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ORIGINAL PAPER

Ectopic adrenal tissue in the kidney: A systematic review

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Summary

Introduction: *Ectopic adrenal tissue in the kidney, including "Ectopic adrenal tissue" and "Adrenal-renal fusion", is a rare event with a specific behavior which may be difficult to distinguish clinically from renal neoplasms. We performed a systematic review on ectopic adrenal tissue variants reported in the literature underlining its clinical aspects.*

Methods: *Manuscripts which presented a case report or case series of ectopic adrenal tissue in the kidney were included even if published in original articles, reviews, or letters to the editor. A specific search on SCOPUS®, PubMed®, and Web of Science® database was performed. Only English language papers published in a period ranging between August 1991 and April 2020 were considered. Additionally, a case we had at our institution is described, and its characteristics are included. Data on clinical presentation, type of adrenal anomaly, location, anatomopathological and immune-histotype characteristics were collected.*

Results: *We identified 888 manuscripts. Among these 29 were included in this systematic review. Overall, 39 patients with renal adrenal fusion or adrenal ectopia were considered. In most cases, the diagnosis was made incidentally, or following investigation for flank pain, abdominal pain, or endocrinological disorders. CT scan frequently identified a solid vascularized lesion that was difficult to distinguish from renal neoplasm. Adrenal fusion was mostly located at the level of the upper pole. Adrenal rest was found in the renal parenchyma, renal hilum, or retroperitoneum in close proximity to the renal peduncle. Often these ectopic adrenal tissue lesions follow a benign behavior and can be classified as functioning or non-functioning adenomas. Rarely, they may experience neoplastic degeneration. The most frequently positive markers were inhibin, vimentin, melan-A, synaptophysin and anti-p450 scc.*

Conclusions: *Ectopic adrenal tissue in the kidney is a rare event with specific clinical characteristics that need to be identified in order to arrive at a correct diagnosis and carry out appropriate treatment management.*

KEY WORDS: *Intrarenal adrenal tissue; Ectopic adrenal tissue; Renal-adrenal fusion; Adrenal rest; Incidental renal masses; Renal cancer; Small renal mass.*

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INTRODUCTION

Renal cancer represents 3% of all neoplasms in western Countries. During the last few years, its incidence increased by 2% due to an increased amount of incidental radiological diagnosis, especially for small renal masses (< 4 cm of diameter) (1, 2), for which nephron sparing surgery is the treatment of choice (3). However, these small lesions can behave biologically different from other renal masses. It is estimated that 20-30% of small renal masses are benign and active surveillance is an acceptable tool that can be used to avoid the surgery and its related risks in this cohort of patients (2-4). The presence of ectopic adrenal tissue in the kidney, while benign, is a rare event that needs to be identified and distinguished from renal cancer. This condition can be divided into two entities based on the pathophysiological origin.

First, "*Ectopic adrenal tissue*" or "*adrenal rest*", initially described by *Morgagni* in 1740, is a congenital anomaly due to the migration, to other organs, of fragments of the primitive adrenal gland, and can be classified as "*true*" or "*accessory*" ectopy depending on the migration of the whole or part of the gland, respectively (5, 6).

Second, "*Adrenal-renal fusion*", first described by *Rokitansky* in 1855 (7), could be divided into a "*congenital*" form when it is caused by failure of the retroperitoneal mesenchymal cells to stimulate adrenal capsule formation, or "*acquired*" form when it is a consequence of inflammation of the perirenal fat. Consequently the adrenal gland becoming fused with the renal parenchyma, and become anatomically indivisible from the kidney (8).

Most ectopic adrenal tissue is located along the migration path of the urogenital system but it could be present also at the level of celiac axis, broad ligament, spinal cord and other retroperitoneal parenchymatous organs (9). Ectopic adrenal tissue can be present in 50% of newborns, usually regressing and persisting in only 1% of the adult population (10). It is not a rare condition and can manifest clinically as endocrine abnormalities due to secretory activity, mass effect or neoplastic transformations. Additionally, due to the location where these lesions can arise, adrenal rest becomes part of the differential diagno-

sis along with renal cell carcinoma and for this reason it must be correctly diagnosed (11). Here, we report a systematic review of the literature on ectopic adrenal tissue while underlining its main clinical aspects.

Methods

We performed a systematic review limited to case reports, case series and all formats reporting a case description on our specific topic. The purpose of this literature review is to describe the salient features of adrenal ectopia in order to assist the differential diagnosis process with renal neoplasms. For this reason, we considered only adrenal ectopias located at the renal level or in the retroperitoneum in close proximity to the renal pelvis in the study. A specific search on *SCOPUS®*, *PubMed®*, and *WEB OF SCIENCE®* database was performed including "[(intrarenal adrenal tissue) OR (ectopic adrenal tissue)] OR [(renal -

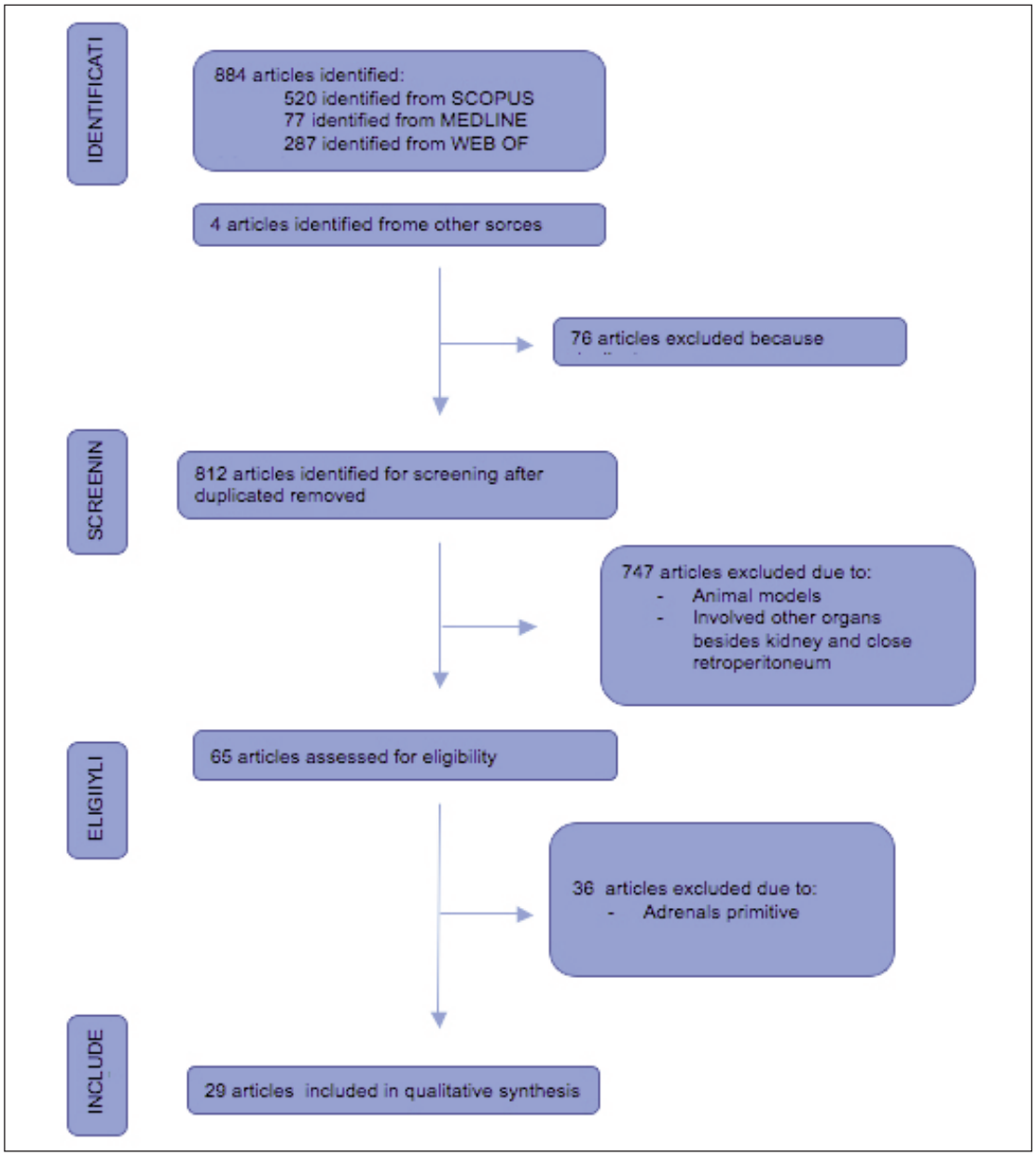


Figure 1. *PRISMA flowchart.*

In November 2017, a 66 year-old man with a previous history of diabetes mellitus, hypertension, and benign prostatic hyperplasia came to our Institution.
Due a single episode of hyperpyrexia associated with left flank pain, he performed an abdomen ultrasound with incidental finding of a left renal mass, and a following abdomen CT scan which confirmed the presence of an exophytic solid lesion of 10 x 14 mm, in the middle lateral margin of the left kidney (R.E.N.A.L. score 6A; P.A.D.U.A. 7 A), (Figure 2 A-B-C-D).
Both adrenal glands had regular morphology, size and location. Complete blood count, creatinine, urine analysis values were all within normal limits.
Given the small size of the neoformation, active surveillance of the neoformation was proposed to the patient but he preferred to remove the mass, and robot assisted left partial nephrectomy was performed in January 2018.
A clampless enucleoresection was performed with a continuous suture on the resection bed by sliding suture technique with Hem-O-Lok.
The post-operative period was regular and uncomplicated. The patient was discharged after three days. The definitive anatomopathological report reports "ectopic adrenal gland with renal tissue where occasional tubular thyroidization and minimal interstitial chromic nephritis" (Figure 3 A-B). The follow up was negative. Ultrasound of the abdomen and blood test with kidney function evaluation was negative.

Box 1. *Case report.*

Table 1.
Clinical and pathological characteristics of adrenal ectopias findings in the included studies.

Author	Type of article	N° of case	Clinical Presentations	Adrenal abnormalities	AP report	Markers
Goren et al. 1991 (14)	Case report	1 case	Left lumbar pain	Adrenal rest	Ectopic adrenocortical adenoma	NS
Chin et al. 1994 (6)	Case report	1 case	Incidental finding in patient with kidney neoplasia	True heterotopia	ectopic adrenocortical adenoma	Anti-P450 scc+
Colberg et al. 1998 (15)	Case report	1 case	abdominal pain and weight loss	Adrenal renal fusion	Adrenocortical adenoma	Pan cytokeratin - cytokeratin 7-
Ayala et al. 2000 (16)	Case report	1 case	Cushing's syndrome	Adrenal rest	Ectopic adrenocortical adenoma	NS
Souverijns et al. 2000 (17)	Case report	1 case	Hypertension	Adrenal rest	Ectopic adrenocortical adenoma	Vimentin +
Szumera et al. 2003 (11)	Case report	1 case	NS	Adrenal rest	Ectopic adrenocortical adenoma	Vimentin + synaptophysin + cytokeratin- EMA -
Fan et al. 2004 (18)	Case report	1 case	Incidental findings in patients with metabolic syndrome	Adrenal renal fusion	Atrophic adrenal gland and renal cyst	NS
Hsu et al. 2005 (19)	Case report	1 case	Incidental findings in Patient with kidney neoplasia	Adrenal rest	Ectopic adrenocortical adenoma	NS
Claahsen-van der Grinten et al. 2008 (20)	Case report	1 case	Abdominal pain in patient with congenital adrenal hyperplasia	Adrenal rest	Adrenal rest tumour	cytokeratins 8/18 + inhibin + AE1/AE3 - epithelial membrane antigen - CD68 - CD10 - placental-like alkaline phosphatase -
Baydar et al. 2008 (32)	Case series	2 cases	Abdominal pain	Adrenal rest	Ectopic adrenocortical adenoma Eterotopic adrenal cortical tissue	melan-A + inhibin + calretinin + EMA- pancytokeratin - melan-A + synaptophysin + calretinin + EMA- CD68-
LInder et al. 2009 (21)	Case report	1 case	Incidental finding	Renal adrenal fusion	Adrenocortical adenoma	MART-1 + MAK-6 + inhibin + CD10 - hmb-45 - AE1/3 - SMA -
Mahadevia et al. 2009 (22)	Case report	1 case	Abdominal pain	Adrenal renal fusion	Adrenocortical adenoma	NS
Ye et al. 2009 (12)	Retrospective cases series	9 cases	-	7 adrenal rest 2 adrenal renal fusion	Ectopic adrenocortical adenoma	NS
Louiset et al. 2010 (23)	Case report	1 case	ACTH-independent Cushing's syndrome due to PPNAD	Bilateral adrenocortical micronodular hyperplasia and adrenal rest	Bilateral adrenocortical micronodular hyperplasia and ectopic adrenocortical adenoma	17-α hydroxylase+ 21-α hydroxylase+
Brčić et al. 2011 (15)	Case report	1 case	Incidental finding	Adrenal rest	Ectopic adrenocortical adenoma	HMB-45 + SMA + melan-A + inhibin + Calretinin+ AE1/3 - CD10 - EMA -
Cardinalli et al. 2012 (24)	Case report	1 case	Incidental finding in Beckwith-Wiedemann syndrome	Adrenal rest	ectopic adrenocortical adenoma	NS
Wang et al. 2012 (9)	Case report	1 case	Cushing's syndrome	Adrenal rest	ectopic adrenocortical adenoma	NS
Yokoyama et al. 2013 (25)	Case report	1 case	Incidental finding	Adrenal rest	adrenocortical carcinoma	P450c17 + SF-1 + DHEA-ST + 3β-HSD +
Tong et al. 2014 (26)	Case report	1 case	Cushing's syndrome	Adrenal rest	Ectopic adrenocortical adenoma	Melan-A+ HSD3B2+ CYP17A1+
Godin et al. 2014 (27)	Case report	1 case	Incidental finding	Adrenal rest	Oncocytic adrenocortical adenoma	NS
Griffin et al. 2015 (28)	Case report	1 case	Hypertension	Adrenal renal fusion	Multinodular adrenal cortical hyperplasia	NS
Clair et al. 2015 (29)	Case report	1 case	Abdominal pain	Adrenal renal fusion	Adrenocortical adenoma	NS
Liu et al. 2016 (33)	Case report and review	1 case	Endocrinological Disorders: Amenorrhea and virilization and obstruction urinary output	Adrenal rest	Ectopic adrenocortical adenoma	Vimentin + Inhibin α+ Melan-A + Synaptophysin + NSE + CD56 + AE1/AE3 +/- PAX 8 - S100 - Chromogranin A -
Zhang et al. 2016 (10)	Case report and review	1 case	Hypertension and bilateral limb weakness	Adrenal rest	Ectopic adrenocortical adenoma	Synaptophysin + CD56 + Vimentin + Ki-67 +(2%) Inhibin α+ Calretinin + chromogranin A - CD117- CD10 - CK7 - EMA - CK-pan - melan-A -
Sappal et al. 2016 (34)	Case report and review	1 case	Incidental finding	Adrenal rest	Ectopic adrenocortical adenoma	Melan-A + PAX 8 -
Zhao et al. 2018 (30)	Case report	1 case	Cushing's syndrome	Adrenal rest	Adrenocortical adenoma with myelolipoma metaplasia	NS
Lee et al. 2018 (31)	Case report	1 case	Back pain	Adrenal rest	Adrenocortical carcinoma	Inhibin α+ Vimentin + Synaptophysin + Melan A focal +
Bamford et al. 2018 (8)	Case report	1 case	Incidental finding in patient with bladder neoplasia	Adrenal renal fusion	-	-
Lu et al. 2018 (35)	Case report and review	1 case	ACTH-independent Cushing's syndrome	Adrenal rest	Ectopic adrenocortical adenoma	Inhibition + Melan-A + Synaptophysin + Vimentin + AE1/AE3 + HMB45 +/- CD34 +
Current case	Case report and systematic review	1 case	Incidental finding	Adrenal rest	Heterotopic adrenocortical adenoma	NS

adrenal fusion) OR (adrenal rest)] AND [(kidney cancer) OR (renal cancer) OR (renal cell carcinoma)]" MeSh terms. Only manuscripts in English language published in a period ranging between August 1991 and April 2020 were considered (Figure 1).

All the manuscripts which presented a case report or case series were included even if published in original articles, reviews, or letters to the editor.

Two authors (D.D.M.) and (G.M.) independently reviewed the literature using inclusion and exclusion criteria. All disagreements about eligibility were resolved by discussion with a third reviewer (A.T.) until consensus was reached.

This study was performed using guidelines set out by *Preferred Reporting Items for Systematic Reviews and meta-analysis* (PRISMA) statement (12).

Additionally, a case at our institution is described, and its characteristics are included in the following evidence synthesis (Box 1, Tables 1-2).

Table 2.
CT characteristics characteristics of adrenal ectopias findings in the included studies.

Author	Location	CT-presentation	Native adrenals	HU	MRI	Differential diagnosis
Goren et al. 1991 (14)	Left renal hilum	8 cm solid mass with contrast enhancement	NS	NS	NS	Oncocytoma, RCC
Chin et al. 1994 (6)	Right upper pole	NS	Normal	NS	NS	NS
Colberg et al. 1998 (15)	Right upper pole	2.9 cm solid mass	NS	NS	NS	NS
Ayala et al. 2000 (16)	Left renal hilum	3.5 cm mass	Normal	NS	NS	Ureteral tumor
Souverijns et al. 2000 (17)	Retroperitoneal mass close to left renal vein	5.5 cm mass with inhomogeneous peripheral contrast enhancement	NS	NS	NS	Lymph node metastasis
Szumera et al. 2003 (11)	Left upper pole	cystic lesion of 7 cm	NS	NS	NS	RCC
Fan et al. 2004 (18)	Right upper pole	Cystic renal mass (Bosniak II)	WISP-like and thin	9-10	NS	Cystic RCC
Hsu et al. 2005 (19)	Retroperitoneal paracaval mass	5 cm contrast enhancing paracaval mass	NS	NS	NS	Lymph node metastasis
Claahsen-van der Grinten et al. 2008 (20)	Retroperitoneal mass beside Rx left kidney	5 cm retroperitoneal mass with multinodular aspect	NS	NS	NS	NS
Baydar et al. 2008 (32)	Right upper pole	1.5 cm solid mass	Normal	NS	NS	RCC
	Left upper pole	2 mm mass at upper pole	NS	NS	NS	RCC
Linder et al. 2009 (21)	Right upper pole	4.5 cm solid mass with minimal amount of fat	NS	NS	NS	AML, RCC
Mahadevia et al. 2009 (22)	Left upper pole	2 cm mass with low attenuation and heterogeneity	Normal	Basal: -19A. Phase: +58V. Phase: +22	NS	AML, RCC
Ye et al. 2009 (12)	1 Mid pole left kidney, 6 superior pole	NS	NS	NS	NS	RCC
	2 superior pole	NS	NS	NS	NS	RCC
Louiset et al. 2010 (23)	Right pararenal adrenal rest close to the renal hilum	3.8 cm pararenal mass	Previous bilateral adrenalectomy	28	NS	NS
Brčić et al. 2011 (15)	Right upper pole	2 cm cystic and solid mass with contrast enhancement	NS	NS	NS	AML, RCC
Cardinalli et al. 2012 (24)	Left renal hilum	NS	NS	NS	NS	NS
Wang et al. 2012 (9)	Left upper pole	NS	Bilateral adrenal atrophy	NS	3 cm mass with fatty component and plentiful vascular supply	NS
Yokoyama et al. 2013 (25)	Retroperitoneal mass between inferior vena cava and right kidney	6,5 cm retroperitoneal mass	Normal	NS	NS	NS
Tong et al. 2014 (26)	Left renal hilum	2.7 mass in the left renal hilum	Atrophic	NS	NS	NS
Godin et al. 2014 (27)	Left upper pole	NS	NS	NS	4,8 cm heterogeneously enhancing mass	RCC, pheocromocytoma
Griffin et al. 2015 (28)	Right superior pole	NS	NS	NS	NS	Cystic RCC
Clair et al. 2015 (29)	Left upper pole	2.5 cm heterogeneous mass with contrast enhancing	NS	NS	Hypointense on T2 than renal cortex	Papillary RCC, AML, RCC
Liu et al. 2016 (33)	Left renal hilum	2.7 cm well-circumscribed soft-tissue mass with contrast enhancement with atrophic bilateral adrenals	Atrophic	35 to 161	NS	AML, oncocytoma, paraganglioma and RCC
Zhang et al. 2016 (10)	Right renal hilum	3*3 cm mass with contrast enhancement	Normal	NS	NS	NS
Sappal et al. 2016 (34)	Right upper pole	2.7 cm mass with contrast enhancement	Lesions appeared inseparable from the right adrenal gland	NS	NS	RCC
Zhao et al. 2018 (30)	Right renal hilum	3.6 cm solid mass with contrast enhancement. Adrenal gland were normal	Normal	NS	NS	NS
Lee et al. 2018 (31)	Mid pole right kidney	13 cm heterogeneous mass	NS	NS	NS	RCC
Bamford et al. 2018 (8)	Bilateral superior pole	Symmetrical well-defined low-attenuation subcapsular lesions each measuring 2.3 cm	No demonstrable fat plan between renal lesions and adrenals	55	NS	NS
Lu et al. 2018 (35)	Left renal hilum	3 cm well-circumscribed mass with athrophic bilateral adrenal glands	Atrophic	NS	NS	NS
Current case	Mid pole of the left kidney	10 x 14 mm, in the middle lateral margin of the left kidney	Normal	Basal: - 5A. Phase: +90 V. Phase: +60	NS	RCC, AML

Results

Our online search identified 888 publications. Sixty-five had all the inclusion criteria, and 29 were included in this systematic review. Among these, 22 were single case reports (6, 8, 9, 13-31), 2 articles reported more than one case (11, 32), 4 were literature reviews with case report (10, 33-35), and 1 article was a letter to the publisher including a case reports (5). We therefore compared the cases present in the literature with one that happened in our center in January 2018 (Box 1), evaluating the main characteristics. Overall, 39 patients with renal adrenal fusion or adrenal ectopia were considered.

The main aspects examined in this review of the literature were the clinical presentation, the type of adrenal anomaly found, the location of this anomaly, the definitive anatomopathological report and the presence of immune-histotypic markers (Table 1).

Type of adrenal anomalies

"*Adrenal rest*" were present in 29 patients, "*adrenal renal fusion*" was present in 9 patients (Table 1). All cases had adrenal cortex tissue, in the absence of heterotopia with regard to the medullary portion.

We found 1 case of "*true heterotopia*" as published by *Chin*

et al. in 1994 (6). In this case, the absence of an adrenal gland on the right side and the presence of normal left gland on the preoperative CT scan suggests a true heterotopia. From our review, it emerged, that the most frequent form of adrenal heterotopia is the adrenal rest, and in alignment with these findings, our clinical case also had this form of adrenal abnormality.

Clinical presentation

In 11 patients the diagnosis was incidental, in 8 patients the mass was found after clinical investigation was performed for flank or abdominal pain, in 7 patients presented with manifestations of endocrinological disorders, and in 3 patients, it was diagnosed during imaging evaluations which were performed for arterial hypertension refractory to therapy or metabolic syndrome.

The onset of symptomatology was not reported in 9 patients derived from a retrospective case series (11).

Most of the clinical cases in the literature have been accidentally diagnosed during clinical investigations for abdominal or lower back pain, high blood pressure, or during diagnostic routines for concomitant neoplasms. Seven cases showed endocrinological disorders such as Cushing syndrome, primary hyperaldosteronism or were present in the context of congenital anomalies such as Beckwith-Wiedemann syndrome (9, 16, 20, 23, 24, 26, 30, 33, 35).

Abdominal pain may be due to an ureteropelvic obstruction due to the mass effect of the neoplasm, as in the case presented by *Goren et al.* (14) and *Lee et al.* (31).

In another five cases the abdominal pain was not motivated by the size or the location of the adrenal abnormalities (15, 20, 22, 29, 32).

Cushing syndrome was the most frequent clinical presentation when a secreting ectopic adrenal adenoma was reported (9, 16, 23, 26, 30, 35). The clinical presentation included moon facies, hirsutism, easy bruising and weakness, polydipsia and polyuria. Elevated blood pressure refractory to anti-hypertensive drugs was also present. In these patients, surgical removal of the adrenal adenoma led to a regression of symptoms except for the case published by *Suverijns et al.* in which the pressure remained high (10, 17, 28).

In one case described by *Cardinalli et al.* in 2012 the adrenal rest was diagnosed during complementary radiological studies in a patient with Beckwith-Wiedemann Syndrome (BWS) (24).

BWS is a growth disorder characterized by macrosomia, macroglossia, organomegaly, abnormalities of the ears, an increased risk for development of embryonal tumors and disorders of the adrenal gland. In this particular case the presence of ectopic adrenal tissue at the level of left renal hilum was associated with a myelolipoma but the authors concluded that a clear relationship between BWS, adrenal adenoma and myelolipoma is unclear (24).

In our case, the diagnosis was incidental during routine investigation. In fact, the patient did not report abdominal pain, and did not manifest any endocrinological abnormalities or elevated blood pressure.

Location and CT-presentation

CT is considered the gold standard for the characterization of renal cancers. Multiphase CT has a sensitivity of 90% to 99% and a specificity of 99% to 100%. In our review, MRI was the method of choice for the study of renal mass only in two cases (9, 27). However, small kidney masses can exhibit similar behaviors making the differential diagnosis process difficult.

Renal adrenal fusion as described by *Rokitansky* is due to the absence of adipose tissue that normally separates the adrenal gland and the upper pole of the kidney. In our review we identified 9 cases of renal adrenal fusion all located at the upper renal pole (Table 2).

Among the 29 patients with adrenal rest, 17 had a localization at the kidney, 7 at the level of the renal hilum and 5 at the level of the retroperitoneum in close proximity to the renal peduncle (Table 2).

In patients with localization at the kidney, the lesion most commonly occurred in the upper pole, while only 3 patients, including our case, had a lesion located in the middle third of the kidney (11, 31).

In this subgroup of patients, the differential diagnosis included *clear cell renal cell carcinoma* (ccRCC), *angiomyolipoma* (AML), oncocytoma, *papillary renal cell carcinoma* (pRCC) and cystic RCC. In the remaining case reports with extra renal localization the differential diagnosis included lymph node metastases and ureteral tumors (Table. 2).

Only 3 case reports present in our review reported the *Hounsfield Units* (HU) of the neoplasms. *Fan et al.* found that the lesion had a HU of 9-10. In this case, given the radiographic characteristics of the lesion, the differential diagnosis included a cystic renal neoplasm (18). *Mahadevia et al.* found a variation in HU depending on the phase of the study from -19 to +58 and +22.

In this case the differential diagnosis was between AML and RCC (22). *Liu et al.*, reported a change in HU from 35 to 161. In this case the differential diagnosis included AML, Oncocytoma, Paraganglioma and RCC (33). In our case, the neoplasm showed a behavior similar to that described by *Mahadevia*. In fact, the neoplasm had different HU -5, +90 and +60 according to the different phases of the CT study. Also, in our case, the main differential diagnoses were AML and RCC.

Anatomopathological report

More frequently these adrenal changes have a benign behavior and can be classified as functioning or non-functioning adenomas. However, in some cases, they may experience neoplastic degeneration as published by *Yokoyama et al.* and *Lee et al.* (25, 31).

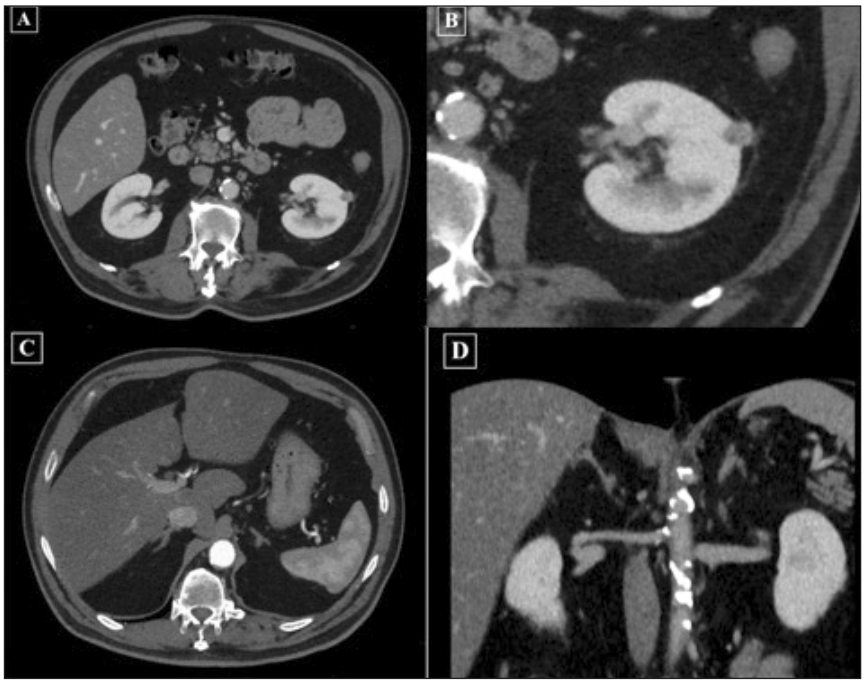
Godin et al. in 2014 published the first case of adrenocortical heterotopic oncocytoma of the kidney. As reported, the additional cases present in the literature had extrarenal locations being localized at the spinal or retroperitoneum level (27). Our case, according with the literature is one with a non-functioning adrenocortical adenoma (Box 1 - Table 1).

Additionally, the absence or poor presence of fibrous tissue between the kidney and heterotopic tissue was commonly reported, and a contact between the adrenal tissue and the renal parenchyma is frequently described. This feature is also present in our case (Figure 2).

Immune-histotypic markers

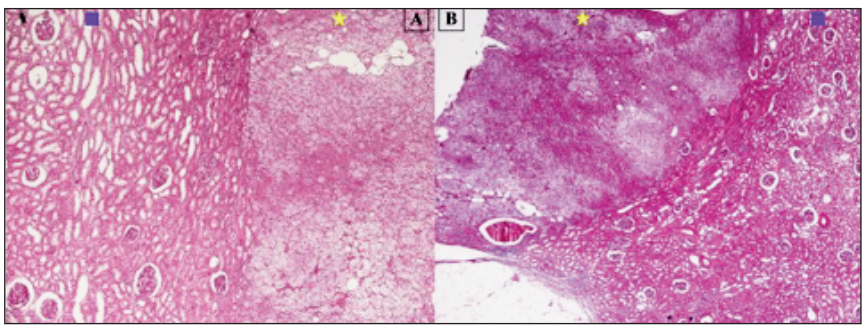
The immunohistochemistry has a pivotal role in the final

Figure 2.
"A-B": renal neoformation localized to the middle third of the left kidney;
"C-D": adrenal glands with regular size, morphology and localization.



diagnosis. In our review, 17 studies investigated the use of immunohistochemistry in the diagnostic phase.
Chin et al. in 1994, first used immunohistochemistry to establish the steroidogenic potential of the sample under examination (6). The kidney was incubated with adrenal ectopic tissue and specific antibodies for cytochrome p 450 scc (a mitochondrial enzyme implicated in the synthesis of steroid hormones), and a high response to the adrenal ectopic tissue was found. Subsequently, further markers were used in the differential diagnosis. The most frequently positive markers were inhibin, vimentin, melan-A, synaptophysin and anti-p450 scc (Table 1).
Our case report did not pose a diagnostic doubt and therefore, was not investigated with immunohistochemistry (Figure 2).
Adrenal heterotopia is a rare condition, present in about 1% of the adult population. The main locations are celiac axis, broad ligament, spinal cord and other retroperitoneal parenchymatous organs and this is due to the embryological development of the adrenal gland.
Adrenal heterotopia is a benign and asymptomatic condition; however, it can become evident clinically when endocrinological disorders manifest, neoplastic transformation occurs, or mass effect arises.
In most cases it presents itself as an incidental finding during routine examinations performed for other causes and can mimic a solid lesion affecting parenchymatous organs, a retroperitoneal lesion compatible with a neoplasm or a metastasis if diagnosed during diagnostic investigations for other malignancies. Having a heightened clinical suspicion for these neoplasms in the setting of small renal masses will improve detection and allow more appropriate therapeutic planning with important clinical implications. In this review, we considered the clinical characteristics of a subgroup of adrenal heterotopias such as those located at the renal, perirenal and retroperitoneal level in order to identify the main differences that can guide clinicians towards to a correct preoperative diagnosis.
As we reported, clinical presentation can be very varied. In most cases, it is silent and diagnosed during routine exams. In other cases, if the adenoma is secreting hormones, it manifests itself with endocrinological disorders, hypertension refractory to medical therapy or abdominal pain.
The most frequently occurring location of this lesion is at the level of the upper pole of the kidney with a typical morphology of solid lesion with fat content, and a hyper-vascularized pattern which includes differential diagnoses of AML or ccRCC (Table 2).
In these, an attenuation of -10 HU or less is similar to AML. A strong contrast during CMP with HU values greater than 100 with subsequent wash-out during the nephrogenic phase is similar to ccRCC. Also, pRCC has a more subtle enhancement pattern than ccRCC, further complicating the list of differentials (36). Finally, it can also present itself as a complex cyst as published by *Fan et al.* and, in this case the differential diagnosis is with cystic RCC (18).
More frequently the anatomopathological report is a benign adenoma, however an adrenocortical neoplasm or other histological subtypes may be

Figure 3.
Histopathological findings of an ectopic adrenal gland. Normal kidney parenchyma with glomeruli and tubules can be seen (BLUE SQUARE).
The right side is occupied by normal tissue of the adrenal gland, where cells belonging to the fasciculata and the reticularis can be spotted (YELLOW STAR).
While the orthotopic adrenal gland is embedded and separated by the renal parenchyma by a fibrous capsule most of the time, in this case the glandular tissue appears to be embedded directly in the renal parenchyma, since it is directly adjacent to it without any visible capsule or connective tissue.



present sporadically as published by *Godin et al.* in 2014 (27). In many of the cases present in this review, immunohistochemical markers were used, in fact the histological structure was not always correctly reported. This is especially true for cases of adrenocortical carcinoma and rarer histological subtypes.

The characteristics that our clinical case carried, correspond to clinical characteristics presented in the literature. The diagnosis was incidental during routine investigation, no painful or endocrinological symptoms were present. When the definitive anatomopathological report showed a well differentiated adrenal adenoma, further immunohistochemical investigations could have been avoided. The main feature that distinguishes our clinical case is the localization at the level of the middle third of the kidney on the lateral margin which is present only in two other clinical cases (11, 31).

In our case, we proposed active surveillance, given the size of the mass, however the patient chose surgery to relieve the anxiety of carrying a cancer diagnosis. We had not proposed a renal biopsy and the EAU guidelines do not recommend a renal biopsy on a mass with contrast enhancement, given the high diagnostic accuracy of radiographic imaging. Furthermore, biopsy is not currently a requirement for initiating active surveillance (3). In a recent systematic review, *Mir et al.* found that less than 30% of patients included in retrospective active surveillance studies had a confirmatory biopsy (4). The diagnostic accuracy and safety of the method, previously controversial, are currently supported by a recent meta-analysis (37).

In the absence of a definitive histology, active surveillance is based on initial dimensions and on its growth estimated as linear grow rate (cm/yr) but unfortunately growth is not an indicative parameter of the biology of a lesion, as even benign lesions can have a volumetric increase (4). On the contrary, a retrospective study done at *Columbia University* showed that low growth rate lesions do not progress to metastatic disease (38).

Although it is a rare condition, adrenal heterotopia at the renal level presents itself as a contrast-enhancing neoplasm and therefore worthy of biopsy to avoid unnecessary surgery.

Certainly, in the presence of a lesion suspected of renal neoplasia, it is difficult to include within the differential diagnosis a condition with such a low incidence, but,the presence of endocrinological disorders, hypertension refractory to medical therapy can guide the differential diagnosis process. Other symptoms such as abdominal pain, appear to be of lesser help in the diagnostic phase as it is linked to the localization of the neoplasm and to its size and not to a peculiar characteristic of the adrenal anomaly. The main location of the adrenal fusion is at the level of the superior pole, and adrenal rest can also be present in the retroperitoneum adjacenct to the renal pelvis. However, in some cases, such as ours, the adrenal ecotopia can also be localized at the level of the lateral margin of the kidney.

This systematic review has intrinsic limitations such as the fact that it examines case series and case reports and the non-homogeneity of the cases taken into consideration. However, it underlines the main characteristics of the types of adrenal ectopic tissue in the kidney. The astute clinician should be cognizant of this condition in the evaluation of small renal masses due to its benign behavior, and its differentiation by renal cancer could require a renal biopsy because active surveillance is indicated in these patients.

Conclusions

The increase in the incidence of small renal masses due to the diffusion of radiological imaging has led to a better understanding of the behavior of these neoformations. Ectopic adrenal tissue in the kidney is a rare event with specific clinical characteristics which can clinically mimic a renal neoplasia and needs to be known in order to arrive at a correct diagnosis and carry out appropriate treatment management.

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