Rebound thymic hyperplasia after adrenalectomy in a patient with Cushing syndrome caused by adrenocortical adenoma

A case report

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Abstract

Rationale: The development of rebound thymic hyperplasia (RTH) has been reported in patients who have recovered from stressful conditions such as surgery and steroid therapy. We report a case of RTH following the resolution of hypercortisolism after adrenalectomy for the treatment of adrenocortical adenoma in a patient with Cushing syndrome.

Patient concerns: A 5-month-old female infant with a history of overeating, hirsutism, and excessive weight gain for the previous 2 months was referred to the hospital. The laboratory results revealed elevated 24-hour urinary free cortisol levels. An overnight dexamethasone suppression test showed no response. Abdominal imaging revealed a right-sided suprarenal mass measuring 4.3 cm. Histology showed an adrenocortical adenoma. Thus, she underwent a right adrenalectomy.

Diagnoses: The patient showed clinical improvement with weight loss and normal cortisol levels over the next 4 months. Six months after the operation, a chest computed tomography showed enlargement of the left thymic lobe, which was previously nonexistent.

Interventions: A fine needle aspiration biopsy was performed, and histological examination revealed diffuse thymic hyperplasia.

Outcomes: At the 1-year follow-up, the chest imaging studies showed resolution of the RTH.

Lessons: An understanding of RTH after adrenalectomy as a treatment for cortisol-producing adrenocortical tumors is important for the prevention of unnecessary surgical intervention and therapy.

Abbreviations: ACTH = adrenocorticotropic hormone, CS = Cushing syndrome, CT = computer tomography, DHEA = dehydroepiandrosterone, FNAC = fine needle aspiration cytology, RTH = rebound thymic hyperplasia

Keywords: adrenalectomy, Cushing syndrome, rebound thymic hyperplasia

1. Introduction

The volume of the thymus may decrease under stressful conditions, depending on their duration and severity. After recovery, the thymus usually returns to its original size or becomes enlarged within 9 months, a phenomenon known as rebound thymic hyperplasia (RTH).[1] The development of RTH has been reported not only in patients with malignancies after the initiation of chemotherapy but also in patients who have recovered from stressful conditions, such as burn,[2] surgery,[3] steroid therapy, and bone marrow transplantation.[1,4]

There are 2 distinct types of thymic hyperplasia that may enlarge the thymus and simulate a neoplasm. RTH represents a form of true thymic hyperplasia, which indicates a diffuse, symmetric thymic growth beyond the age-appropriate range with conservation of the thymic architecture. On imaging studies, the gland is diffusely enlarged and preserves its normal shape, showing a homogenous appearance similar to normal thymic tissue on computed tomography (CT). Lymphoid follicular hyperplasia, on the contrary, is generally defined by the presence of proliferation of lymphoid follicles with active germinal centers and increased numbers of lymphocytes. It is usually seen in patients with myasthenia gravis or other autoimmune diseases.[5–7]

Although RTH may occur as a rebound phenomenon during the recovery phase of chemotherapy, the occurrence of a mediastinal mass after treatment completion in pediatric patients with malignancies is alarming and challenging for clinicians. The discovery of a thymic mass in patients with Cushing syndrome (CS) who have undergone adrenalectomy may also not be easily discerned from thymic hyperplasia and ectopic tumors of the thoracic region.

Herein, we report the case of a 5-month-old infant with RTH following the resolution of hypercortisolism after adrenalectomy treatment for an adrenocortical tumor. This case highlights the importance of recognizing RTH because the rapid enlargement of the thymus may present a misleading tumoral appearance, particularly in cases of altered chest anatomy. An understanding of this unusual side effect may prevent unnecessary assessment and therapy.
2. Case report

A 5-month-old female infant with a history of overeating, hirsutism, and excessive weight gain over the previous 2 months was referred to our hospital. The infant was born to Bangladeshi parents at 37 + 2 weeks with a birth weight of 3100g via Cesarean section at a local hospital. A maternal history of polycystic ovary syndrome and oligohydramnios was reported. The infant was healthy with no unusual medical history, and her development was normal. There was no medical history of disorders such as metabolic or endocrine diseases, cancer, and genetic diseases. Written informed consent was obtained from the patient’s parents. Institution ethical review board approval is not required for observational case reports that do not alter patient management.

Physical examination revealed a overweight baby with a moon face, buffalo hump, and protruding abdomen (Fig. 1). Increased body hair was also noted. The patient’s body length was 61.0 cm (5–10th percentile) and her weight was 10.4 kg (>97th percentile). Her blood pressure was within the normal range (100/60 mm Hg).

Complete blood cell counts showed leukocytosis (white blood cell count of 29,220 cells/μL, 44% lymphocytes), but the other cell counts were all normal. The results of the blood chemistry analysis, including serum glucose levels and liver and kidney function tests, were normal. After a low-dose (1 mg) dexamethasone suppression test, a morning serum cortisol level of 49.7 μg/dL was obtained, which showed no suppression (cut-off point, <1.8 μg/dL). Anelevated 24-hour urinary free cortisol level was noted (872.4 μg/dl), and the concomitant plasma adrenocorticotropic hormone (ACTH) level was within the lower limits of the normal range (12.1 pg/mL). These results were compatible with a diagnosis of ACTH-independent CS.

Regarding the results of the imaging studies, a chest x-ray showed nonspecific findings with normal thymic and cardiac shadows. However, abdominal magnetic resonance imaging (MRI) revealed a 3.8 × 2.8 cm right adrenal mass with homogenous enhancement and diffusion restriction. The margin was smooth with distinct borders, showing no invasion to adjacent organs, which was suggestive of adrenocortical adenoma; however, adrenocortical carcinoma could not be fully excluded due to restrictions in diffusion (Fig. 2).

**Figure 1.** Physical examination of the patient upon admission, showing the typical features of Cushing syndrome.

**Figure 2.** Diagnosis of adrenocortical adenoma. (A) Magnetic resonance imaging (MRI) of the abdomen showed a right-sided suprarenal mass measuring 4 × 3 cm with a smooth margin and no invasions. (B) T1 image showing homogenous enhancement of the mass. (C) A right adrenal mass in the coronal view of the MRI. (D) Gross appearance of the adrenocortical adenoma. The cut surface is darkly pigmented. (E) Histological features of adrenocortical adenoma, including an increased nucleo-cytoplasmic ratio and prominent nucleoli of the adrenal cells and no evidence of vascular invasion (hematoxylin and eosin, ×400).
The right adrenalectomy revealed a soft, movable suprarenal mass that measured $4.2 \times 3.9 \times 2.4$ cm with a dystrophic calcification of the capsule (Fig. 2). No lymphadenopathy or adhesions to the adjacent organs were observed. Histopathology revealed findings suggestive of adrenal adenoma, including adrenal cells with uniform round nuclei and increased nucleocytoplasmic ratio separated by fibrous septae. No evidence of necrosis or infiltration was found (Fig. 2).

Postoperatively, the patient was administered hydrocortisone via intravenous infusion for 2 days; the treatment was then changed to an oral physiologic replacement dose ($10 \text{mg/m}^2/\text{d}$) with sequential tapering and was discontinued after 6 months. The patient was regularly followed up at our oncology department and showed clinical improvement with weight normalization and resolution of her Cushingoid appearance over the next 4 months. The elevated cortisol level had also returned to normal at $18.2 \mu\text{g/dL}$ at the 4-month follow-up.

Six months after adrenalectomy, a mediastinal mass, which was previously nonexistent, was detected on a routine chest x-ray (Fig. 3). For further evaluation, chest CT was performed and an enlargement of the left thymic lobe ($45.51 \times 72.97 \times 51.76$ mm) with homogenous attenuation was confirmed. To exclude the possibility of a residual adrenal lesion or misdiagnosis, an abdomen CT scan was performed and showed no abnormal findings. To further investigate the mass, a fine needle aspiration (FNA) biopsy was performed. Histopathology revealed benign thymic tissue without evidence of malignancy. Thymic architecture consisting of corticomedullary differentiation with presence of Hassall corpuscles in the medulla was conserved, thus confirming that the thymic tissue was benign, which is characteristic of RTH (Fig. 4). Thereafter, she did not undergo surgical exploration and only basic assessments were performed during regular follow-up check-ups.

The 6-month follow-up chest x-ray after the diagnosis of RTH still showed mediastinal widening. However, at the 1-year follow-up, the chest x-ray showed resolution of the RTH (Fig. 3).

Figure 3. (A) Normal chest x-ray findings before the right adrenalectomy. (B) Six months after adrenalectomy, an enlarged mediastinal mass was visible on chest x-ray, which was previously nonexistent. (C) Six-month follow-up chest x-ray after the diagnosis of rebound thymic hyperplasia (RTH). (D) One-year follow-up chest x-ray after the diagnosis of RTH, showing its resolution.
In addition, the size of the thymus on the follow-up CT findings has gradually decreased since the diagnosis. After 1 year, the size of the thymus had decreased from 45.51 × 72.97 × 51.76 mm to 37.01 × 61.99 × 41.24 mm (Fig. 5). The length and width were measured perpendicularly as the maximum diameter, and the height was measured from the sternoclavicular junction level based on the proximal clavicular end.

3. Discussion

Development of rebound hyperplasia has been observed in patients who undergo chemotherapy within 2 years from the initiation of the treatment. The diagnostic challenge in patients with known neoplasms is to differentiate thymic hyperplasia from recurrent or metastatic tumors. RTH typically shows a diffuse enlargement, a fine mixture of lymphoid tissue and fat, a smooth contour, and normal vessels; in contrast, thymic neoplasia is usually associated with a nodular contour and frequently contains necrotic or calcified foci.

As in our patient, RTH may also occur after a resection of a primary pituitary or ectopic ACTH-secreting tumor without administration of chemotherapy, sometimes leading to an inappropriate removal of the thymus. Doppman et al reported that after the removal of cortisol or ACTH-producing tumors, a period of relative adrenal insufficiency occurs after a sudden decrease in cortisol levels despite routine postoperative replacement steroid therapy. This period of relative adrenal insufficiency physiologically resembles the termination of stress associated with recovery from chemotherapy, burns, and surgery.

The underlying mechanism may involve a depletion of thymus lymphocytes caused by high cortisol concentration in the plasma, leading to RTH, when the cortisol level decreases. Such cases have been particularly reported in children who received corticosteroid treatment for lymphoma or other malignancies. Its average duration varies. However, the condition spontaneously normalizes within 1 year.

The first diagnostic tool for the evaluation of thymic lesions is a chest CT with possible imaging findings overlapping between

**Figure 4.** Fine-needle aspiration biopsy was performed, and histological examinations showed a benign thymic tissue (hematoxylin and eosin, ×100, ×400).

**Figure 5.** Diagnosis of rebound thymic hyperplasia (RTH), (A) computed tomography (CT) imaging of the thorax showing enlargement of the left thymic lobe. A large thymus with a quadrilateral appearance is visible at the anterior mediastinum with homogenous attenuation. (B) Six-month follow-up CT after the diagnosis of RTH. (C) One-year follow-up CT after the diagnosis of RTH, showing decreased thymus size.
normal thymic variants, ectopic thymic tissue, malignancy, and non-neoplastic conditions, such as RTH.\cite{14} The determination of thymic hyperplasia is a diagnostic challenge and most patients undergo surgical exploration. In some reports, FNA cytology (FNAC) was not appropriate for the differentiation of RTH from malignancy.\cite{13} Recently, a few cases of thymic hyperplasia have been confirmed through ultrasound-guided FNAC of the thymus, which is a simpler and less invasive method than thymus biopsy via videothoracoscopy or surgical procedures.\cite{16} This suggests that FNAC should be used as a front-line diagnostic tool for RTH.\cite{15}

The mean recovery time of RTH is not clearly specified. Zhen et al reported that most cases of enlarged thymus in RTH returned to normal size within 6 to 9 months, but in a few patients, the enlarged thymus persisted for as long as 5 years.\cite{17} Another case showed spontaneous regression of the thymus 38 months after the initial diagnosis of RTH.\cite{18} Therefore, the duration of the follow-up for RTH should vary depending on the patient; however, due to its gradual change, at least a 1-year of follow-up is recommended.

The detection of a mediastinal mass is usually distressing. However, as RTH can be expected once we are familiar with the normal variation, we should be aware that an abrupt decline in serum cortisol levels due to several factors can lead to RTH. This phenomenon should be recalled, and a conservative approach for follow-up examinations should be permitted.\cite{19} A complete knowledge of thymic embryology, anatomy, normal variations, ectopic locations, and constant change is essential to prevent the performance of unnecessary invasive procedures.

4. Conclusions

Knowledge regarding RTH after adrenalectomy for the treatment of cortisol-producing adrenocortical tumors is important to prevent inappropriate surgical intervention and overtreatment due to its benign course and spontaneous recovery. Therefore, despite its rareness, RTH should also be considered as a cause of mediastinal mass after the resolution of hypercortisolism. Pediatricians should be familiar with the pathophysiological changes caused by a precipitous decrease in cortisol levels to prevent diagnostic errors and unnecessary operations.

Author contributions

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