Clinical case

Adrenal tuberculosis after a pheochromocytoma: a misleading tumoral presentation

Tuberculose surrénalienne succédant à un phéochromocytome : une présentation tumorale trompeuse

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Abstract

Adrenal gland involvement could account for 6% of active tuberculosis. The diagnosis of this extrapulmonary form of tuberculosis is difficult, especially when presenting as unilateral adrenal tumor. This report describes an unusual case of adrenal tuberculosis presenting as a tumor occurring shortly after surgical removal of an adrenal pheochromocytoma located in the opposite gland, in a 63-year-old woman with a previous history of breast cancer. At initial presentation, the patient suffered from symptomatic paroxysmal hypertension. A pheochromocytoma in the left adrenal was diagnosed and resected. One year later, while physical examination and biological parameters were unremarkable, an enhanced adrenal computed tomography (CT) scan showed a right adrenal mass mimicking the CT features of the resected pheochromocytoma. A peripheral tissular rim delineating a central hypodensity characterized this tumor. Magnetic resonance imaging (MRI) showed the same findings on gadolinium-enhanced T1-weighted slices, while the mass was not seen on T2-weighted images. No tumor signal loss was observed on out of

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phase images when using the in phase-out of phase T1-weighted sequence. Because of the tumoral evolution and the uncertainty of the nature of that lesion, the patient underwent a second adrenalectomy. Definitive diagnosis was provided by culture of tissue sample, which resulted in the identification of Mycobacterium tuberculosis. In an era of tuberculosis resurgence, this unusual case underscores the necessity of keeping in mind adrenal tuberculosis as a possible differential diagnosis in adrenal tumors of uncertainty nature. It stresses the importance of culture of biopsy tumor, whenever feasible, to avoid unnecessary operations. In the near future, interferon-γ assay could be a valuable means to recognize extra-pulmonary forms of tuberculosis.

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1. Introduction

The most common clinical manifestation of tuberculosis is pulmonary disease. In immunocompetent people, extrapulmonary forms of tuberculosis (EPTB) account for about 15–20% of all cases and are often diagnosed many years after primary infection [16]. However, in studies involving human immunodeficiency virus (HIV)-infected patients, it may represent up to 50% of cases [16]. The diagnosis of EPTB is difficult, especially when biopsy is difficult because of the deep or hard to reach location of sites involved. These sites include in order decreasing frequency the lymph nodes, pleura, liver, spleen, kidney, bone, meninges and adrenals [1,8,16].

The adrenal gland is the most commonly involved endocrine organ in tuberculosis [5], which may also affect the hypothalamus, pituitary and thyroid glands. Clinical presentations of adrenal tuberculosis are variable, including adrenal insufficiency with enlargement of one or both adrenal glands [7,15] and adrenal incidentaloma [4,14]. While the diagnosis of tuberculosis should be entertained for any space-occupying lesion of various organs, such as adrenal mass [8], definitive diagnosis requires histological examination and specific cultures of the operative specimen after adrenalectomy or biopsy. Furthermore, studies have shown that adrenal tuberculosis has not infrequently been diagnosed postmortem by autopsy [8]. In this report, we present a challenging case of adrenal tuberculosis diagnosed after the surgical removal of a contralateral adrenal pheochromocytoma. In an era of tuberculosis resurgence, this unusual case illustrates that the diagnosis of tuberculosis should always be entertained in the case of adrenal tumor.

2. Case report

In February 2002, a 63-year-old woman presented to a heart specialist complaining of acute malaise with palpitations, headaches and hot flushes. Since a few months, she was treated for hypertension with labetolol. Her past medical history was remarkable for primitive breast cancer at 59 years of age treated with breast-conserving surgery and radiotherapy followed by tamoxifen treatment. She had a family history of breast, kidney and bladder cancers. Ambulatory blood pressure monitoring confirmed paroxysmal hypertension, synchronous with symptoms. Urinary catecholamines and metanephrines assay (HPLC) showed a marked increase in the excretion of free noradrenaline, 9.26 μmol/24 hours (N: 0.5–2). Plasma noradrenaline concentration was markedly elevated at 40 nmol/l (N: 0.5–2) while the excretion of adrenaline, dopamine and their metabolites was within the normal range. Enhanced abdominal computed tomography (CT) scan revealed a 2.5 × 3 cm inhomogeneous mass located in the left adrenal gland characterized by a hypervascularized peripheral rim and a central area of low attenuation (Fig. 1). No other abnormality was observed on this CT scan at any sites including the right adrenal gland. A whole-body (131I) meta-iodobenzylguanidine (MIBG) scintigraphy did not demonstrate any abnormal uptake, but was performed while the patient was under labetolol medication. The diagnosis of adrenal pheochromocytoma secreting noradrenaline was highly suspected. The patient underwent video-laparoscopic surgery to remove the entire left adrenal gland. This gland weighed 15 g and contained a well-circumscribed tumor of 2.5 × 1.5 cm size with central necrotic area. Pathological examination confirmed a pheochromocytoma with 3/10 high power field mitotic rate with no capsular or vascular invasion. One month after surgery, the patient was asymptomatic, blood pressure was normalized without oxynoradrenaline, 9.26 μmol/24 hours (N: 0.5–2). Plasma noradrenaline concentration was markedly elevated at 40 nmol/l (N: 0.5–2) while the excretion of adrenaline, dopamine and their metabolites was within the normal range. Enhanced abdominal computed tomography (CT) scan revealed a 2.5 × 3 cm inhomogeneous mass located in the left adrenal gland characterized by a hypervascularized peripheral rim and a central area of low attenuation (Fig. 1). No other abnormality was observed on this CT scan at any sites including the right adrenal gland. A whole-body (131I) meta-iodobenzylguanidine (MIBG) scintigraphy did not demonstrate any abnormal uptake, but was performed while the patient was under labetolol medication. The diagnosis of adrenal pheochromocytoma secreting noradrenaline was highly suspected. The patient underwent video-laparoscopic surgery to remove the entire left adrenal gland. This gland weighed 15 g and contained a well-circumscribed tumor of 2.5 × 1.5 cm size with central necrotic area. Pathological examination confirmed a pheochromocytoma with 3/10 high power field mitotic rate with no capsular or vascular invasion. One month after surgery, the patient was asymptomatic, blood pressure was normalized without

Fig. 1. Contrast-enhanced axial CT scan showing a 3-cm in diameter left adrenal tumor composed by a hypervascularized peripheral rim limiting a central low attenuation area (white arrow).

Fig. 1. Scanner avec injection montrant une tumeur surrénalienne gauche de 3 cm de diamètre hypervascularisée en périphérie et hypodense au centre (flèche blanche).
treatment and levels of urinary noradrenaline and methoxynoradrenaline had returned within the normal range, 407 and 0.56 μmol/24 hours, respectively. Based on clinical and biological findings, a genetic disease such as multiple endocrine neoplasia type 2, Von Hippel-Lindau’s disease or neurofibromatosis was ruled out.

The patient remained asymptomatic for 1 year, then returned complaining again of hot flushes and headaches. At first, a recurrence of pheochromocytoma was suspected. Physical examination was unremarkable. Ambulatory blood pressure monitoring demonstrated normal blood pressure profile. Repeat laboratory investigation did not give further evidence of relapse: catecholamines and metanephrines assayed both in plasma and urine remained within the normal range, serum chromogranin A was normal 60 μg/l (N: 20–100). However, an enhanced adrenal CT scan showed a newly occurring right adrenal mass measuring 1.5 cm in the longest diameter, mimicking the CT features of the left resected pheochromocytoma. Indeed, this tumor was characterized by a peripheral tissular rim delineating a central hypodensity (Fig. 2). Magnetic resonance imaging (MRI) showed the same findings on gadolinium-enhanced T1-weighted slices, while the adrenal mass was not seen on T2-weighted images. No tumoral signal loss was observed on out of phase images when using the in phase-out of phase T1-weighted sequence (chemical shift sequence).

Tamoxifen was suspected to contribute to hot flushes. Indeed the withdrawal of this treatment resulted in the disappearance of symptoms. A repeat adrenal CT scan performed 4 months later revealed a slight increase in volume of the right adrenal mass. Attenuation values in Hounsfield units were 35 on unenhanced CT and 43 on enhanced CT. Considering the previous history of breast cancer; the diagnosis of adrenal metastasis was entertained at this time. Mammography showed no evidence of local recurrence. Total bone scintigraphy was normal as were CT scans of chest, abdomen and pelvis. Biological parameters were unremarkable including inflammatory and tumoral markers such as CRP, 1 mg/l (N < 5), ACE, 2 μg/l (N: 0–5), CA15.3, 18 U/ml (N < 25). Morning serum cortisol was normal, 180 μg/l (normal range, 70–250) as was corticotropin/ACTH, 40 ng/l (N: 0–52). HIV serology was negative.

Because of the tumoral evolutivity and the uncertainty of the nature of that lesion, the patient underwent a new video-laparoscopic surgery to remove the entire right adrenal gland. The gland contained two adjacent firm whitish tumors measuring, respectively, 1 and 2 cm in the longest diameter. Immuno-histological analysis showed granulomatous inflammation with central caseous necrosis strongly suggesting tuberculosis (Fig. 3). Ziehl–Neelsen stain on microscopic section was negative. However, bacterial investigation confirmed the suspicion of tuberculosis infection. Cultures of adrenal specimen in specific middlebrook 7H12 medium by radiometric procedure were positive after 3 weeks. Mycobacterium tuberculosis was identified by Geno-type MTBC Test (Hain Lifescience, Germany). Retrospectively, the patient disclosed that she had presented a tuberculosis primo-infection at 10 years of age.

The resulting adrenal insufficiency was treated with hydrocortisone and fludrocortisone replacement. Triple antituberculous therapy (rifampicin, isoniazid, pyrazinamide) was initiated for 4 months, then switched to a bitherapy for 2 months.
3. Discussion

This report describes a case of adrenal tuberculosis presenting as a tumor occurring after surgical removal of an adrenal pheochromocytoma located in the opposite gland. This observation is highly unusual because of coincidence of two different adrenal pathologies in the same patient. Initially, all the clues pointed to the diagnosis of recurring pheochromocytoma. Later, the history of breast cancer was a red herring misleading us towards potential adrenal metastasis.

While in past decades adrenal tuberculosis was the most common cause of Addison’s disease, only a few cases have been reported in recent years, especially in countries with a low incidence of tuberculosis [6]. However, adrenal gland involvement could account for 6% of active tuberculosis as reported in a very large retrospective analysis of autopsies and adrenalectomies performed in Hong Kong [8]. In this study, tuberculosis affecting the adrenal gland has contributed to the cause of death in 83% of patients and the diagnosis was not suspected in 47% of patients before death, illustrating diagnostic difficulties and severity of affection.

After ingestion by alveolar macrophage, most of Mycobacterium are destroyed in immune cells. However, in some cases the Mycobacterium escapes from the intracellular destruction process resulting in primary infection in the lung and/or hematogenous dissemination in any organ including adrenal glands. Usually, the host immune response is highly effective to contain the disease and maintain latent infection. When immune defenses are compromised, active disease can occur most frequently in lung but also in any others remote sites. HIV coinfection is the greatest risk factor for progression to active disease, especially in extrapulmonary forms [16]. Other medical conditions, including poorly controlled diabetes mellitus, chemotherapy, and corticosteroid therapy, underlying malignant disease can also compromise the immune system. In addition, as reported in the literature, a history of recent surgery could have contributed in our patient’s reactivation of a latent adrenal infection [8]. Finally, previous pulmonary tuberculosis constitutes a well-known risk factor for EPTB [1].

Usually, tuberculosis in the adrenals can result in the progressive destruction of the glands. When 90% of the tissue is destroyed, adrenocortical insufficiency characterized as Addison’s syndrome would appear. In the developing countries, tuberculosis is still an important cause of adrenocortical failure. Moreover, it has been recently shown that patients with active tuberculosis can have subclinical adrenal insufficiency revealed by ACTH stimulation test, both in pulmonary and extrapulmonary forms of the disease [17]. This insufficiency reverses with therapy in most patients on long-term follow-up.

In rare and atypical cases like our own, adrenal tuberculosis appears as a unilateral adrenal tumor more or less incidentally discovered [4,14]. Patients are otherwise asymptomatic. In some cases, clinical presentation can also mimic neoplasia [3].

Imaging features are also variable. CT-findings typically include bilateral adrenal enlargement with a central necrotic area of hypoattenuation and peripheral rim enhancement [19]. When present, small calcification dots can be suggestive of the diagnosis [18,19]. In unusual cases with unilateral involvement, contrast-enhanced CT features, such as contour preservation, low attenuation in the center with peripheral enhancement and calcification can be used as discriminators of tuberculosis from primary tumors in the adrenal gland [18,19].

MRI imaging is particularly useful in patients with suspected pheochromocytomas as pheochromocytomas exhibit high signal intensity on the enhanced T2-weighted image whereas non-functioning adenomas appear similar to normal adrenal tissue. Chemical shift imaging can also offer substantial information to help discriminate between benign and malignant adrenal lesions. Benign adrenal adenomas lose signal on out of phase images compared to the in phase slices. In our case, the imaging phenotype was not suggestive of a benign lesion as there was no tumoral signal loss on out of phase slices.

Positron emission tomography (PET) with CT was not performed in this case, though it could be a better exam than conventional CT for the detection of adrenal metastases. As tuberculosis is known to cause false positive, PET images may have been misleading in our case. Current recommendations emphasize the need to interpret positive PET scans with caution when differentiating benign from malignant anomalies [2,11], especially in geographical areas with a high prevalence of granulomatous lesions. Conversely, this new radionuclide imaging procedure might become helpful in the diagnosis of infection and inflammation [10].

Definitive diagnosis of tuberculosis involves demonstration of M. tuberculosis by microbiological, cytopathological or histopathological methods. The first challenge for the physician is to suspect EPTB as a possible diagnosis. Frequently, an unnecessary surgical procedure is performed because EPTB has not been suspected [15,16]. A thorough anamnesis of tuberculosis is an important clue, as well as evidence of tuberculosis on chest X-ray. A highly positive tuberculin skin test (TST) usually involves active tuberculosis. However in abdominal tuberculosis, the sensitivity of this test is variable and rather low [4,15,16]. So TST result alone is not sufficient evidence to diagnose EPTB in adults, particularly in patient with BCG immunization. Recently, interferon-γ assays based on detection of interferon-γ produced by T-lymphocytes when activated by specific tuberculosis antigens 6-kDa early secreted antigenic target (ESAT6) and culture filtrate protein 10 (CFP-10), have been developed. More sensitive and specific than the TST, interferon-γ assays could be a better way to suspect EPTB [12]. Further, every attempt should be made to obtain tissue for histopathological and microbiological diagnosis. Pheochromocytoma being ruled out, percutaneous biopsy using CT could have been considered in our patient. This procedure is most often performed to evaluate the presence of metastatic disease to the adrenal gland in patients with a known extra-adrenal primary malignancy. Although pathological findings may be suggestive of “granulomatous infection”, only a few cases of adrenal tuberculosis have been diagnosed in the literature using fine-needle biopsy [9,13,20]. Correct diagnosis is
most often made after adrenalectomy. Caseous necrosis is commonly observed although granulomatous inflammation with Langhans giant-cells seems particularly frequent in patients with adrenal insufficiency [8]. Culture of tissue sample resulting in growth of *M. tuberculosis* provides definitive diagnosis. In addition, it allows test to the susceptibility to antituberculosis drugs. Whenever feasible, culture of biopsy or surgical specimen is mandatory. Increased awareness among specialists, who encounter this clinical problem, is needed to increase the diagnostic yield and avoid unnecessary operations.

In conclusion, high index of clinical suspicion, CT-findings and culture of the biopsy material are the key to the successful diagnosis of adrenal tuberculosis. In the near future, interferon-γ assay (ELISPOT) could be a valuable means to recognize EPTB. This diagnosis should be considered in the diagnosis of patients with adrenal tumor of uncertainty nature.

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References