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A case of leg pain and weakness in a man with diabetes

A 61-year-old man presented to his general practitioner in June 2001 with pain and weakness in both legs. He had a 31-year history of type 2 diabetes, treated with insulin for the previous 5 years. He had been treated with cerivastatin since October 2000 for hypercholesterolaemia. His serum creatine kinase (CK) was raised at 1040 IU/l (normal range 25-195). Renal function was normal. The cerivastatin was stopped. Two weeks later his CK had fallen to 734. A diagnosis of cerivastatin induced myositis was made.

In August 2001 he attended the diabetic clinic. He still had pain and weakness in his legs. He had felt well enough to go on a walking holiday in July. This had resulted in an elevation of his CK to 1033 although this had fallen to 770 by August. HbA1c was 6.9% and total:HDL cholesterol ratio was 3.9. The rise in CK was presumed to be a worsening of his myositis following the walking holiday.

By September 2001 the patient was no better and was referred to the rheumatology clinic. Although the pain was settling, he had continuing weakness in his legs which had resulted in two falls. Cardiovascular, respiratory, abdominal and musculoskeletal examinations were normal. There were no skin rashes. Neurological examination of his upper limbs was normal but there was bilateral wasting of his lower limb muscles. The muscle tone was normal. Power was reduced to 4/5 bilaterally, worse proximally than distally. Plantar responses were normal. Deep tendon reflexes were normal at the ankles but reduced at the knees. No muscle fasciculations were apparent. Sensation was normal.

Further blood testing revealed CK was 598. The erythrocyte sedimentation rate was 3 mm and C-reactive protein <2 mg/l. A chest x ray, full blood count, renal, hepatic and thyroid function, calcium, serum vitamin D, rheumatoid factor, autoimmune profile, anti-JO antibodies, complement levels and serum electrophoresis were all normal. The differential diagnosis at that time was a prolonged myositis secondary to cerivastatin or diabetic amyotrophy.

In December 2001 he underwent nerve conduction studies (NCS) and electromyography (EMG). The upper limbs were normal. Sensory and motor nerve conduction in the lower limbs had decreased amplitude and conduction velocity. Needle electromyography of the lower limbs showed large action potentials but no fibrillations or fasciculations. These changes were reported to be compatible with amyotrophy with sensory peripheral neuropathy or possibly with multiple radiculopathy or motor neurone disease. There were no myopathic changes on the EMG to explain the raised CK.

In February 2002 he underwent a muscle biopsy. This revealed atrophic and hypertrophic fibres, characteristic of denervation. There was no evidence of muscle fibre destruction. There was an increased proportion of type 2a muscle fibres, possibly indicative of reinnervation. This was compatible with diabetic amyotrophy but not myopathy or myositis. A diagnosis of diabetic amyotrophy was made but the raised CK was still unexplained. Testing for macro-CK was negative. In July 2002 there was little improvement in his symptoms. He was referred for a neurological opinion.

He was reviewed in the neurology outpatient department in October 2002. By now his symptoms were progressing such that he had developed weakness affecting the left arm and his wife thought there may be some change in his voice. He had no problems swallowing. Examination revealed a mild slurring dysarthria and a weakness affecting the triceps muscles but otherwise normal upper limbs. Examination of his lower limbs revealed power reduced to 3/5 for hip flexors, 4/5 for knee flexors and 1/5 for ankle dorsiflexion. Reflexes were maintained throughout despite muscle atrophy. Vibration and pinprick sensation in his feet were intact. He had fasciculations affecting all four limbs and his tongue. A diagnosis of motor neurone disease was made. The patient deteriorated gradually and died in September 2004.

Discussion

This case illustrates some of the diagnostic problems of motor neurone disease in a man with long-standing diabetes and hypercholesterolaemia. The raised CK with muscle pain and weakness initially suggested statin induced myositis but failed to resolve with withdrawal of cerivastatin. A mild diabetic peripheral neuropathy and absence of fibrillations resulted in a mixed picture on the nerve conduction studies and electromyography. The muscle biopsy suggested denervation which was presumed to be a complication of his long-standing diabetes.

Motor neurone disease has an incidence of 2 per 100 000 people.¹ Typical clinical findings are normal sensation with mixed upper and lower motor neurone signs: muscle weakness and wasting with fasciculation, increased tone, brisk tendon reflexes and extensor plantar

responses. Approximately 10% of patients present without upper motor neurone involvement,¹ as was the case with this patient. Although there are no definitive diagnostic tests for motor neurone disease, nerve conduction studies and electromyography are often used to support a clinical diagnosis. Classical signs on NCS and EMG are fibrillations, large action potentials and normal conduction velocity in motor nerves.² Sensory nerves are not affected in motor neurone disease. The presence of a subclinical, presumed diabetic, peripheral sensory neuropathy, abnormalities of motor nerve conduction and the absence of fibrillations or fasciculations on electrophysiological studies made the diagnosis of diabetic amyotrophy seem more likely than motor neurone disease in this patient. Up to 40% of patients with motor neurone disease may initially be misdiagnosed and time from onset of symptoms to diagnosis is on average 12 months.²

Although, like diabetic amyotrophy, the muscle symptoms are secondary to a neurological disease, there is a recognised association between raised CK and motor neurone disease.³ A Medline search revealed no reports of a raised CK in diabetic amyotrophy. The concentrations of CK in motor neurone disease are thought to be exercise related and are not related to prognosis.³ A raised CK occurs in 3-5% of patients taking hydroxyl-methyl-glutaryl-Co-enzyme A reductase inhibitors (statins), although most patients are asymptomatic.⁴ Elevations of CK would be expected to resolve within a few days of stopping the drug.⁵ A high serum concentration of CK may be found in healthy individuals or those with autoimmune diseases due to the presence of macro-CK, a complex of CK bound to immunoglobulins.^{6,7}

This case illustrates the importance of considering diagnoses other than diabetic complications in patients presenting with neurological symptoms, especially in the presence of non-typical features such as high serum CK. Earlier referral to a neurologist would not have altered the prognosis but may have avoided the repeated changes of diagnosis and prognosis given to the patient.

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Ovarian lipoleiomyoma: a rare benign tumour

There are only two published case reports of lipoleiomyoma in the English literature. We report a case of lipoleiomyoma of the ovary in a woman who was in her fifties. She presented with a gradually progressive abdominal mass of 8 months duration. Abdominal imaging showed a large mass that was fed by right ovarian pedicle. Right ovary was not visualised. The excised mass was nodular and encapsulated; the cut section was yellowish with scant grey-white whorled areas. Microsections showed a mature adipose tissue admixed with leiomyomatous areas without cellular atypia and adjacent compressed ovarian tissue. Immunohistochemical staining showed diffuse positive reaction for desmin confirming that spindle cells were smooth muscle cells. A diagnosis of lipoleiomyoma of the ovary was made based on the radiological, histopathological and immunohistochemical findings.

Primary leiomyoma is a rare tumour of the ovary.¹ Lipoleiomyoma of the ovary is even more uncommon. There are only two published case reports of lipoleiomyoma of the ovary in the English language literature.^{2,3} We report here a case of primary lipoleiomyoma of the ovary because of its rarity. It can also be occasionally misdiagnosed as sarcoma on clinical and radiological examination.

Case history

A woman in her fifties presented with a gradually progressive abdominal mass of 8 months duration. Abdominal CT and ultrasound scan revealed a large mass suspected to be a liposarcoma. The CT scan demonstrated a huge fat density in the right adnexa with few solid enhancing components and minimal fluid. The right ovary was not visualised separately but the right ovarian pedicle was feeding the mass. The ultrasound scan showed a large intraperitoneal echogenic mass with hypoechoic areas and fluid pockets. The uterus was normal in size and had no fibroids in both the scans.

Figure 1 A cut section of the tumour shows yellow and grey-white whorled areas.

Figure 2 Tumour composed of predominantly smooth muscle cells in fascicles and adipose tissue (H&E ×100).

Histopathological findings

The mass weighed 4.5 kg and comprised of four well-encapsulated nodules attached to one another. Three nodules were large and each measured approximately 18×15×12 cm. A fourth central small grey-white nodular mass measured 4×2×2 cm. Cut sections of the two large nodules showed uniform yellow lobules; the third large nodule was also yellowish but had a central grey-white whorled mass that measured 6 cm across (fig 1). The cut section of the small nodule had a whorled appearance. One of the nodules had a pearly white area on the external surface suggestive of a compressed ovary.

Multiple representative sections from the smaller central nodule and the grey-white area in one of the larger nodules showed a tumour comprising predominantly smooth muscle cells arranged in interlacing fascicles admixed with small foci of mature adipose cells (fig 2). The sections from the large yellowish masses showed extensive mature adipose tissue in the form of lobules separated by thin fibrovascular septae. Intimately admixed with these adipose lobules were multiple leiomyomatous areas (fig 3). Stroma showed scattered lymphocytes, plasma cells and eosinophils. Also seen were focal areas of hyaline degeneration. Sections from the pearly white area showed compressed ovarian stroma with few adipose cells. To confirm that spindle cells were smooth muscle cells, immunohistochemistry was performed using desmin, which showed a diffuse positive reaction (fig 4).

Discussion

Primary leiomyoma of the ovary is uncommon and they account for about 1% of the benign neoplasms.⁴ Lipoleiomyoma is even rarer. To the best of our knowledge, this is the third case reported.

We made a diagnosis of lipoleiomyoma of the ovary based on the presence of intimately

Figure 3 Tumour showing predominantly mature adipose tissue admixed with smooth muscle cells (H&E ×100).

Figure 4 Immunohistochemical staining for desmin showing diffuse positive reaction (×100).

Take-home messages

- Lipoleiomyoma is a very rare benign tumour of the ovary.
- The tumour is identified by the presence of mature adipose tissue intimately admixed with smooth muscle cells.
- Lipoleiomyoma may mimic sarcoma clinically.

admixed mature fat and smooth muscle cells. It was considered to be of ovarian origin based on 1) the presence of ovarian tissue closely adherent to the excised mass, 2) presence of adipose tissue within the ovary and 3) CT scan showing the right ovarian pedicle feeding the mass and non-visualisation of the right ovary.

Microscopic features are similar to leiomyoma, but in addition they have mature adipose tissue. The amount of fat may range from being a minor component in what is otherwise leiomyoma to being a neoplasm composed entirely of mature adipocytes.⁵ Primary ovarian leiomyoma most likely originates from smooth muscle cells in the walls of the arterial vessels within the cortical stroma, corpus luteum and in the ovarian ligaments at their point of attachment to the ovary.⁶ Its precise histogenesis is, however, uncertain.⁷ The theories on histogenesis of adipose tissue are unresolved even in the case of the uterus where these tumours are relatively more common than in the ovary. In uterine origin, they most probably represent tumour metaplasia within a leiomyoma.^{5,8} In ovary too, presence of adipose tissue might represent metaplasia.

Fatty tumours of the ovary are very rare and almost invariably benign.⁴ The tumours are usually found in menopausal and post-menopausal women. Clinically, the tumours are asymptomatic and discovered either incidentally or when they attain huge sizes with attendant complications. The only puzzle for the pathologists could be the unexpected presence of fat in the ovary. Occasionally, the clinical presentation and macroscopic appearance may mimic sarcoma, as in this case, and create diagnostic confusion.³ Primary leiomyoma must also be differentiated from pedunculated subserosal parasitic uterine leiomyoma, which has lost its attachment from the uterus and is instead attached to the ovary.⁹ Lastly, it should be differentiated from ovarian fibroma, which is more common.⁹

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