Computed Tomography Findings Used to Discriminate Between Atypical Renal Angiomyolipoma and Renal Cell Carcinoma

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ABSTRACT

Objective: Differentiate the atypical angiomyolipoma from the renal cell carcinoma of the same size by computed tomographic findings.

Introduction: A solid renal mass is a lesion without macroscopic fat that enhances regardless of its pattern. It is important to detect the malignant one and differentiate them from the benign one, especially when they are small. To maximize its detection and characterization, CT includes images obtained before and after the administration of intravenous contrast.

Materials and methods: A prospective study was carried out with 45 patients (7) with atypical angiomyolipomas and (38) with renal cell carcinoma, all cases had been nephrectomized (total or partial) for the resection of the lesion with subsequent evaluation of it in the pathology center, using three-phase computed tomography (phases without contrast, corticomedullary and early excretory) for renal cell carcinoma less than 50 mm. Two expert radiologists individually evaluate the characteristics of the tumor, its attenuation in phase without contrast and the characteristics of its enhancement to differentiate the atypical angiomyolipoma from renal cell carcinoma

Results: There was a predominance of women with atypical AML (57.1% of the total; n = 4) and of men with RCC (65.15%; n = 25), but no significant difference seen between them. Significant difference is seen between atypical AML and RCC regarding their contour (p-value = 0.043). In the post-contrast phase, atypical AMLs had a homogeneous distribution enhancement in 6 cases (85.7%) and a prolonged enhancement pattern over time in most of cases (71.4%, n= 5); regarding the RCCs presented heterogeneity in most of cases (92.1%, n= 35) and early wash out enhancement pattern in (81.6%, n= 31), with significant difference between them.

Conclusion: Three-phase helical CT is the standard modality for evaluate the SRM less than 50 mm. It serves to differentiate the Atypical AML from the RCC, with the more valuable tomographic findings are homogeneity and pattern of enhancement of renal mass.

Keywords: atypical AML, RCC, single renal mass.

INTRODUCTION

A solid renal mass (SRM) is a lesion without macroscopic fat, that enhances regardless of its pattern. It is important to detect the malignant one and differentiate them from the benign one, especially when they are small (Herts et al., 2002; Jinzaki et al., 2000; Ruppert-Kohlmayr et al., 2004). Computed tomography (CT) is the most sensitive technique in the distinction of subtypes of renal cell carcinoma (RCC) in large SRM and in the analysis of the small one. To date, enhancement patterns have not been rigorously evaluated to characterize malignant versus benign nature of a small SRM and the different RCC subtypes (Sheir et al., 2005; Zhang et al., 2007; Pierorazio et al, 2013). Although most SRM are RCC, 20-30% is benign. Therapeutic options for small MRS include close follow up, partial nephrectomy, or ablative surgeries (Kutikov et al., 2006; Campbell et al., 2006; Israel and Bosniak, 2008). To maximize its detection and characterization, CT includes images obtained before and after the administration of intravenous contrast (different phases), comparing their Hounsfield Units (HU). When there is a controversy about the degree of enhancement, a change of 20 HU or more constitutes a strong enhancement (Israel and Bosniak, 2005). Angiomyolipoma (AML) is the most common benign SRM of the kidney and occurs in 0.3-3% of the population. Corresponds to a hamartoma (ie, histologically normal tissues in location, but of abnormal proportions), composed by variable amounts of vascular, muscular tissue and lipid. The frequency of hemorrhage, necrosis, perirenal extension and myomatous pleomorphism can cause an erroneous anatomopathological diagnosis of malignancy (Kim et al.,2004; Simpfendorfer et al.,2009; Fernandez et al.,2009). There is typical and atypical AML, the first (or classic) represents the majority and is defined in a preoperative stage as AML with typical tomographic findings of fat (Milner et al., 2006). On the other hand, those with a minimum fatty component (Atypical AML) constitute an unusual manifestation (3-4.5%) and characterized by the absence of fat inside a lesion that enhances post intravenous contrast. Currently, the diagnosis of renal AML is made in non-invasive and precise way by CT, ultrasound (US) and magnetic resonance imaging (MRI) (Hafron et al., 2005). CT presents greater sensitivity in the detection of fat inside the AML for its

ability to discriminate small differences of density, as well as being useful for determining frequent complications, such as perirenal extension and hemorrhage. The CT appearance of AML depends largely of the type, reflecting variable pathological findings (Sheir et al., 2004). In some cases, SRM biopsy may be indicated (if any secondary imaging findings are present) to make a certain diagnosis and avoid surgery (Silverman et al., 2006; Silverman, et al., 2007). With regard to RCC, it represents almost 3% of solid tumors. Most SRM with enhancement found by means of imaging corresponds to RCC, being less common than benign entities, such as oncocytomas and Atypical AML. Among the subtypes (clear cells, papillary, and chromophobe), the clear cell RCC is the most common in adults (70%), and each one has its implications in the treatment and prognosis (Eble et al.,2004; Vikram et al.,2009; Prasad et al.,2006; Cheville et al.,2003). Given the technological advances, particularly in the multidetector helical CT (MDCT), in recent years has been have more frequently detected small SRM (<3 cm in diameter) and very small (<1.5 cm) (Yoshimitsu et al., 2004) It is currently known that 20% of all small, reinforcing SRM are benign and that the size of the tumor alone is not enough information to decide treatment (Millet et al., 2011). The objective of our study is to differentiate between atypical AML and RCC of the same size using computed tomography.

MATERIALS AND METHODS

A prospective study was conducted between February 2018 and January 2020 in the Radiology department of Imam Hussein teaching hospital in Nasiriya city/Iraq. Patient of both sexes were referred from Urology department with preoperative diagnosis of RCC of size less than 50 mm, diagnosed using MDCT in our center. All the cases had a nephrectomy (total or partial) for the resection of the lesion with subsequent evaluation of it in the pathology center. Tumors up to 50 mm in diameter were assessed to compare the two types of lesions of similar size. In our study we exclude patients with single-phase MDCT, CT performed in another center of images, CT that could not be recovered in digital files, and typical AML diagnosed prospectively in MDCT based on the intratumoral fat content. Multiphasic CT scans were performed with Toshiba Aquilion (64 slices) under the study protocol of the center, consisting of phases without contrast material, then patients received 50-100 ml of non-ionic water-soluble low osmolarity iodine contrast (Iohexol) intravenously, the corticomedullary phase (whose differentiation was also happens at 20-30 s after contrast), the nephrographic (whose maximum enhancement with homogeneous nephrogram is at 60- 80 s postcontrast) and the early excretory (which begins at 120 s after injection of the contrast.

All the images were analyzed by two senior radiologists with experience in renal CT. First, each specialist visually evaluated the images of the lesions in non-contrast phase to determine if any tumor presented areas of low attenuation, associated with an attenuation value negative due to the presence of fat inside the lesion. The tissue was considered fat when it had the same density of the subcutaneous or retroperitoneal fatty tissue or objectively by measuring its density. A work station was used to calculate the diameter of the tumor and assess the attenuation in the region of interest (ROI) through the available measurement tools.

In each tumor, two features were analyzed: its general characteristics, its attenuation in pre and post- contrast phases. Regarding its general characteristics, they were determined in nephrographic phase: its margin (smooth or irregular), the location from the center (extracapsular, with at least 75% of the tumor center located outside the renal contour; or intracapsular, with the tumor center located 50% or more below the renal contour), intratumoral calcification (presence or absence) and perirenal changes (presence or absence; that is, perinephric soft tissue stranding and thickening of the Gerota fascia). The attenuation of the tumor in non-contrast phase was estimated subjectively, and was compared with that of the surrounding renal parenchyma. It was classified as hypoattenuation (if it was lower to the adjacent renal parenchyma), as isoattenuation (when it was similar) and as hyperatenuation (if it was higher). Finally, the characteristics of the tumor enhancement, defined significant if there is an increase in the attenuation of more than 20 UH, They included:

- Tumor enhancement distribution: homogeneous (when the Most areas showed uniform enhancement in the corticomedullary phase and in the early excretory phase) or heterogeneous (if non-uniform). If the attenuation was heterogeneous, it was assessed subjectively using the zone with the highest attenuation for classification..
- Pattern of enhancement in time: lesional behavior of the intravenous iodinated contrast. This was subclassified as:
  - Early washout: when the tumor showed a peak of enhancement in the corticomedullary phase and then had a washing at least 20 UH in the early excretory phase.
  - Gradual: when the value of tumor attenuation in the early excretory phase was at least 20 UH more of what it was in the corticomedullary phase.
  - Prolonged: when the difference between the values of attenuation of the corticomedullary phase tumor and the early excretory oscillated between -20 and 20 UH.
- Degree of tumor enhancement in the corticomedullary phase and early excretory phase in HU. The difference in the average attenuation values between the images without and with contrast. For its analysis, a round ROI was used, of at least 1 cm2, with identical location and size in the three phases of examination. To minimize the volume partial averaged with the surrounding renal parenchyma, the ROI was placed near the center of the tumor. CT scans showing the largest surfaces of the lesion and the renal parenchyma were selected, and the largest possible region of interest was obtained in these.

The ideal location of the ROI was agreed, according to the homogeneity or heterogeneity of the tumor. In the first case, it selected a solid area of enhancement in the corticomedullary phase, while in heterogeneous lesions, as there are multiple areas of enhancement, the greatest possible number of suspicious portions was included within the ROI (areas of enhancement greater than 1 cm in

diameter on the short axis) and at least three regions of interest were analyzed for each phase to ensure the presence of unequivocal enhancement and then calculate the average values. An attempt was made to include the greatest amount of enhancement area in the ROI and to exclude the surrounding renal parenchyma and any intratumoral areas with cystic degeneration or calcification.

Statistical analysis was performed using IBM SPSS v 23.0 software. The paired t- test and correlation coefficients were calculated. In all tests, p values of ≤ 0.05 were considered significant.

RESULTS

45 adults with renal masses less than 50 mm in diameter (average: 33 mm; range: 13-50 mm) were found, diagnosed by MDCT as RCC. Of the total, 28 were men (62.2%) and 17 women (37.8%). Histopathology diagnosed 7 atypical AMLs (15.5%) and 38 RCC (84.5%). There was a predominance of women with atypical AML (57.1% of the total; n = 4) and of men with RCC (65.15%; n = 25), but no significant difference seen between them (Figure 1). Patients age is between 28 and 76 years (mean: 52 years). All atypical AMLs showed smooth contours (100%), intratumoral calcifications (28.57%, n=2), intracapsular location (71.42%, n= 5) and absence of perirenal changes (85.7%, n= 6); at the same time that the majority of the RCC revealed irregular contours (79%, n=30), extracapsular location (68,4%, n=26), presence of perirenal changes (86.84%, n=33) and absence of intratumoral calcifications (92.1%, n= 35). Significant difference is only seen between atypical AML and RCC regarding their contour (p-value = 0.043) (Table 1).

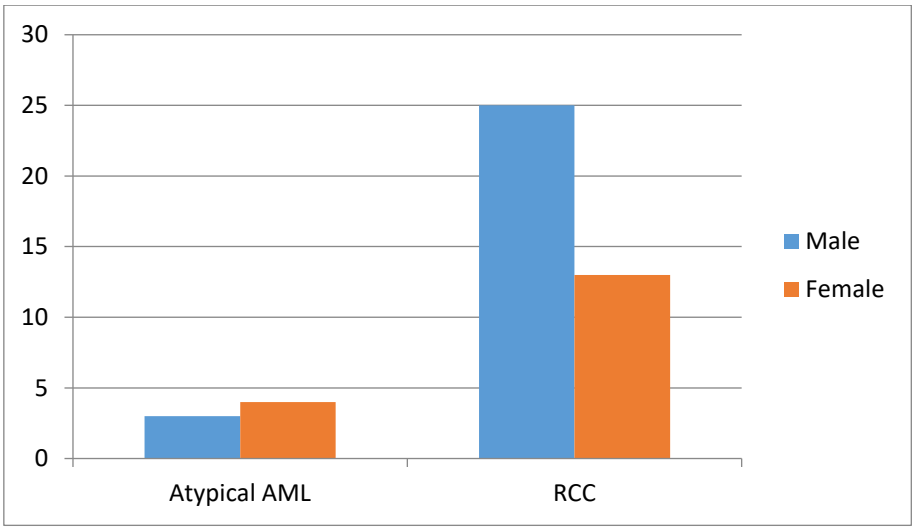

Figure 1: Gender distribution for both atypical AML and RCC

Table 1: Shows general characteristics of atypical AML and RCC

	Number	Gender		Contour		Calcification	Location		Perirenal fat stranding
		Male	Female	Smooth	Irregular		Intracapsular	Extracapsular	
Atypical AML	7 (15.5%)	3 (42.9%)	4 (57.1%)	7 (100%)	0	2 (28.57%)	5 (71.4%)	2 (28.6%)	1 (14.3%)
RCC	38 (84.5%)	25 (65.8%)	13 (34.2%)	8 (21%)	30 (79%)	3 (7.9%)	12 (31.6%)	26 (68.4)	33 (86.845)
P-value	0.12	0.5		0.043		0.47	0.1		0.2

In the non-contrast phase, the atypical AMLs were hyperdense in 2 cases (28.6%), isodense in 4 cases (57.1%), and hypodense in 1 case (14.3%); and the RCCs were hyperdense in 5 cases (13.2%), isodense in 21 cases (55.3%), and hypodense in 12 cases (31.6%). On the other hand, in the post-contrast phase, atypical AMLs had a homogeneous distribution enhancement in 6 cases (85.7%) and heterogeneous enhancement in 1 case (14.3%), and a prolonged enhancement pattern over time in most of cases (71.4%, n= 5), while 1 case shows early washout and 1 case shows gradual enhancement ; regarding the RCCs presented heterogeneity in most of cases (92.1%, n= 35) and homogenous in only 3 cases (7.9%), most of RCCs show early wash out enhancement pattern in (81.6%, n= 31), while gradual enhancement in 5 cases (13.1%) and prolonged enhancement only in 1 case (5.3 %). Significant difference between atypical AML and RCC was seen in postcontrast enhancement pattern and homogeneity (Table 2) (Figure 4-7).

Table 2: Shows patters of post contrast enhancement of atypical AML and RCC

	Pre contrast density			Post contrast enhancement		Pattern of enhancement		
	Hyperdense	Isodense	Hypodense	Homogeneous	Heterogeneous	Early washout	Gradual	Prolonged
Atypical AML	2 (28.6%)	4 (57.1%)	1 (14.3%)	6 (85.7%)	1 (14.3%)	1 (14.3%)	1 (14.3%)	5 (71.4%)
RCC	5 (13.1%)	21 (55.3%)	12 (31.6%)	3 (7.9%)	35 (92.1%)	31 (81.6%)	5 (13.1%)	2 (5.3%)
P-value	0.12			0.02		0.05		

For atypical AMLs, the mean value of tumor attenuation in the phase without contrast was 32 HU (range: 20-44 HU), in the corticomedullary phase of 61 HU (range: 45-72 UH), and in the early excretory phase of 73 HU (range: 48-89 HU). Regarding the RCC, these had an average value of tumor attenuation in the phase without contrast of 36 HU (range: 28-49 UH), in the corticomedullary phase of 98 UH (range: 79-140 HU) and in the early excretory phase of 68 HU (range: 55-101 UH). (Figure 2)

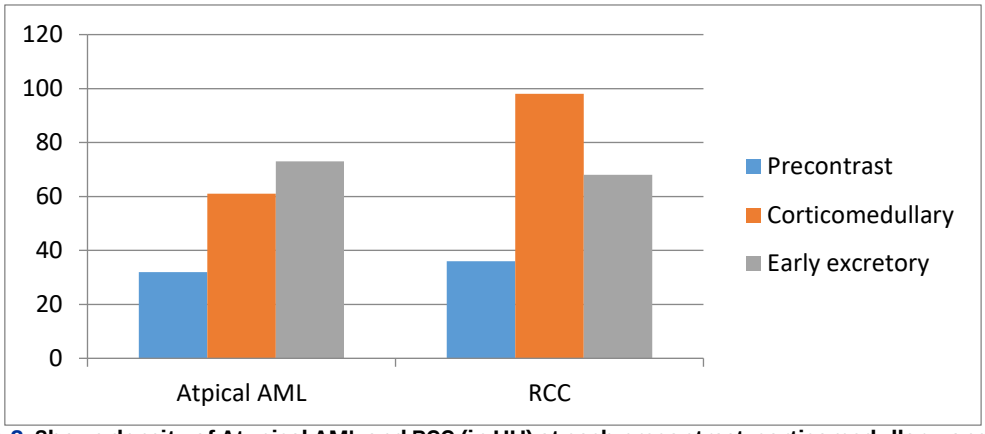

Figure 2: Shows density of Atypical AML and RCC (in HU) at each precontrast, corticomedullary, and early postcontrast excretory phases

On histological examination: of the 38 cases of RCCs, 30 (78.9%) were clear cell RCC, while the remaining 8 (21.1%) were found to be papillary RCC. (Figure 3)

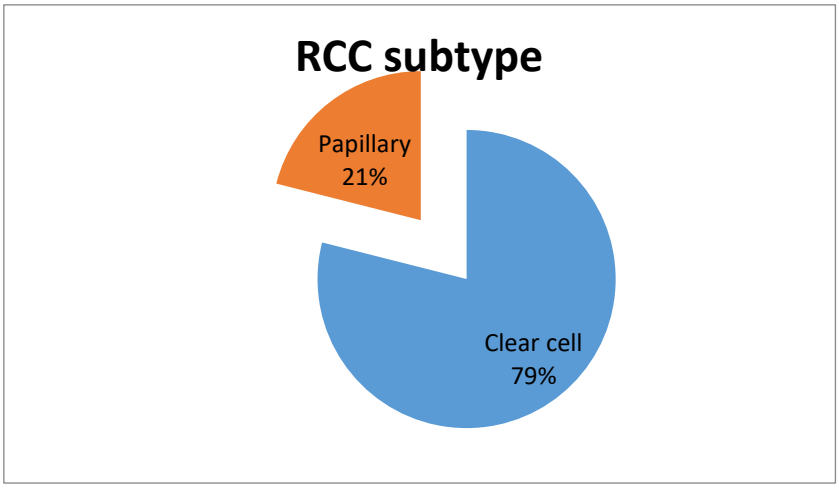

Figure 3: Shows percentage of each subtype of RCC on histopathology

DISCUSSION

Renal parenchymal tumors are a group of lesions which vary from benign to very aggressive. In consequence, its morphological characteristics and the degree and pattern of enhancement vary significantly according to architecture and the subtype. Therefore, the characterization of renal parenchymal tumors using imaging techniques raises its difficulties (Choi et al., 2012). Although it is important to differentiate in the pre-surgical stage an SRM to plan the treatment and advise the patient, there are no well-established imaging criteria to classify its histological subtypes. Thus, the diagnosis defined based on the results of the biopsy is a challenge, as it can be difficult to distinguish a RCC from an oncocytoma or a RCC with sarcomatoid component with an atypical AML (Zhang et al., 2007). In

one study, 6.9% of patients undergoing partial nephrectomy for suspected CCR with an average diameter of 2.3 cm (range: 1.2 - 4.3 cm) had pathological confirmation of AML (Simpfendorfer et al., 2009). This entity represents 1% of all renal tumors that are surgically explored. They occur isolated or associated with tuberous sclerosis, and can be found incidentally in US or CT, or presenting with chronic pain, acute retroperitoneal hemorrhage, shock, palpable mass or hematuria (Fernandez et al., 2009). In the US they are round or oval lesions, well circumscribed and hyperechoic. With regarding the renal sinus, typical AML are hyperechogenic, while the atypical ones present homogeneous isoechogenicity, so it should be considered as diagnostic differential to the RCC. While it is very suggestive of AML, hyperechogenicity of an intrarenal mass is not pathognomonic, so the CT must confirm the presence of fat and excludea potentially curable RCC (Kim et al., 2004; Milner et al.,2006). Regarding CT, the typical AML has enough fat to be recognized and, in general, the RCC can be excluded. In phase without contrast it is a hypodense SRM characterized by the presence of macroscopic fat (similar to normal subcutaneous or retroperitoneal fat) with attenuation values negative (between -10 and -120 UH), and within it are interspersed elements of soft tissue density in the form of striations, which represent smooth muscle, blood vessels or hemorrhages. Some authors consider that CT absolute values are relatively reliable although it may be affected by factors, such as parameters of analysis (kilovolts and milliamperes), ROI orientation and CT values of the surrounding tissues. In the postcontrast phases, these lesions show enhancement (Israel et al., 2005; Kim et al.,2004; Neville et al.,2011). Likewise, atypical AML are difficult to diagnose because CT doesn't demonstrate intratumoral fat (for lack of macroscopic fat or presence of minimum quantities), besides that they are indistinguishable from other neoplasms kidney disease (including RCC), leading to unnecessary surgery with subsequent histopathological diagnosis of atypical AML. Some studies show that in the precontrast phase CT atypical AML are always hyperdense in relation to the renal parenchyma, while postcontrast show a homogeneous enhancement and prolonged, which evidences large vascular components or relevant fibromuscular contents; or on the contrary reveal mild enhancement, in proportion to the accumulation of fat and minorization of the vessel pattern (all nonspecific findings for an accurate diagnosis of atypical AML). Fat is not detectable in axial images may be hidden by the intratumoral hemorrhage, be composed mainly by muscular, vascular or immature fatty tissue, or by the dispersion of a small amount of fat inside other components. The radiologist's most important role is to differentiate the RCC entity and other malignancies through CT, non-invasively and accurately, being vital to determine the therapeutic strategies, since in the asymptomatic AML behavior is conservative (observation) especially for smaller lesions, while in the RCC, according to its size and location, the management is surgical (radical or partial nephrectomy) or proceeds to angiographic embolization (Obuz et al.,2000; Zagoria, et al.,2000). In MRI, the typical AML is hyperintense in precontrast T1 weighted for its fatty component, with similar signal to perirenal fat in T2 weighted sequences in; While that the atypical ones are hypointense in T2 weighted images with remarkable focal or diffuse decrease in signal strength in the opposite phases. This does not indicate necessarily an AML, since some RCCs can also show these characteristics due to the presence of abundant microscopic fat (Pierorazio et al., 2013; Silverman et al.,2007; Yoshimitsu et al.,2004). Anyway, there are some imaging peculiarities that differentiate to the RCC from the AML both in precontrast and postcontrast phases. In multiple works the scarcity or absence of fat was verified in certain AML defined histologically, so that these authors recommend that, given the suspicion of a small amount of fat in an SRM, the CT is used adapting the collimation and the advance of the table to obtain an effective cutting thickness (1.5-5 mm). In this regard, some propose to register in the precontrast stage the value of attenuation (HU sampling by ROI) if necessary, while others suggest a multiphase study for the detection (Hosokawa et al., 2002). Jinzaki M. et al. (Jinzaki et al., 2014) determined that a negative attenuation coefficient is characteristic of renal AML with mature adipose elements, while a positive, despite being suggestive of RCC, can also be found in AML with a small amount of mature fat or a high proportion of immature fat. To identify the latter, the CT has a relative disability, so it may be a limitation for the preoperative diagnosis of AML. The positive attenuation coefficient of the atypical AML can be explained if the fraction of fat is considered between 5-15% of the total amount of the tumor and / or increase the proportion of immature adipocytes with respect to mature adipocytes. In this regard, Winkler considers that a fat fraction greater than 50% allows a diagnosis reliable of typical AML (Garant et al., 1998). Regarding the precontrast phase, in our study was found no significant tomographic finding regarding density of tumor attenuation, which were isodense for both atypical AML and RCC (Table 2). The tumor enhancement between AML and CCR has also been compared. With respect to the utility of the phases in the detection of SRM, this varies according to the different authors. For some, the nephrographic is superior by the maximum enhancement and homogenous of the parenchyma, while this is more difficult in the corticomedullary and the early excretory phases (Suarez-Ibarrola et al.,2020). Others, such as Smith et al., detected 20-30% more SRM using the early excretory phase than using the corticomedullary phase; but one review found the sensitivity is comparable in the detection of SRM both in the corticomedullary as in the early excretory phase (Garant et al.,1998). In this regard, Cohan et al (1995) detected 1.5 times more SRM, when interpreting together the images in phase without contrast and in nephrographic phase than those in phase without contrast and corticomedullary phase. As for Millet et al. (2011), they determined the absence of useful tomographic, morphological or enhancement criteria to differentiate small malignant and benign SRM. There are also discrepancies regarding the attenuation value and the enhancement pattern to differentiate these tumors. In our experience, the significant tomographic finding was the pattern of homogeneity and prolonged enhancement over time for

atypical AML, while heterogeneity and early washout enhancement in RCCs, in agreement with Kim et al. (2002).

In the work of Hosokawa et al (2002), hyperdense renal tumors in precontrast phase, with moderate enhancement and without showing a fatty component, suggested an atypical AML, which is not comparable with our study which reveals that most cases are isodense to renal parenchyma for both atypical AML and RCC; while Pierorazio et al (2013) determined that a small SRM with high and early enhancement is more likely to be a RCCs than an oncocytoma, or an AML, which is comparable with our study. On the other hand also our study is comparable with that of Bird et al. (34) which demonstrated that the RCC showed a high wash out of 50%.

In our work all the atypical AML showed smooth contours, while most of cases (79%) of RCC showed irregular contour and there was a significant difference between the two entities. Also most cases of atypical show intracapsular localization, absence of perirenal changes, while most of the RCCs revealed extracapsular localization and presence of perirenal changes which is comparable to results of (Alshumrani et al.,2009; Hrescak et al.,2016)

We have some limitations in our work including small number of atypical AML which is already is a rare entity, also choosing a small size of the mass limit the number of the studies cases (Kim et al.,2004; Milner et al.,2006).

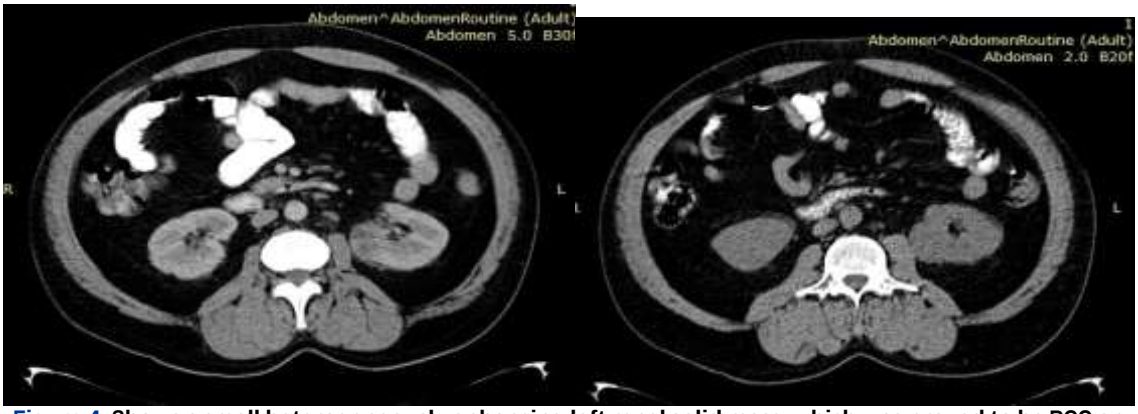

Figure 4: Shows a small heterogeneously enhancing left renal solid mass, which was proved to be RCC on histopathology

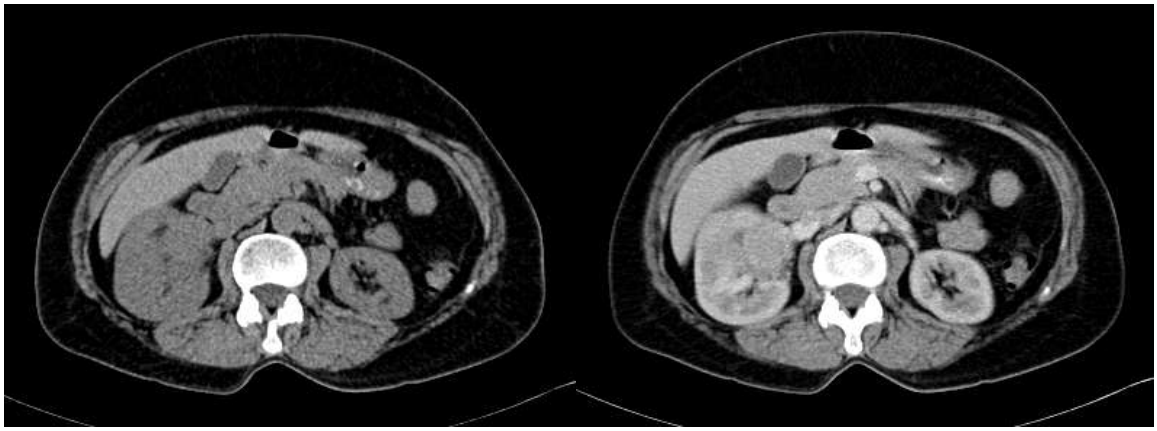

Figure 5: Shows a small homogeneously enhancing right renal solid mass, which was proved to be atypical AML on histopathology

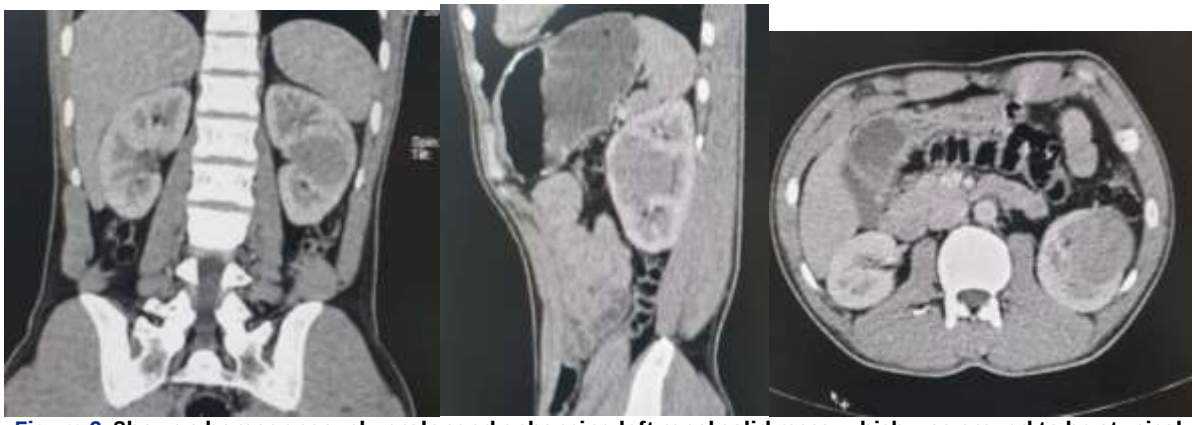

Figure 6: Shows a homogeneously prolonged enhancing left renal solid mass, which was proved to be atypical AML on histopathology

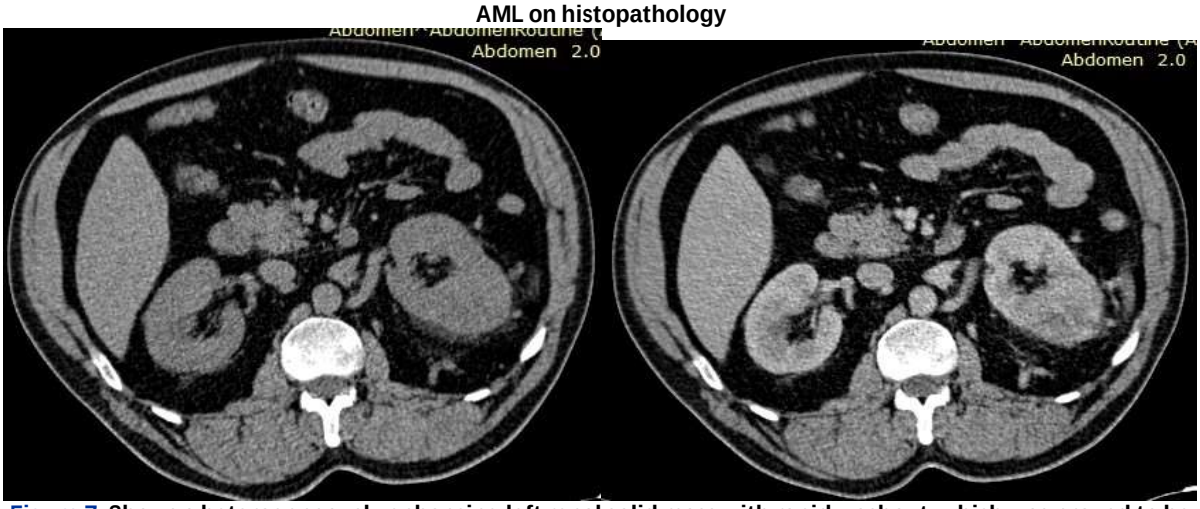

Figure 7: Shows a heterogeneously enhancing left renal solid mass with rapid washout, which was proved to be RCC on histopathology

CONCLUSION

Three-phase helical CT is the standard modality for evaluate the SRM less than 50 mm. It serves to differentiate the Atypical AML from the RCC, with the more valuable tomographic findings are homogeneity and pattern of enhancement of renal mass. However, future studies should include larger populations, involving other imaging modalities for diagnosis like ultrasonography or MRI.

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