CASE REPORT

Diffuse large B-cell lymphoma of the adrenal gland: a rare cause of primary adrenal insufficiency

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SUMMARY

Although it is a rare entity, primary lymphoma of the adrenal gland should be considered in the differential diagnosis of bilateral nodular adrenal lesions, particularly when there is evidence of associated adrenal insufficiency. We describe the case of an 83-year-old woman admitted to the emergency department due to a month's history of asthenia, weight loss, anorexia and nausea. Abdominopelvic CT showed bilateral nodular lesions of adrenal glands and a stimulation test with tetracosactide was compatible with primary adrenal insufficiency. CT-guided biopsy of the left adrenal gland was performed, and histopathological results were consistent with diffuse large B-cell lymphoma. Positron emission tomography ^{18}F -fluorodeoxyglucose detected two intensely hypermetabolic lesions limited to both adrenal glands. Replacement therapy with hydrocortisone 15 mg/day and fludrocortisone 0.1 mg/day was promptly started and chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone was initiated after haematology-oncology consultation.

BACKGROUND

Diffuse large B-cell lymphoma (DLBCL) of the adrenal gland is an uncommon condition and clinical presentation as primary adrenal cortical insufficiency is rare. Thus, high suspicion associated with early diagnosis enables appropriate and early treatment with favourable impact on prognosis.

CASE PRESENTATION

An 83-year-old woman with a known medical history of hypertension, dyslipidaemia, type 2 diabetes mellitus, obstructive sleep apnoea syndrome and nodular thyroid disease, was admitted to the emergency department due to asthenia, weight loss (>10% body weight), anorexia and nausea for the past month. There were no additional respiratory, gastrointestinal or neurological symptoms reported within that period.

INVESTIGATIONS

Physical examination was normal with no lymphadenopathies and no cutaneous hyperpigmentation. No laboratory abnormalities were identified besides an elevation of lactate dehydrogenase (LDH) 254 U/L (normal range (NR) <247 U/L) and normocytic normochromic anaemia (haemoglobin 11.1 g/dL; NR 12–15 g/dL).

CT of the abdomen showed two adrenal masses with a maximal diameter of 4.6 and 4.7 cm on left and right gland, respectively. The patient was

admitted for evaluation at the endocrinology department.

Laboratory workup revealed an adrenocorticotrophic hormone (ACTH) value at 8/9 h of 298 pg/mL, cortisol at 8/9 h of 8.5 µg/dL and a stimulation test with tetracosactide was compatible with primary adrenal insufficiency (ACTH basis 557 pg/mL; cortisol—0': 7.2 µg/dL; 30': 8 µg/dL; 60': 8.5 µg/dL).

Adrenal androgens (dehydroepiandrosterone SO_4 <0.2 µg/mL, NR 0.35–4.3 µg/mL; androstenedione 0.8 ng/mL, NR 0.5–3.4 ng/mL), plasma renin (62 µU/mL, NR 7–79 µU/mL), plasma aldosterone (40.1 pg/mL, NR 40–310 pg/mL), plasma metanephrines (8.2 pg/mL, NR <60 pg/mL) and plasma normetanephrines (31.1 pg/mL, NR <120 pg/mL) were normal.

Tumour markers carcinoembryonic antigen, α -fetoprotein and CA-125; interferon γ (Quantiferon) and serology for hepatitis B virus, hepatitis C virus and HIV 1/2 were negative. Breast ultrasound and colonoscopy did not show any abnormality.

A second thoracoabdominopelvic CT, 1 month later, confirmed the previously described lesions, with a maximal diameter of 6.3 and 7.3 cm, on the right and left adrenal glands, respectively. These nodules presented a heterogeneous texture, with precontrast density of 35 Hounsfield unit and absolute washout of 35%, with neither lymphadenopathy nor abdominopelvic expansive lesions (figure 1). MRI revealed abdominal nodular lesions with moderate hyperintensity on T2 and hypointensity on T1, strongly suggestive of a malignant aetiology (figure 2A, B).

CT-guided biopsy directed to the left adrenal gland was performed, and histopathological results

Figure 1 Thoracoabdominopelvic CT: nodular lesions on the right and left of 6.3–7.3 cm at major axis; heterogeneous texture; spontaneous density of 35 Hounsfield unit and absolute washout of 35%.

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Figure 2 Abdominal MRI ((A) transverse plane; (B) coronal plane—acquisition in T2)—nodular lesions with moderate hyperintensity on T2 strongly suggestive of a malignant aetiology.

were consistent with involvement of the left adrenal gland, with DLBCL: LCA+, CD20+, CD10+, BCL-2+, BCL-6+; AE1/AE3–, CD56– and Melan A–. (figure 3A–C).

Positron emission tomography with ^{18}F -fluorodeoxyglucose detected two bulky intensely hypermetabolic lesions, compatible with highly metabolic neoplastic disease activity, limited to both adrenal glands (figure 4).

Bone marrow aspiration study showed no evidence of abnormal lymphoid infiltration.

DIFFERENTIAL DIAGNOSIS

Nodular lesions of adrenal glands may be related to metastatic disease (mostly from solid tumours of the lung and breast, renal conditions, melanoma and rarely from tumours of the colon), primary malignant adrenal disease (lymphoma, pheochromocytoma, adrenocortical carcinoma or neuroblastoma), non-functioning or functioning adenoma, adrenal macronodular hyperplasia, congenital adrenal hyperplasia, infiltrative causes (amyloidosis), infectious causes (tuberculosis, histoplasmosis and cryptococcosis) or haemorrhagic causes.

TREATMENT

Replacement therapy was initiated for the primary adrenal insufficiency with 15 mg/day of hydrocortisone and 0.1 mg/day of fludrocortisone. The patient was subsequently oriented to haematology-oncology consultation and has been proposed for chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP).

OUTCOME AND FOLLOW-UP

The patient is on the second cycle of chemotherapy with R-CHOP. No complications were observed during the systemic treatment and no acute adrenal insufficiency episodes were registered since hormone replacement treatment was initiated.

DISCUSSION

The adrenal glands are frequent sites of secondary lesions of solid tumours, particularly those originating in the breast, lung

Figure 4 Positron emission tomography ^{18}F -fluorodeoxyglucose—two bulky intensely hypermetabolic lesions, compatible with highly metabolic neoplastic disease activity, limited to both adrenal glands.

and kidney and from melanoma.^{1 2} Among the lymphoproliferative neoplasms, non-Hodgkin's lymphomas, particularly DLBCL, are the most commonly identified.³ Clinical presentation as primary adrenal cortical insufficiency is rare, usually only becoming evident when there is destruction of about 90% of the glandular parenchyma, as occurs in advanced stages of the primary disease.⁴

Bilateral, bulky masses of adrenal glands are highly suspicious of granulomatous disease, haemorrhage, lymphoma or metastatic lesions.^{1 5}

Involvement of adrenal glands by extranodal lymphoma is uncommon, with <200 cases reported in the literature.^{6–12}

The rare association between the described nosological entities justifies that the diagnosis is often delayed and that their overall frequency is underestimated.¹³

To clarify the aetiology of a nodular lesion of the adrenal gland, a detailed medical history and complete physical examination are needed, as well as biochemical evaluation (to exclude functional tumours) and imagiological characterisation. CT scan is the preferred imaging method and, although there are no pathognomonic radiological features of adrenal lymphoma, masses >4 cm with a heterogeneous texture are highly suggestive of malignancy.^{8 14} On MRI, lymphomas typically have a signal intensity lower than that of the liver on T1-weighted sequences and are heterogeneously hyperintense on T2-weighted sequences.²

The definitive diagnosis depends on histopathological diagnosis. Ultrasound/CT scan guided needle biopsy is reserved for selected cases with high clinical suspicion of primary lymphoma or metastatic lesions. Adrenalectomy has been performed mostly when lymphoma was not considered in the initial differential diagnosis and may be a factor that delays systemic therapy in these cases, thereby adversely affecting prognosis.^{3 6 14}

Median survival of these patients stands at 13 months and prognostic factors such as advanced age, large tumour size, elevated LDH and germinal centre phenotype have negative

Figure 3 Histological images obtained through CT-guided biopsy of the left adrenal gland: (A) H&E stain cellular detail (x400)—large cells with scant cytoplasm and irregular nuclear contour; (B) immunostaining positive for CD45 (leucocyte common antigen)—recognising a haematolymphoid origin; (C) immunostaining for CD20 (x400) showing large CD20+ B lymphocytes.

impact on survival. Association with adrenal insufficiency worsens the overall prognosis, especially if there is bilateral gland involvement. Therefore, it is critical to consider and screen patients with a stimulation test using tetracosactide and initiate appropriate hormone replacement to prevent the development of acute adrenal insufficiency even during oncological treatment.^{15 8}

The most widely accepted therapy is chemotherapy with an R-CHOP regimen with progression-free survival and overall survival rates exceeding 50% at 2-year follow-up.^{7 12 15}

Learning points

- Primary lymphoma of the adrenal gland is a rare entity but should be considered in the differential diagnosis of bilateral nodular lesions especially when there is evidence of associated adrenal insufficiency.
- Imaging and analytical study support the diagnosis, but the definitive diagnosis requires histological evaluation.
- The high suspicion associated with early diagnosis enables appropriate treatment with favourable impact on prognosis.

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Contributors ASL followed the patient while she was electively admitted for investigation at the endocrinology department, doing so under the tutelage of PO; and was also responsible for conception, interpretation of data and drafting the article, which was reviewed by MB and PO and subsequently by FC. MB followed the patient in their endocrinology consultation and added substantial contribution by revising the manuscript critically for important intellectual content. FC reviewed, guided and approved all the processes of investigation and all the medical decisions applied and gave final approval of the version to be published. All the authors read and approved the final manuscript.

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