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6 Article type : Case Report

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9 **Title**

10 Ectopic adrenal adenoma causing gross hematuria: steroidogenic enzyme profiling and
11 literature review

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34 **Running title:** Ectopic Adrenal with Gross Hematuria

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45 **Abstract**

46 **Introduction:** Aberrant cortical adrenal tissues are not generally identified in adults.

47 Herein, we present a very rare case of an ectopic adrenal tumor located in the renal

48 hilum that caused gross hematuria.

49 **Case Presentation:** A 33-year-old man suddenly presented with asymptomatic gross
50 hematuria. Abdominal computed tomography revealed a 35-mm mass in the left renal
51 hilum encroaching the renal vein. Following the surgical removal with frozen section of
52 the mass, his gross hematuria immediately improved. Pathological analysis of the
53 specimen revealed the features adrenal adenoma. Immunohistochemical staining for key
54 steroidogenic enzymes confirmed the adrenocortical origin without excessive hormone
55 production.

56 **Conclusion:** This is the first case of an ectopic adrenocortical adenoma in the renal
57 hilum that caused gross hematuria without hormonal symptoms.

58

59 **Keywords:** ectopic adrenal adenoma, gross hematuria, renal hilum tumor, steroidogenic
60 enzyme

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62 **Key note message**

63 This is the first case of an ectopic adrenocortical adenoma in the renal hilum that caused
64 gross hematuria without excessive hormone production. To further investigate the
65 etiology and hormonal function of the mass, we performed immunohistochemical
66 analysis of key steroidogenic enzymes with literature review.

67

68 **Text**

69 **Introduction:** Aberrant cortical adrenal tissues might descend with the primordial
70 gonads along the course of their supplying arteries but are not commonly encountered in
71 adults [1]. We describe an unexpected case of gross hematuria caused by an ectopic

72 adrenocortical adenoma located in the renal hilum of an otherwise healthy adult.

73 **Case Presentation:** A 33-year-old man presented to the hospital with a complaint of
74 sudden gross hematuria. He had no associated pain or additional complaints. His
75 laboratory workup revealed normal levels of hemoglobin and tumor markers (CEA,
76 CA19-9, NSE, SCC, sIL-2R, and IgG4). Atypical urothelial cells were not detected in
77 the urinary cytological test. In a cystoscopic examination, gross hematuria from the left
78 ureteral orifice was found, although no apparent abnormalities were observed in bladder
79 mucosa. In contrast, enhanced computed tomography (CT) revealed a 35-mm mass with
80 slight enhancement, which significantly compressed the left renal vein (Fig. 1a, b).
81 Collateral vessels were not apparent between renal parenchyma and inferior vena cava.
82 Abdominal enhanced magnetic resonance imaging identified a low signal intensity of
83 tumor at T1 as well as T2-weighted images with a slight enhancement and an almost
84 normal intensity in diffusion weighted image suggesting a benign tumor. A CT-guided
85 needle biopsy was not performed because the tumor was encroaching the renal vein,
86 thus having a possible risk of hemorrhage. After obtaining the informed consent
87 concerning surgery and subsequent publication, the patient underwent open tumor
88 resection through retroperitoneal approach for easy extension of the resecting area in
89 case the frozen section identified malignancy. During surgery, a yellowish, non-necrotic
90 tumor compressing the renal vein was identified corresponding to the CT findings. The
91 result of the intraoperative rapid pathological analysis suggested a benign tumor.
92 Therefore, the left kidney was spared and the surgery was completed.

93 Pathological examination identified the mass was directly surrounded by
94 adipose tissue, lacking a distinct capsule, and was composed of adrenocortical-like cells.
95 Medullary cells were not observed. The final pathological diagnosis was adrenocortical

96 adenoma (Fig. 2).

97 According to the Weiss criteria [2], the estimated malignant potential of the
98 tumor was low, with only one of the nine criteria met, which was clear cells comprising
99 $\leq 25\%$ of the tumor. Accordingly, the tumor was diagnosed as benign. The hematuria
100 improved immediately after surgery, and no evidence of tumor recurrence was found
101 during the 2-years follow-up, supporting the benign nature of the tumor.

102 To further investigate the etiology and hormonal function of the mass, we
103 performed immunohistochemical analysis of key steroidogenic enzymes, as previously
104 reported [3, 4]: 3β HSD, CYP11B2, CYP17 and CYP11B1 (Fig. 3). The positive cell
105 area (PCA) per total area (TA) of each stained section was measured by using the Color
106 Deconvolution software and the ImageJ software. The PCA/TA ratio of 3β HSD and
107 CYP11B1 were 39.4% and 93.4%, respectively. The latter indicated that the tissue was
108 of an adrenocortical origin. The PCA/TA of CYP17 was 10.0%, suggesting that some
109 cells might have produced cortisol. The CYP11B2 staining result was positive only in a
110 few cells (0.3%), indicating that the mass unlikely produced aldosterone.

111 After removal of the tumor, the narrowing of left renal vein disappeared in the
112 CT image (Fig. 1c). At present, more than 2 years after the operation, there is no
113 recurrence, nor even microscopic hematuria.

114 **Discussion:** We herein report an intriguing case of gross hematuria caused by an
115 ectopic adrenocortical mass. Ectopic adrenocortical tissue can be found in children and
116 usually regresses by puberty [1]. The most common sites of ectopic adrenocortical
117 tumors are the celiac axis (32%), broad ligament (23%), adnexa of the testis (7.5%), and
118 spermatic cord (3–8%) [5]. The growth of such ectopic adrenal rest tissue is promoted
119 by excessive and sustained elevations of adrenocorticotrophic hormone levels, such as

120 those in patients with congenital adrenal hyperplasia, but is otherwise uncommon in
121 adults. Presumably, ectopic adrenal tissue might undergo somatic mutations that lead to
122 adenomatous growth. Malignant transformation of ectopic adrenal tissue has been
123 previously reported, however, benign ectopic adrenal masses that cause hematuria have
124 never been reported.

125 Based on image diagnosis and macroscopic findings during surgery, we assumed
126 the nut-cracker mechanism would be the cause of hematuria in this case. Furthermore,
127 the complete disappearance of hematuria after tumor removal also supported this
128 assumption. In a typical case with nut-cracker phenomenon, the left renal vein is
129 compressed between the superior mesenteric artery and the aorta. Therefore, it is easy to
130 detect left renal vein because its diameters before and after narrowing are relatively
131 wide. In the present case, we could not measure renal venous pressures due to technical
132 difficulty in detecting renal side of left renal vein.

133 We reviewed the summary of the manuscripts involved in ectopic adrenal tumor
134 located in renal hilum. We identified 5 related articles and considered them (Table 1).
135 Among the reported cases of ectopic adrenal tissue in the renal sinus; a 27-year-old
136 woman presented amenorrhea with borderline elevation of testosterone [6], a
137 37-year-old woman with possible primary aldosteronism [7], a 38-year-old man with
138 Cushing's syndrome [8], and a 63-year-old woman with Cushing's syndrome [9]. Only
139 one report, a 53-year-old woman with Cushing's syndrome, the mRNA levels of
140 3 β HSD, CYP17, CYP11B2, and CYP11B1 were analyzed by using quantitative reverse
141 transcription polymerase chain reaction and were suggestive of cortisol excess [10]. All
142 but this case has been identified because of hormonal symptoms accompanied by
143 hormonally active tumors. We performed immunohistochemical analysis and obtained

144 that 3 β HSD and CYP17 are highly expressed throughout the tumor. Conversely, in our
145 case, the tumor had high 3 β HSD (39.4%) and CYP11B1 expression levels (93.4%) but
146 low CYP17 (10.0%) and CYP11B2 expression levels (0.3%), indicating that the tumor
147 was presumably non-functional. The immunohistochemical analysis of steroidogenic
148 enzymes was useful for identifying true nature of the mass suggesting adrenal origin.
149 In conclusion, we here report for the first time a case of ectopic adrenal tumor in the
150 renal hilum that was hormonally silent but, despite its benign nature, caused gross
151 hematuria.

152

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163 **Conflict of interest declaration**

164 The authors declare no conflict of interest.

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193 adrenocortical adenoma in the renal hilum: histopathological features and
194 steroidogenic enzyme profile. *Int J Clin Exp Pathol* 2014, 7(7):4415-4421.

195

196 **Figure legends**

197 **Figure 1. Contrast-enhanced computed tomographic image.**

198 It shows anatomical tumor localization. A mass (*) is compressing the renal vein (#)
199 (Fig. 1a: transverse view and Fig. 1b: coronal view). Fig. 1c demonstrates postoperative
200 transverse view of the same slice.

201 **Figure 2. Pathological features.**

202 The tumor consists predominantly of cells with eosinophilic cytoplasm in more than
203 75% of the mass (bottom right), while the remainder of the tissue consists of islands
204 with vesicular or clear cytoplasm (upper left). Bar: 100 μ m.

205 **Figure 3. Immunohistochemical analysis of key steroidogenic enzymes.**

206 High-resolution images (2400 dots/in) of immunostained sections for 3 β -hydroxysteroid
207 dehydrogenase (3 β HSD) (A), 17 α -hydroxylase/17,20 lyase (CYP17) (B), aldosterone
208 synthase (CYP11B2) (C), and steroid 11 β -hydroxylase (CYP11B1) (D). Bars: 5 mm.

209

210 **Table 1. Literatures related to ectopic adrenal adenoma in the renal hilum.**

211 M: Male, F: Female.

212

213 **Abbreviations**

214 CEA = carcinoembryonic antigen

215 CA19-9 = carbohydrate antigen 19-9

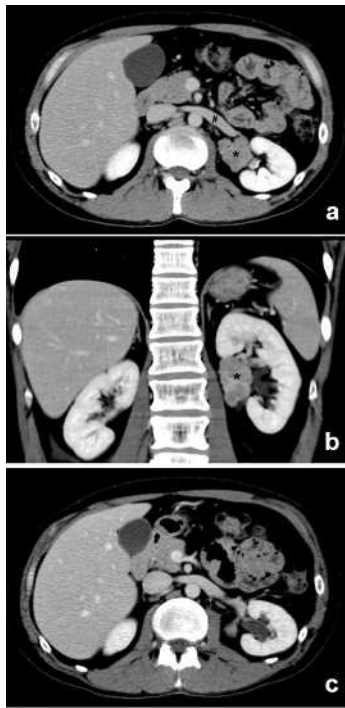
- 216 NSE = neuron-specific enolase
- 217 SCC = squamous cell carcinoma antigen
- 218 sIL-2R = soluble interleukin-2 receptor
- 219 IgG4 = immunoglobulin G4
- 220 3 β HSD = 3 β -hydroxysteroid dehydrogenase
- 221 CYP11B2 = aldosterone synthase
- 222 CYP17 = 17 α -hydroxylase/17,20 lyase
- 223 CYP11B1 = steroid 11 β -hydroxylase

Table 1. Literatures related to ectopic adrenal adenoma in the renal hilum.

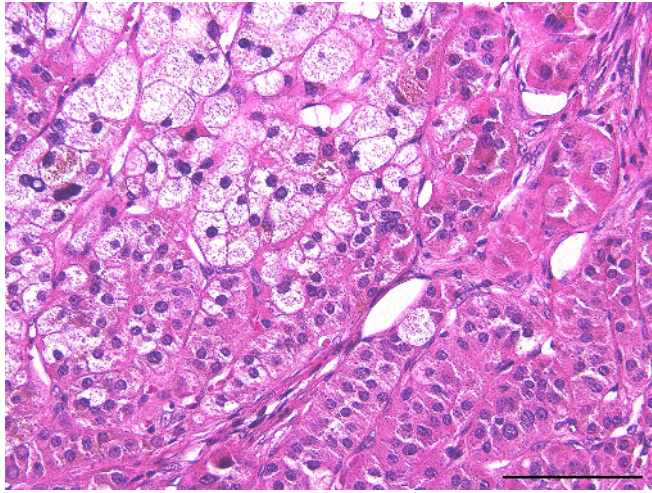
Case	Title	Author	Journal	Age/Sex	Symptoms	Complications Endocrine disorder	Largest diameter
1	Ectopic adrenocortical adenoma in the renal hilum: a case report and literature review.	Liu Y et al.	Diagn Pathol. 19; 11:40, Apr 2016.	27/F	Amenorrhea	Borderline elevation of testosterone	2.5cm
2	An ectopic adrenocortical adenoma of the renal sinus: a case report and literature review.	Zhang J et al.	BMC Urol. 16; 16:3, Jan 2016.	37/F	Hypertension Bilateral limb weakness	Possible primary aldosteronism with mild cortisol excess	3.4cm
3	Ectopic cortisol-producing adrenocortical adenoma in the renal hilum: histopathological features and steroidogenic enzyme profile.	Tong A et al.	Int J Clin Exp Pathol. 15; 7(7): 4415-21, Jun 2014.	53/F	Hypertension Weight gain Moon face Thin skin Systemic edema	Cushing's syndrome	3.5cm
4	Laparoscope resection of ectopic corticosteroid-secreting adrenal	Wang XL et al.	Neuro Endocrinol Lett. 33(3):	38/M	Cushingoid appearance	Cushing's syndrome	5.3cm

	adenoma.		265-7, 2012.				
5	Corticotropin-independent Cushing's syndrome caused by an ectopic adrenal adenoma.	Ayala AR et al.	J Clin Endocrinol Metab. 85(8): 2903-6, Aug 2000.	63/F	Hirsutism, Facial plethora, Hypertension, Centripetal obesity, Proximal myopathy	Cushing's syndrome	3.5cm
Current case	Ectopic adrenal adenoma causing gross hematuria: steroidogenic enzyme profiling and literature review.	Ashikari D et al.		33/M	Gross hematuria	No endocrinology disorders	3.5cm

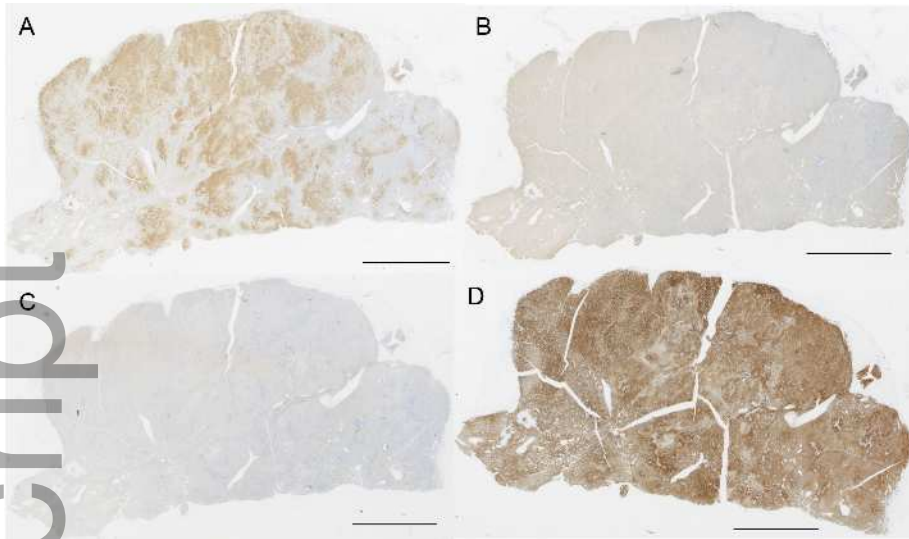
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