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Case Report

Spontaneously reversible adrenal nodules in primary diffuse large B-cell testicular lymphoma mimicking an extranodal involvement: A case report ☆,☆☆

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ABSTRACT

In the staging of cancer patients, transient and spontaneously reversible bilateral adrenal hypertrophy may mimic a secondary localization of the disease. We discuss the case of an 82-year-old male patient with suspected testicular neoplasia in which abdominal CT examination reveals the onset of a bilateral macronodular adrenal enlargement, suggesting the diagnostic hypothesis of primary testicular neoplasia with secondary adrenal localization. The subsequent ¹⁸FDG-PET/CT study showed hyper-metabolism of the testicular mass, while the adrenal glands, surprisingly, did not show increased uptake of the radiotracer. After right orchifuniclectomy, primary testicular diffuse large B-cell lymphoma was diagnosed. The subsequent staging PET/CT study with iodine contrast medium, three months after the first CT examination, showed spontaneous complete regression of the adrenal hypertrophy without any use of drug therapy. The differential diagnosis of this finding considered the lack of hypermetabolism and the densitometric characteristics of the adrenal glands, the absence of possible pharmacological interactions throughout the time of the diagnostic procedures, and the available clinical-laboratory data. By excluding the main causes of adrenal hypertrophy, the most likely diagnostic hypothesis was transient adrenal hypertrophy due to stress induced by testicular lymphoma, meaning by stress a disturbance not only

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emotional but also an alteration of organic homeostasis. Our case suggests that the analysis of adrenal lesions appeared in cancer patients should take into account non-metastatic conditions that must be studied with a multimodal approach and with serial investigations.

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Introduction

Incidental adrenal masses are common imaging findings found in approximately 3-7% of adults [1]. Adrenal incidentalomas are mostly benign and compatible with non-functioning adenomas [2]. The characterization of an adrenal mass as benign or malignant is critical, and imaging plays a key role in influencing the clinical management of patients. Considering the high prevalence of benign adrenal masses in the general population, an incidental adrenal mass in a cancer patient is also most likely benign [3,4]. However, the adrenal gland is also a common site of metastases [5] and, less frequently, of primary adrenal tumors, including pheochromocytomas, aldosteronomas and adrenal cortical carcinomas [1]. Secondary adrenal involvement by lymphomatous disease systemic has been reported in 25% of patients with Non-Hodgkin lymphoma [6]. Therefore, in patients with known or suspected neoplasm, the appearance of adrenal lesions raises the suspicion of a secondary adrenal localization [7]. Adrenal hypertrophy is radiologically defined as a non-malignant glandular enlargement, with increased thickness of one or more areas (i.e. body and limbs), which histologically corresponds to an increase in cell size, or in the number of cells in case of hyperplasia [8]. Unlike unilateral adrenal incidentalomas, which concern 4% of CT exams performed [9], the incidental finding of bilateral adrenal hypertrophy is infrequent, and the literature on such finding is lacking. Our report concerns the history of a patient with primary testicular diffuse large B-cell lymphoma with the appearance of macronodular enlargement of the adrenals in a staging CT survey, with the resulting initial diagnostic hypothesis of a secondary localization of the disease. The subsequent spontaneous regression of these adrenal nodules together with the absence of adrenal hypermetabolism made us reconsider the differential diagnosis, which finally led towards a transient bilateral adrenal hypertrophy likely related to lymphoma induced organic stress.

Case presentation

An 82-year-old male patient presented at the Emergency Department for painless right testicular swelling in the absence of systemic symptoms. His medical records showed left eye glaucoma, transvesical prostatic adenomectomy, episode of acute urinary retention, appendectomy and left inguinal hernioplasty. Prior medical treatments included dorzolamide, lansoprazole and dutasteride. The testicular ultrasound examination showed enlargement and ecostructural inhomogeneity of the right didymus and epididymis and the presence of ipsilateral corpuscular hydrocele. To treat a suspected or-

chiepididymitis, the patient was treated with antibiotic therapy (amoxicilin/clavulanic acid for 10 days). At the end of the treatment, the swelling persisted, so the patient underwent a CT scan with iodinated contrast medium. Abdominal CT examination confirmed the testicular pathological findings and revealed the presence of bilateral macronodular adrenal hypertrophy (15 × 12 mm on the right and 27 × 18 mm on the left), with homogeneous attenuation (Fig. 1). Notably, bilateral nodules were not present in a CT scan performed 3 years earlier. To complete the testicular and adrenal evaluation, a ¹⁸F-FDG PET/CT showed a focal hyperfixation of the right testis only (SUVmax 25.5) and the absence of adrenal uptake (Fig. 2). Blood chemistry showed normal electrolyte, blood count, martial profile, protein electrophoresis, glycemia, kidney and liver function. The thyroid profile and cell proliferative indices (LDH and Beta2 microglobulin) were within the normal range. Serology was negative for active HCV and EBV infection and positive for previous EBV infection, viruses involved in the development of some NHL histotypes. Clinically, the patient did not complain of asthenia, headache, or abdominal pain, nor did he have abdominal striae or nuchal hump (“buffalo hump”). The blood pressure values were equal to 130/80 mmHg and there were no pressure peaks in the 24-hours blood pressure monitoring. The patient underwent a right orchifunicectomy on the basis of a diagnosis of diffuse large B-cell malignant lymphoma (DLBCL) of the testis with high proliferative activity (Ki-67 index = 80%), not infiltrating the adjacent structures. The subsequent staging PET/CT examination with iodine contrast agent, performed 3 months after the first CT examination, documented the total regression of adrenal hypertrophy without the use of any drug therapy and the absence of fixation of the PET radiotracer (Fig. 3). Following the PET/CT staging, the patient was treated with R-CHOP chemotherapy protocol at monthly intervals and contralateral scrotal radiotherapy.

Discussion

We presented the case of an 82-year-old patient with primary testicular lymphoma and a finding of transient and spontaneously reversible bilateral adrenal hypertrophy. From the radiological point of view, the contextual evidence of a testicular mass, later revealed to be lymphomatous; and the onset of adrenal bilateral macronodular enlargement requires detailed differential diagnosis to exclude extranodal adrenal involvement of testicular lymphoma and other causes of bilateral enlargement. A correct radiological differential diagnosis may help the clinician to evaluate correctly the proper treatment strategy and reduce surgical risks correlated with wrong

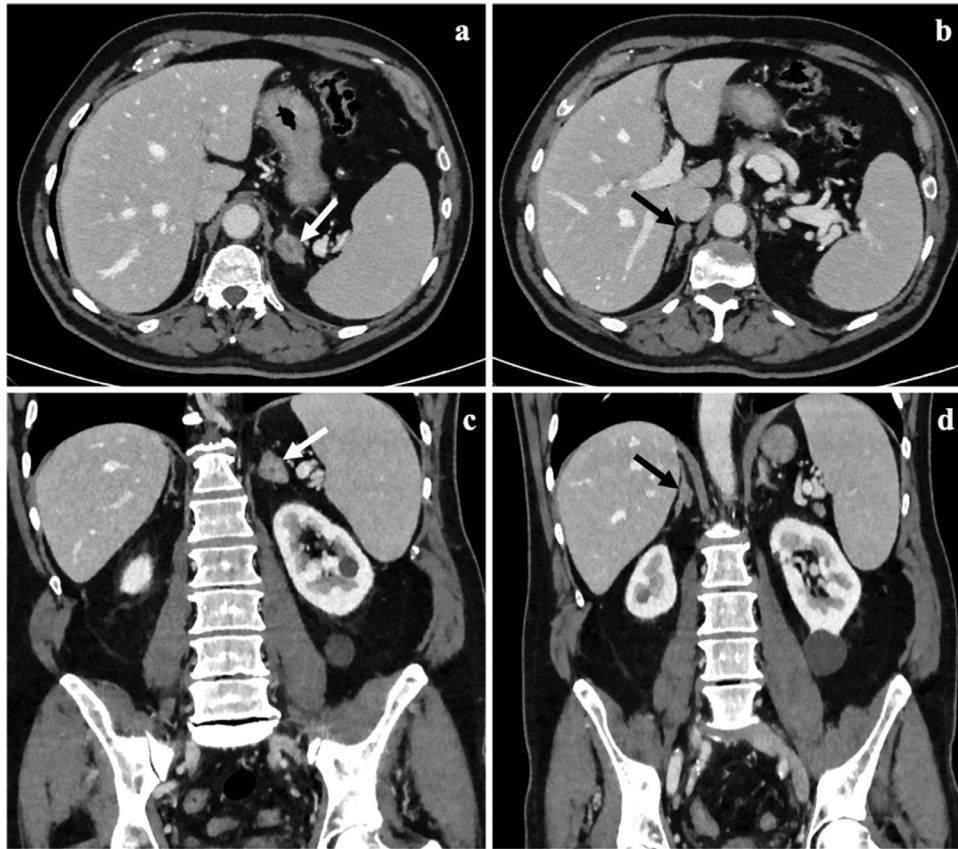


Fig. 1 – First contrast-enhanced CT exam performed to investigate testicular swelling. Axial (a-b) and coronal (c-d) images of the abdomen, show bilateral adrenal enlargement with large nodules replacing the left (white arrow) and the right adrenal gland (black arrow). (Colour version of the figure is available online).

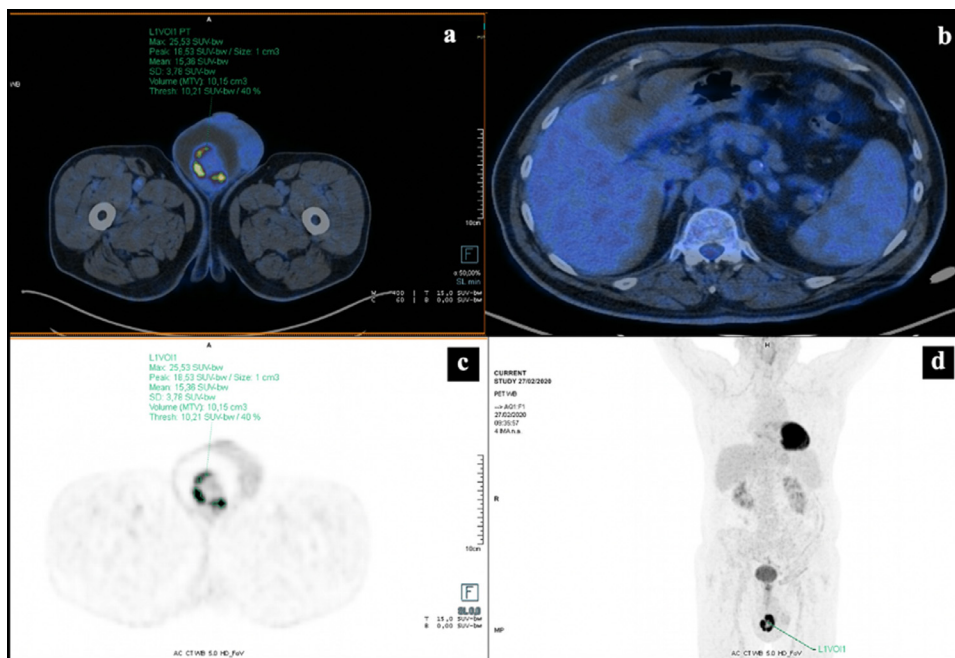


Fig. 2 – First PET-CT exam. Axial fused FDG PET/CT images (a-b) and maximum-intensity-projection PET images (c-d) show increased absorption of ^{18}F FDG (standardized maximum absorption value, 25.5) in the right testis, consistent with avid malignant lesion without significant FDG uptake in the enlarged adrenal glands.

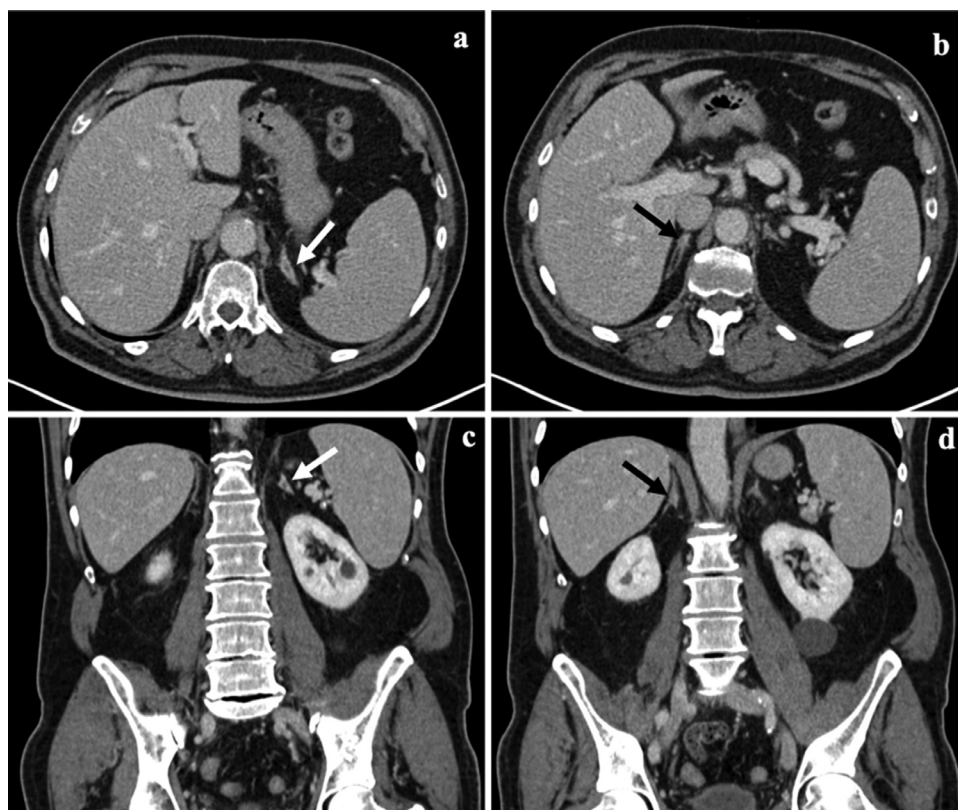


Fig. 3 – Staging contrast-enhanced CT exam, 3 months after the first CT examination. Axial (a-b) and coronal (c-d) images of the abdomen, show complete resolution of bilateral macronodular adrenal enlargement with smooth and normal sized of the left (white arrow) and right (black arrow) adrenal glands. (Colour version of the figure is available online).

diagnoses (i.e. hypertensive crisis during surgery in case of non diagnosed pheochromocytoma).

Primary and secondary adrenal DLBCL

There are two histotypes of primary adrenal lymphoma (PAL): diffuse large B-cell lymphoma and peripheral large T-cell lymphoma, but both are hypermetabolic and FDG avid [10]. Therefore, the possibility of a primary DLBCL lymphoma synchronous to the testicular neoplasm should be excluded not only for its rarity but especially for the absence of FDG uptake [11]. Furthermore, any secondary localization of the disease, even in case of extranodal primitive lymphomas, have to show FDG PET hypermetabolism [12]. Finally, the spontaneous regression of the adrenal finding supports the exclusion of these diagnostic hypothesis.

Cushing's syndrome

There are two categories of bilateral cortical hyperplasia: ACTH-dependent or ACTH-independent. However, neither is spontaneously reversible. For our patient, in order to exclude this diagnostic hypothesis, an endocrinological consultation with ACTH and cortisol dosage, urinary free cortisol and salivary cortisol were scheduled, but no longer performed because of the spontaneous regression of hyperplasia. We underline that our patient had no signs and/or symptoms of hy-

percortisolism, nor electrolyte/glycemic alterations. Finally, it is also possible to exclude the hypothesis of a paraneoplastic ectopic corticotrophic secretion by testicular lymphoma. In fact, even though the ectopic testicular secretion may justify the regression of adrenal hypertrophy following the orchifunicectomy, the only tumors capable of secreting ACTH originate from cells of the APUD system, not from lymphocytes [13].

Congenital bilateral cortical hyperplasia and bilateral pheochromocytoma

Congenital adrenal hyperplasias are a group of autosomal recessive diseases caused by mutations in genes that code for enzymes in pathways involved in cortisol biosynthesis. The most common form derives from mutations/deletions of CYP21A, determining a 21-hydroxylase deficiency. Clinical presentations comprise a wide clinical spectrum that vary from neonatal salt wasting and virilization of genitalia in females newborns to male precocious puberty and female late-onset rise of hirsutism and irregular menses [14]. Bilateral pheochromocytomas also occur more often as components of genetic syndromes such as multiple endocrine neoplasia (MEN) type 2a and type 2b, Succinate Dehydrogenase associated mutations and von Hippel-Lindau disease. Pheochromocytomas are associated with specific clinical stigmata such as severe hypertension, palpitations, headaches,

sweating lasting from only minutes to hours, occurring periodically [15]. In our clinical case, these diagnostic hypotheses have been excluded because of the absence of clinical symptoms suspected for pheochromocytoma and because these forms do not show spontaneous regression. In fact, we note the complete absence of pathological adrenal findings in clinical-radiological history of the patient and pathological and familiar anamnesis were also silent for precocious puberty, primary hyperparathyroidism/medullary carcinoma (associated with MEN2A) or conditions associated with VHL.

Bilateral adrenal hematoma or cystic lesions

Adrenal haemorrhage can occur in an atraumatic manner in case of coagulopathy, sepsis, hypotension or abdominal surgery. Acute bleeding is manifested by symptoms of adrenal insufficiency. In our case, in addition to the lack of suggestive clinical elements, the CT densitometry of the glands did not show the hyperattenuation (50-90 HU) typical for haemorrhage. Furthermore, in the resolution phase of the hypertrophy, the adrenal morphology, in our clinical case, was not typical for post-haemorrhagic evolution, as it showed neither cystic nor calcific involution [16]. Finally, bilateral cystic lesions are rare finding, which can be excluded due to the CT densitometry not compatible with fluid lesions [9].

Bilateral infectious adrenalitis

The abundant vascularization of the adrenal glands makes them the target of hematogenous infection by various pathogens (viruses, bacteria, fungi, parasites). A patient with adrenalitis is not necessarily immunocompromised. The infection is typically underdiagnosed due to the indolent and nonspecific clinic, mostly resulting from the depression of the adrenal function (asthenia, hypotension, hypoglycemia, hyperkalaemia). However, in our case, there was no suggestive clinical data for adrenalitis. Furthermore, the infection often leaves calcified relics in the glandular parenchyma, which we did not found [17].

Adrenocortical pharmacotoxicity

Some compounds, such as etomidate and aminoglutethimide, cause the inhibition of specific cytochromes involved in adrenal steroidogenesis, resulting in a decrease in the circulating free fraction of corticosteroids. Thus, the servo system at the base of the HPA axis thus activates an increase in corticotropic stimulation on the adrenal glands, which become hyperplastic [8]. In our patient, the medical history did not reveal compounds capable of causing adrenal toxicity.

Stress

After the exclusion of the main organic and functional causes of adrenal hypertrophy, the most likely possibility is that of stress-related hypertrophy whereby stress resulted in a disturbance of organic homeostasis, due to lymphomatous proliferation. In this regard, we recall the natural immunosuppressive and anti-inflammatory function of corticosteroids produced by the adrenal gland, and the recent scientific evidence of a

pro-inflammatory state created by DLBCL [18]. Vincent et al. already demonstrated in 1994, a statistically significant correlation between adrenal hyperplasia and the presence of neoplasia, both carcinomatous and lymphomatous, suggesting the activation of the HPA axis by hormone-like bioactive factors secreted by lymphomatous / tumor cells as the cause [19]. It has been demonstrated that DLBCL lymphomas may induce the activation of pro-inflammatory genes, creating a pro-inflammatory microenvironment favorable to lymphomatous proliferation [18]. In conclusion, adrenal hyperplasia may be a paraneoplastic condition, and the concept of stress should be evaluated as organic and biochemical changes [19]. Emotional stress, determined by the onset of disease, may also be considered a contributing factor in the activation of the HPA axis and the consequent adrenal hypertrophy. In a study conducted on rats, prolonged depressive-anxious stress induces the activation of the paraventricular hypothalamic nucleus, located at the apex of the HPA axis, resulting in bilateral adrenal hyperplasia downstream [20]. In literature, there are no data on acute stress as a cause for transient adrenal growth even though it is described a clinical case of bilateral adrenal incidentalomas (without hormonal overproduction) disappearing completely and spontaneously after 3 months [9]. The patient described was affected by ileus, developed erysipelas of the right foot with fever and chills during hospitalization. In conclusion, organic stress induced by neoplasms may be the cause for the development of transient adrenal hypertrophy. Other existing differential diagnosis for bilateral adrenal enlargement were not sufficient to explain the findings in our case. This report is the second case described for disappearing adrenal masses not compatible with hematomas so our experience may be useful for other Clinicians. In presence of bilateral undetermined adrenal lesions it is necessary to perform a good differential diagnosis. Therefore, a strict collaboration between Radiologist and Endocrinologist and a multidisciplinary approach are necessary for a proper diagnosis and to evaluate the best treatment strategy. Our case suggests also that the analysis of adrenal lesions appeared in cancer patients should take into account non-metastatic conditions that must be studied with a multimodal approach and with serial investigations.

Patient Consent

Written consent was taken for the case report publication from the patient. No personal information has been provided and if required informed consent with documentation can be transmitted when publication is accepted for publication.

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