

A CASE OF ADRENAL MYELOLIPOMA A PATIENT WITH BREAST CANCER

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Abstract

Background. Adrenal myelolipoma is a rare benign tumor composed of adipose tissue and hematopoietic elements resembling bone marrow. The majority of myelolipoma do not produce adrenal hormones and are only found as a result of evaluation for another disorder. With the widespread use of non-invasive abdominal imaging for various reasons, its incidental detection has become more common. There are a few cases of breast cancer with concomitant adrenal myelolipoma in the literature.

Case. A 43-year-old woman presented to endocrine clinic due to presurgical assessment of adrenal mass prior breast cancer surgery. Abdominal CT showed a 9 x 8 cm sized, lobulated contour heterogeneous fatty density mass with peripheral calcification in right adrenal gland. Hormonal studies for adrenal incidentaloma revealed: Aldosterone/Renin ratio, 0.70 ([normal range < 30]; normal DHEA-S, 85.0 µg/dL ([normal range, 80 -560 µg/dL]), ACTH 25 pg/mL ([normal range, 10 - 60 pg/mL]), morning serum cortisol 8.9 µg/dL ([normal range, 5 - 12 µg/dL]). In 24-hour urine, there revealed free cortisol 21.6 µg/day ([normal range, 10 - 50 µg/day]); metanephrine 0.19 mg/day ([normal range < 0.8 mg/day]); 17-ketosteroid 14.06 mg/day ([normal range, 7 - 20 mg/day]). The hormonal results of adrenal mass revealed as nonfunctioning. The adrenal mass was surgically resected in order to rule out malignancy. Pathology report showed myelolipoma.

Conclusion. We reported a case of adrenal myelolipoma coexisting with breast cancer where the diagnosis was made incidentally based on radiological features, treated with surgical resection.

Key words: adrenal Myelolipoma, breast cancer, adrenal incidentaloma.

INTRODUCTION

Adrenal myelolipoma is a rare benign tumor composed of adipose tissue and hematopoietic elements resembling bone marrow. The incidence of adrenal myelolipoma varies from 0.08 to 0.8% at autopsy (1).

It is found incidentally during abdominal imaging study of patients. With the vast use of non-invasive abdominal imaging for various reasons the incidence rate was estimated to be at 3% with abdominal CT scan. They are usually unilateral but may be bilateral and may also be present in extra-adrenal sites such as the retroperitoneum, thorax and pelvis. Most of the adrenal myelolipomas are usually non-functioning and asymptomatic; however some patients have abdominal discomfort or acute abdominal emergency due to mechanical compression from a huge mass or hemorrhage or necrosis (2). Although non-functioning, there have been a few reports of adrenal myelolipoma associated with endocrine dysfunction, such as Cushing's syndrome, congenital adrenal hyperplasia, Conn's syndrome and pheochromocytoma (3-5). There are few cases of malignancy with concomitant adrenal myelolipoma in the literature. Simultaneous breast cancer and adrenal myelolipoma are uncommon.

In this report, we describe a case with incidental finding of a giant adrenal myelolipoma coexistent with breast cancer.

CASE REPORT

A 43-year-old previously healthy woman was referred to the endocrine clinic for pre-surgical evaluation of an adrenal mass that was found incidentally by abdominal CT scan prior breast cancer surgery. Past medical history was unremarkable. Her father had hypertension and mother had diabetes. Patient was asymptomatic except for facial hot flushes and irregular menses. Patient's blood pressure and heart rate showed 110/70 mmHg and 72 beats/min respectively. There was a firm, non-tender right breast mass, sizing 2 × 1.5 cm. There was no palpable mass and tenderness on the abdomen. The rest of the physical examinations were unremarkable.

Mammography showed a 2.0 cm speculated

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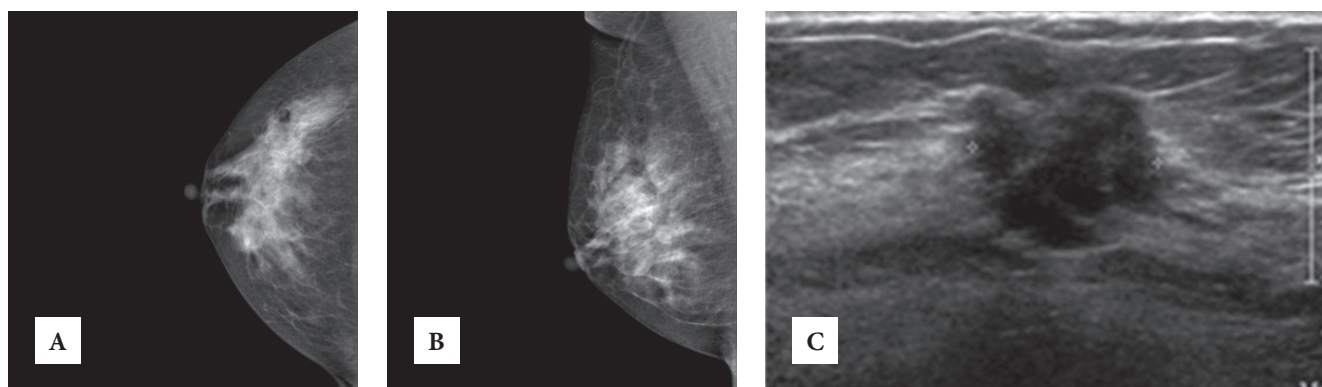


Figure 1. Mammographic and Ultrasonographic finding of breast. (A),(B) : There is a 2.0 cm spiculated isodense nodule at right mid outer portion. (C): There is a 1.7×2.0 cm spiculated low echoic nodule with invasion to retro mammary fat at 2 cm from right nipple.

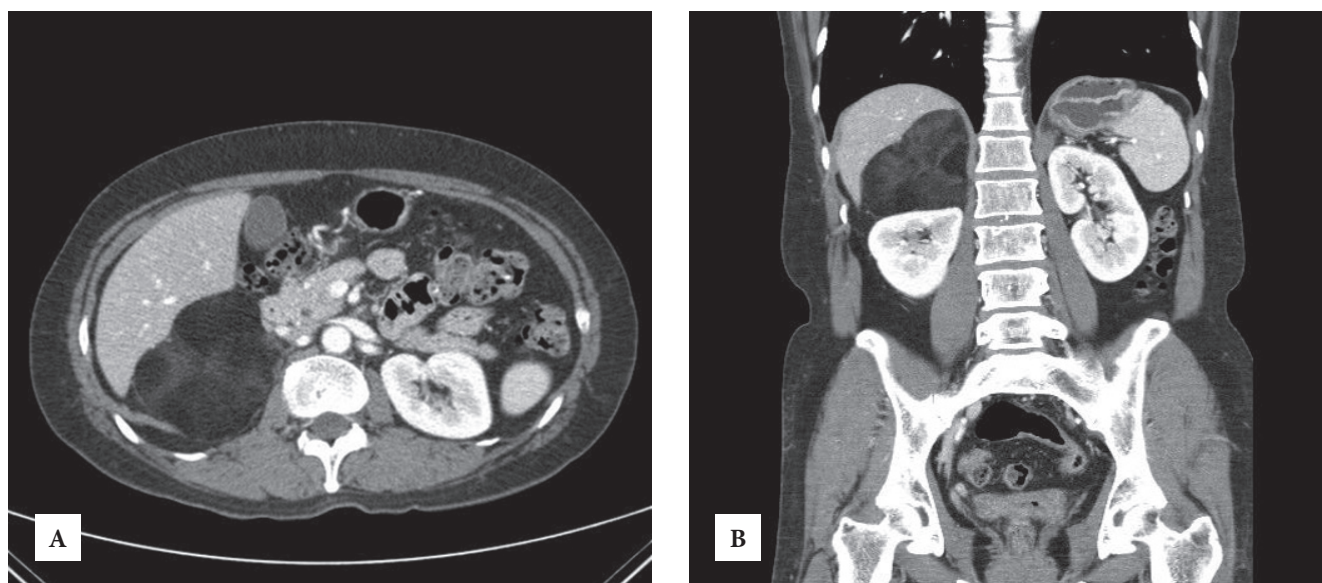


Figure 2. Abdomen pelvic computed tomography. (A),(B): Abdomen CT shows a lobulated contour heterogeneous fatty density mass with peripheral calcifications in right adrenal gland (maximum diameter 8.9 cm).

isodense lesion at the mid outer portion of the right breast (Fig. 1). Ultrasonography of the right breast showed a 1.7 × 2.0 cm spiculated low echoic nodule with invasion to retromammary fat at 2 cm from right nipple (Fig. 2). Abdominal CT showed a 9×8 cm sized, lobulated contour heterogeneous fatty density mass with peripheral calcification in the right adrenal gland (Fig. 3).

The laboratory biochemical studies showed normal results including glucose, blood urea nitrogen, creatinine, cholesterol, triglycerides, alkaline phosphatase, glutamic oxaloacetic transaminase, glutamicpyruvictransaminase and total bilirubin except for normocytic normochromic anemia (Hb 10.9 g/dL). To evaluate the functionality of adrenal mass, we performed screening tests of Cushing's syndrome, primary aldosteronism and pheochromocytoma. Cushing's syndrome was excluded by the tests for

morning ACTH (20 pg/mL ([normal range 15-60 pg/mL]), 1 mg overnight dexamethasone suppression test (cortisol 1.0 µg/dL) and 24 hour urine free cortisol (free cortisol, 21.6 µg/day [normal range, 10-50 µg/day]). Primary aldosteronism was excluded by Aldosterone/Renin ratio 0.70. 24 hour urine collection of metanephrine (0.19 mg/day [normal range < 0.8 mg/day]) was performed to exclude the possibility of pheochromocytoma. Due to huge size of adrenal mass, we also evaluated the possibility of primary adrenal carcinoma. The results of serum DHEA-S (85.0 µg/dL, [normal range, 80 - 560 µg/dL]), 24 hour urine 17-ketosteroid (14.06 mg/day [normal range, 7-20 mg/day]) were in normal range.

We did not perform fine needle aspiration of adrenal mass due to size and radiologic feature. Although the adrenal mass revealed as non-functioning and benign feature, it was too large and malignancy

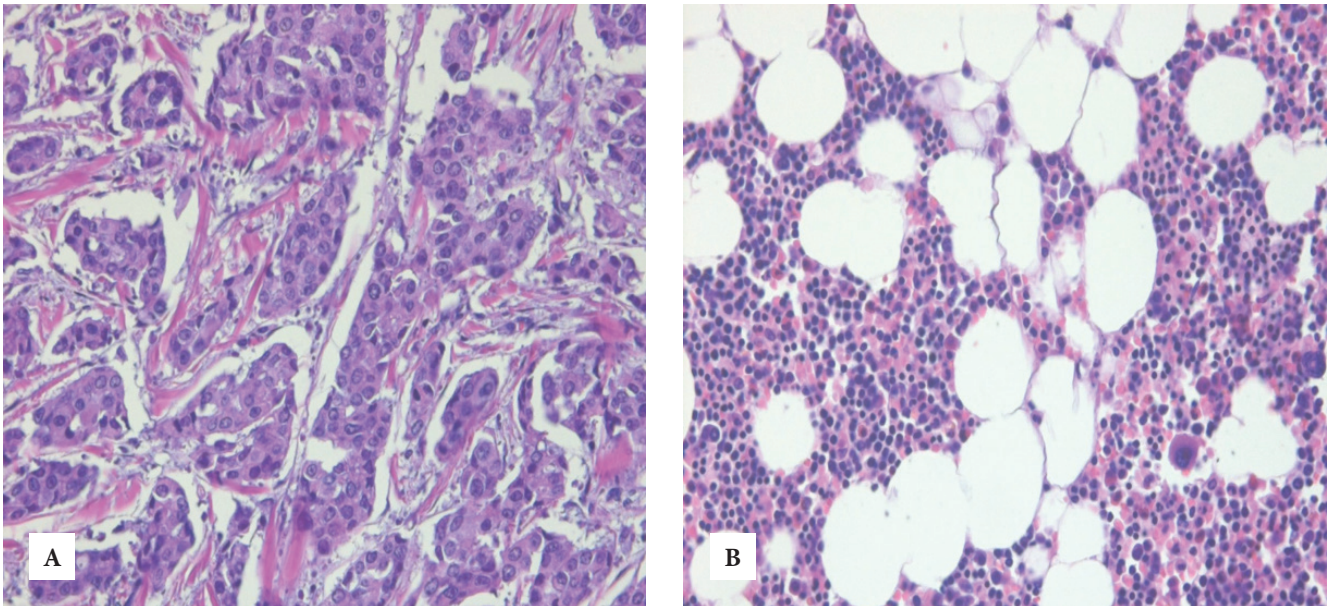


Figure 3. Pathologic finding with hematoxylin and eosin stain shows. (A) Breast : nest formation with atypical cell invading in surrounding tissue, invasive ductal carcinoma (X 400). (B) Adrenal gland: mature adipose tissue admixed with a central cellular area filled with haematopoietic elements including megakaryocytes, accompanied by myeloid and erythroid precursors confirming the presence of myelolipoma (X 400).

could not be ruled out. We examined PET-CT for staging work up of breast cancer and the possibility of malignant component of huge adrenal mass. PET-CT showed that there were significant FDG uptakes in the mid inner portion and mid outer portion of right breast in the same location as breast ultrasonography. But there was no definitive FDG uptake in right adrenal gland like breast mass. Even though biochemical studies did not show increased catecholamine, we need to evaluate the adrenal mass about asymptomatic pheochromocytoma. We also examined ^{131}I -MIBG to evaluate pheochromocytoma. ^{131}I -MIBG scan showed there was no evidence of abnormal uptake in adrenal gland.

Therefore, she was transferred to the surgery ward for further surgical treatment. She underwent right modified radical mastectomy with lymph node dissection and also right adrenalectomy. Biopsy results of breast mass showed that nest formation with atypical cell invades surrounding tissue, with diagnosis of invasive ductal carcinoma. Resection margins were free from carcinoma and chest wall or skin involvement was not identified. Although metastatic cells were identified in axillary and sentinel lymph nodes. Breast cancer biomarkers, including HER2 receptor, estrogen receptor, progesterone receptor (PR), Cerb B2, Ki-67 and P53 were assessed to determine appropriate treatment regimen of breast cancer by immunohistochemistry. PR and P53 was positive and other biomarkers including HER2

receptor were negative in breast cancer. We also examined adrenal mass about the biomarkers of breast cancer by immunohistochemistry. All biomarkers of breast cancer were negative in adrenal mass.

The tumor was well-encapsulated and adhering to the right adrenal gland. Postoperative histological examination showed nest formation with atypical cell invading the surrounding tissue, with diagnosis of invasive ductal carcinoma (Fig. 4). Frozen section of the right adrenal mass, sizing $9\times 8\times 5$ cm, revealed mature adipose tissue and normal appearing trilineage hematopoietic tissue (Fig. 5). There was no evidence of malignant cells in the right adrenal mass. Grossly, there was no evidence of abnormal mass like lesion in the left adrenal gland.

Postoperatively, she did not develop any symptoms of adrenal insufficiency. She underwent rapid ACTH stimulation test to evaluate the possibility of adrenal insufficiency after adrenalectomy. Basal, 30min and 60 min cortisol were $8.9\ \mu\text{g/dL}$, $18.2\ \mu\text{g/dL}$ and $20.4\ \mu\text{g/dL}$ respectively. Rapid ACTH stimulation test showed normal adrenal response. After 3 months, she had rapid ACTH stimulation test again to evaluate adrenal insufficiency. The rapid ACTH stimulation test showed normal response. She underwent adjuvant chemotherapy and radiotherapy for breast cancer. She was followed up regularly without any sign of recurrence of breast cancer.

DISCUSSION

Adrenal myelolipoma is a rare benign tumor of the adrenal gland. Most myelolipomas are asymptomatic and hormonally inactive. They are discovered incidentally as a result of widespread noninvasive abdominal imaging for other reasons that are not related to adrenal gland, thus its incidence rate is higher than in the past. Adrenal myelolipoma occurs in late adult life (age range: the 5th to 7th decades of life) and in both genders with an equal frequency. Most tumors originated from the right adrenal gland (R:L=3:2) while bilateral involvement is rarely reported (2). In this case, it also occurred in the right adrenal gland. Myelolipomas have been commonly discovered in adrenal glands, extra-adrenal myelolipoma and also reported in various sites, including mediastinum, thoracic spine, presacral retroperitoneal space, peri-renal or infra renal retroperitoneal space and pelvic cavity (2). There are a few cases of malignancy with concomitant adrenal myelolipoma in the literature. Only 9 cases of malignancy were being reported, such as urinary bladder cancer, collecting duct carcinoma of the kidney and adrenal carcinoma with a concomitant adrenal myelolipoma and the adrenal carcinoma being the most common cause of malignancy (Table 1)(6-11). Incidental adrenal myelolipoma was usually discovered on the same side of malignancy, mainly the left side. Although this case showed that adrenal myelolipoma was located on the right side, it was on the same side with the right breast mass.

Generally the adrenal gland is a common location for metastatic invasion of various malignant tumors. In nononcologic population, the prevalence of adrenal metastasis is 0 – 20%; however, the prevalence of adrenal metastasis in oncologic patients is higher in the range of 32 – 73% (12). Lung cancer is the most common cause of adrenal gland metastasis and then breast, ovary and malignant melanoma are also frequently involved (12). The incidence of adrenal metastasis of breast cancer varies based on different tissue type of breast cancer (13). Invasive ductal

carcinoma of breast cancer can metastasize to the lungs, liver, bones and brain, but rarely to the adrenal gland. In contrast, the adrenal metastasis of infiltrating ductal carcinoma of breast cancer is common. When adrenal mass is found in oncologic patients, it is important to evaluate the possibility of metastasis for treatment planning and prediction of prognosis. As our case was diagnosed with infiltrating ductal carcinoma of breast, it is essential to differentiate between metastasis and benign lesion of adrenal mass. As mentioned above it, the prevalence of adrenal metastasis in oncologic patients is higher than in nononcologic patients, therefore radiographic diagnosis is important for the detection of adrenal mass in oncologic patients. Mass size, wash out of contrast dye, and Housefield units (HU) are used for distinguishing between benign and malignant lesion. Radiographic features of malignant adrenal lesions include a mass size > 4 cm, a cut off values < 10 HU, irregular borders, heterogeneous enhancement, and < 40 % of the relative percentage washout (14). Lee *et al.* reported that the pre-contrast HU > 20 can be used as a diagnostic reference to suggest metastasis in cancer patients with adrenal masses (15).

Most adrenal gland metastases are asymptomatic, while some cases present adrenal insufficiency if the large portion of malignant cells replace or both adrenal glands are involved (16). Hematogenous spread is the main pathophysiology of adrenal metastasis. Kennecke *et al.* reported that HER2 subtype of breast cancer had a higher incidence of spreading into the brain, liver, bone and lungs while metastases in other organs that originate from HER2 subtype were less frequent (17). It suggested that metastatic involvement is affected by cancer subtype. In addition, Erin *et al.* showed that the vagus nerve plays a significant role in defense against cancer by inhibiting cancer metastasis (18). The vagus nerve directly regulates the immune system. It suggested that adrenal metastasis is controlled by interaction of the nervous and immune system.

There was a case of breast fibroadenoma combined with adrenal myelolipoma reported in

Table 1. Comparison of clinical characteristics of adrenal myelolipoma with concomitant carcinoma

Author	Case	Underlying cancer	Size	Site of adrenal myelolipoma	Endocrine symptoms
Nicolás Torralba <i>et al.</i> (10)	F/64	Urinary bladder cancer	7 cm	Left	Absence
Sakamoto <i>et al.</i> (11)	M/67	Urinary bladder cancer	5 cm	Left	Absence
Li <i>et al.</i> (8)	F/70	Collecting duct carcinoma (left)	7 cm	Left	Absence
Kim <i>et al.</i> (6)	F/76	Adrenal carcinoma (left)	2 cm	Left	Absence
Sun <i>et al.</i> (9)	M/43	Adrenal carcinoma (left)	4 cm	Left	Hyperaldosteronism
Banik <i>et al.</i> (32)	F/57	Adrenal carcinoma (right)	325 g	Right	MEN type 1
Goetz <i>et al.</i> (30)	F/24	Adrenal carcinoma	Unknown	Unknown	Cushing's syndrome

MEN: Multiple Endocrine Neoplasia

the past, yet, no cases of breast cancer with adrenal myelolipoma have ever been reported (3). To our knowledge, this is the first reported case of breast cancer with concomitant adrenal myelolipoma.

Most adrenal myelolipomas are asymptomatic. In our case she also did not have any symptoms. Occasionally, some patients have abdominal discomfort due to large size of myelolipoma. Rarely, patient can also present with hematuria, flank pain and abdominal mass as well. Hemorrhage, necrosis, intestinal obstruction can be possible complications of huge myelolipoma (19). Adrenal myelolipomas manifest as a well-defined suprarenal mass with attenuation below -30 HU on CT scan (20).

The size and radiological characteristics of an adrenal mass are major factors of differential diagnosis between benign and malignant lesions (14). Generally benign lesions are characterized by smooth, well-defined borders, size less than 4 cm and HU of less than 10. In this case, size of adrenal mass was 9×8 cm with lobulating lesion with peripheral calcification. Due to the large size and peripheral calcification of adrenal mass and underlying breast cancer, we should evaluate giant adrenal mass, especially benign adenoma, primary adrenal carcinoma and metastasis.

The differential diagnosis of adrenal mass includes benign non-functioning adenoma, functioning adenoma, metastatic and primary adrenal carcinoma. The first step in the evaluation of an adrenal mass is to classify it as a metabolically active adrenal lesions: cortisol secreting adenoma, pheochromocytoma, primary hyperaldosteronism. In the second step the mass should be examined for the risk of malignancy. Main causes of giant adrenal mass are pheochromocytoma, primary adrenal carcinoma and adrenal myelolipoma (21). Most pheochromocytoma have typical clinical signs and symptoms including headache, hypertension or sweating. However, small minority of (about 8%) pheochromocytoma has no typical clinical signs and symptoms (22). These silent pheochromocytoma showed normal biochemical results due to periodic secretion of catecholamines in the blood (23). Until recently ¹³¹I-MIBG scan is a golden standard functional imaging study for highly sensitive and specific diagnosis of pheochromocytoma. ¹³¹I-MIBG is a useful study to evaluate a biochemically normal phenotype of pheochromocytoma. In our study, we also examined ¹³¹I-MIBG to rule out a possibility of silent pheochromocytoma.

The biopsy of a huge adrenal mass should be made with caution, especially when the mass contains

hemorrhage, calcification or low lipid content. Despite of diagnostic imaging, fine needle biopsy is indicated when the mass cannot be adequately characterized by imaging or appear to be malignant on imaging studies (24).

Especially in the patient with underlying cancer for whom the physician is deciding treatment modality it is important to confirm diagnosis in order to prevent unnecessary operation. Despite clinically inactive, the hormone status should be evaluated especially catecholamines prior fine needle aspiration of adrenal mass. Although, there was a possibility of silent pheochromocytoma and risk of infection, hemorrhage, pneumothorax and possible seeding of the cancer so we did not perform fine needle aspiration of adrenal mass. Primary adrenal carcinoma is also the main cause of giant adrenal mass. It is a rare disease but fatal prognosis.

Fine needle biopsy of a suspected primary adrenal insufficiency is almost never justified because of anticipated tumor spill (25).

In our case, a large adrenal mass sizing 9×8 cm with lobulated contour heterogenous fatty density mass and peripheral calcification, we decided to perform laparoscopic adrenalectomy to rule out metastatic lesion from breast cancer.

The pathogenesis of adrenal myelolipoma is still unknown. Several theories regarding the mechanism of adrenal myelolipoma have been described. Selye *et al.* (26) showed that they were able to produce myeloid tissue in the adrenal gland by the injection of necrotic tissue of adrenal gland and hormones. Most widely accepted the theory is metaplastic change in the reticuloendothelial cells of blood capillaries in response to stimuli, including necrosis, infection, and stress. Some studies suggested that ACTH is a possible factor to induce adrenal myelolipoma, evidenced by an increase in the relative frequency of myelolipoma in patients with excessive ACTH such as Cushing's disease, congenital adrenal hyperplasia and Addison's disease (27). A patient under a long period of intense stress can develop myeloid metaplasia in the adrenal cortex such as severely burned or cancer patients. Nevertheless, it seems these factors might have influence on adrenal myelolipoma development with malignancy by a complex process. Although, our case did not have any level elevation on ACTH and cortisol. There are a few cases of cytogenetic studies of adrenal myelolipoma. The chromosomal dislocation t(3;21)(q25;p11) has been found in adrenal myelolipoma (28). The hematopoietic elements and adipose tissue of adrenal myelolipoma have nonrandom X-chromosome inactivation, suggesting a clonal proliferation from a common mesenchymal stem cell (29).

Myelolipoma does not usually secrete hormones; however cases with Conn's syndrome, Cushing's syndrome and congenital adrenal hyperplasia and pheochromocytoma, Addison disease, virilism have been reported (3). Three cases of hormone producing adrenal myelolipoma concomitant malignancy were reported: hyperaldosterone, Cushing's syndrome and multiple endocrine neoplasm type 1, all of them are associated with adrenal carcinoma (9, 30-32).

The management of adrenal myelolipoma should be individualized. Patients with lesion < 4 cm and asymptomatic can manage conservatively for 1- 2 years with CT. If a patient is symptomatic or has a significant tumor growth, then surgery is recommended. Surgery is indicated when patients have symptoms, tumor size bigger than 4–5 cm or are suspicious of malignancy (33).

In conclusion, we reported a case of adrenal myelolipoma coexistent with breast cancer, where the diagnosis was made incidentally based on radiological features, treated with surgical resection.

Conflict of interest

The authors declare that they have no conflict of interest concerning this article.

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