

Spinal epidural lipomatosis: a rare association of Cushing's disease

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Summary

Excess cortisol is associated with hypertrophy and redistribution of adipose tissue leading to central obesity which is classically seen in Cushing's syndrome. Abnormal accumulation of fatty tissue in the spinal canal is most commonly associated with chronic steroid therapy and rarely reported with endogenous Cushing's syndrome. Herein, we describe a case of spinal epidural lipomatosis (SEL) associated with Cushing's disease. A 17-year-old man was referred with lower limb weakness, weight gain, multiple stretch marks, back pain and loss of height. He had clinical and biochemical features of Cushing's syndrome. MRI and Inferior Petrosal Sinus Sampling (IPSS) confirmed a pituitary adenoma as the source. On day 1 post trans-sphenoidal adenectomy he developed spastic paraparesis with a sensory deficit to the level of T5. MRI spine showed increased fat deposition in the spinal canal from T2 to T9 consistent with a diagnosis of SEL. He was managed conservatively and made a good recovery following restoration of eucortisolism and a period of rehabilitation.

Learning points:

- SEL is a serious complication of glucocorticoid excess and should be considered in any patient presenting with new lower limb neurological symptoms associated with hypercortisolism.
- It is important to distinguish symptomatic SEL from cortisol-induced proximal myopathy by good history and clinical examination.
- MRI of the spine is the gold standard investigation for making a diagnosis of SEL.
- Restoration of eucortisolism can lead to resolution of fat accumulation and good neurological outcome.

Background

Spinal epidural lipomatosis (SEL) is a rare and complex condition characterised by pathological deposition of adipose tissue in the extradural space. For reasons that are unclear, males are affected three times more commonly than females (1). The clinical presentation typically involves progressive lower back pain, radiating leg pain and lower limb neurological deficits. Long-term glucocorticoid therapy is the most common cause of this condition but association with endogenous steroid

excess is very rare. We report a case of SEL in a teenage patient with Cushing's disease who developed spastic paraparesis post-trans-sphenoidal surgery and aim to review the current literature. To our knowledge this is only the third reported case and the youngest patient described to develop SEL secondary to Cushing's disease. Clinicians should be familiar with this condition as it can potentially cause catastrophic neurological complications if not identified and managed quickly.

Case presentation

A 17-year-old man was referred with a 2-month history of increasing limb weakness leading to poor mobility, particularly on climbing stairs. This progressed to the point that he became wheelchair-bound and could not attend school. He had also noticed stretch marks on his body for the last year with associated weight gain of 2 stones within 6 months, leg swelling, back pain and loss of height.

His past medical history included bronchial asthma which was well-controlled with Beclomethasone and Salbutamol inhalers. There was no significant family history of endocrinopathy. On examination, he was obese (106 kg) and displayed typical Cushingoid features, including central obesity, facial plethora, widespread purple striae over his arms and abdomen and significant proximal myopathy. He was hypertensive with a blood pressure of 176/102 mmHg.

Investigations revealed hypokalaemia (3.3 mmol/L; normal range (NR): 3.5–5.0), low testosterone (5.5 nmol/L; NR: 8–30) and suppressed gonadotrophins (follicle stimulating hormone 0.6 IU/L (NR: 1–11); luteinizing hormone 0.1 IU/L (NR: 2–13)). 24-h urinary free cortisol was elevated at 4411 nmol/L (NR: 30–250) and cortisol post 48-h low dose dexamethasone suppression test was unsuppressed (696 nmol/L). ACTH was elevated at 146 ng/L (NR: 7–63) confirming ACTH-dependent Cushing's syndrome. Thyroid function and prolactin levels were normal. Initial MRI failed to show a pituitary adenoma but subsequent Spoiled Gradient (SPGR) MRI confirmed a 5 mm right sided pituitary microadenoma (Fig. 1). Inferior petrosal sinus sampling (IPSS) confirmed a central source of ACTH excess.

A DEXA scan showed a Z score of -3.2 at the spine confirming osteoporosis. He was commenced on block-and-replace therapy with metyrapone and dexamethasone whilst awaiting trans-sphenoidal surgery.

Pituitary surgery was uneventful apart from the development of hypotension intra-operatively. On the recovery ward he became more hypotensive (70/40 mmHg) and tachycardic (120 b.p.m.), and developed paraparesis with hypertonicity, reduced power of 2/5 and a sensory deficit from below the mid-thoracic region. MRI brain did not show any evidence of intracranial bleeding. MRI spine showed no evidence of spinal cord haemorrhage or infarction; however, there was loss of height and wedging of vertebral bodies from T1 to L1 and increased fat deposition in the spinal canal from T2 to T9 with high signal intensity in the thoracic cord causing

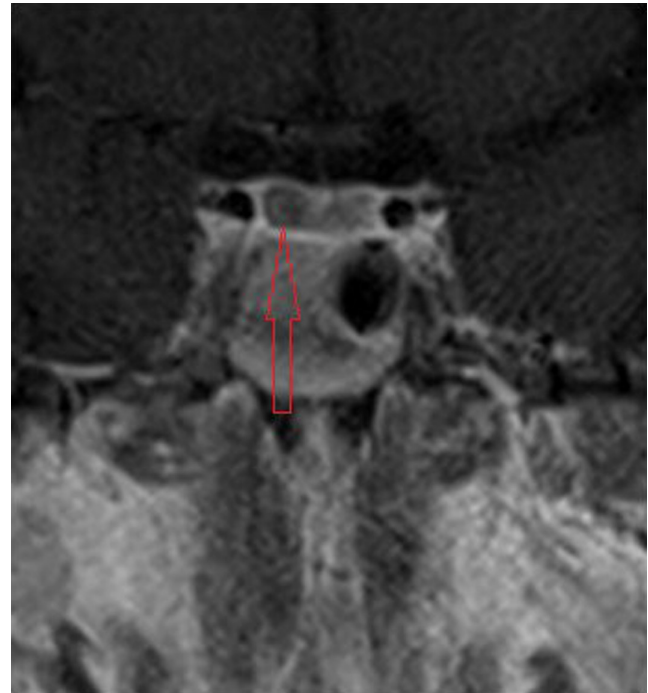


Figure 1
MRI pituitary demonstrating a pituitary microadenoma (Red arrow).

spinal cord compression (Fig. 2). This was consistent with a diagnosis of spinal epidural lipomatosis.

Due to multi-level cord compression and no single surgical target, the spinal surgical team recommended a conservative approach with bed rest for 6 weeks and spinal rehabilitation. Post-operative 9am cortisol at day 5 was 70 nmol/L suggestive of remission of Cushing's disease.

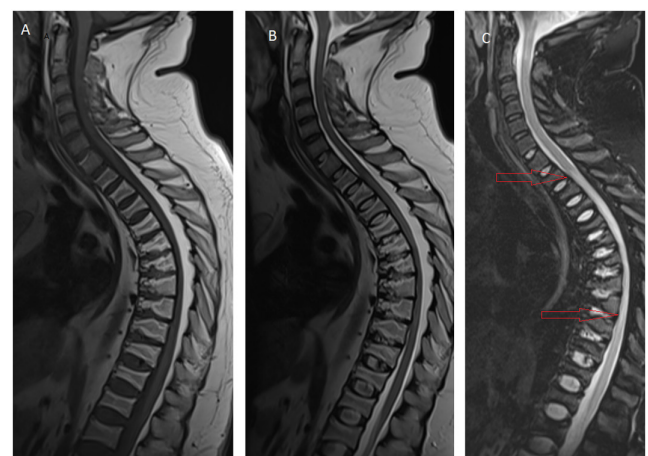


Figure 2
Sagittal T1 weighted (A), Sagittal T2 weighted (B) and STIR (Short T1 Inversion Recovery) sequence (C) demonstrating excessive epidural lipomatosis, multiple vertebral fractures and compression of the thoracic spinal cord. (Red arrows).

He was commenced on glucocorticoid replacement. A short synacthen test 6-weeks post-operatively confirmed a suboptimal cortisol response and he was consequently continued on prednisolone replacement.

Pituitary histology demonstrated a corticotroph adenoma with ACTH immunopositivity. The Ki67 proliferative index was significantly elevated (at 20% in parts).

Treatment

While awaiting pituitary surgery, he was commenced on Metyrapone 1 g three times a day and Dexamethasone (initially 0.5 mg daily and briefly 1 mg daily on account of possible symptomatic hypoadrenalism). Ramipril 10 mg daily and Amiloride 10 mg daily were also commenced for hypertension and hypokalaemia. Metyrapone therapy resulted in a significant reduction in urinary free cortisol (from 4411 nmol/24 h to 1117 nmol/24 h) accompanied by improved anxiety, myopathy, insomnia and leg oedema.

After discussion in the pituitary-neurosurgical multi-disciplinary team meeting, he underwent trans-sphenoidal pituitary adenectomy. On account of hypotension and low cortisol post-operatively, he was commenced on Hydrocortisone which was weaned off over 10 days to a maintenance dose of oral prednisolone of 3 mg daily. His osteoporosis was managed with Bisphosphonate and vitamin D supplements. The SEL was managed conservatively.

Outcome and follow-up

At 1 month post-operatively, he had lost 20 kg in weight, from 106 kg pre-operative to 86 kg. Anti-hypertensive therapy was stopped due to normalisation of his blood pressure. He remained on the spinal rehabilitation unit for 4 months where he made a good recovery and was able to walk with crutches on discharge. He continued to have physiotherapy in the community. Pituitary MRI 4 months after pituitary surgery showed no evidence of recurrence. One year post-operatively, he had lost 30 kg in weight, was able to walk independently and had returned to school. Repeat MRI of the spine a year after the initial finding of SEL showed reduction in the extent and size of the thoracic and lumbar lipomatosis (Fig. 3). Repeat DEXA scan at 14 months showed an improvement in his bone mineral density from a Z score of -3.2 to -2.6 at the spine. At 2 years post-surgery prednisolone was discontinued following a normal synacthen test. He is followed-up

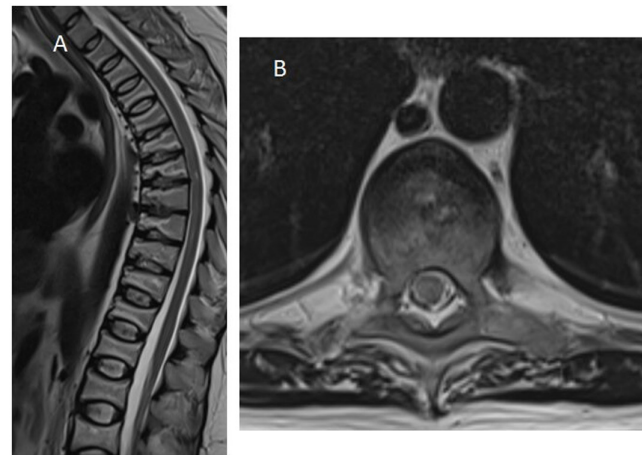


Figure 3

One year follow-up MRI spine showing reduction of the excessive epidural fat and compression of the spinal cord. (A) Sagittal T2 weighted MRI showing a sliver of brighter CSF signal between the cord and the bright fat signal. (B) Axial T2 at T6/7 showing thecal sac separation from the cord with CSF more evident.

closely in our endocrine clinic for possible recurrence of Cushing's disease in view of the high Ki67 proliferative index but is currently eupituitary and in remission at 2.5 years post-surgery.

Discussion

Spinal Epidural Lipomatosis (SEL) is a rare condition characterised by the pathological deposition of non-encapsulated adipose tissue within the extradural space of the spinal canal which can result in symptoms related to spinal cord or nerve root compression (2).

The pathogenesis of SEL is complex and poorly understood. There is evidence that steroids act on cytosolic glucocorticoid receptors within adipose tissue to cause hypertrophy and ultimately spinal cord or nerve compression (2). It is unclear whether this is a localised expansion of adipose tissue or a reflection of more generalised adipogenesis. Ishihara *et al.* observed in their study that the extent of epidural fat accumulation correlated with BMI, abdominal circumference and visceral fat area. They therefore concluded that metabolic syndrome may be associated with SEL (3). Our patient had evidence of metabolic syndrome (obesity, hypertension, fatty liver disease and high urate levels) related to Cushing's syndrome. However, there are case reports of symptomatic SEL with normal body weight and no evidence of exogenous or endogenous cortisol excess, which suggests that other mechanisms may be involved. Exogenous steroid use appears to be the most common



cause of SEL and accounts for about 55% of cases (4). Other causes include obesity (25%), Cushing's syndrome (3%) and idiopathic (17%) (4).

In 2017, Theyskens *et al.* retrospectively examined 28 902 spinal MRIs performed for any purpose and found that about 1 in 40 patients (2.5%) had some evidence of SEL. Twenty-three percent had no symptoms, 72% had spinal symptoms, but only 5% showed symptoms specific for SEL (5). Symptomatic SEL associated with endogenous Cushing's syndrome is rare, with only seven cases reported to our knowledge. Of these, only two were secondary to Cushing's disease while the other five were due to Cushing's syndrome (related to adrenal adenoma in two cases and ectopic ACTH from neuroendocrine tumours in the other 3). Our case is the third related to Cushing's disease and the youngest to have Cushing's disease-related SEL. The characteristics of all seven cases are summarised in Table 1. It is unclear why SEL is rarely diagnosed in patients with endogenous steroid excess, although Doppman argued that this may be due to early diagnosis and treatment of hypercortisolism before SEL develops (6). In contrast, epidural fat is often allowed to accumulate longer in patients on chronic steroids because early SEL symptoms may be easily mistaken for complications of steroid treatment (i.e. myopathy, osteoporotic fractures) (6). It is interesting to note that in spite of their rarity ectopic ACTH-related Cushing's syndrome cases account for a relatively high proportion

of the total, potentially as a result of the high cortisol burden usually observed.

MRI is the gold standard investigation as it can also visualise other pathologies such as compression fractures, osteoporosis and degenerative disc disease (7). Depending on the degree of spinal cord or nerve compression and presenting neurological symptoms SEL can be managed either surgically or conservatively. In patients with exogenous steroid excess a reduction in the dose of steroid medication and weight loss can help to improve neurological symptoms (8). Surgical management involves a decompressive laminectomy and excision of epidural adipose tissue. The main therapeutic approach for patients with endogenous steroid excess, as in our case, is treatment of the underlying disease, typically involving resection of the endocrine tumour to achieve eucortisolism (7). All seven previous cases of endogenous steroid excess treated with surgery to remove the primary tumour showed partial or complete resolution of neurological symptoms within 6 months. Only one case, presenting with acute cord compression due to ectopic ACTH-related SEL, required laminectomy (9). The remainder were managed conservatively with good neurological outcome.

The site of fat accumulation in SEL may vary but Al-Khawaja *et al.* in their review of 111 cases found that in the 62 cases of SEL attributed to steroid excess that lipomatosis was more frequent in the thoracic spine

Table 1 Seven previous reported cases of SEL related to endogenous steroid excess.

Reference	Age/Sex	Aetiology	Neurology	Treatment	Outcome
Noël <i>et al.</i> (11)	35/Male	Cortical adrenal tumour	T3 spinal cord compression	Resection of adrenal tumour	Partial relief of neurological symptoms after 6 months
Sivakamur <i>et al.</i> (12)	33/Male	Cushing's disease	T8/T9 paraparesis	Resection of pituitary tumour	Partial relief of neurological symptoms after 2 months
Dumont-Fischer <i>et al.</i> (13)	49/Female	Adrenal adenoma	Low back pain, sciatica L5 nerve root	Resection of adrenal adenoma	Asymptomatic after 4 months
Benamou <i>et al.</i> (14)	58/Female	Cushing's disease	Low back pain, sciatica, S1 nerve root	Mitotane, intradural glucocorticoid injection	Asymptomatic after 6 months
Koch <i>et al.</i> (2)	36/Male	ACTH-secreting bronchial Carcinoid	T6 sensory level, lower limb weakness	resection of bronchial tumour, steroid synthesis inhibitors,	Asymptomatic after 5 months
Bodelier <i>et al.</i> (6)	30/Male	ACTH-secreting Thymic carcinoid	Low back pain, lower limb weakness	Resection of Thymic carcinoid tumour	Asymptomatic after 6 months
Bhatia <i>et al.</i> (9)	34 male	ACTH-secreting bronchial carcinoid	T3–T8 spinal cord compression	Laminectomy and resection of carcinoids	Asymptomatic after 2 years



(1), as in our case. The thoracic spinal canal is narrower than the lumbar canal, hence only a small increase in fat deposition might cause cord compression. Nevertheless, it is not clear why steroid-induced SEL has a particular proclivity for the thoracic spine.

Our patient did not develop signs of spinal cord compression until in the immediate post-operative period. With the benefit of hindsight, it is conceivable that some of his presenting symptoms of back pain and lower limb weakness may have related to a degree of cord compression rather than osteoporotic fractures and proximal myopathy respectively. We therefore recommend that a careful neurological examination be undertaken in such cases. Nevertheless, the immediate pre-operative neurological examination documented proximal muscle weakness but no sensory level. It is thus not entirely clear why he developed acute cord compression in the immediate post-operative period and not pre-operatively. One possible explanation may be vascular insult from hypotension-related spinal cord ischaemia on the background of an already compromised spinal canal due to SEL and multiple osteoporotic wedge fractures. Greenish et al. reported a case of acute cauda equina syndrome secondary to L5/S1 SEL 2 days after bilateral spinal (L4/L5) decompression surgery for severe canal stenosis. Pre-operative MRI spine had not revealed SEL. They could not provide an explanation but recommended this to be included in the recognised post-operative complications of spinal surgery (10).

Two other features of our case are worthy of discussion in relation to possible contributory factors for the development of his SEL. First, our patient had asthma since early childhood and had been on steroid inhalers since the age of 2. We recognise that long-term high dose steroid inhalers can cause iatrogenic Cushing's syndrome and potentially could contribute to the development of SEL, particularly in the presence of obesity. Secondly, he was given a relatively high dose of dexamethasone as part of his block-and-replace treatment preoperatively, albeit that this was only in the short-term. However, whilst it's conceivable that these may have contributed to SEL in our patient, he was entirely asymptomatic until the year he was diagnosed with Cushing's disease making inhaler-induced SEL less likely. Additionally, he presented with florid Cushing's syndrome, as evidenced by the very high urinary free cortisol levels, hence this was very likely to have been the main driver. The relatively rapid resolution of the lipomatosis on MRI post-operatively provides additional support for this view.

In conclusion, we describe a rare case of a young male who developed acute spinal cord compression in the immediate post-operative period following trans-sphenoidal surgery for Cushing's disease. Investigations showed that this was due to SEL. Our report emphasises that SEL should be considered in the differential diagnosis of lower limb weakness in patients with hypercortisolism and that good neurological outcomes can be achieved with rehabilitation and restoration of eucortisolism.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

A full written consent has been obtained from the patient.

Author contribution statement

Dr Sajjad Ahmad wrote case report and performed literature search for writing discussion with references, Dr Thomas Best helped in writing the case report, Dr Andrew Lansdown reviewed the case report and provided the tables and images, Miss Caroline Hayhurst was the responsible neurosurgeon for this patient and authorised the final version of the case report, Dr Fiona Smeeton was the primary endocrinologist of this patient and authorised the final version of the case report, Prof Steve Davies authorised the final version of the case report, Prof Aled Rees critically reviewed the case report and provided suggestions for further improvement.

References

- 1 Al-Khawaja D, Seex K & Eslick GD. Spinal epidural lipomatosis – a brief review. *Journal of Clinical Neuroscience* 2008 **15** 1323–1326 (<https://doi.org/10.1016/j.jocn.2008.03.001>)
- 2 Koch CA, Doppman JL, Patronas NJ, Nieman LK & Chrousos GP. Do glucocorticoids cause spinal epidural lipomatosis? When endocrinology and spinal surgery meet. *Trends in Endocrinology and Metabolism* 2000 **11** 86–90 ([https://doi.org/10.1016/s1043-2760\(00\)00236-8](https://doi.org/10.1016/s1043-2760(00)00236-8))
- 3 Fogel GR, Cunningham PY, 3rd & Esses SI. Spinal epidural lipomatosis: case reports, literature review and meta-analysis. *Spine Journal* 2005 **5** 202–211. (<https://doi.org/10.1016/j.spinee.2004.05.252>)
- 4 Theyskens NC, Paulino Pereira NR, Janssen SJ, Bono CM, Schwab JH & Cha TD. The prevalence of spinal epidural lipomatosis on magnetic resonance imaging. *Spine Journal* 2017 **17** 969–976. (<https://doi.org/10.1016/j.spinee.2017.02.010>)
- 5 Doppman JL. Epidural lipomatosis. *Radiology* 1989 **171** 581–582. (<https://doi.org/10.1148/radiology.171.2.2704829>)



- 6 Bodelier AG, Groeneveld W, van der Linden AN & Haak HR. Symptomatic epidural lipomatosis in ectopic Cushing's syndrome. *European Journal of Endocrinology* 2004 **151** 765–769. (<https://doi.org/10.1530/eje.0.1510765>)
- 7 Kim K, Mendelis J & Cho W. Spinal epidural lipomatosis: a review of pathogenesis, characteristics, clinical presentation, and management. *Global Spine Journal* 2018. (doi:[10.1177/2192568218793617](https://doi.org/10.1177/2192568218793617))
- 8 Ishihara S, Fujita N, Azuma K, Michikawa T, Yagi M, Tsuji T, Takayama M, Matsumoto H, Nakamura M, Matsumoto M, *et al.* Spinal epidural lipomatosis is a previously unrecognized manifestation of metabolic syndrome. *Spine Journal* 2019 **19** 493–500. (<https://doi.org/10.1016/j.spinee.2018.07.022>)
- 9 Bhatia K, Frydenberg E, Steel T, Ow-Yang M, Ho K & Grainger E. Spinal epidural lipomatosis due to a bronchial ACTH-secreting carcinoid tumour. *Journal of Clinical Neuroscience* 2010 **17** 1461–1462. (<https://doi.org/10.1016/j.jocn.2010.04.008>)
- 10 Greenish D, Watura K & Harding I. Acute spinal epidural lipomatosis following bilateral spinal decompression. *BMJ Case Reports* 2019 **12** e226985. (<https://doi.org/10.1136/bcr-2018>)
- 11 Noël P, Peppersack T, Vanbinst A & Allé JL Spinal epidural lipomatosis in Cushing's syndrome secondary to an adrenal tumor. *Neurology* 1992 **42** 1250–1251. (<https://doi.org/10.1212/wnl.42.6.1250>)
- 12 Sivakumar K, Sheinart K, Lidov M & Cohen B Symptomatic spinal epidural lipomatosis in a patient with Cushing's disease. *Neurology* 1995 **45** 2281–2283. (<https://doi.org/10.1212/wnl.45.12.2281>)
- 13 Dumont-Fischer D, Rat AC, Saidenberg-Kermanac'h N, Laurent S, Cohen R & Boissier MC Spinal epidural lipomatosis revealing endogenous Cushing's syndrome. *Joint Bone Spine* 2002 **69** 222–225. ([https://doi.org/10.1016/s1297-319x\(02\)00382-2](https://doi.org/10.1016/s1297-319x(02)00382-2))
- 14 Benamou PH, Hilliquin P, Chemla N, Chevrot A, Cormier C & Menkès CJ Epidural lipomatosis not induced by corticosteroid therapy. Three cases including one in a patient with primary Cushing's disease (review of the literature). *Revue du rhumatisme (English ed.)* 1996 **63** 207–212.

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