiopathic inflammatory myopathies (PM and dermatomyositis (DM)), is estimated at about eight per 100 000 in the general population. It is important to establish a correct diagnosis of IIM to avoid unnecessary exposure of potentially toxic immunosuppressive drugs as highlighted in our cases. The diagnosis of PM may be confused with dystrophinopathies in particular BMD, isolated female carriers of Duchenne muscular dystrophy (DMD) and the recently described dysferlinopathies as the clinical presentation of these disorders can be similar. The late onset presentation of the dysferlinopathies and milder form of the two dystrophinopathies can often be misdiagnosed as PM.

There are pitfalls in the interpretation of a muscle biopsy that could lead to a clinical misdiagnosis. Recent routine molecular diagnostic testing for dystrophies has highlighted the overlap histological features of IIM with some muscular dystrophies [2]. Endomysial lymphocytic infiltrates are considered to be a key pathologic feature of PM but can also occur in DMD, BMD, dysferlinopathies and facioscapulohumeral dystrophy leading to an initial incorrect diagnosis of PM [3].

Another frequent error in interpreting muscle biopsies is not performing immunocytochemistry to assess for deficiency of sarcolemmal proteins that can cause muscular dystrophies. An assessment of class I major histocompatibility complex antigen with immunocytochemistry is important as it is a consistent finding in PM [4]. Although this is helpful, it is not specific and has also been found in patients with dystrophies [5]. Recent advances have led to the availability of genetic testing which can be extremely helpful [6].

The presence of auto-antibodies may help in distinguishing IIM from muscular dystrophies. ANA are present in up to 89% of patients with IIM [7]. Thus, the absence of a positive anti-nuclear antibody should raise doubt about the diagnosis. However, the presence of auto-antibodies does not completely exclude non-inflammatory myopathies as illustrated in the second case.

There was no family history of muscle disease in the three cases presented suggesting the sporadic nature of some forms of muscular dystrophies.

In conclusion, neuromuscular diseases can mimic IIM. In patients thought to have IIM, the absence of ANA and a poor response to immunosuppression should prompt re-consideration of the diagnosis and re-biopsy.

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Severe disabling tendinopathy caused by anastrozole

SIR, Aromatase inhibitors are a group of drugs that are used in the adjuvant treatment of oestrogen receptor-positive breast cancer. Musculoskeletal symptoms are frequently observed during treatment with aromatase inhibitors [1]. Mostly, the complaints consist of arthralgias, muscle weakness, morning stiffness and bone pain. Also osteoporosis and arthritis may occur. Recently, tenosynovitis...
occurring during treatment with aromatase inhibitors has been described [2].

In this case report, we describe a patient with severe, disabling tendinopathy during treatment with the aromatase inhibitor anastrozole (Arimidex®).

Case report
A 55-yr-old woman was referred to our Department of Rheumatology for severe, disabling pain and swelling at the wrists. A year before she had started treatment with anastrozole because of oestrogen receptor-positive breast cancer. Since then, she experienced non-severe myalgias and morning stiffness. Pain and swelling at the radial side of the right wrist occurred after 5 months of treatment with anastrozole and had worsened since. In addition, she had pain in the Achilles tendons, but no pain or swelling of joints. She did not use drugs other than anastrozole. Non-steroid anti-inflammatory drugs and splintage had no effect. The week before presentation, pain and swelling also occurred in the left wrist.

At physical examination there was a tender swelling on the radial side of both wrists (Fig. 1A). Resisted extension and abduction of the thumbs was also very painful. Finkelstein’s test was negative. Both Achilles tendons were tender. There were no signs of arthritis, and no further abnormalities at physical examination.

Laboratory tests revealed a normal ESR (2 mm in first hour) and CRP (<5 mg/l). Blood count, renal function, liver enzymes and rheumatoid factor were normal. There were no anti-CCP antibodies. Thyroid function was normal. There was no hypercholesterolaemia. Radiographs of hands and wrists showed no abnormalities, neither did skeletal scintigraphy. Ultrasound showed a thickening and irregular aspect of the tendon of the abductor pollicis longus muscle on the right wrist (Fig. 1B). There were no signs of tenosynovitis such as a peri-tendinous fluid collection or swelling. Power Doppler revealed an increased vascularity of the tendon, confirming active inflammation. Based on these findings, the diagnosis of tendinopathy of the tendon of the abductor pollicis longus muscle was made. Treatment with anastrozole was discontinued. After this, the pain in the Achilles tendons resolved completely, but an additional local corticosteroid injection was needed for further improvement of the wrist symptoms.

Discussion
Aromatase inhibitors are increasingly used as adjuvant hormonal therapy in post-menopausal patients with oestrogen-positive breast cancer. These drugs cause a depletion of oestrogen and thereby prevent progression of the disease. Musculoskeletal symptoms, especially arthralgias and myalgias, have been reported in up to 5.4–35.6% of patients during use of aromatase inhibitors [1]. Mostly, these complaints diminished in the first year after start of treatment, but, in some cases, the drugs had to be discontinued because of severe arthralgias [3]. Also carpal-tunnel syndrome has been reported [4]. It has been suggested that aromatase inhibitors inhibit the antinociceptive effects of oestrogen by depleting oestrogen levels, thereby decreasing the threshold for painful stimuli. Furthermore, oestrogen might exert effect on inflammation in the joint [5]. Recently, Morales et al. reported tenosynovitis in 12 patients treated with either letrozole or exemestane [2]. Six of these patients had to discontinue treatment because of disabling pain.

In our patient, a De Quervain’s tenosynovitis appeared to be unlikely because there was no peri-tendinous fluid or swelling at ultrasound, as is often seen in the De Quervain’s tenosynovitis [6]. The involvement of both wrists and the Achilles tendons suggest the presence of a (diffuse) tendinopathy.

Possible causes of tendinopathy were reviewed by Riley in 2004 [7]. Inherited disorders can lead to deficient or abnormal collagen or abnormal fibril structure. Endocrine and metabolic disorders may lead to altered collagen metabolism or deposits between fibrils. Finally, rheumatologic diseases may cause destruction of collagen by inflammation. Also other intrinsic factors, like age and joint laxity and extrinsic factors like occupation and sport may be implicated in chronic tendinopathy.

Tendinopathy of the Achilles tendon is often associated with vigorous physical activity or use of drugs like fluoroquinolone antibiotics or steroids [8].

In our patient there were no signs of underlying systemic disease, there was no abnormal physical activity preceding the complaints and she used no other drugs beside anastrozole. Furthermore, the complaints improved after discontinuation of anastrozole. Therefore, the anastrozole is thought to be the cause of the tendinopathy in this patient.

To our knowledge, this is the first case describing a tendinopathy caused by an aromatase inhibitor. As complaints caused by tendinopathy can be severe and aromatase inhibitors are increasingly used in the treatment of breast cancer, one has to be aware of this possible side effect.

Rheumatology key message

- Aromatase inhibitors can cause a painful, disabling tendinopathy.

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Successful treatment of refractory lupus-associated haemophagocytic lymphohistiocytosis with infliximab

Sir, Tolerance of tumor necrosis factor-α (TNF-α) inhibitors is usually excellent, but a number of recent publications call attention to some potentially paradoxical reactions to TNF-α inhibitor therapy, worsening or new-onset palmo-plantar pustulosis or psoriasis [1], as well as lupus-like syndrome and inflammatory bowel disease. It is puzzling that medications used to treat one disease may induce the same disease, suggesting a complex role of TNF-α inhibitors. Recently, some case reports of haemophagocytic lymphohistiocytosis (HLH) after treatment with TNF-α inhibitors were published [2, 3]. Here, we report a case of refractory HLH who was treated successfully with a TNF-α inhibitor, infliximab (IFX).

The activity of SLE was considered to be high because of fever, arthralgia, headache and fatigue increased to 25 mg/day on day 3 of admission, but her fever, headache, fatigue and pancytopenia did not improve, with a further increase in the serum ferritin level of 2943 ng/ml on day 13. HLH [4] was suspected, and a bone marrow aspiration was done, which showed marked haemophagocytosis (myeloid/erythroid ratio: 4.8). Several treatments including two courses of methylprednisolone (mPSL) pulse, cyclosporin-A (CSA), intravenous cyclophosphamide pulse (IVCY, 500 mg/day) and intravenous immunoglobulin (IVIG, 15 g/day) for 3 days did not improve her condition. Then, we decided upon a trial of anti-TNF-α monoclonal antibody therapy, infliximab (IFX; 5 mg/kg/day, total 200 mg) on day 55. Three days after IFX therapy, her fever subsided and constitutional symptoms including headache and fatigue decreased markedly. Her pancytopenia gradually recovered. Increased levels of inflammatory cytokines and haemoglobin (HO-I) [5] normalized on day 70 (15 days after IFX) (Fig. 1). In June 2007, she was in a good condition with PSL 8 mg/day and CSA 50 mg/day after single administration of IFX.

It is well known that TNF-α is an early co-ordinator of the cytokine response to injury and is elevated in inflammatory diseases such as rheumatoid arthritis (RA). However, chronic TNF-α stimulation has the paradoxical consequences of both acting as an anti-inflammatory and down-regulating T cell responses. Ablation of TNF-α signalling by genetic TNF-α receptor deletion accelerates autoimmunity in lupus-prone NZB mice [6]. This dichotomy is also reflected in the clinical response to TNF-α inhibition.

TNF-α is one of the major pro-inflammatory cytokines that have been suspected to be responsible for the pathogenesis of HLH. TNF-α binds to soluble TNF-α receptors (sTNF-R1 and/or sTNF-R2) that are shed into the circulation, and TNF-α bound to its soluble receptor is not detected by the immunoassay for TNF-α [7]. Thus, rather than measuring TNF-α, the concentrations were examined of sTNF-R1 and/or sTNF-R2, which are the natural homeostatic regulator of the action of TNF-α and which provide a better indication of the true biological activity of TNF-α [8]. Our patient revealed significantly high levels of sTNF-R1 and sTNF-R2 regardless of low level of TNF-α, which indicated highly activated TNF-α.

To date, anti-TNF-α therapy has been reported in five patients including our case for diseases involving histiocytic-lineage cells [9, 10]. All patients were young (4–29 yrs), and anti-TNF-α therapy was dramatically effective (duration to remission ranged from 24 h to 40 days). Two patients were treated with IFX, in whom remission was introduced by only one or two administrations of IFX.

On the other hand, there are four reports of anti-TNF-α therapy being implicated as potential triggers for HLH. Two case reports describe anti-TNF-α induced infection associated HLH [2]. In other two case reports, the causes of HLH were unknown [3]. These case reports suggest that immunosuppression induced by the anti-TNF-α treatment may favour the occurrence of serious infectious events leading to HLH [10]. Seen from another standpoint, in the same way of psoriasis, paradoxical function of TNF-α might induce new-onset HLH. Anti-cytokine therapies are remarkably effective for some HLH patients; however, they should be administered carefully to infection-associated HLH.

In our highly refractory lupus-associated HLH, IFX dramatically improved the patient’s condition. Anti-TNF-α drugs could be an effective therapy for some refractory lupus-associated HLH.