ISSN 2472-1972

Sclerosing Angiomatoid Nodular Transformation of the Adrenal Gland: A Case Report of a Novel Histopathological Entity

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The finding of an indeterminate adrenal mass at radiological investigations is a challenge for physicians. Complex diagnostic work-up, periodic follow-up, or surgical intervention are therefore needed to rule out malignant lesions. Tertiary care hospitals are provided with ^{18}F-fludeoxyglucose (^{18}F-FDG) positron emission tomography (PET) and ^{18}F-dihydroxyphenylalanine (^{18}F-DOPA) PET, which aid in the characterization of indeterminate adrenal masses. Nevertheless, the histopathological examination may be required to exclude malignancy or rare etiologies. A 54-year-old woman presented to our clinic 6 months after a cerebral hemorrhage. She was hypertensive and had recently discovered a left adrenal mass of 15 mm during an abdominal ultrasound. Contrast-enhanced CT, following adrenal protocol, revealed a 14-mm adrenal mass without characteristics suggestive of an adrenal adenoma. Tumor markers were negative. Functional tests excluded hormone hypersecretion. An ^{18}F-DOPA PET was negative. An ^{18}F-FDG PET showed mild uptake of both the adrenal glands, with a more circumscribed pattern in the left one (maximum standardized uptake value = 4). As the clinical diagnosis was still indeterminate, we performed laparoscopic left adrenalectomy. The histopathological examination described a sclerosing angiomatoid nodular transformation (SANT) of the adrenal gland, a benign lesion already described as a rare occurrence only in the spleen. IgG4 levels were reduced. In conclusion, this is a report of a SANT of the adrenal gland, a novel entity that should be taken into consideration in the differential diagnosis of indeterminate adrenal masses at CT scan.

Freeform/Key Words: sclerosing angiomatoid nodular transformation, adrenal, mass, ^{18}F-fludeoxyglucose positron emission tomography, computed tomography

The clinical diagnosis of an incidentally discovered adrenal mass requires multiple laboratory tests and imaging investigations [1]. Nevertheless, in certain circumstances, a definitive diagnosis is hard to achieve, meaning that only the histopathological examination represents the

Abbreviations: ^{18}F-DOPA, ^{18}F-dihydroxyphenylalanine; ^{18}F-FDG, ^{18}F-fludeoxyglucose; HU, Hounsfield unit; PET, positron emission tomography; SANT, sclerosing angiomatoid nodular transformation; SUV_{max}, maximum standardized uptake value.

Received 9 January 2019
Accepted 1 May 2019
First Published Online 7 May 2019

Case Report
June 2019 | Vol. 3, Iss. 6
doi: 10.1210/js.2019-00013 | Journal of the Endocrine Society | 1207–1213

last step in the diagnostic work-up. Multidisciplinary teams are therefore needed to identify all of the possible differential diagnoses and decide the best treatment options.

Radiological imaging for the diagnosis of adrenal malignancy is often cumbersome and requires an expert radiologist [2]. Tumor size, margins, and homogeneity may help in the decision to bring the patient to surgical attention. Noncontrast CT scan appears to be highly sensitive in the diagnosis of adrenal cancer but shows poor specificity when nonenhanced tumor density cut-off is set at 10 Hounsfield unit (HU). Moreover, there are still limited data on the additional diagnostic role of the evaluation of the contrast medium washout at CT scan and the added value of positron emission tomography (PET) scan imaging.

Here, we report the case of a middle-aged woman who sought our attention for an adrenal mass of uncertain origin. Written consent for publication of this Case Report was obtained from the patient.

1. Case Description

A. Clinical History

A 54-year-old woman was referred to the Outpatient Clinic of the Division of Endocrinology of the Sant'Orsola-Malpighi Hospital (Bologna, Italy) in July 2017. She had been in menopause for 3 years. Her smoking history was negative. In 2000 and 2003, she had two pregnancies without complications. She had a positive family history of hypertension and ischemic heart disease by her father. In November 2016, she underwent right parietal craniotomy for the evacuation of a hematoma as a result of intraparietal right hemorrhage with signs of sylvan subarachnoid hemorrhage. The cerebral contrast-CT was unremarkable. Specifically, there was no evidence of arteriovenous malformation or aneurisms of cerebral arteries. Before the cerebrovascular accident occurred, she had been found with elevated blood pressure values that had been under treatment with homeopathic products. During hospital admission in 2016, urinary tests showed a mild elevation of adrenaline (64 μg/day; normal range 1.7 to 22.4 μg/day), whereas noradrenaline (56.2 μg/day; normal range 12.1 to 85.5 μg/day) and dopamine (358 μg/day; normal values $<$500 μg/day) were normal. The patient underwent an abdominal ultrasound, showing a 15-mm left adrenal mass. Random aldosterone levels were within the normal range (9.4 ng/dL; normal range 3.7 to 31.0 ng/dL). After hospital discharge, she began antihypertensive treatment: ramipril 5 mg, amlodipine 10 mg, doxazosin 4 mg, and metoprolol 50 mg twice per day. Anticonvulsant therapy with lamotrigine 100 mg twice per day was also started, as a result of an episode of seizures after the neurosurgical intervention.

On first admission to our Outpatient Clinic, the physical examination was unremarkable: no signs of hypercortisolism nor neurologic deficits were detected. Body mass index was 21.2 kg/m^2, blood pressure 130/85 mmHg, and heart rate 60 beats per minute. We performed a contrast-CT scan with adrenal protocol, which confirmed an adrenal mass of 14 × 13 mm, without features resembling an adenoma (noncontrast density: 32 HU; venous-phase density: 157 HU; late-phase density: 93 HU; absolute wash-out: 51%; relative wash-out 40%; Fig. 1). Morphology of the right adrenal gland was normal. Serum cortisol after a 1-mg dexamethasone test was normal (0.9 μg/dL), as well as androgens (Table 1). Blood levels of carcinoembryonic antigen, carbohydrate antigen 19-9, carbohydrate antigen 15-3, carbohydrate antigen 125, neuron-specific enolase, cytokeratin 19 fragments, α-fetoprotein, and chromogranin A were also within the normal ranges. Upright aldosterone and renin determination was not done as a result of the unfavorable risk/benefit ratio in the withdrawal of the interfering antihypertensive treatment. With the consideration of the elevation of urinary epinephrine, we performed an ^{18}F-dihydroxyphenylalanine (^{18}F-DOPA) PET scan, which did not detect abnormalities. A CT scan was repeated 6 months later, showing the stability of the adrenal mass size. An ^{18}F-fludeoxyglucose (^{18}F-FDG) PET scan revealed a diffuse hyperfixation of both adrenal glands (Fig. 1), with a more circumscribed pattern in the left one [maximum standardized uptake value (SUV_{max}) adrenal/liver = 4:2.4].

The case was discussed in our Multidisciplinary Adrenal Team meeting. We decided for surgical removal of such an undetermined adrenal mass. In March 2018, the patient

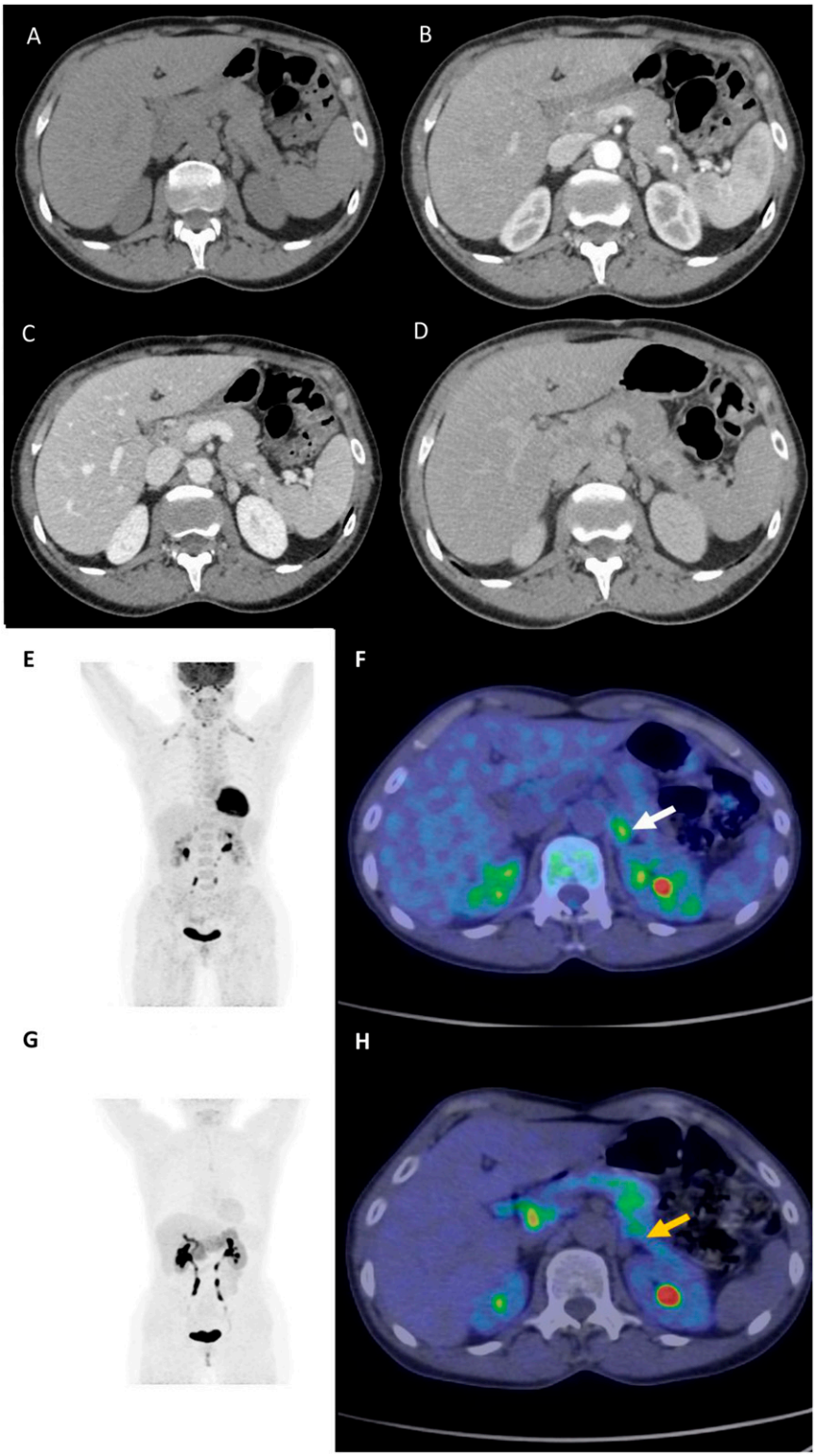

Figure 1. Radiological and nuclear imaging. (A–D) CT scan. Lesion of the medial limb of the left adrenal gland (dimension 13 × 14 mm). The region of interest for the assessment of the density was placed over two-thirds of the surface area of the mass in the axial view. The attenuation value assessment shows a density of (A) 32 HU on unenhanced CT, (C) 157 HU in the venous phase (at 70 to 80 seconds), and (D) 93 HU in the delayed phase (at 15 minutes) with absolute wash-out of 51% and relative wash-out of 40%. (E and F) ^{18}F-Fludeoxyglucose (^{18}F-FDG) PET scan: diffuse hyperfixation of both adrenal glands, with a

more circumscribed pattern in the left one [maximum standardized uptake value (SUV_{max}) adrenal/liver = 4:2.4]. The white arrow indicates the left adrenal gland. (G and H) ^{18}F-Dihydroxyphenylalanine (^{18}F-DOPA) PET showing no uptake from the adrenal glands. The yellow arrow indicates the left adrenal gland.

underwent laparoscopic left adrenalectomy without complications. The histopathological examination showed a solid, white-tan mass (0.8 cm maximum diameter; (Fig. 2). The nodular lesion was predominantly constituted by fibrosclerotic stroma with hemosiderophages, fibroblasts, and lymphomononuclear cells. The lesion showed a storiform growth with relatively sharp demarcation and was composed of epithelioid cells arranged in strands with a storiform pattern. The cells often showed a histiocytoid appearance; the nuclei were commonly vesicular without distinct nucleoli. Mild nuclear atypia was only focally observed. Mitoses were absent. Furthermore, the cells showed an abundant hyaline cytoplasm with variable intracytoplasmic vacuoles, and some elements presented lumina occluded by hyaline thrombi. A dense hyaline stroma was diffusely present. Necrosis and calcification were not observed. The lesion was composed of cells that were diffusely positive for CD34, factor XIIIa, and Friend leukemia integration 1 with a focal expression of CD31, indicating derivation from sinusoidal, capillary-like, and vein-like elements. The CD34-immunonegative cells were stained for CD68 (sparse histiocytes). Expression of adrenal markers (inhibin, synaptophysin, Melan A, GATA-3) and all types of cytokeratins, including epithelial membrane antigen, were performed and resulted negative. S-100, D-240, signal transducer and activator of transcription 6, human melanoma black 45, calretinin, anaplastic lymphoma kinase 1, and IgG4 were negative. CD3, CD4, and CD8 highlighted sparse T-lymphocytes, mostly CD8 positive. The Ki-67 proliferative index was <1%. The rest of the adrenal gland had a preserved architecture.

Table 1. Biochemical, Hormonal, and Radiological Characteristics

Characteristics	
Laboratory values	
Sodium, mM	143
Potassium, mM	4.5
Aldosterone, ng/dL	9.4
ACTH, pg/mL	20
Cortisol, ng/mL	160
1 mg-DST cortisol, μg/dL	0.9
Testosterone, ng/mL	0.33
Dehydroepiandrosterone sulfate, μg/dL	119
Dehydroepiandrosterone, ng/mL	6.1
Androstenedione, ng/dL	298
17-Hydroxyprogesterone, ng/dL	76
TSH, μU/mL	1.98
Free thyroxine, pg/mL	9.6
IgG4, mg/dL (normal range 39.2 to 86.4)	17.4
Imaging findings	
CT Basal, HU	32
CT Venous phase, HU	157
CT Late phase, 15 min, HU	93
CT Absolute wash-out, %	51
CT Relative wash-out, %	40
^{18}F-FDG PET: SUV_{max} left adrenal gland	4.0
^{18}F-FDG PET: SUV_{max} right adrenal gland	4.0
^{18}F-FDG PET: SUV_{max} liver	2.4
^{18}F-DOPA PET	Negative

Abbreviations: ACTH, adrenocorticotrophic hormone; DST, dexamethasone; TSH, thyrotropin hormone.

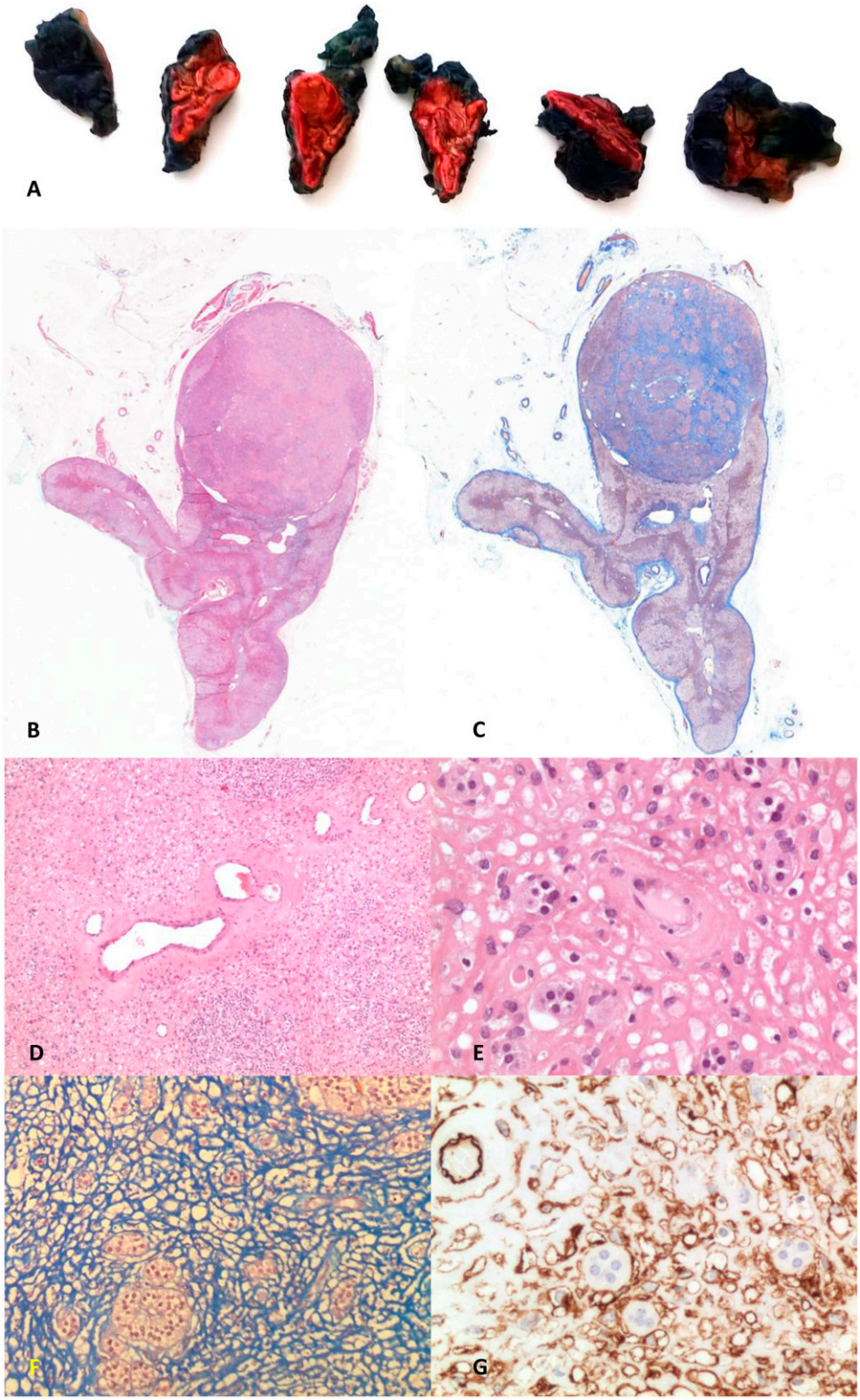

Figure 2. (A) Gross appearance of the adrenal gland with a nodule of 0.8 cm. (B and C) The lesion appeared nodular and predominantly fibrosclerotic: (B) hematoxylin and eosin; (C) Weigert -von Gieson, ×10. (D and E) Epithelioid cells arranged in strands with a storiform pattern, with vesicular nuclei and intracytoplasmic vacuoles (hematoxylin and eosin, ×50, ×200). (F) Abundant collagenized stroma (Weigert -von Gieson, ×100). (G) Diffuse CD34 expression (×200).

The microscopic appearance of the lesion and the protein expression pattern resembled that of the sclerosing angiomatoid nodular transformation (SANT), a rare pathological finding that has been described in the spleen in a few Case Reports worldwide so far [3–6]. Splenectomy is the treatment of choice for the management of splenic SANT. Patients have a good prognosis with no recurrence. The pathogenesis is still unclear. It has been proposed that SANT may represent a splenic hamartoma undergoing an unusual form of sclerosis, a peculiar reactionary transformation of red pulp, as a result of an exaggerated stromal response [4]. It appears that SANT is probably a reactive lesion rather than a true neoplastic process, a theory supported by the high prevalence of concurrent conditions in SANT patients. Recently, a number of authors have suggested that the proliferation seen in SANT may be associated with IgG4-related sclerosing lesions as a result of the presence of plasma cells found in its stroma [6]. The splenic lesion is commonly described in middle-aged adults after being found incidentally on radiographic imaging [4].

With the consideration that such a lesion has been found in the context of IgG4-related disease, we measured circulating IgG4 levels in our patient, which were under the lower reference range (17.4 mg/dL; normal range 39.2 to 86.4 mg/dL). Ten months after surgery, at last follow-up, the physical examination of the patient was unremarkable. Currently, our report represents a description of SANT outside of the spleen, and with the consideration of the benign appearance, such as the negativity for IgG4, we may speculate that the described lesion could represent an incidental hamartoma or a reactive process.

2. Conclusion

This Case Report describes a case of SANT reported in the adrenal gland. The clinical and the radiological characteristics of this entity are not specific, except for a radiological appearance of a nonadenomatous lesion at abdominal CT-scan. The role of the ^{18}F-FDG PET scan is uncertain, even though a mild uptake may be detected, as previously reported in spleen lesions [5]. Therefore, adrenal malignancy and pheochromocytoma should be considered in the differential diagnosis of this condition, which can be diagnosed only after histopathological examination.

Acknowledgments

The Multidisciplinary Adrenal Team–Bologna (MAT-BO) includes the following medical specialists: Valentina Vicennati, Uberto Pagotto, Guido Di Dalmazi, Guido Zavatta, and Barbara Bergonzoni (Division of Endocrinology, Department of Medical and Surgical Sciences, University of Bologna); Cristina Mosconi, Caterina Balacchi, and Rita Golfieri (Division of Radiology, Sant'Orsola-Malpighi Hospital, Bologna); Eugenio Roberto Cosentino and Claudio Borghi (Hypertension Unit, Department of Medical and Surgical Sciences, University of Bologna); Cristina Nanni (Metropolitan Nuclear Medicine, Sant'Orsola-Malpighi Hospital, Bologna); Saverio Selva and Francesco Minni (General Surgery, Department of Medical and Surgical Sciences, University of Bologna); Antonio De Leo and Donatella Santini (Pathology Unit, University of Bologna); and Maria Abbondanza Pantaleo (Department of Experimental, Diagnostic and Specialty Medicine, Sant'Orsola-Malpighi Hospital, and "G. Prodi" Interdepartmental Center for Cancer Research, University of Bologna).

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Disclosure Summary: The authors have nothing to disclose.

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