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May an adrenal incidentaloma change its nature?

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15 cancer.

16

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18 review: EB; Drafting of the Manuscript: AM, EI; Critical Review of the Manuscript: SP, AP, GR,
19 MT; Supervision: AP, GR, MT.

20 **Abstract**

21 Up to 70% of adrenal masses detected in patients affected by extra-adrenal malignancy are metastatic
22 lesions. Therefore, detection of an adrenal mass in patients with active or previous malignancy
23 requires a careful differential diagnostic work-up. ¹⁸F-Fluorodeoxyglucose-positron emission
24 tomography/computed tomography (¹⁸F-FDG-PET/CT) is increasingly used to determine the
25 malignant potential of adrenal lesions.

26 We report the case of a 64-year-old man who had a single adrenal metastasis due to non-small-cell
27 lung carcinoma developing on a pre-existing benign adrenal lesion. This metastasis occurred in a
28 phase of perceived oncological remission and was detected thanks to ¹⁸F-FDG-PET/CT showing a
29 focal adrenal uptake. Contrast-enhanced computed tomography (CT), performed as part of
30 oncological follow-up, and MRI with chemical shift sequences did not lead to the correct diagnosis.
31 The patient underwent laparoscopic adrenalectomy and the pathological evaluation confirmed a lung
32 carcinoma metastasis.

33 The present case highlights the peculiarity of the follow-up of adrenal masses in cancer patients and
34 the primary role of ¹⁸F-FDG-PET/CT in the management of such patients.

35

36 **Background**

37 About 2% of all incidentally detected adrenal masses are of metastatic nature. This percentage rises
38 to 30-70% in patients affected by an extra-adrenal malignancy [1] . The adrenal gland represents
39 indeed a frequent site of metastasis, due to its rich sinusoidal vascularization. Lung cancer followed
40 by breast cancer and melanoma are most likely to spread to the adrenal gland [2] . Rare cases of
41 collision tumors, defined as the coexistence of two different tumors in an adrenal gland, such as an
42 adrenal adenoma and an adrenal cancer or a metastatic tumor, have been described [3].

43 Although no randomized study comparing imaging tests has been performed, non-contrast computed
44 tomography (CT) is generally considered as the first-line imaging test to make a differential
45 diagnosis between benign and malignant adrenal masses. Whenever the mass is considered of
46 indeterminate nature after non-contrast CT, second-line imaging tests, including CT with delayed
47 contrast media washout, chemical shift MRI, and ¹⁸F-FDG-PET/CT, are needed to define the
48 diagnosis [4]. Once that an adrenal incidentaloma is considered to be a benign lesion after an
49 appropriate work-up, it is not recommended to pursue a specific follow-up with repeated imaging
50 studies [4]. The recommendation is based on the very low chance that a benign adrenal lesion may
51 turn in a malignant one during follow-up [5].

52 We report here in a case that represents an exception to this general rule and underlines the
53 challenges that may arise in the diagnosis of adrenal metastases.

54

55 **Case presentation**

56 The patient is a 64-year-old man, ex-smoker (10 cigarettes/day), with an occupational exposure to
57 silica dust and asbestos and a clinical history of chronic obstructive pulmonary disease and arterial
58 hypertension. In 2008, a left adrenal nodule was occasionally detected and investigated with

59 endocrinological workup and non-contrast CT, which were suggestive for a benign, non-functioning,
60 adrenal adenoma. The lesion was of 30 mm in size with a density < 0 Hounsfield Units (HU) [Figure
61 1].

62 In August 2015, a squamous cell carcinoma of the upper lobe of the right lung with mediastinal
63 lymphadenopathy was diagnosed. The patient was treated with chemo- and radiotherapy with
64 complete disease response and subsequent negative radiological follow-up.

65 In September 2017, a follow-up total body contrast-enhanced CT scan showed multiple pulmonary
66 lesions and a slight enlargement of the known left adrenal nodule (37 mm diameter) [Figures 2a and
67 2b]. Hounsfield Units and morphological characteristics were not reported. Due to the suspect of
68 disease recurrence a ¹⁸F-FDG-PET/CT scan was performed and it showed a focal pathological uptake
69 in the left adrenal region without relevant uptakes in other sites (absolute SUV value 7.8,
70 adrenal/liver ratio 3.5) [Figure 2c], while the pulmonary lesions resolved after antibiotic therapy.

71 The patient was then referred to our outpatient unit. A hormonal workup was negative for
72 hypercortisolism, primary hyperaldosteronism and catecholamine excess. All the available CT scans
73 were re-evaluated by an expert radiologist, who confirmed the increase in size (7 mm) and described
74 the adrenal mass as inhomogeneous with faintly irregular borders. Due to the changed radiological
75 characteristics an adrenal magnetic resonance imaging (MRI) with chemical shift sequences was
76 performed but was not conclusive in the differential diagnosis between a lipid-poor adenoma and a
77 malignant lesion, showing incomplete, inhomogeneous signal intensity loss in out-of-phase
78 sequences [Figures 3a and 3b].

79 Following the pathological adrenal uptake at FDG-PET scan, not justified by an autonomous
80 hormone production, and the undetermined radiological characteristics at MRI the patient underwent
81 left laparoscopic adrenalectomy with an uneventful course. The pathological exam revealed that the
82 adrenal parenchyma was completely replaced by squamous carcinoma cells, with typical
83 adenomatous cells surrounding the central neoplastic core [Figures 4a and 4b].

85 Discussion

86 Whether most adrenal masses detected in patients affected by extra-adrenal malignancies are of
87 secondary nature, adrenal metastases are rarely found in non-oncological patients [1]. Therefore, a
88 history of known extra-adrenal malignancy requires a particular attention to the possibility of an
89 adrenal metastasis. A new adrenal lesion developing during oncological follow-up should also be
90 viewed as suspicious.

91 In clinical practice, the most commonly used imaging techniques to assess the risk of malignancy are:
92 non-contrast CT, MRI with chemical shift sequences, and ^{18}F -FDG-PET/CT. The recent
93 ESE/ENSAT guidelines on the management of adrenal incidentalomas recommended non-contrast
94 CT as the first radiological test [4]. Adrenal lesions that are homogeneous, smaller than 4 cm, with
95 density < 10 Hounsfield units (HU) are considered benign, lipid-rich adenomas. However, about 30%
96 of adrenal adenomas are lipid-poor and show an attenuation value > 10 HU that overlaps with
97 malignant lesions and pheochromocytomas [6-8]. The use of MRI with chemical shift sequences is
98 based on the typical loss of signal intensity shown by intracellular lipid-rich lesions in out-of-phase
99 sequences, while lipid-poor adenomas, malignant lesions and pheochromocytomas remain unchanged
100 [9-11]. In patients with history of extra-adrenal malignancy, the ESE/ENSAT guidelines suggest the
101 use of ^{18}F -FDG-PET/CT performed as part of oncological follow-up [4]. ^{18}F -FDG-PET/CT has the
102 advantage of being able to detect malignant adrenal lesions with a low rate of false negatives (mainly
103 metastases from tumors with low FDG-uptake, i.e. kidney cancer [12]) and a certain rate of false
104 positives (i.e., functional adenomas [13]) [14]. Routine use of ^{18}F -FDG-PET/CT in patients without
105 history or suspect of malignancy is currently not recommended, but a recent prospective study
106 showed that it has an excellent negative predictive value in the characterization of indeterminate
107 and/or large adrenal masses in non-cancer patients [15].

108 In our patient, the contrast-enhanced CT performed during the oncological follow-up reported only a
109 slight enlargement of the known adrenal lesion and only the radiological revision, requested after the
110 ¹⁸F-FDG-PET/CT, showed changes of the lesion's features. The ¹⁸F-FDG-PET/CT was done
111 primarily for the suspect of pulmonary progression of disease but showed a single, focal uptake of
112 the known adrenal lesion. Since the mass has been previously recognized as benign, further
113 diagnostic tests were done. Hormone assessment was unrewarding, and MRI was still compatible
114 with a lipid-poor adenoma. Our case represents a “real-life” demonstration of the limits of
115 radiological and functional imaging in defining adrenal masses nature, especially in patients with
116 known oncological history. These limits have been widely analyzed in a systematic review and meta-
117 analysis [16] which laid the groundwork for the recommendations given by the ESE/ENSAT
118 guidelines, especially when second-line imaging techniques are used in indeterminate adrenal
119 masses. Despite the great potential of available radiological and functional imaging, there are not
120 only difficulties related to the heterogeneity of both benign and malignant adrenal lesions and to the
121 frequent overlap in imaging features [17], but also the expertise of the single radiologist and clinician
122 influence the patient's diagnostic pathway in clinical practice.

123 In our patient, since radiological and functional imaging were not conclusive in defining the nature of
124 the adrenal lesion's changes, a histopathological evaluation was considered essential. The
125 multidisciplinary team discussion considered the adrenal biopsy a possible choice, but since we had
126 a consistent suspicion of malignancy and the patient was in excellent clinical conditions with a
127 prolonged disease-free interval following oncological treatment of his non-small cell lung cancer
128 (NSCLC), we decided to be proactive and recommended surgical removal of the adrenal lesion. Our
129 choice was also supported by the expertise of our surgeon and the notion of a favorable outcome of
130 patients who underwent removal of solitary adrenal metastases from different cancer types, including
131 NSCLC.

132 Since the first description of adrenalectomy for isolated metastasis in 1982 [18], many retrospective
133 series showed a potential benefit in survival in well-selected patients undergoing surgical treatment
134 [19-26].

135 In recent years, there is growing evidence in support of use of laparoscopic approach in malignant
136 adrenal lesions ensuring an adequate oncologic result, in addition to the advantages of mini-invasive
137 surgery in terms of safety and post-operative recovery [27-30]. Therefore, laparoscopic
138 adrenalectomy represents the first-choice surgical option in these patients.

139 Given the low probability that a benign adrenal lesion becomes malignant during follow-up [5], an
140 active imaging surveillance of adrenal incidentalomas that are characterized to be benign is currently
141 not recommended [4, 31]. However, oncological patients may represent a possible exception to the
142 rule because neoplastic cells may be seeded in a pre-existing benign lesion. **Whether the coexistence**
143 **of a metastasis in an adrenal benign lesion is an incidental occurrence or represents the result of**
144 **changes in the local environment that may favor hematogenous metastatization in an adrenal**
145 **adenoma is not still clear. In 2014, Untch and colleagues [3] reviewed 11 histopathologically-proved**
146 **adrenal collision tumors described in literature. In the last five years other 14 case reports of adrenal**
147 **collision tumors have been published [3, 32-51]. The 25 cases are summarized in Table 1. In 18**
148 **cases, an adrenal adenoma was present. In 17 cases a malignant component was described, in 6 cases**
149 **of primitive adrenal origin, in 11 cases of metastatic nature. 3 cases were lung cancer metastases, one**
150 **small cell lung carcinoma (SCLC) and two NSCLC.**

151

152 **Conclusions**

153 In conclusion, we have reported the development of a solitary adrenal metastasis on a pre-existing
154 benign adrenal lesion in a patient with a NSCLC in apparent clinical remission. **Although oncologists**

155 and pneumologists, familiar with the way of metastatic spreading of lung carcinoma, are used to
156 follow up patients with total body CT, this case report highlights the peculiarity of the follow-up of
157 adrenal masses in cancer patients. While imaging follow-up of adrenal incidentalomas is seldom
158 recommended [4, 5, 31] any adrenal lesion in a patient with known oncological disease should be
159 carefully evaluated at any restaging, even if the mass has been previously labelled as benign. This is
160 of utmost importance when a complete response of the primary cancer has been obtained after
161 treatment, since the detection of new adrenal metastasis may change the management plan. In this
162 clinical scenario, ¹⁸F-FDG-PET/CT represents a valid tool to guide clinicians in the decision-making
163 process [52].

164

165 **Conflict of Interest**

166 On behalf of all authors, the corresponding author states that there is no conflict of interest.

167

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