CASE REPORT

Primary adrenal lymphoma: a case of hiccups

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Abstract
Approximately 250 cases of primary adrenal lymphoma have been reported. We describe an unusual presentation of this condition. Our patient is a 65-year-old male whom presented to the emergency department with 4 days of severe persistent hiccups. He had lost 26 kg in weight in the preceding 4 months. Computed tomography abdomen revealed large invasive bilateral adrenal masses. Biochemical evaluation confirmed adrenal insufficiency. Hiccups resolved within 24 h of steroid replacement. Adrenal biopsy confirmed a diffuse large B-cell lymphoma. Hypotheses for the aetiology of his hiccups include diaphragmatic irritation and primary adrenal insufficiency. This case is interesting for its rarity involving bilateral adrenal glands, Addison’s disease from the primary adrenal tumour and rapid resolution of hiccups with corticosteroid therapy.

INTRODUCTION
Hiccups (Latin: singultus) are spasmodic, involuntary contractions of the diaphragmatic and intercostal muscles. The majority of cases spontaneously resolve within 48 h. Causes of hiccups are diverse ranging from trivial causes to malignancy and neurological disorders. Intractable and prolonged hiccups may require prompt investigation to ascertain an underlying trigger.

Primary adrenal lymphomas (PALs) are rare and account for <1% of all non-Hodgkin lymphomas. Patients with adrenal failure have bilateral pathology. These malignancies are typically highly aggressive with poor 2-year survival rates.

We report an interesting patient who presented with hiccups.

CASE REPORT
A 65-year-old male presented with persistent hiccups for 4 days and 26 kg weight loss in 4 months. His past medical history and family history were both unremarkable. Relevant negative symptoms included abdominal discomfort, fevers and night sweats. A diagnosis of haemochromatosis had been made in the community based on a raised ferritin and heterozygosity for the H63D gene. He was venesected twice prior to this presentation.

Physical examination revealed a tall gentleman with blood pressure of 104/75, heart rate of 90 bpm and weight of 89 kg. Bilateral flank masses were palpated but no lymphadenopathy was identified. Admission blood tests were indicative of impaired renal function, hyperkalaemia and hyponatraemia (Table 1). An adrenocorticotropic hormone (ACTH) stimulation test confirmed adrenal insufficiency.

Computed tomography (CT) chest, abdomen and pelvis revealed large bilateral suprarenal masses measuring 135 × 125 mm on the left 115 × 85 mm on the right (Figs 1 and 2) with several sub centimetre retroperitoneal lymph nodes. Associated visceral invasion was noted with displacement of the renal vasculature and inferior vena cava (IVC) on the left and encasement of the left renal hilum, left renal vasculature and proximal ureter on the right. Postero-medially, the left lesion was not separable from the diaphragmatic crus. No nodal disease was identified above the diaphragm. Positron emission tomography (PET) scan confirmed fludeoxyglucose (FDG) avidity of these
Table 1: Initial biochemical evaluation

| Parameter                      | Value       | Reference range |
|--------------------------------|-------------|-----------------|
| Sodium                         | 122 mmol/L  | 135–145         |
| Potassium                      | 5.8 mmol/L  | 3.5–5.2         |
| Creatinine                     | 211 μmol/L  | 60–110          |
| Urea                           | 11 mmol/L   | 3–9             |
| Baseline ACTH                  | 621 pg/ml   | <46             |
| Baseline cortisol              | 232 nmol/L  | 110–550         |
| 30 min cortisol post ACTH      | 308 nmol/L  |                 |
| 60 min cortisol post ACTH      | 282 nmol/L  |                 |
| Plasma metanephrines           | <70 pmol/L  | <300            |
| Plasma normetanephrines        | 710 pmol/L  | <1050           |
| Lactate dehydrogenase          | 389 U/L     | 120–250         |
| Iron                           | 3.1 μmol/L  | 10–30           |
| Transferrin                    | 2.06 g/L    | 2.1–3.8         |
| Transferrin saturation         | 6%          | 15–50           |
| Ferritin                       | 1936 μg/L   | 30–500          |

Figure 1: Axial CT imaging demonstrating bilateral large adrenal masses with displacement of adjacent viscera.

masses with an additional FDG-avid right-sided para-aortic lymph node (Fig. 3). Lumbar puncture and MRI brain and whole spine excluded CNS involvement.

Following the exclusion of pheochromocytoma biochemically, to avoid insurgence of catecholamine and hypertensive crisis following biopsy, ultrasound biopsy of the right adrenal gland was undertaken. This demonstrated a diffuse large B-cell lymphoma of activated type (Fig. 4). Concurrent flow cytometry on the adrenal sample revealed a monoclonal B-cell population with CD5/CD10 negativity consistent with B-cell lymphoma. Immunohistochemical testing demonstrated positivity for B-cell lymphoma 2 (BCL-2), patchy positivity for BCL-6 and negative for C-MYK (Fig. 5). Ki-67 was estimated at 90% exhibiting a very high mitotic rate (Fig. 6). A bone marrow biopsy was not performed as haemophagocytic lymphohistiocytosis was felt unlikely given an unremarkable full blood count and a ferritin count of 1936 μg/L.

Initially, chlorpromazine was used for symptomatic control of hiccups with mild effect. Intravenous and subsequent oral hydrocortisone was commenced for primary adrenal insufficiency with clinical and biochemical improvement. Fludrocortisone was added at a later stage. Full resolution of hiccups was observed within 24 h of commencing corticosteroid therapy.

After three of six cycles of R-CHOP-21 chemotherapy, PET imaging has demonstrated significant interval regression of bilateral masses (70 × 76 × 50 mm on the right and 131 × 92 × 46 mm on the left). There has been no further recurrence of hiccups and renal function has since normalized.

DISCUSSION

Differential diagnoses of bilateral adrenal masses include congenital bilateral adrenal hyperplasia, metastases especially from...
Primary adrenal lymphoma

Breast and lung and melanoma, infective causes such as tuberculosis and histoplasmosis, infiltrative conditions and primary neoplastic lesions such as pheochromocytoma and PAL.

PAL is rare with ~250 cases reported [1]. PAL is characteristically a highly aggressive malignancy with diffuse large B cell (78%) comprising the most common subtype [2]. Diagnosis requires lymphomatous involvement of one or both adrenal glands with no prior history of lymphoma. In patients with extra-adrenal involvement, the adrenal glands must be the unequivocal dominant lesion. While metastatic disease into the adrenal gland is a rare cause for Addison’s disease, adrenal insufficiency in PAL is common occurring in over 50% of cases [1, 3]. Outcome remains poor with a 61.5% overall 2-year survival according to a recent multicentre case series of 50 patients [1].

The patient’s presentation shared many features consistent with the reported literature. This includes age of presentation, male predominance, high lactate dehydrogenase, hyperferritinaemia, bilateral adrenal involvement, adrenal failure, high Ki-67 mitotic rate and diffuse large B-cell characterization [1–4].

To our knowledge, this case represents the first presentation of PAL with hiccups.

Hiccups are caused by abrupt spasmodic contractions of both diaphragmatic and intercostal muscles. Potential causes are wide ranging and include central nervous disorders, gastrooesophageal conditions, metabolic (including hyponatraemia), psychogenic and medication induced [5, 6]. Hiccups have been reported in four patients with Addison’s disease. Interestingly in all cases, steroid replacement resulted in complete resolution of hiccups [7–9].

The most plausible explanation for hiccups in this patient is from direct tumour irritation. The left mass was inseparable from the left diaphragmatic crus and lower oesophageal compression was evident. However, such marked and complete resolution of symptoms with corticosteroids raises the possibility of Addison’s disease as the underlying aetiology. Numerous reports in the literature have associated steroids, especially dexamethasone, with the onset rather than resolution of hiccups [6]. On the contrary, it is certainly possible that the high-grade masses described would shrink with steroid administration with subsequent reduction with direct tumour irritation while resolution within a day of hydrocortisone use is unexplainable.

Diagnostic delay in malignant conditions has marked consequences with morbidity and mortality. Significant unintentional weight loss should always prompt further investigation. Unfortunately, a raised ferritin level and heterozygosity for the H63D gene led to delayed diagnosis. Haemochromatosis is diagnosed with a raised ferritin level in the absence of inflammation or infection and with transferrin saturations of >45%. Iron studies and inflammatory markers in this case clearly point towards inflammation as the cause of hyperferritinaemia. Clinicians should be aware of the broad range of causes of high ferritin levels including chronic alcohol consumption, liver injury, haemophagocytic lymphohistiocytosis, systemic infection and chronic inflammatory conditions and malignancy should not be forgotten [10].

CONFLICT OF INTEREST STATEMENT

None declared.

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ETHICAL APPROVAL

Ethical approval was not required and therefore not obtained.

CONSENT

Verbal and written consent has been gained for this report (including publication of images).

GUARANTOR

The first author accepts official responsibility for the overall integrity of the manuscript.
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