

Cushing's Disease Presenting with Lower Extremity Insufficiency Fracture, and Complicated by Cavernous sinus Syndrome and Pituitary Macroadenoma Infarction Following Bilateral Inferior Petrosal Sampling

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Abstract

Osteoporosis is a common manifestation of Cushing's syndrome, and fractures, particularly of vertebra and ribs, are frequent complications. Lower extremity insufficiency fractures, in the absence of other overt Cushingoid features, are a rarely reported presenting feature of endogenous Cushing's syndrome. Adrenocorticotrophic hormone (ACTH) dependent Cushing's syndrome accounts for the majority of endogenous Cushing's syndrome, and includes ACTH-secreting pituitary adenomas, ectopic ACTH production and corticotrophin releasing hormone (CRH)-producing tumors. Bilateral Inferior Petrosal Sinus Sampling (BIPSS) is the gold standard to confirm ACTH excess of pituitary origin and lateralization within the gland. It is generally regarded as an accurate and safe procedure, and serious adverse effects are rare. We report a case of Cushing's Disease presenting with a metatarsal fracture with minimal other clinical signs of hypercortisolism, and a novel case of cavernous sinus syndrome and pituitary macroadenoma infarction complicating BIPSS, with subsequent temporary improvement of hypercortisolism.

Keywords: Bilateral Inferior Petrosal Sinus Sampling (BIPSS); Cushing's disease; Cavernous sinus syndrome; Cavernous sinus thrombosis

Key Clinical Message

Lower extremity insufficiency fractures in the absence of other overt clinical manifestations of hypercortisolism, are a rare presenting feature of Cushing's disease. Cavernous sinus thrombosis and pituitary macroadenoma infarction is a rare complication of bilateral inferior petrosal sampling.

Case Report

A 40-year-old female was referred for investigation and management of osteoporosis following a low-trauma metatarsal fracture and low bone mineral density (lumbar spine Z-score -3.0 and femoral neck Z-score -2.7). Past medical history included endometriosis and two previous successful pregnancies. There was no history of previous fractures or risk factors for osteoporosis. Medications included cholecalciferol 25 mcg daily and calcium carbonate 1200 mg daily. She had experienced 4 kg of weight gain over the preceding year following her fracture with subtle increased central weight distribution, mild proximal weakness and mood irritability. She had normal menstrual cycles. Clinical examination revealed height 1.70 m, weight 57.8 kg, BMI 20.0 and blood pressure 110/70 mmHg. She had mild facial plethora and mild proximal muscle weakness but no other signs of overt Cushing's syndrome.

Investigations

Investigations demonstrated failure of cortisol suppression following 1 mg dexamethasone (490 to 260 nmol/L; normal <50 nmol/L), while 24-hour urine free cortisol and midnight salivary cortisol were elevated to more than three times the upper limit of normal. Adrenocorticotrophic hormone (ACTH) was elevated (65-71 ng/L; normal 5-50 ng/L). There was partial cortisol suppression (400 nmol/L to 182 nmol/L) following administration of 8mg dexamethasone; however there was no significant ACTH or cortisol response to corticotrophin releasing hormone (CRH) stimulation. Pituitary MRI revealed a 14 × 14 × 12 mm-enhancing lesion encapsulating the right internal carotid artery and invading the right cavernous sinus (Figure 1). Baseline visual field testing was

normal. The remaining anterior pituitary profile was within normal ranges. Bilateral inferior petrosal sinus sampling (BIPSS) with CRH stimulation was performed to confirm Cushing's disease. Following jugular vein catheterization, unfractionated heparin (5000 units) was administered intravenously. Cannulation of the inferior petrosal sinuses (IPS) was difficult due to small caliber vasculature. Microcatheters were directed into each IPS however blood aspiration was unsuccessful and blood samples were obtained from catheters at the IPS origins. Baseline samples showed extraordinarily high ACTH levels with lateralization to the right IPS (Table 1). ACTH levels declined over the course of the procedure and showed no response to CRH stimulation.

The peri- and post-BIPSS course were complicated by the immediate onset at BIPSS cannulation of headache, nausea, partial oculomotor nerve palsy, partial right abducens nerve palsy, sensation loss in the ophthalmic division of the trigeminal nerve and post-ganglionic Horner's syndrome, consistent with cavernous sinus syndrome. Post-BIPSS computed tomography (CT) was not consistent with pituitary apoplexy. Magnetic resonance imaging (MRI) on day 1 post-BIPSS revealed increased size of the macroadenoma, now measuring 22 × 20 × 18 mm with new susceptibility weighted image (SWI) blooming suggestive of either intratumoural haemorrhage or cavernous sinus thrombosis. The patient was treated conservatively with dexamethasone and prophylactic doses of heparin. MRI on day 10 post-BIPSS showed decreased macroadenoma size (8 × 11 × 11 mm) with reduced SWI signaling, favouring a resolving cavernous sinus thrombosis (Figure 2).

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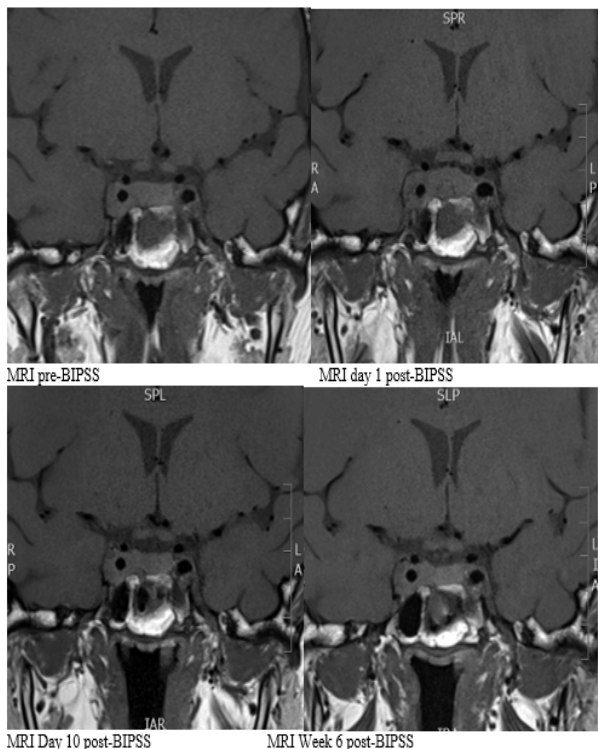


Figure 1: MRI pre and Day 1, Day 10 and Week 6 post BIPSS (Coronal T1 post GAD).

Time (min)*	ACTH level (ng/L)				
	Right [†]	Left [†]	Periphery [‡]	PPR (Right)	PPR (Left)
-2	254630	9100	4300	59.2	2.11
0	169954	13710	3100	54.8	4.4
2	186413	10105	3400	53.9	3.0
5	48477	18573	3200	15.1	5.8
10	43981	5100	3100	14.2	1.6
15	35062	4000	2800	12.5	1.42

*Time since CRH injection (1 ug/kg)

[†]Reference range 10-50 ng/L

[‡]Blood samples were obtained from catheters at the IPS origins

PPR: Petrosal sinus to peripheral gradient (≥ 2 in basal conditions and ≥ 3 following CRH simulation suggests pituitary ACTH hypersecretion)

Table 1: Assessment of Bilateral Inferior Petrosal Sinus Sampling (BIPSS).

Laboratory investigations post-BIPSS demonstrated improvement of hypercortisolism, with normalization of midnight salivary and 24-hour urine free cortisol but failure of cortisol suppression following 1mg dexamethasone. The remaining pituitary function remained intact (Figure 3).

Outcomes and Follow-up

We hypothesize that BIPSS cannulation was complicated by venous infarction or cavernous sinus thrombosis and subsequent cavernous sinus syndrome and pituitary macroadenoma infarction. The extraordinarily high ACTH levels intra-procedurally likely reflect excess hormone release in the context of tumour infarction. The patient had complete resolution of neurological deficits and improvement in hypercortisolism over the following days and weeks. MRI 6 weeks post-BIPSS showed stable appearance of the pituitary macroadenoma and again favored to represent recent cavernous sinus thrombosis.

The patient was commenced on cabergoline and monitored for hypercortisolism and macroadenoma progression. Repeat biochemistry nine months post-BIPSS showed relapse of overt hypercortisolism and fluconazole was subsequently commenced. Transphenoidal biopsy was performed and immunohistochemistry confirmed a densely granulated corticotroph adenoma. The patient underwent Gamma-knife radiotherapy and pituitary function continues to be monitored.

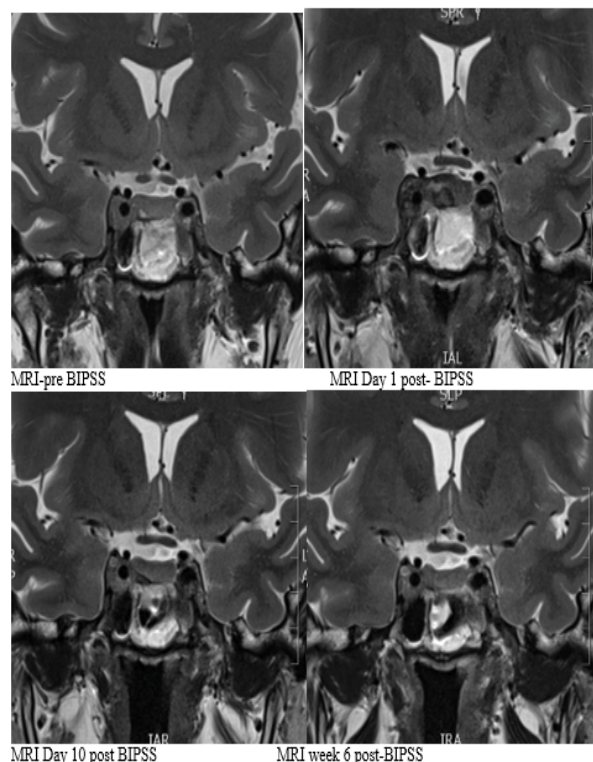


Figure 2: MRI pre and Day 1, Day 10 and Week 6 post BIPSS (Coronal T2).

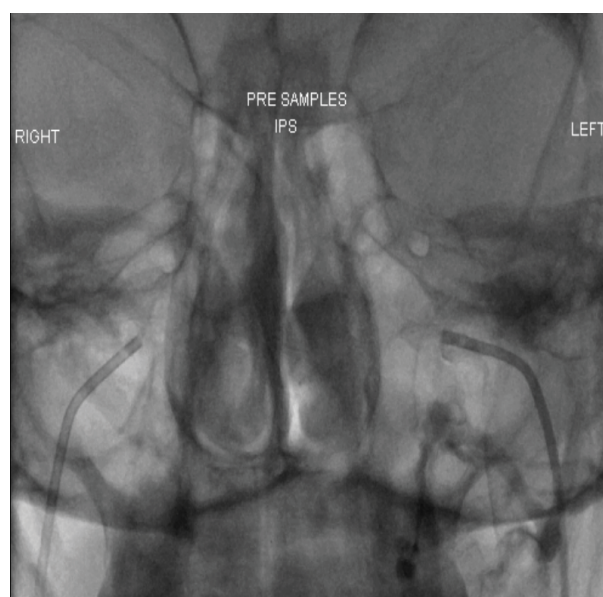


Figure 3: Angiogram performed during BIPSS showing cannulas positioning.

Discussion

We describe a case of Cushing's disease which initially presented with the rare manifestation of a lower extremity insufficiency fracture, with minimal other clinical signs of hypercortisolism. To our knowledge this is also the first reported case of cavernous sinus syndrome, likely a result of venous infarction or cavernous sinus thrombosis complicating BIPSS cannulation, and pituitary ACTH-secreting macroadenoma infarction. Osteoporosis is a well-known manifestation of overt Cushing's syndrome, and fractures, particularly vertebral and rib fractures, are common complications of hypercortisolism. There are limited reports in the literature of lower extremity insufficiency fractures as the initial manifestation of endogenous Cushing's syndrome, with many of these patients having no other clinical features of overt hypercortisolism [1].

BIPSS with CRH stimulation is the gold standard to confirm ACTH excess of pituitary origin and is generally considered to be a safe procedure when performed in experienced centres [2]. The incidence of severe adverse events is <1% [3]. These include brainstem injury, subarachnoid haemorrhage, deep venous thrombosis, pulmonary embolism and cranial nerve IV palsy [2,3]. Patients with Cushing's syndrome have an increased risk of venous thromboembolic events due to the associated hypercoagulable state with hypercortisolism [2]. Periprocedural heparinisation and avoiding central IPS cannulation are important in preventing venous thromboembolism and IPS and cavernous sinus thrombosis [2].

Cavernous sinus thrombosis is extremely rare with an estimated incidence of 0.1-1.6 per 100,000 per year [4], with the majority of cases associated with infection. Aseptic cavernous sinus thrombosis is much less common and can occur secondary to trauma, surgery and pregnancy. Other risk factors include immunosuppression, corticosteroid use, increased estrogen states, obesity, dehydration and inherited and acquired thrombophilia [4].

The risk of pituitary apoplexy increases with adenoma size and has been reported more frequently in macroadenomas with extrasellar extension [5]. ACTH-secreting adenomas are usually microadenomas, with macroadenomas accounting for <15% of cases and apoplexy in these tumours is very rare [6]. In this case, the presence of hypercortisolism, small caliber venous vasculature, cannulation difficulties and the location and size of the macroadenoma in the

cavernous sinus likely increased the risk of cavernous sinus thrombosis and subsequent tumour infarction.

Dynamic endocrine testing can precipitate pituitary apoplexy, and has been reported following CRH administration, including in a patient with an ACTH-secreting macroadenoma [5,7]. However, the peri-procedural symptom onset and the initial extraordinarily high central ACTH levels with right lateralization in our patient suggest macroadenoma infarction occurred prior to CRH administration. The rate of remission in ACTH-secreting macroadenomas is high with apoplexy. However, relapses can occur and long-term follow-up is essential [6].

Conclusion

We describe a case of Cushing's disease presenting with the rare initial manifestation of metatarsal fracture, and the first published case of cavernous sinus syndrome likely secondary to venous infarction or cavernous sinus thrombosis and resulting in pituitary ACTH-secreting macroadenoma infarction complicating BIPSS cannulation. It is important to consider the possibility of Cushing's syndrome in patients with lower extremity insufficiency fractures, even in the absence of overt clinical features of hypercortisolism. A comprehensive work up of any patient with suspected Cushing's disease and discussion at a multidisciplinary team meeting is recommended. BIPSS is not a benign procedure and rare and serious neurological complications can occur.

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