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RESEARCH ARTICLE

DIFFERENTIATION OF RENAL AML (ANGIOMYOLIPOMA) WITH MINIMAL FAT FROM RCC (RENAL CELL CARCINOMA) BY ANALYSIS ON CT IMAGES.

Munezero Champion, Prof Deng Gang, Dipsundar Limbu, Suman Rouniyar and Kwizera Ghyslaine.
Center of Interventional Radiology and Vascular Surgery, Department of Radiology, ZhongDa Hospital.

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Abstract

Introduction:-

Angiomyolipomas (AMLs) belong to a group of tumors broadly referred to as neoplasms with perivascular epithelioid differentiation, which were previously called perivascular epithelioid cell tumors and are now referred to as PE-Comas [1] . These tumors arise by clonal proliferation of epithelioid cells distributed around blood vessels. Renal AMLs may appear in connection with tuberous sclerosis complex (TSC) or pulmonary lymphangioleiomyomatosis (LAM) or arise as occasional finding among subjects who have neither TSC nor pulmonary LAM [2] .

AML characteristically expresses melanocytic markers including HMB-45 and Melan-A. The availability of melanocytic markers to diagnose AML produced more precise categorization of tumors of exceptional histology that previously may have been miscategorized [3] . Monophasic AMLs contrast histologically from triphasic AMLs in that they are made of predominantly or completely of 1 component some of which are smooth muscle or fat. The epithelioid variant of AML is distinguished from classic AML by the presence of an epithelioid characteristic. These tumors have been reported to exhibit a tendency toward malignant conversion and infrequently are reported to metastasize [4] .

Renal AML is a relatively rare neoplasm that is encountered in less than 0.2% of the public. Histo-pathologically renal AML is normally made of variable amounts of smooth muscle cells, malformed blood vessels and adipose tissue [5] . Typical AML is radiologically diagnosed by detecting a renal mass that contain a low attenuation component which is consistent with fat on CT or MR imaging. Although the manifestation of fat is characteristic of AML, many pathologically proven AMLs are not suspected on preoperative imaging because of an absence of radiographically evident fat due to the fact that they have only microscopically visible fat hence the designated name fat poor AML. In these fat poor AMLs, the histological reports are generally common and clinical outcomes in patients with fat poor AMLs have been proven to be excellent in considerable small series [6] .

The preoperative radiological diagnosis of AMLs with unusual histological features present a diagnostic problem because atypical or “fat poor” AML share many overlapping imaging characteristics with RCC

Corresponding Author:- Munezero Champion.
Address:-Center of Interventional Radiology and Vascular Surgery, Department of Radiology, ZhongDa Hospital.

Diagnosis:-
Various imaging modalities have been used to identify characteristic findings of fat-poor AML; these include sonography, CT, and MRI. Because of the importance of CT in clinical practice in the evaluation of renal masses, our focus will be mostly directed on CT scan. CT is one of the commodity mostly used in diagnosis of renal masses. A CT image eliminates the overlapping structures and make the internal anatomy more apparent, which allow radiologists to identify internal organs, their shape, size, density, texture and other characteristics.

Classic Renal angiomolipomas are composed of proliferation of blood vessels, adipose tissue and smooth muscle. Simple evaluation of attenuation is used in diagnosing classic renal AML by detecting visible or macroscopic fat within the mass. Malignant renal tumors that contained fat have been published in case reports though all of these had areas of calcification [7] . Studies done by Bosniak et al have shown that a threshold attenuation of -10 HU is considered specific for the presence of fat cells and therefore diagnostic of AML [1] . However, in approximately 5% of the cases, there are kinds of angiomyolipoma known as fat poor angiomyolipoma who are not detected with conventional imaging techniques because they contain only a microscopically detectable amount of fat and therefore their intra-tumoral fat are too small to be detected on CT images, even with the use of thin (1.5–3 mm) sections and their appearance on non-contrast CT will mimic RCC [8].

Fat poor AML can be divided into 3 subtypes: Hyper-attenuating AML, iso-attenuating AML and epithelioid AML [4] .

Classification Of Fat Poor Renal Angiomyolipoma:-

Hyper-attenuating AML:-
With an average of 3 cm in diameter, hyperattenuating AMLs are naturally small [9, 10] . On CT, they are diagnosed by identifying a portion of the mass with an attenuation of 45 HU or more which is indicative of smooth muscle [2] . At pathology, these AML consist mostly of smooth muscle components and scanty to no amount of fat cells, with the tumor cells staining positively for HMB-45 [10] .

Iso-attenuating AML:-
At unenhanced CT, Iso-attenuating AML contain CT attenuation close to renal parenchyma that range from -10 to 45 HU. This subtype of fat-poor AML is very rare and no specific feature that differentiate them from RCC is fully known. Differentiation from RCC is problematic as they have similar attenuation and enhancement at CT. Several investigations have been attempted to differentiate iso-attenuating AMLs from RCC using different quantitative feature analysis, with iso-attenuating angiomyolipoma exhibiting a greater quantitative area of negative CT attenuation compared to RCC [11, 12] . Pathologically, they generally contain few but diffuse and scattered fat cells among the smooth-muscle and vessel components hence their iso-attenuating appearance on unenhanced CT [13] .

Epithelioid AML:-
Epithelioid angiomyolipoma is an another extremely rare subtype with an unknown etiology. It is characterized by numerous atypical epithelioid muscle cells and less or no adipose tissue. [14-16] . The expression of the P53, TSC1, and TSC2 differentiate the epithelioid AML from other fat poor AML. In contrast with other AML, the epithelioid AML is potentially malignant and can be locally aggressive however no histological criteria of malignancy have been made so far with only some metastasizes accepted as a definite sign of malignancy [17] . Radiologically, epithelioid angiomyolipomas generally present as large masses of soft tissue lesion with higher density than normal parenchyma, intra-tumoral hemorrhage and necrosis [18, 19] . The enhancement pattern of most epithelioid angiomyolipomas include: hyperattenuating on unenhanced CT (typically more than 45 HU), rapid wash in and slow wash out. Differentiation of the epithelioid AML from RCC preoperatively may not be crucial as both lesions treatments remained surgical resection. However, some studies have reported treatment with mTOR inhibitors, such as sirolimus or temsirolimus may represent an effective treatment option against epithelioid angiomyolipoma [20, 21] . For that reason, the pre-operative diagnosis of EAML may become important in the future.

Ct Scan Imaging Pattern Of Fat Poor Angiomyolipoma:-
Non-contrast CT:-
Renal AML can be single, multiple or associated with TSC [4] . Fat poor AML is similar to RCC radiographically due to the lack or very few amount of lipid component and may result in radiographic misdiagnosis. Differentiation of fat poor AML from RCC have been a very challenging task with different patterns of enhancement being

analyzed to distinguish the two entities. Unenhanced CT lesion attenuation has been proposed as diagnostic features of fat poor angiomyolipoma with promising initial results criteria. In previous studies, nearly all cases of AML with minimal fat showed homogeneously high attenuation on unenhanced CT scans [2, 22, 23] . However, Kim et al [6] reported that tumor attenuation on unenhanced CT scans may vary with both AML and RCC showing hyper-attenuation. In his study, high attenuation was found in 53% of AMLs with minimal fat and 22% of RCCs respectively. These results imply that tumor attenuation on unenhanced scans may vary, reason why high tumor attenuation on unenhanced scans should not be used as a definitive finding for AML with minimal fat. Yang et al categorized lipid-poor AML based on homogeneity with a homogeneous enhancement pattern for fat poor AML and a heterogeneous enhancement pattern for clear-cell RCC [3] nevertheless the majority of chromophobe RCC and papillary RCC tumors revealed a homogeneous pattern [2, 6] . Calcification was also another criteria used to differentiate fat poor AML from RCC in non-contrast CT as intra-tumoral calcification is a common finding in RCCs and may be seen in about 30% of cases [11] , whereas it is rare in AML [5, 24] . Yang et al examined morphologic appearance with potential significance in differentiating AML from RCC and found that hypodense rim (low density rim at the peripheral area of a tumor) had a high positive predict value (PPV) and specificity for the diagnosis of fat poor AML [6] . However, a study conducted by Schieda Et al concluded that there is no histologic basis for a predominance of fat in poor-fat angiomyolipoma to be located at the periphery of the lesion. [25] .

Different types of CT scans have been used to improve the detection of fat in small renal masses to allow more diagnosis of angiomyolipomas. In practice, conventional CT and helical CT are used to diagnose small renal masses and a density of ≤ -10 unit is diagnostic of AML on unenhanced CT. However, helical CT yields better results for AML which attenuation value differ by more than 6 HU [1, 26] . In addition, helical CT is more sensitive in revealing fat in masses less than 2cm with a sensitivity of 86%.

Various region of interest (ROI) and pixel mapping threshold have been proposed for the CT diagnosis of AML with some disagreements over the optimum threshold value [27] . E Simpson et al compared the accuracy of the various threshold values of ROI versus pixel mapping in diagnosing lipid poor AML and reported a threshold unit of -10 or less being the most accurate with a high specificity but a modest sensitivity of 100% and 73% respectively for ROI but a high sensitivity of 86% for pixel mapping [27]. However, even with pixel mapping and ROI criteria some proven AMLs could not be identified on imaging. One approach to these suspected fat less AML on both ROI assessment and pixel mapping was to follow up the growth rate. RCCs (or at least the clinically aggressive RCCs) are distinguished by a more rapid growth rate compared with AMLs. [28]

Another method used for diagnosis of fat poor AML is CT histogram analysis. Kim et al evaluated the diagnostic performance of CT histogram analysis by comparing the percentages of voxels and pixels according to the CT number categories and reported that AML had significant greater percentages of voxels and pixels with a CT number ≥ -30 HU, ≥-20 HU, ≥-10 HU and ≥0 HU compared to RCC with a high specificity of 100%. [12]

Contrast CT:-

Tumor enhancement pattern have been used to distinguish fat poor AML from RCC, since most RCC show early enhancement and rapid wash out [9] , gradual, or prolonged enhancement on CT have been suggested for differentiating fat poor angiomyolipoma from RCC with a positive and negative predictive values of 91% and 87% respectively [11] . However, K Sasiwimonphan et al maintained that most angiomyolipomas show an arterial to-delayed enhancement ratio greater than 1.5 [29] .

Lipid-poor AMLs show entirely high attenuation on unenhanced CT and moderate and homogeneous enhancement in the nephrographic phase. However, partially high attenuation area is not uncommon for RCC reason why, partially high attenuation mass may not be suggestive of AML [30] .

Biphasic CT contrast can be used to differentiate fat poor AML from RCC, using this technique, fat poor AML showed higher tumor attenuation than normal renal parenchyma on unenhanced CT and moderate and homogeneous enhancement on nephrographic phase whereas RCC showed a higher degree of enhancement on nephrographic phase. These features had a positive predictive value of 91% and a negative predictive value of 87% [6] .

In the study by Kim et al 2013, an MDCT based scoring system was used to differentiate fpAML from RCC [31] . Among the different MDCT and clinical findings, the ratio of long-to-short axis diameter was the most significant in differentiating fpAML from RCC with fpAML showing greater ratio than malignant RCCs. Female predominance

were also significant findings favoring fat poor AML over RCC. Female predominance of AML is suggested to have genetic background [32, 33] .

Morphologic analysis with CT have been used to help differentiate fat poor AML from RCC. Reportedly, the prevalence of RCC is much higher than that of fat poor AML in patients with a small renal mass [29, 34] . In a recent study conducted by Kim et all 2017 [35] , predictive values of CT parameters have been analyzed with both angular interface (narrow, angular configuration within the renal parenchyma) and overflowing beer sign (certain degree of free extension of bulging-out portion along the renal surface) as the independent parameters in differentiating fat poor AML from RCC with overflowing beer sign to be a more specific biomarker imaging of fat poor AML whereas absence of both angular interface and overflowing beer sign on contrast-enhanced CT being more likely suggestive of RCC than fat poor AML.

Treatments:-

Indication of treatment:-

Radiographic size and associated clinical symptoms determine the diagnosis and treatment of renal AMLs. When a mass is large and asymptomatic, active surveillance should be encouraged [36] . However, when a mass reach more than 8 cm in size treatment should be performed even in the absence of symptoms [37] .

The recommendations of treatment of an AML are based on the patient's symptoms or the size of the lesions with hemorrhage, pain or reduction of mass effect as the main indications for treatment. Several studies have suggested 4 cm as the limit above which elective treatment of an AML should be considered due to their high predisposition of hemorrhage, pain and hematuria [37] . Asymptomatic AMLs of 4 cm or less should be observed every 12 months with ultrasound [38] . Recent literature implies that although tumour size is important, size of associated aneurysms may be more significant. Yamakado et al. reported a significant association between tumour size and aneurysm size with rupture. Using aneurysm size of 5 mm as a predictor of rupture, the sensitivity and specificity were of 100% and 86% respectively compared to 100% and 38% respectively when only tumor size was considered [24] .

Surgery and embolization are the 2 mainstays treatment for AML. Nephrectomy and partial nephrectomy have been used as first line treatment of renal AML because of the rare recurrent rates after surgery compared to renal angioembolization which has a high recurrence of repeat procedures. However, renal embolization has the advantage of maintaining maximal renal function and is a less invasive treatment option with a very short hospital stay of less than 24 hours compared to 2 days and more for surgery.

U. Rimon et al adopted a grading system for renal AMLs of 4cm and more to classify them according to their angiogenic component and assess their eligibility of treatment with embolization. In their series, grade 1 tumor which are tumors with only minimal angiogenic components were not indicated for prophylactic treatment, whereas for grade 2 and grade 3 tumors which are tumors of moderate and marked vascularity respectively, prophylactic treatments and surveillance were highly suggested [39] .

Conclusion:-

Renal AML can be encountered as single or multiple masses or present in association with TSC. Fat poor AML is hard to distinguish from RCC on CT considering their similarities on CT scan images. When evaluating patients with atypical renal masses, a thorough analysis of all available radiographic information by the managing physician is of great importance.

There are several key imaging features in CT to assist in distinguishing fat poor AML from RCC. Moreover, it is advised to consult radiology professionals/colleagues/expert about these miscellaneous parameters to gain additional insight. Fat poor AML will always present a difficult problem in preoperative diagnosis; however, this should improve with an increased refinement in radiological scanning and will minimize unexpected surgical resection of fat poor AML in most cases.

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