

Spontaneous resolution of avascular necrosis of femoral heads following cure of Cushing's syndrome

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Summary

Avascular necrosis (AVN) is a rare presenting feature of endogenous hypercortisolism. If left untreated, complete collapse of the femoral head may ensue, necessitating hip replacement in up to 70% of patients. The majority of the described patients with AVN due to endogenous hypercortisolaemia required surgical intervention. A 36-year-old female, investigated for right leg pain, reported rapid weight gain, bruising and secondary amenorrhoea. She had abdominal adiposity with violaceous striae, facial plethora and hirsutism, atrophic skin, ecchymosis and proximal myopathy. Investigations confirmed cortisol excess (cortisol following low-dose 48 h dexamethasone suppression test 807 nmol/L; 24 h urinary free cortisol 1443 nmol (normal < 290 nmol)). Adrenocorticotrophic hormone (ACTH) was <5.0 pg/mL. CT demonstrated subtle left adrenal gland hypertrophy. Hypercortisolaemia persisted after left adrenalectomy. Histology revealed primary pigmented micronodular adrenal disease. Post-operatively, right leg pain worsened and left leg pain developed, affecting mobility. MRI showed bilateral femoral head AVN. She underwent right adrenalectomy and steroid replacement was commenced. Four months after surgery, leg pain had resolved and mobility was normal. Repeat MRI showed marked improvement of radiological abnormalities in both femoral heads, consistent with spontaneous healing of AVN. We report a case of Cushing's syndrome due to primary pigmented nodular adrenocortical disease, presenting with symptomatic AVN of both hips. This was managed conservatively from an orthopaedic perspective. Following cure of hypercortisolaemia, the patient experienced excellent recovery and remains symptom free 4 years after adrenalectomy. This is the first report of a favourable outcome over long-term follow-up of a patient with bilateral AVN of the hip, which reversed with treatment of endogenous hypercortisolaemia.

Learning points:

- AVN of femoral head can be a presenting feature of hypercortisolism, both endogenous and exogenous.
- Rarely, treatment of hypercortisolaemia can reverse AVN without the need for orthopaedic intervention.
- Primary pigmented nodular adrenal disease is a rare cause of ACTH-independent Cushing's syndrome.

Background

Our case will be of interest to other clinicians in the field as it has a number of unique elements. Avascular necrosis (AVN) is a very rare presenting feature of endogenous hypercortisolaemia. Previously published cases almost

exclusively reported outcomes requiring orthopaedic intervention; in our case, AVN resolved with treatment of the underlying pathology causing cortisol excess. Furthermore, to our knowledge, this is the first case to report long-term follow-up of non-surgical management of AVN of the hip due to endogenous hypercortisolaemia.



Case presentation

A 36-year-old female was admitted under orthopaedic surgery to investigate right leg pain. Lumbar spine MRI showed a left paracentral disc herniation at L4/L5 level. She underwent L4/L5 discectomy with modest symptomatic improvement. Incidental findings of an early L1 compression fracture and multiple rib fractures were made; there was no history of trauma.

Given her premature osteoporosis, an endocrinology opinion was sought. The patient reported weight gain, secondary amenorrhoea of 2 year duration and a recent onset of facial hirsutism. On examination, she had abdominal adiposity with violaceous striae, facial plethora and hirsutism, atrophic skin, multiple ecchymoses and proximal muscle weakness consistent with Cushing's syndrome. She had never used exogenous steroids.

Investigation

Biochemical investigations confirmed cortisol excess with 09:00 h cortisol following a 1 mg overnight dexamethasone suppression test of 747 nmol/L and cortisol following low-dose 48 h dexamethasone suppression test of 807 nmol/L. Two 24 h urinary collections showed free cortisol of 1263 and 1443 nmol (reference ≤ 290 nmol/24 h). Adrenocorticotrophic hormone (ACTH) was suppressed at <5.0 pg/mL consistent with an ACTH-independent source of Cushing's syndrome. Non-contrast dedicated CT adrenal glands showed possible subtle hypertrophy of the left adrenal gland and a radiologically normal right adrenal gland.

The diagnosis of micronodular adrenal hyperplasia was considered, and the patient underwent sequential low-dose, high-dose dexamethasone suppression test with 24 h urine collection for measurements of free cortisol (Liddle's test: collection on day 1–2 for baseline measurement, day 3–4 during low-dose dexamethasone suppression test and day 5–6 during high-dose dexamethasone suppression test). In 69–75% of patients with cortisol excess due to primary pigmented nodular adrenocortical disease, there is a paradoxical 50% rise in 24 h urinary cortisol excretion on day 6 of the test (1). However, in our patient, Liddle's test failed to show a rise in cortisol excretion (day 1 – 1443 nmol, day 2 – 1700 nmol, day 3 – 1526 nmol, day 4 – 1071 nmol, day 5 – 945 nmol and day 6 – 877 nmol).

Treatment

She underwent laparoscopic left adrenalectomy but remained hypercortisolaemic after surgery: morning

cortisol on day 4 post surgery was 293 nmol/L; cortisol post 1 mg dexamethasone suppression test was 306 nmol/L. Post-operatively, her right leg pain worsened and left leg pain developed, affecting ambulation. MRI of hips showed bilateral AVN of the femoral heads with early bone fragmentation on the left (Fig. 1A and B). Surgical core decompression of the left femoral head was deferred, in favour of a right-sided adrenalectomy. Histology of both adrenal glands showed multifocal nodular hyperplasia and brown pigment consistent with a diagnosis of primary pigmented micronodular adrenal disease, which is a rare cause of ACTH-independent Cushing's syndrome causing bilateral adrenal pathology. Long-term steroid replacement with 15 mg hydrocortisone was commenced.

Outcome and follow-up

Following adrenalectomy, the patient was under regular orthopaedic follow-up, and as symptoms of bilateral leg pain continued to improve, orthopaedic intervention was withheld in keeping with the patient's preference. This approach seems to be justified in this case and supported by the growing literature of conservative management of AVN at pre-collapse stage (2, 3, 4). Four months later, the patient was able to walk 6 km daily and attend the gym regularly. Repeat MRI showed marked improvement in high signal intensity in both femoral heads, consistent with spontaneous healing of AVN (Fig. 1C and D). She remains symptoms free 4 years after adrenalectomy.

Given the histopathological diagnosis and its known association with Carney complex (CNC), genetic testing was performed but did not reveal a mutation in protein kinase A, regulatory subunit, type I, alpha (*PRKARIA*) gene.

Discussion

Atraumatic AVN of the hip is typically associated with exogenous glucocorticoid treatment. To date, there have been less than 20 reports where AVN was the presenting feature of endogenous cortisol excess (5, 6). In the largest series to date of patients with glucocorticoid-induced AVN, only 3 of 77 patients had evidence of endogenous steroid excess (7). The mechanism by which glucocorticoid-induced AVN develops is not fully understood. It has been reported that glucocorticoids induce osteocyte apoptosis, the first histopathological feature of AVN, leading in turn to impairment in bone remodelling (8). One of the

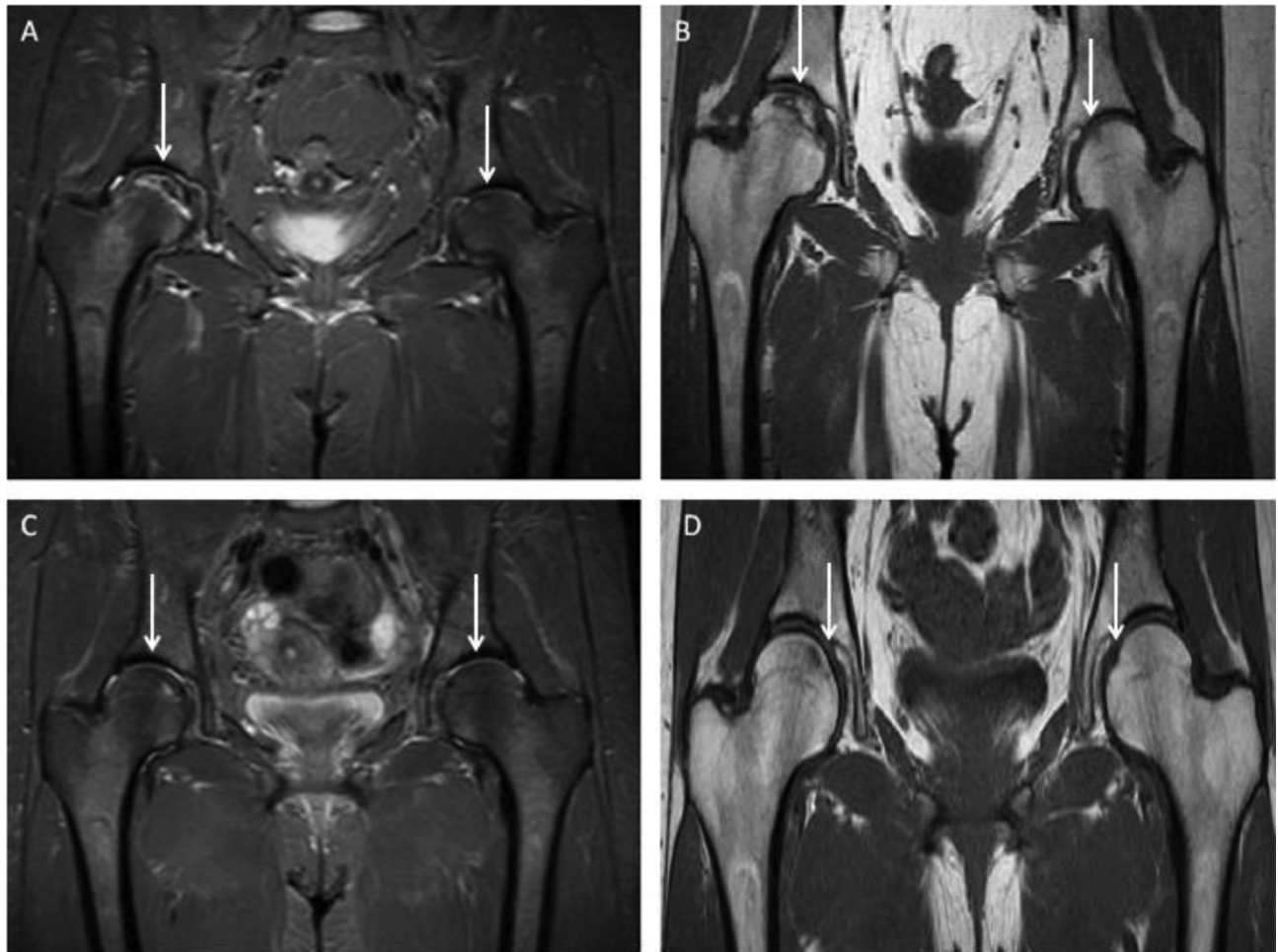


Figure 1

MRI pelvis – pre-treatment: (A) Coronal Short-T1 Inversion Recovery (STIR); (B) coronal T1. Right femoral head inner bright hyperintense and outer dark hypointense signal lines on the STR sequence and dark hypointense signal line on the T1 sequence compatible with osteonecrosis. Post-treatment: (C) coronal STR; (D) coronal T1. Near-complete resolution of right femoral head pre-treatment signal abnormality with now only a small residual bright hyperintense STR sequence and dark T1 sequence hypointense signal focus. No evidence of cortical collapse.

plausible mechanisms of steroid-induced osteonecrosis is microvascular ischaemia due to intravascular thrombosis and lipid microemboli with resultant tissue necrosis (9). The association between glucocorticoid excess and a hypercoagulable state has been known for long. In addition to this, glucocorticoids are associated with fat-cell hypertrophy in the bone marrow, leading to increased bone marrow pressure and compromised venous return (10). A recently published study reported that treatment with low-molecular-weight heparin (LMWH) prevents AVN in animal models of steroid-induced osteonecrosis supporting the theory that intravascular thrombosis plays a major role in its pathophysiology (11). Counterintuitively, two case reports have described the development of AVN following successful treatment of hypercortisolism (12)

(13). However, either no information on replacement doses of steroids was given or a supraphysiological steroid replacement regimen with prednisolone was used. It has been shown that steroid doses equivalent to less than 5 mg of prednisolone daily can lead to abnormal ACTH and cortisol responses to Corticotropin Releasing Hormone (CRH) in normal subjects, indicating that such doses are supraphysiological (14). Although osteonecrosis of the hip is reported typically in association with prolonged courses of high doses of glucocorticoids, it has been shown that up to 2.4% of patients on replacement doses of glucocorticoids can develop this complication of hypercortisolaemia (15).

It has been suggested that, if left untreated, AVN leads to a complete collapse of the femoral head necessitating



total hip replacement in up to 70% of patients (8). The majority of the described patients with AVN due to endogenous hypercortisolaemia were treated surgically with core decompression surgeries, osteotomies or total hip arthroplasties (6, 12, 16, 17). Although hip-preserving surgical procedures remain the mainstay of treatment in cases of atraumatic AVN, a number of medical therapies targeting pathophysiological pathways in this condition, such as bisphosphonates, non-steroidal anti-inflammatories and LMWH, have been evaluated with varying clinical outcomes (3, 4, 18). Although our patient was treated with prophylactic LMWH during her hospital stay, we do not think that this influenced the outcome as the study showing delay in progression of osteonecrosis utilised much higher doses of this medication for a longer duration (3). There is some evidence suggesting that statins can prevent osteonecrosis, but it is of note that our patient was never exposed to such treatment (19).

Here, we report the case of a 36-year-old woman with Cushing's syndrome due to primary pigmented nodular adrenocortical disease, presenting with symptomatic AVN of both hips. PPAND is associated with CNC, a rare endocrine neoplasia syndrome caused in 70–80% of cases by a mutation in the *PRKARIA* gene (20). Patients with CNC have a constellation of abnormalities, including cardiac and other myxomas, spotty skin pigmentation and endocrine organ tumours (21). Evaluation of our patient revealed some skin freckling, and it was thought that this could be a feature of CNC. Because of this and the histopathological diagnosis, we performed genetic testing given the known association of this condition with tumours, including a small risk of malignancy (22). Genetic diagnosis would also have implications for the patient's family members and the patient's family planning as the condition is inherited in an autosomal dominant manner (20). It is possible that the patient might possess a somatic mutation in the *PRKARIA* gene in the adrenal cells as this has been described in a significant proportion of patients with adrenal Cushing's syndrome (23), but this would not have any clinical implications for her or her family.

AVN in our case was managed conservatively from an orthopaedic perspective, and the patient's hypercortisolaemia was cured following bilateral adrenalectomy. With this approach, she experienced excellent and sustained functional recovery, and marked improvement in radiological findings was observed on MRI.

In this case, similar to others in the literature, the initial presenting symptoms were attributed to another pathology. AVN frequently evades early diagnosis, and a high index of clinical suspicion is required for its accurate

identification. This case highlights that AVN can be a presenting feature of hypercortisolaemia, both endogenous and exogenous, and as such should prompt consideration of a work-up for same. This is the first report of a favourable long-term outcome following non-surgical management of AVN of the hip due to endogenous hypercortisolaemia.

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

Written informed consent has been obtained from the patient for publication of the submitted article and accompanying images.

Author contribution statement

A Pazderska wrote the manuscript and was involved in the care of the patient. M Sherlock provided critical review of the manuscript and was involved in the care of the patient. S Crowther, P Govender and K C Conlon provided pathological, radiological and surgical input into the patient's care. J Gibney was the primary physician of the patient.

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