practice was followed in that histological examination of the resected adrenal gland was confirmed to be normal by two pathologists, one an endocrine specialist. There was no clinical evidence of an extra-adrenal lesion. The normal blood pressure and normal catecholamine excretion observed when the patient was well led us to conclude that her intermittent hypertension and raised catecholamines were a direct consequence of her AIP.

The biochemical investigations gave ''false positive'' results because of the activity of her underlying disease, i.e. AIP. When performing such tests it is essential to consider coexisting conditions which may produce abnormal results, rendering the investigation at best uninformative, and at worst dangerous. This patient illustrates the need for specialists in inherited metabolic disease who can advise at an early stage on the management of rare conditions such as acute porphyria and prevent inappropriate treatment.

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Leucocyte common antigen (CD45) and CD5 positivity in an ''undifferentiated'' carcinoma: a potential diagnostic pitfall

CD45 is a transmembrane protein tyrosine phosphatase located on most haematopoietic cells. It has several isoforms, and haematopoietic cells express one or more of the isoforms—CD45RO, CD45RA and CD45RB.[1 2] CD45 immunoreactivity is recognised to be highly specific for non–Hodgkin's lymphomas.[3 4] CD45-expressing non-haemopoietic tumours are very rare. This was first noted by McDonnell *et al*[5] in 1987, who reported a primitive sarcoma expressing CD45. Subsequently, Nandedkar *et al*[6] reported three cases of undifferentiated large-cell, possibly neuroendocrine, carcinomas expressing CD45. Two of them were lymph node metastasis and one was a pulmonary tumour. All the three cases expressed both CD45 and cytokeratin. Two of the cases behaved in an aggressive manner.[6]

In contrast to CD45, CD5 is expressed in thymic carcinoma and malignant mesothelioma.[7 8] To the best of our knowledge, this is the first reported case of a carcinoma expressing both CD45 and CD5.

Case report

We report a patient in their 60s who presented initially with weight loss over 1 month and bilateral leg weakness with deterioration in mobility of 2 weeks' duration. On examination, the patient was found to have bilateral cervical lymphadenopathy. Furthermore, the patient was an ex-smoker, and had been treated for chest infection 1 month earlier, but was otherwise not taking any regular medication.

On admission, an epigastric mass, ascites and jaundice were noted. Blood tests showed low albumin, abnormal liver function tests, and normal blood counts, serum calcium, total cholesterol and thyroid-stimulating hormone.

Upper gastrointestinal endoscopy showed a normal oesophagus and stomach. However, there was a polypoidal lesion in the pharynx, just above the epiglottis, which was biopsied. Furthermore, radiological findings suggested that there was a liver lesion with the appearance of metastasis.

The patient died within a few weeks of diagnosis before any treatment could be instituted. Autopsy was not performed.

Materials and methods

The biopsy specimen was processed for routine paraffin embedding, and 4 μm paraffin sections were stained with H&E stain and used for immunohistochemical analysis with appropriate retrieval techniques, antibody dilutions and controls (table 1).

Pathological findings

Biopsy showed squamous mucosa with a poorly differentiated malignant tumour. The cells were large, with vesicular nuclei, prominent nucleoli and moderate amounts of eosinophilic cytoplasm, which in some cells was more opaque and fibrillar. Cellular cohesion and pleomorphism were observed. However, there was no discernible pattern. The overlying epithelium did not show dysplasia. Small

Table 1 Details of the antibodies used

Antibody	Dilution	Company
MNF-116	1:150	Dako, Cambridgeshire, UK
TTF-1	1:50	Novocastra (Vision Biosystems), Newcastle, UK
CD45	1:10	Dako
CD5 (Leu-1)	1:50	Novocastra (Vision Biosystems)
CAM5.2	1:10	ICRF(CRUK), UK
CD15	1:10	Dako
Synaptophysin	1:40	Dako
EMA	1:100	Dako
Ki-67	1:50	Novocastra (Vision Biosystems)
CD20	1:250	Dako
CD79a	1:10	Dako
Pax-5	1:50	Santa Cruz, Heidelberg, Germany
CD10	1:20	Novocastra (Vision Biosystems)
CD2	1:50	Novocastra (Vision Biosystems)
CD3	1:50	Novocastra (Vision Biosystems)
CD4	1:400	Novocastra (Vision Biosystems)
CD7	1:50	Novocastra (Vision Biosystems)
CD8	1:50	Novocastra (Vision Biosystems)
CD30	1:50	Novocastra (Vision Biosystems)
CD56	1:100	Novocastra (Vision Biosystems)
Alk	1:10	Dako
CD138	1:100	Serotec, Oxford, UK
CD38	1:50	Novocastra (Vision Biosystems)
Myeloperoxidase	1:2000	Dako
CD34	1:200	Dako
CK5/6	1:300	Dako
CK20	1:100	Dako
CK14	1:100	Dako
CK19	1:200	Dako
CK10	1:100	Novocastra (Vision Biosystems)
CA19.9	1:300	Novocastra (Vision Biosystems)
CEA polyclonal	1:1000	Dako
CA125	1:200	Dako
Chromogranin	1:200	Biogenex (Via Launch), Kent, UK
Calretinin	1:100	Zymed (Invitrogen), Paisley, UK
Melan-A	1:50	Novocastra (Vision Biosystems)

EMA, epithelial membrane antigen; TTF-1, thyroid transcription factor 1.

lymphoid cells, plasma cells and histiocytic cells were seen in the background (fig 1).

The tumour cells expressed MNF-116, thyroid transcription factor 1, CD45 and CD5. Focal staining for CAM5.2 was observed. Extreme focal staining with CD15, synaptophysin and EMA (epithelial membrane antigen) was also noted. Ki-67 expression was seen in >80% of cells (fig 1). They were negative for CD20, CD79a, Pax-5, CD10, CD2, CD3, CD4, CD7, CD8, CD30, CD56, Alk, CD138, CD38, myeloperoxidase, CD34, CK5/6, CK20, CK14, CK19, CK10, CA19.9, CEA polyclonal antibody, CA125, chromogranin, calretinin and melan-A.

The features suggested an undifferentiated carcinoma with an aberrant immunophenotype, and possibly having its origin in the lung. The expression of CD45 and CD5 seemed to be aberrant.

Discussion

CD45-positive carcinomas are extremely rare.[6] In this report, we document the first reported case of an undifferentiated carcinoma expressing both CD45 and CD5. In addition to expression of keratins, the tumour cells also expressed thyroid transcription factor 1, raising the possibility of an origin in the lung.

CD45 is uniformly distributed on the cytoplasmic membrane of most haematopoietic cells, and is thought to enrich regions of T cell and B cell contact.[2] CD5 is predominantly a T cell marker, but is also expressed in a few B cell lymphoproliferative disorders, such as chronic lymphocytic leukaemia and mantle cell lymphoma. Furthermore, as the CD5 antibody used in our laboratory is the 4C7 clone, apart from thymic carcinoma and malignant mesothelioma, it is also known to show immunoreactivity in gastric adenocarcinomas, endometrial carcinomas, small bowel carcinoids, adenocarcinomas of the salivary glands, papillary carcinoma of the thyroid gland, chordomas and uterine leiomyomas.[9]

With respect to the current case, what are the plausible reasons for the aberrant expression of CD45 and CD5? False positivity of CD45 can be excluded, as the biopsy specimen was immunostained in two separate laboratories. There is a very small possibility that if immunohistochemistry was performed on fresh frozen tissues, the results may have differed. But it seems doubtful that fixation and processing could have resulted in the aberrant phenotype, as both CD45 and CD5 antibodies used in our laboratory have been extensively evaluated in other studies using paraffin sections. Passive acquisition of CD45 and CD5 antigens from the surrounding tumour-infiltrating T cells and their expression on the cell membrane of the neoplastic epithelial cells could be one explanation. Experimental studies have shown that epithelial cells are able to passively acquire leucocyte antigens and major histocompatibility complex class II molecules.[10 11] In the current case, however, the volume of reactive lymphoid infiltrate was small. Furthermore, the tumour cells did not express other T cell/lymphoid cell antigens. Hence, the latter possibility is unlikely.

Therefore, like the CD5 expression in epithelial tumours, CD45 expression, in the current case, is likely to be a true aberrant antigen expression.

The use of PCR-based clonality analysis for T cell receptor genes and immunoglobulin heavy-chain gene could be helpful in establishing the correct diagnosis in such cases.[12] In fact, PCR was attempted in this case. However, as tissue was depleted in the paraffin block, we could not obtain DNA of adequate quality and concentration to perform the analysis.

While interpreting immunohistochemistry in an undifferentiated malignant tumour, two aspects need to be emphasised. (1) Immunostains should be interpreted in the morphological context. Attention to detail is essential and subtle morphological clues should not be overlooked. (2) It is important to use a wide panel of immunohistochemical analyses to include various lineage-specific leucocyte and epithelial antibodies so as to avoid misdiagnosis.

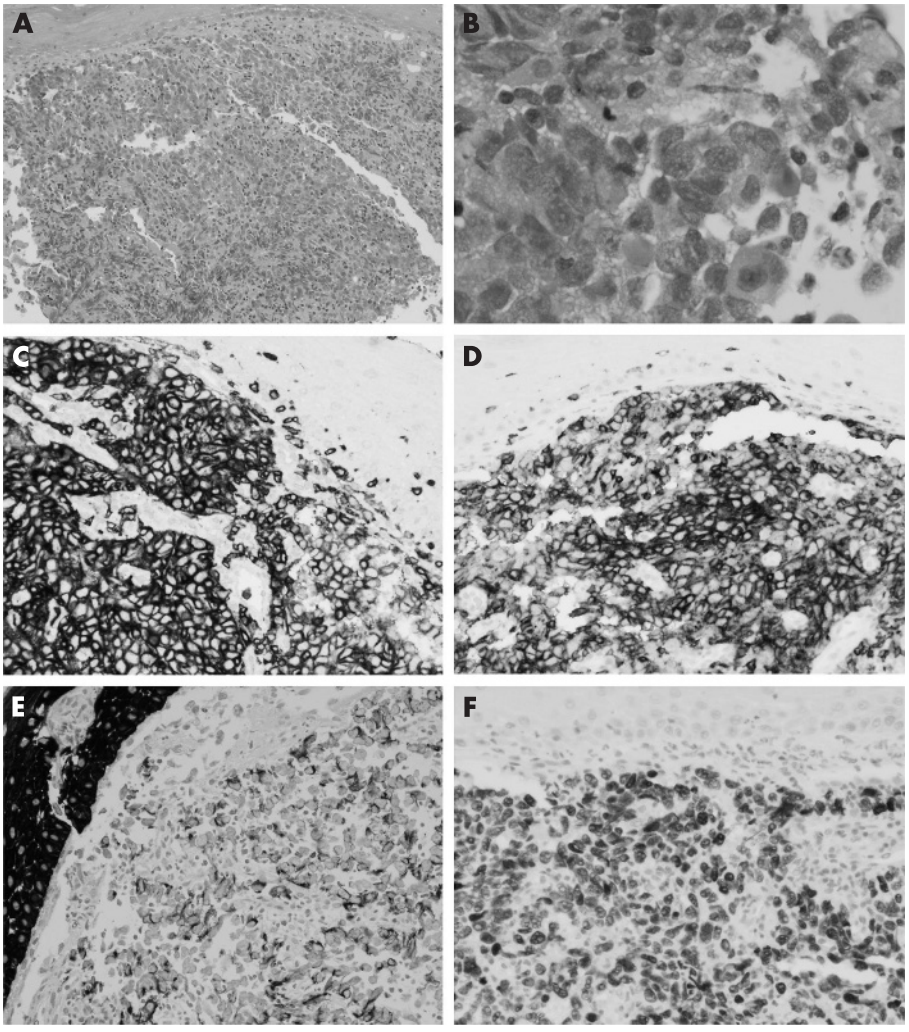

Figure 1 (A) Biopsy showing uninvolved squamous mucosa with a poorly differentiated malignant tumour beneath (H&E ×100). (B) The tumour cells are large, with vesicular nuclei, prominent nucleoli and moderate amounts of eosinophilic cytoplasm. The cells are cohesive (H&E ×400). Immunostaining shows expression of (C) CD45 (×200), (D) CD5 (×200), (E) MNF-116 (pan-keratin; ×200) and (F) thyroid transcription factor 1 (×200).

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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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