CASE REPORT

Symptomatic epidural lipomatosis in ectopic Cushing's syndrome

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Abstract

We report a case of spinal epidural lipomatosis (SEL) caused by ectopic Cushing's syndrome and give a review of the literature. The most common cause of SEL is prolonged therapy with glucocorticoids, only a very few cases are related to endogenous Cushing's syndrome. The pathophysiological mechanism is not clear but there is a possible role for the autonomic nervous system in the stimulation of growth of epidural fat. Severe neurological symptoms which indicate myelopathy and radiculopathy can occur, but there is often a delay in diagnosis because the non-specific initial symptoms are not recognized. The epidural fat is mostly located in the thoracic and lumbar region. Magnetic resonance imaging can establish the diagnosis rapidly. In patients with severe neurological symptoms, surgical decompression of the myelum and removal of the epidural fat is the treatment of choice. Most patients have partial or complete recovery of neurological deficits after surgical treatment or after discontinuing glucocorticoid therapy; mild cases can also be treated conservatively. Routine imaging for the detection of epidural-located lipomatosis in patients at risk is probably useful.

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Introduction

Spinal epidural lipomatosis (SEL) is an excessive fat deposition in the spinal canal which can lead to compression of nervous structures. SEL is a rare but well-documented complication of long-term glucocorticoid therapy with more than 50 reported cases in the literature. Only a very few cases describe SEL related to endogenous Cushing's syndrome. We present a patient with SEL related to the ectopic Cushing's syndrome. The literature on SEL is reviewed and possible pathophysiological mechanisms are considered. In view of the possibly severe neurological deficits and therapeutic consequences, SEL should be considered in all patients on steroid therapy and with endogenous Cushing's syndrome who present with symptoms of spinal cord or cauda equina compression, or even vague muscle complaints.

Case report

A 30-year-old man was admitted to our department for evaluation of hypertension and hypokalemia. He had used combination therapy with beta-blocker/thiazide diuretic for several months and had recently switched to angiotensin-converting enzyme (ACE)-inhibitor therapy. He suffered from polydipsia and had progressive pain and edema in both legs. There was no significant weight gain. On physical examination he was

found to have a moonface, a buffalo hump, acne and centripetal obesity. His abdomen was distended and painful in the left upper quadrant. Blood pressure at that time was 140/100 mmHg. His body mass index (BMI) measured 24 kg/m². We considered Cushing's syndrome, possibly due to adrenocortical carcinoma, based on the Cushing's stigmata combined with the distended and painful left upper quadrant of the abdomen. Computed tomography (CT) scanning showed prominent adrenal glands but no adrenocortical tumor mass. Routine laboratory tests showed a glucose level of 16.7 mmol/l and a decreased level of potassium (3.3 mmol/l). Serum cortisol at 1500 h was increased to 2.34 µmol/l, plasma adrenocorticotrophic hormone (ACTH) was 71 pmol/l (normal 1.5–9 pmol/l); 24-h urinary excretion of cortisol was markedly elevated at 20 079 nmol. After administering 7 mg i.v. dexamethasone, cortisol and ACTH levels were suppressed to 1.44 µmol/l and 32 pmol/l respectively. Magnetic resonance imaging (MRI) of the pituitary region did not reveal a pituitary tumor. Levels of ACTH sampled from the left (134 pmol/l) and right (144 pmol/l) petrosal vein showed no substantial difference to the internal jugular vein (130 pmol/l) and peripheral forearm vein (124 pmol/l). After injection of corticotropin-releasing hormone, no stimulation of ACTH levels was observed in the left (170 pmol/l) and right (152 pmol/l) petrosal veins. An extrapituitary source of ACTH was suspected. Somatostatin receptor scintigraphy (Fig. 1)

Figure 1 Somatostatin receptor scintigraphy and CT scan. The arrow on the left shows pathological enhancement in the upper mediastinum, the arrow on the right indicates tumor mass visualized with CT scanning.

and subsequent CT scanning visualized a 4 cm tumor mass in the upper mediastinum. Fine-needle aspiration was performed and a neuroendocrine tumor was suspected. During the diagnostic work-up our patient rapidly developed lower back pain, progressive weakness in both legs and diminished pain perception below the levels of Th3–Th4 dermatomes. MRI of the thoracolumbar spine was performed which showed a peridural lipomatosis from the first to the tenth thoracic vertebra with myelum compression, a diffuse osteoporotic spine and a compression fracture of the Th10 vertebral body (Figs 2a and 3a). The epidural fat thickness was 14 mm at Th6 level in sagittal view.

Because of grade 4 paresis of his lower extremities the patient became wheelchair dependent. Decompressive laminectomy with debulking of the epidural fat was initially considered but thought too great a risk of spine instability because of extensive osteoporosis and subsequent risk of further damaging the myelum. The hypercortisolism was treated, while awaiting the definitive surgical treatment, with ketoconazole in a maximum dosage of 600 mg twice a day and metyrapone 750 mg three times a day. Cortisol levels normalized within 1.5 months. A subsequent smaller dosage of antihypertensive medication was required and insulin therapy could gradually be diminished and eventually stopped. During this period no clinical improvement or deterioration of his neurological deficits occurred.

The ACTH-producing tumor in the upper mediastinum was resected via sternotomy and was diagnosed as atypical thymic carcinoid. The histological diameter of the tumor was 4.5 cm. The diagnosis of atypical carcinoid was based on histological characteristics with central necrosis and multiple mitoses according to the 1999 WHO definition. No metastatic lymph nodes were present. Additional radiotherapy was performed. Within 3 months after surgery his condition and symptoms significantly improved and gradually he regained mobility. After 6 months he walked without appliances and went to work on a bike. Follow-up radiological studies showed a significant reduction in the amount of epidural fat (Figs 2b and 3b), 8 mm thickness at Th6 level vs 14 mm before treatment. The Cushing's syndrome is in complete remission. Glucocorticoid supplementation could be stopped 8 months after surgery. Thymic carcinoid tumors can be an unusual presentation of the genetic syndrome multiple endocrine neoplasia (MEN) type 1 which is characterized by neoplasia of the parathyroid, pituitary and pancreatic islet cells. Our patient had no family history of endocrine tumors and there was no clinical, biochemical or radiological evidence for the MEN 1 syndrome.

Discussion

SEL is defined as an abnormal increase in the amount of non-encapsulated fat within the epidural space of the spinal canal. Compression of the spinal cord or nerve roots can lead to neurological symptoms such as muscle weakness, sensory loss and abnormal reflexes. The frequency of this excessive fat accumulation in the epidural space is unknown. SEL as a complication of endogenous Cushing's disease or syndrome is very rare. We found five additional cases in the literature (1–5); the characteristics of these cases are shown in Table 1. In 1992, Noël *et al.* (1) reported a 35-year-old patient with SEL and an adrenal tumor. Dumont-Fischer *et al.* (2) documented a similar case in 2002. The first case of SEL caused by ectopic ACTH production was described by Koch *et al.* in 1999 (3). The majority of case reports on SEL are in patients receiving long-term corticosteroid therapy (6–14). Idiopathic lipomatosis has been described, mostly in patients with marked obesity (4, 6). SEL caused by local epidural corticosteroid injections has also been reported (15). The pathogenesis of this possible harmful condition is not fully understood. It is thought that the pre-existing epidural fat responds to the excess of steroids by progressive hypertrophy in a similar manner to the centripetal fat in Cushing's disease (6, 15). Exogenous glucocorticoid administration seems to be the major cause of symptomatic SEL. The underlying disorders in patients with SEL for which corticosteroid therapy was indicated are very heterogeneous and include systemic lupus erythematosus, rheumatoid arthritis, chronic active hepatitis, renal and cardiac

Figure 2 MRI of midline sagittal section, T1 weighed sequence. Scans were carried out at diagnosis (a) and 6 months after resection of carcinoid (b). The arrow indicates the accumulation of fat in the epidural space from the first to the tenth thoracic vertebra with compression of the dural sac. Extended osteoporosis and compression fracture of the tenth thoracic vertebra are also evident.

transplantation, multiple sclerosis, bronchial asthma, chronic obstructive pulmonary disease, ulcerative colitis, Graves' disease and atopic dermatitis (6–14). In all these patients, the development of SEL was independent of the glucocorticoid dosage and even occurred in patients who received a prednisone dosage as low as 10 mg/day. Time to onset of symptoms of SEL varied between 2 months and 30 years after initiation of glucocorticoid treatment. BMI and tissue sensitivity to glucocorticoids are probably important factors in the development of SEL. There seems to be a direct correlation between the concentration of the glucocorticoid receptor in a cell and the sensitivity of the cell to glucocorticoids. Obese patients might be more at risk of developing SEL during corticosteroid therapy (16). Only one case reports on SEL in hypothyroidism and

is possibly a coincidental finding (17). SEL related to endogenous Cushing's syndrome is very rare, our patient is the sixth reported case in the literature and the second on ectopic Cushing's syndrome. The etiology of the Cushing's syndrome of the five previous cases can be found in Table 1. The prevalence of SEL in endogenous hypercortisolism is unknown. A higher prevalence might be expected in patients with ectopic Cushing's syndrome because of the generally higher cortisol levels (16). Recent discoveries show that adipose tissue has metabolic and endocrine functions. The adipocyte produces several hormones and is part of an endocrine regulatory system (18). Adipose tissue is connected via the hypothalamus, by branches of the sympathetic and parasympathetic nervous system, with the autonomic nervous system. Different

Figure 3 MRI of transversal section, T1 weighed sequence. Scans were carried out at diagnosis (a) and 6 months after resection of carcinoid (b). The black arrow indicates the accumulation of fat in the posterior epidural space.

Table 1 Five previous reported cases of SEL related to endogenous Cushing's disease or syndrome.

Reference	Age/sex	Etiology	Symptoms	Treatment	Outcome
Noël <i>et al.</i> (1)	35/M	Adrenal tumor	Bilateral Babinski, Th3 sensory level	Removal of adrenal tumor	Partial relief of neurological symptoms, reduction of lipomatosis on MRI
Dumont-Fischer <i>et al.</i> (2)	49/F	Adrenal tumor	Low back pain, sciatica L5 nerve root	Removal of adrenal tumor	Complete symptom relief after 4 months, decrease in epidural fat
Koch <i>et al.</i> (3)	36/F	Bronchial carcinoid ectopic ACTH	T6 sensory level, weakness in lower extremities	Removal of carcinoid, laminectomy, steroid synthesis inhibitors	Complete symptom relief, no visible epidural fat after 5 months
Benamou <i>et al.</i> (4)	58/F	Recurrent Cushing's disease	Low back pain, sciatica left S1 nerve root	Op' DDD, intradural corticosteroid injections	Complete symptom relief after 6 months
Sivakamur <i>et al.</i> (5)	33/M	Cushing's disease	Bilateral Babinski, weakness in lower extremities, diminished pain perception below Th8–Th9	Trans-sphenoidal removal of pituitary, tumor, no laminectomy possible	Partial relief, muscle strength regained after 2 months

Op' DDD, mitotane (therapy for adrenocortical carcinoma).

fat compartments (subcutaneous/intra-abdominal) are separately innervated by both branches of the sympathetic and parasympathetic system and are represented by specific autonomic motor neurons. This neuro-endocrine circuit with a feedback mechanism on the central nervous system is a possible neuro-anatomical basis for fat distribution in the body (19, 20). Growth of epidural fat can possibly be explained because of direct stimulation by cortisol or indirect stimulation by the autonomic nervous system.

The diagnosis of SEL is often made late, especially in patients on prolonged steroid therapy. The presenting symptoms are often mild and non-specific and can easily be mistaken for side effects of glucocorticoid therapy such as osteoporosis and myopathy (2, 7). Compression of the nerve roots or spinal cord causes signs of radiculopathy and myelopathy; lower back pain is often present. The thoracic and lumbar spine are most commonly affected, cervical involvement has never been reported. In addition, the thoracic spinal canal is narrower than the lumbar spinal canal so a smaller amount of fat is needed before compressive effects occur. The preferred imaging technique is MRI; the advantage of MRI over CT is that other lesions can be visualized, such as degenerative disc disease and osteoporosis with compression fractures, which can possibly be involved in the patient's symptoms (2). The traditional treatment for patients with severe neurological deficits and progressive symptoms is surgical decompression via laminectomy with debulking of the epidural fat (7). The majority of published cases show partial or complete relief of symptoms after surgery. Correction of underlying endocrinopathy in cases of Cushing's disease is imperative. Conservative management, e.g. reduction of steroid dosage and weight loss, has also been reported as being successful in mild and non-progressive cases (6, 8).

In conclusion, epidural localization of lipomatosis should be considered in patients with endogenous Cushing's syndrome and those who are receiving

glucocorticoid therapy. Severe neurological symptoms can occur for which surgical intervention may be necessary. Screening for spinal lipomatosis in high-risk patients is possibly a useful tool for early detection.

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