CLINICAL CASE

EXOGENOUS CUSHING'S SYNDROME, ADDICTION TO ORAL DEXAMETHASONE AS PAIN KILLER: PITFALLS OF SKELETON EFFECTS AND DECISION MAKING

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ABSTRACT

Chronic use of glucocorticoids, either as medical recommendation or as self-administration for bone and joint long-standing pain, might cause negative effects such as inducing Cushing's syndrome that embraces a large panel of clinical manifestations and bone impact might be one of them. We aim to introduce an adult male case who developed Cushing's syndrome following the daily use of oral dexamethasone for chronic spine pain after undergoing spine surgery. Additionally, he developed vertebral fractures requiring neurosurgery, but continued to voluntarily use the drug. However, DXA (Dual-Energy X-Ray Absorptiometry) assessment was non usable for lumbar spine evaluation and proved no lowering of the bone mineral density at non-lumbar sites. Despite discordances between DXA results and prevalent fractures, a difficult decision amid specific medication against osteoporosis was taken, including the acumen of following the expected improvement of bone status over the time. Prolonged self-administration of corticoids for persistent post-operatory pain might bring negative bone effects in terms of multiple fractures requiring second time surgery that add to the already present component of persistent back pain. However, the tools we currently have to assess glucocorticoids-induced osteoporosis such as DXA and trabecular bone score might not be applicable in certain cases, thus the decision of medication against osteoporosis is based on the clinical panel (exogenous Cushing's syndrome) and suppressed serum bone turnover markers. Poor compliance to glucocorticoids withdrawal as well as adherence to medication against osteoporosis represented another issue in this instance.

KEYWORDS: *Cushing's syndrome, osteoporosis, fracture, DXA, surgery, dexamethasone*

INTRODUCTION

Exogenous glucocorticoids have a variety of administration routes, including oral, topical, intravenous, intramuscular and inhaled since they are useful in treating many conditions, such as rheumatologic, respiratory, oncological, and neurological [1,2]. However, excessive long-term use of glucocorticoids can have side effects on bone, cardio-vascular system, glycaemic status, and many other physiological functions, leading to iatrogenic Cushing's syndrome regardless of the way of administration, but depending on the route, dose, time of exposure, and particular features of one patient, for instance, the co-presence of other secondary elements prone to bone loss such as uncorrected hypogonadism, primary hyperparathyroidism, vitamin D deficiency, anti-cancer drugs exposure, secretory endocrine tumors, and neuroendocrine neoplasia [3-5].

Most commonly, exogenous Cushing's syndrome is caused by the glucocorticoids that are orally taken for various inflammatory conditions due to their effect on reducing inflammation and modulating the immune system. However, an addiction to a corticosteroids-based drug might also add a negative effect to the psychological profile of an individual, a part from the underlying medical indication itself [6,7].

A particular aspect that clinicians must take into consideration when evaluating a patient after prolonged use of synthetic glucocorticoids is represented by the bone health in addition to the menopausal status in females (nevertheless, glucocorticoid-induced osteoporosis represents one of the most frequent causes of secondary bone loss in males, too) [8,9]. Therefore, when iatrogenic Cushing's syndrome is diagnosed on time, an adequate management must be applied in order to prevent the decrease of bone mineral density (BMD) and associated high fracture risk; of note, a subject might display the entire panel of Cushing's syndrome or be selectively affected at skeleton level, thus displaying complications such as (low trauma or spontaneous) fragility fractures [10,11].

We aim to introduce an adult male case who developed Cushing's syndrome following the daily use of oral dexamethasone for chronic spine pain after he underwent spine surgery.

CASE PRESENTATION

This was a 50-year-old male patient admitted for the evaluation of multiple vertebral fractures. His symptoms included chronic, intense lumbar and non-specific, intermittent hip pain, a tendency to weight gain, and chronic fatigue. Clinically, he had a body mass index of 31.32 kg/m2 (obesity grade I), and a round moon faces suggestive for a Cushing's syndrome. His family medical history was irrelevant.

His medical history revealed surgery for lumbar L3-L4 disc hernia 7 years prior; after surgery he progressively started using oral dexamethasone (a dose of at least 8 mg/day, at least 10 days per month for the latest 4 years) due to post-operatory persistent pain. Under these circumstances, he suffered vertebral fractures and further on he underwent a vertebroplasty at thoracic vertebra T12, respectively, lumbar L2 and L3 (3 years prior to current admission). In addition, lower-limb deep vein thrombosis was diagnosed within the following year after spine surgery. No specific endocrine or rheumatologic evaluation was performed in the meantime. Of note, he did not resist to stop using glucocorticoids as pain killer despite recommendations of his primary care physician and some unsuccessful rehabilitation methods.

On the first admission (6 months ago), the biochemistry panel showed high values of total cholesterol, LDL (low-density lipoprotein) - cholesterol and glycated hemoglobin HbA1c. A mild inflammatory syndrome was confirmed by an increased fibrinogen, erythrocyte sedimentation rate (ESR) and white blood cell count (WBC) (Table 1).

Endocrine evaluation revealed suppressed levels of ACTH (Adrenocorticotropic Hormone) and plasma morning cortisol, suggestive for exogenous exposure to glucocorticoids (and consistent with the diagnosis of iatrogenic Cushing's syndrome). No hypogonadism was confirmed in terms of normal FSH (Follicular Stimulating Hormone), LH (Luteinizing Hormone), and plasma total testosterone, (respectively, prolactin).

The mineral metabolism assessments showed normal serum total/ionic calcium and phosphorus levels with a vitamin D deficiency as reflected by the low serum 25-hydroxivitamin D (25OHD) of 18 ng/mL (normal levels above the

value of 30 ng/mL) without secondary hyperparathyroidism. Bone turnover markers were also assessed at serum level, showing decreased osteocalcin and P1NP (bone formation markers) and CrossLaps (bone resorption marker) (Table 2).

Parameter	Value	Normal range	Units
Uric acid	6.1	3.5-7.2	mg/dL
ALT (alanine aminotransferase)	25	0-55	U/L
AST (aspartate aminotransferase)	11	5-34	U/L
Creatinine	0.76	0.5-1.2	mg/dL
Total serum calcium	10.1	8.4-10.2	mg/dL
Ionic serum calcium	4.23	3.9-4.9	mg/dL
Phosphorus	3.7	2.3-4.7	mg/dL
Sodium	139	136-145	mmol/L
Potassium	4.2	3.5-5.1	mmol/L
Magnesium	1.94	1.6-2.6	mg/dL
Total cholesterol	**330**	0-200	mg/dL
LDL-cholesterol	**254**	60-160	mg/dL
Fasting glycaemia	101	70-105	mg/dL
HBA1c (glycated haemoglobin A1c)	**6.3**	4.8-5.9	%
Fibrinogen	**502**	200-500	mg/dL
ESR (erythrocyte sedimentation rate)	**28.6**	1-25	mm/1-h
WBC (white blood cell count)	**12.36**	4-10	10^3/uL

Table 1 – Biochemistry parameters in a patient with chronic back pain and long-term use of oral dexamethasone as pain killer (of note, the admission was done amid COVID-19 pandemic and testing for coronavirus was negative)

Central DXA (Dual-Energy X-Ray Absorptiometry) was performed via a GE Lunar Prodigy device. Unfortunately, prior spine surgery did not allow an adequate interpretation of lumbar L1-L4 BMD and TBS (trabecular bone score). No osteoporosis was consistent with current guidelines criteria solely based on DXA evaluation (Table 3, Figure 1).

Parameter	Value	Normal range	Units
ACTH	**1**	3-66	pg/mL
Plasma morning cortisol	**0.39**	4.82-19.5	µg/dL
FSH	6.2	1.5-12.4	mUI/mL
LH	5.48	1.7-8.6	mUI/mL
Total testosterone	2.01	1.93-7.4	ng/mL
Prolactin	7.3	4.04-15.2	ng/mL
IGF 1	162.7	66-225	ng/mL
Osteocalcin	**3.5**	14-46	ng/mL
Alkaline phosphatase	54	40-150	U/L
P1NP	**8.9**	20.25-76.31	ng/mL
CrossLaps	**0.09**	0.104-0.504	ng/mL
PTH	48.56	15-65	pg/mL
25-OHD	**18**	30-100	ng/mL

Table 2 - Endocrine assays in a 50-year-old male patient with vertebral fractures and long-term administration of dexamethasone. ACTH (Adrenocorticotropic Hormone); FSH (Follicular Stimulating Hormone); LH (Luteinizing Hormone); IGF 1(Insulin-like Growth Factor 1); PTH (parathormone); 25-OHD (25-hydroxyvitamin D)

Imaging evaluations also included profile lumbar-thoracic spine X-ray showing vertebral fractures at thoracic T6 (biconcave aspect, 14.5 mm) and T12 levels, with osteosynthesis material migrated above and below T12. Demineralization was also confirmed in association with vertebral fractures at L2, L3, L4 and L5. The hip did not have any significant changes, except for the osteosclerosis of the acetabular surfaces (Figure 2).

Intravenous contrast computed tomography of the abdomen was conclusive a right adrenal gland with size at the upper normal range and left adrenal gland with normal size, minimally convex contour at medial limb. The mentioned vertebral compression fractures were confirmed, as well (at T12, L2, L3, and L4). The pituitary gland displayed a moderately hypodense micro-nodule of 0.77 by 0.3 cm in the right latero-sellar region (that was considered a pituitary incidentaloma) and visible Gasser ganglion postero-sellar on the median line.

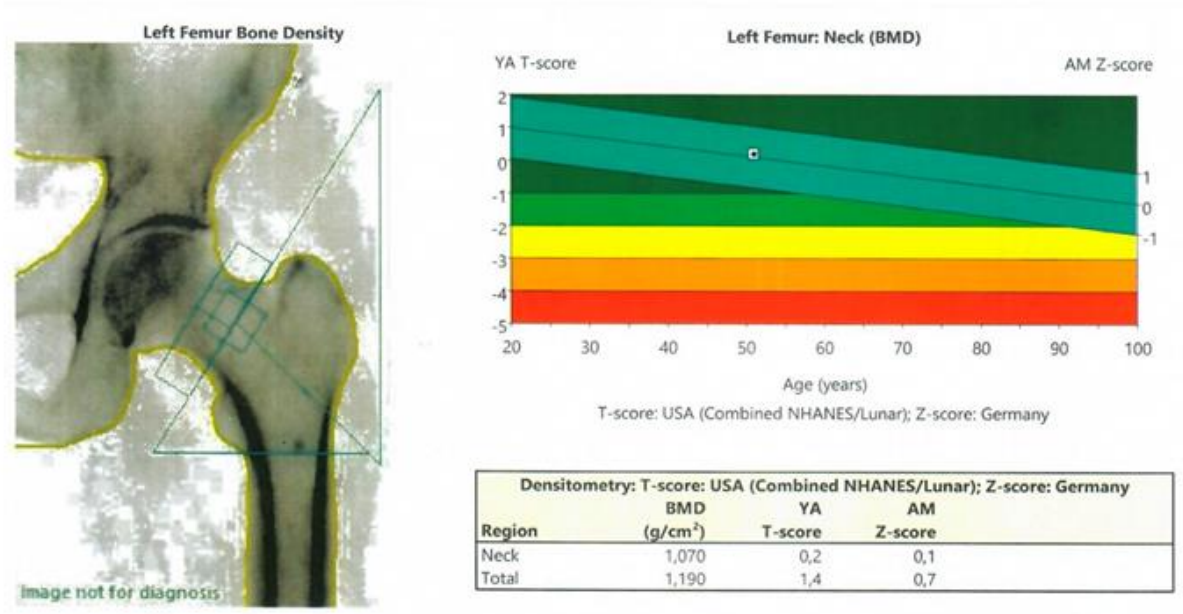

Figure 1 - DXA (GE Lunar Prodigy) results at total hip and total neck in 50-year-old patient with glucocorticoid-induced osteoporosis complicated with low trauma vertebral fractures

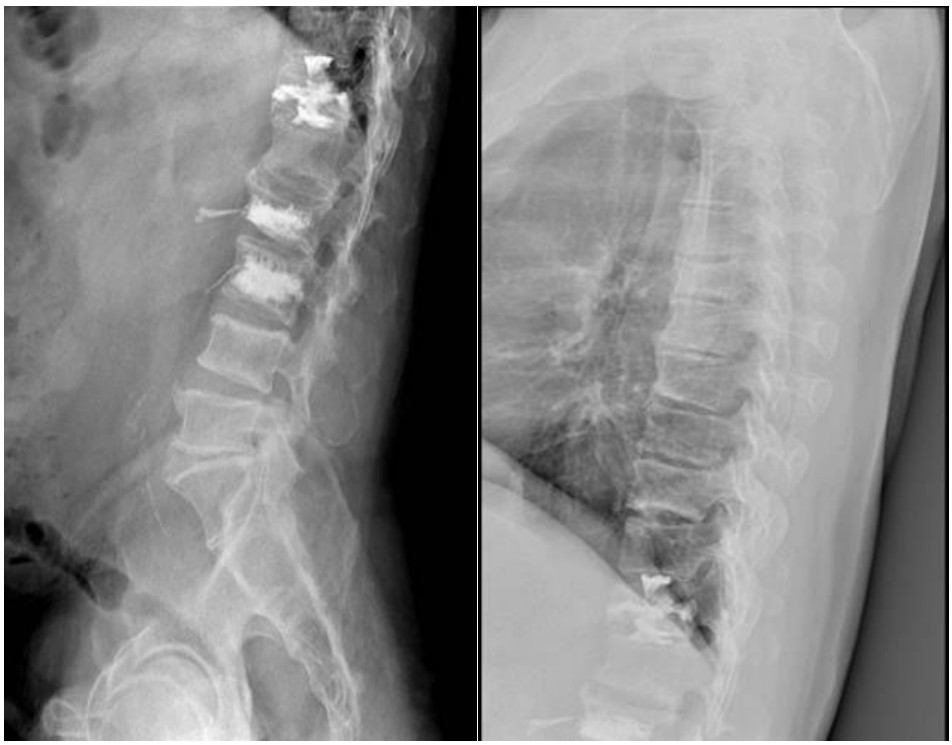

Figure 2 - Profile lumbar (left) and thoracic (right) plane X-Ray showing vertebral fractures

Region	BMD (g/cm²)	T-score (SD)	Z-score (SD)
Femoral neck	1.07	0.2	0.1
Total hip	1.19	1.4	0.7
1/3 distal radius	1.012	1.6	0.3

Table 3 - DXA results on a male patient with low trauma vertebral fractures and associated surgery (non-interpretable lumbar site)

The patient was instructed that it is mandatory to stop dexamethasone medication and was referred to alternative rehabilitation methods to alleviate the chronic lumbar pain (including non-steroidal anti-inflammatory drugs - both systemic and topical). Despite irrelevant central DXA results, a decision of specific medication against osteoporosis was taken based on the prevalent fractures profile. Thus, oral ibandronate 150 mg per month was recommended. Other recommendations included vitamin D supplements cholecalciferol 2000 IU/day in order to achieve normal levels of

25OHD and ensure further skeleton health. Moreover, metformin at a daily dose of 1000 mg was initiated for normalizing the glucose profile in addition to atorvastatin 20 mg/day for dyslipidaemia.

After 6 months, the patient presented for a clinical and laboratory exam. He mentioned that he did not stop dexamethasone administration since the last evaluation because no other method was effective for reducing his pain and continued taking an average daily dose of 8 mg/day. Moreover, he did not initiate the anti-osteoporotic and anti-diabetic treatment regime that was recommended on the previous admission. Blood assays were repeated and, as expected, they showed persistently high cholesterol and HBA1c (Table 4).

Parameter	Value	Normal range	Units
Total cholesterol	253	0-200	mg/dL
LDL-cholesterol	167	60-160	mg/dL
HBA1c	5.97	4.8-5.9	%

Table 4 - Persistently modified parameters after the patient did not follow the anti-diabetic and anti-dyslipidaemia treatment indication

Endocrine reassessment was consistent with suppressed ACTH and serum morning cortisol levels. Vitamin D levels remained low, as he did not start the supplements and bone turnover markers were also decreased, while other parameters were unremarkable (Table 5).

Parameter	Value	Normal range	Units
ACTH	<1.5	3-66	pg/mL
Plasma morning cortisol	0.31	4.82-19.5	µg/dL
Osteocalcin	4.28	14-46	ng/mL
Alkaline phosphatase	50	38-129	U/L
P1NP	10.6	20.25-76.31	ng/mL
CrossLaps	0.09	0.104-0.504	ng/mL
PTH (parathormone)	50.57	15-65	pg/mL
25-OHD	18.29	20-100	ng/mL

Table 5 - Endocrine re-evaluation after the patient did not stop dexamethasone intake, nor start anti-resorptive medication

The abovementioned recommendations remained valid. In addition, he was encouraged to pursue psychological evaluation for glucocorticoid dependency, and to initiate alternative pain-relief methods.

DISCUSSION

The present case highlights several important aspects with concern to real-life-medicine issues amidst glucocorticoid-induced osteoporosis.

Bone damage following long term dexamethasone addiction

Treatment with high doses of glucocorticoids leads to BMD loss (and consecutive high fragility fracture risk), especially at lumbar spine level and more prominent within the first year of administration [12,13]. The particularities are represented by the presence of osteoporosis in a male patient and the severity of it, reflected by multiple vertebral fractures, in association with a long history of oral glucocorticoid intake being the cause, while not specific evaluation of bone status was done for a few years; during surveillance, however, the patient turned out to be non-compliant to recommendations. The treatment of glucocorticoid-induced osteoporosis includes bisphosphonates, denosumab, and teriparatide, but adequate calcium and vitamin D supplementation are also important, as glucocorticoids interfere with the intestinal calcium absorption (in addition to the management of the underlying disease and associated complications) [14,15].

After stopping dexamethasone, the patient should be evaluated for tertiary adrenal insufficiency (so-called glucocorticoids-induced adrenal insufficiency), as the higher is the dose and duration of glucocorticoid administration, the greater is the risk of developing this complication [16-18]. Therefore, special steps must be taken when these patients stop the medication completely, in order to properly manage the recovery of the adrenal function after glucocorticoid withdrawal [19,20]. Generally, 3% of the population is under different regimes of glucocorticoids, hence, an adrenal failure (potentially life threatening) might be registered after stopping them, but many cases might remain actually underdiagnosed and become clinically obvious at different triggers such as trauma or infections [21,22]. This risk is registered irrespective of the route and doses (an exposure less to 4 weeks of a lower dose such than 5 mg of prednisone per day might not be

prone for developing this complication at glucocorticoids withdrawal [23,24]. In this particular instance, an adherence to glucocorticoids withdrawal is to be expected.

From chrono-pharmacology to limits of the fracture risk assessment

In this sample case, one of the challenges involved the skeleton assessment that was actually inconclusive in terms of BMD-DXA and TBS results in order to capture the true essence of the fracture risk. This was not necessarily related to the glucocorticoids exposure and their timing, but to the patient's features such as the presence of obesity, type 2 diabetes mellitus, and arthrosis which might increase BMD in addition to the surgery-related technique issues [25,26]. A next logical step of this matter is the difficultly of assessing the response to medication against osteoporosis (considering that the subject will eventually start it) [27,28]. Of note, the initiation of specific drugs belonging to this category might be limited to national protocols of reimbursement in cases with "abnormally normal" DXA results. The glucocorticoids effects on skeleton levels are reflected by the history of multiple complicated vertebral fractures, also, by the bone turnover markers profile, yet, not by DXA which represents a practical pitfall of not recommending anti-osteoporotic medication [29,30].

Non-compliance as part of real-life-medicine issues

This case from our daily practice showed that a complete endocrine and metabolic check-up was eventually done only a few years following the surgery and long-time dexamethasone use; despite complications, the patient was not compliant to initial recommendations, not only to associate drugs that might lower the fracture risk, but, also, the cardiovascular and metabolic secondary events, and to reduce and eventually stop the stop administration of the glucocorticoids. Additionally, the difficulty imposed by the physiological, not only physical, dependency requires a meticulous multidisciplinary follow-up [31,32].

CONCLUSION

Prolonged self-administration of dexamethasone for persistent post-operatory pain might bring negative bone effects in terms of multiple vertebral fractures requiring surgery that add to the already present component of persistent back pain. However, the tools we currently have to assess glucocorticoids-induced osteoporosis such as DXA and TBS might not be applicable in certain cases, thus the decision of medication against osteoporosis is based on the clinical panel (exogenous Cushing's syndrome) and suppressed serum bone turnover markers. Poor compliance to glucocorticoids withdrawal as well as adherence to medication against osteoporosis represented another issue in this instance.

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