PostScript

Why a positive genetic test for myotonic dystrophy type I does not always imply the right diagnosis

As the clinical symptoms and some diagnostic findings were suspicious for myotonic dystrophy type 1 (DM1), genetic testing of the patient's peripheral blood cells was carried out,⁴ although the family history at this time point was negative for genetic myopathies. Routine Southern-blot analysis from blood DNA² showed 350–450 cytosine–thymine–guanine (CTG) repeats of the myotonic dystrophy protein kinase locus (fig 1A). These findings formally proved the diagnosis of DM1. However, neither of the patient's parents had DM1. Therefore, we challenged this diagnosis and collected a detailed medical history of the patient's family. This unearthed that the patient's cousin (the above-mentioned bone marrow donor) and uncle had symptoms compatible with a myotonic disorder—for example, progressive muscle weakness, muscle atrophy and "eye problems"—which could not be further specified. We assumed that peripheral blood cells carrying a CTG-repeat expansion might have been transferred to the patient from the bone marrow donor, who himself had DM1.

DM1 usually comprises characteristic clinical signs and diagnostic features such as distally accentuated muscle weakness with myotonia, attendant endocrinological disturbances and a positive family history for the disease. However, symptoms and disease course can vary noticeably among different patients from the same family owing to variable gene expression and gene penetration. In addition, spontaneous mutations can occur in previously unaffected collectives. Therefore, the

Muscle tissue is affected in some people with chronic graft-versus-host disease.⁵ In line with our report, symptoms can include muscle cramps, paresis and atrophy. In addition,

Figure 1 (A) Long-range polymerase chain reaction (PCR) products of the cytosine–thymine–guanine (CTG) repeat at the dystrophy protein kinase locus (DMPK) as detected by Southern blot. (B) Genealogical tree indicating the relationship of the reported patient with the bone marrow donor. C, controls; P, patients with DML; arrows, blood DNA (b) and deltoid muscle DNA (m) of the index patient; SM, size marker; light grey square, index patient; dark grey boxes, patients with DML.

unspecific symptoms such as weight loss have been described. Histological changes can comprise muscle fibre loss or atrophy and interstitial immune cell infiltration, thus corroborating our biopsy findings.

Taken together, this case illustrates that a detailed family history is essential in patients having myopathic symptoms and can help to avoid expensive diagnostic tests.

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Myotonic dystrophy type 1 (DM1) is a progressive muscle disease with characteristic neurological symptoms such as distally accentuated paresis and myotonia. Diagnostic hallmarks include a positive family history (autosomal-dominant inheritance), myotonic discharges in the electromyogram and attendant metabolic disturbances.

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Panniculitis and lipoatrophy after subcutaneous injection of interferon β -1b in a patient with multiple sclerosis

Recombinant interferon (IFN) β is currently the most commonly prescribed treatment for long-term immunomodulation in multiple sclerosis, and is generally a well-tolerated treatment. Reactions to IFN β at the injection site are a common side effect, ranging from the frequently observed transient erythema to a more severe cutaneous necrosis in 5% of patients.¹ We describe a patient presenting with panniculitis and subsequent lipoatrophy, secondary to IFN β -1b treatment for multiple sclerosis. To our knowledge, this

case is the first to show this syndrome in relation to IFN β -1b injections.

A 37-year-old man with relapsing–remitting multiple sclerosis presented with a 5-day history of pain in the left thigh, diaphoresis and rigors. This had started 6 days after subcutaneously injecting IFN β -1b (Betaferon, Schering, AG, Berlin, Germany), which he had been using for 27 months, at that site. He did not have arthralgia or myalgia. He had been diagnosed with multiple sclerosis 3 years earlier after an episode of transverse myelitis, and had had four relapses in the interim. Flu-like symptoms and mild reactions at the injection site had developed after initiation of IFN β treatment, but had resolved spontaneously. He also had a diagnosis of migraine, for which he took sumatriptan and diclofenac. There was no history of drug allergies. He did not smoke. He denied previous tuberculosis infection, or a history of connective tissue disorders. On examination, the patient was febrile, and the anteromedial left thigh was swollen, warm, erythematous and tender, with inguinal lymphadenopathy on the same side. Fluctuance was not elicited. Full blood count showed a white cell count of $13.8 \times 10^9/l$, with neutrophilia.

Cellulitis secondary to subcutaneous injection was diagnosed, and he was treated with intravenous flucloxacillin and benzylpenicillin. IFN β was stopped temporarily. An attempt at aspirating the area did not produce any pus, and blood cultures were negative. Ultrasound of the thigh showed an abnormal hypo-echoic area 2.5 cm long and up to 1 cm deep, with some oedema of the surrounding soft tissues. The lesion gradually improved and he was discharged. On review 1 month later, swelling was still evident, although it continued to improve. Interferon was restarted 1 month later.

Four months after the initial episode, the patient had similar symptoms and physical findings, which did not improve with oral antibiotics and a cyclo-oxygenase-2 inhibitor. Again, cellulitis was diagnosed, and IFN β was stopped. A venogram was carried out to rule out an underlying venous thrombosis. The lesion slowly improved after treatment with antibiotics and the patient was discharged. One month later, he started treatment with glatiramer acetate, which he did not inject into the left thigh.

However, the patient presented with pain and swelling of the left thigh on two further occasions, 14 and 19 months after the initial episode. On both occasions, he was treated with intravenous antibiotics. A dermatology opinion was requested, and a skin biopsy was carried out during the second of these episodes. This showed a septal panniculitis, with septal fibrosis and paraseptal lymphohistiocytic inflammation, consistent with erythema nodosum (fig 1). No evidence of vasculitis, neutrophilic infiltrate or histological evidence of deep vein thrombosis was seen on biopsy. The serum angiotensin-converting enzyme (ACE) concentration was moderately raised at 92 U/l (normal range 0–45 U/l). Mantoux test was negative and chest x ray was normal. Serum calcium, urinary calcium excretion, α -1-antitrypsin levels, autoimmune serology, pulmonary function tests and bronchoscopy were also normal. Endobronchial biopsy was normal and did not show any granulomas. We diagnosed panniculitis secondary to IFN β injection. One year after diagnosis, the patient has not had a recurrence; however, the anterior left thigh

Figure 1 Punch biopsy of skin and subcutaneous fat, showing septal fibrosis and paraseptal lymphohistiocytic inflammation.

Figure 2 Lipoatrophy postpanniculitis.

shows marked lipoatrophy (fig 2), which does not affect the other injection sites where he continues to administer glatiramer.

The panniculitides are a group of heterogeneous inflammatory diseases involving the subcutaneous fat, of which erythema nodosum is the most common type. Numerous drugs including sulphonamides, oral contraceptives, phenytoin and salicylates have been associated with panniculitis. Connective tissue diseases such as systemic lupus erythematosus, pancreatic diseases and α -1-antitrypsin deficiency are also associated with panniculitis. Panniculitis may be seen in infections or trauma involving subcutaneous fat. Lipoatrophy is the loss of subcutaneous fat due to a previous inflammatory process involving the subcutis, and it may be the late-stage lesion of several types of panniculitis.²

On literature review, we identified another case of panniculitis after IFN β injections in a patient with multiple sclerosis.³ This patient was taking IFN β -1b for 4 years before the development of panniculitis, with a history of erythematous patches developing at injection sites shortly after the initiation of IFN β treatment. Vasculitis was not seen on dermis and fatty tissue biopsy, and subsequent lipoatrophy was not documented. Although glatiramer acetate has been associated with lipoatrophy, only one recent report describes non-reversible lipoatrophy occurring in a patient with multiple sclerosis during IFN β -1a treatment.⁴

Buttmann *et al*⁵ discuss theories of how IFN β -1a may induce cellular skin infiltration by at least three different pathways: (1) IFN β itself may exert a chemotactic effect on immune cells; (2) IFN β may directly stimulate local adhesion molecule and chemokine expression; and (3) IFN β may indirectly stimulate local adhesion molecule and