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Case Report

Metastatic Renal Epithelioid Angiomyolipoma: An Interesting and Rare Case Report

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Abstract

Angiomyolipomas are the most common clonal mesenchymal tumors of the kidney. Metastatic renal epithelioid angiomyolipomas (MREA) are a less common variant that are found to have malignant potential. We present a case of a 59-year old female diagnosed and treated for MREA which was initially thought to be a benign renal mass. The patient was being followed with serial abdominal imaging which showed subsequent development of two large abdominal masses. Appropriate surgical intervention was performed, the patient tolerated the procedure with minimal complications, and the post-operative microscopic evaluation of biopsied specimens confirmed the diagnosis of MREA. Unlike commonly benign renal angiomyolipomas, MREA is a highly aggressive lesion. It is imperative for clinicians to identify and differentiate this life-threatening lesion from renal cell carcinoma (RCC). A multimodality treatment approach including resection of tumor and adjuvant therapy may provide optimum treatment for MREA.

Keywords: Renal Cell Carcinoma (RCC); Metastatic Renal Epithelioid Angiomyolipomas (MREA); Carcinoembryonic Antigen (CEA)

Introduction

Renal angiomyolipomas (AML) are the most common clonal mesenchymal tumors of the kidney and account for approximately 1% of all renal tumors [1]. Classic renal angiomyolipoma is a benign mesenchymal tumor containing adipose, smooth muscle cells and thick-walled vasculature [1]. In 80% of cases, AMLs are found to be sporadic, but in the remainder of cases they can be associated with tuberous sclerosis [2]. Renal epithelioid angiomyolipomas, described initially in 1998 by Pea., *et al*. are predominantly composed of epithelioid cells in the absence of both adipocytes and abnormal vessels. With this epithelioid variant being adipose poor, identification on imaging can present some challenges. Unlike the classic AML, the epithelioid variant is a rare variant that has the potential to undergo malignant transformation [1]. The epithelioid variant is defined by the 2004 World Health Organization (WHO) Classification of Renal Neoplasms as a potentially malignant neoplasm, characterized by a proliferation of predominantly epithelioid cells, with approximately one third of patients experiencing local or distant metastases [3]. In order to add to the literature, we report our experience of diagnosing and treating a 59-year-old female with metastatic renal epithelioid angiomyolipoma (MREA) who was initially thought to have a benign renal mass.

Case Details

A 59- year-old female, who previously underwent surgical intervention for a mass involving the left kidney, with surgical pathology demonstrating AML, was being followed by a medical oncologist, who had been obtaining routine serial abdominal imaging. No symptoms were present at that time, but serial imaging showed subsequent development of two large abdominal masses. The largest mass measuring 8.1 cm was located between the left lobe of the liver and the lesser curvature of the stomach while the smallest mass measuring 5 cm, was located behind the stomach, raising the clinical suspicion of a metastatic residual primary tumor (Figure 1 and 2). The preoperative diagnostic workup was unremarkable outside of leukocytosis. Preoperative Carcinoembryonic Antigen (CEA) was 6.3 and CA 19-9 level was within normal limits.

Figure 1: Axial view of CT abdomen/pelvis demonstrating 8.1 cm and 5 cm mass.

Figure 2: Coronal view of CT abdomen/pelvis also demonstrating the two previously mentioned masses.

During the subsequent curative surgical intervention, the tumor was found to be invading the left lobe of the liver, both the right and left crus of the diaphragm, and extended down into the lesser sac and the tail of the pancreas. Surgical procedures performed included large abdominal and retroperitoneal tumor resection, en bloc left lateral hepatic segmentectomy, resection of the tail of pancreas and excisional biopsy of metastatic tumor in the omentum. Appropriate surgical intervention was performed with complete resection (R0). The patient tolerated the procedure well.

The post-operative microscopic evaluation of the biopsied specimens confirmed the diagnosis of MREA. In the final pathology report, it was mentioned that the tumor was composed of epithelioid cells with focal areas of spindling and abundant eosinophilic cytoplasm with prominent nuclei. Microscopic tumor necrosis was seen with the mitotic rate up to 5/10 HPFs. Immunohistochemical (IHC) stains showed the tumor cells diffusely and strongly positive for HMB-45.

Discussion

As previously mentioned, renal angiomyolipomas (AML) are the most common clonal mesenchymal tumors of the kidney. AMLs are more common in women than men and are typically found in middle-aged individuals, most commonly in their fifth decade of life [4]. In our case, the patient did fall into this category, being a 59-year-old female. AMLs are often found incidentally as most patients are asymptomatic. Lesions of larger sizes (> 4 cm) may cause symptoms in 68 - 80% of patients. Among the symptomatic patients, flank pain is most commonly described, with hematuria or hemorrhage also been documented, but occurring less frequently [2,5]. Similar to AMLs, renal epithelioid angiomyolipomas (EAML) are also most commonly found incidentally on imaging [1]. This too was true in our patient as she was asymptomatic, and the masses had been found on serial imaging, which was obtained due to her history of AML.

Important diagnostic features of AMLs for all imaging modalities is the presence of fat in the lesion. The epithelioid variant however, is often fat poor and can be challenging to diagnose on imaging. They can present as larger masses with hemorrhage, tumor necrosis, heterogeneous enhancement on CT, or as hypo-echoic lesions on ultrasound (US) [6,7]. A study conducted by Jinzaki., *et al.* did compare minimal fat AMLs to renal cell carcinoma (RCC) using US and found that the homogenous isoreflectivity of AMLs was not replicated in RCCs [2]. This could potentially provide a radiographic feature to be cognizant of on imaging to help with differentiation of the two lesions. Ultimately, differentiating EAML lesions from RCC can still present as a challenge as they can often mimic one another on imaging [5]. Even with the advancement in imaging, diagnosis still often depends on pathology.

Although rare, epithelial variant does have the potential to undergo malignant transformation. Due to its lack of adipocytes, it is difficult to differentiate on imaging but does contain potential histological features that could guide clinicians and at minimum raise suspicion for a more aggressive tumor. The following are histologic features of epithelioid variant which are suspicious for higher malignant potential including ≥ 70 percent epithelioid cells, tumor

size > 7 cm, vascular invasion, ≥ 2 mitotic figures per 10 high-power fields (HPFs), atypical mitotic figures, and necrosis on histological exam [1,8].

These histologic features have been noted in some studies to be potential indicators for risk of malignant transformation [1]. In a study that examined similar histological features, a model was created and used to better predict the risk of malignant transformation. It was highly predictive of malignancy if three or more of the following features were identified: > 70 percent atypical epithelioid cells, two or more mitotic figures per 10 HPFs, atypical mitotic figures or necrosis [2]. The MREA that was excised in our case did have some of the previously mentioned histologic characteristics, which could be predictive of malignant potential.

Of the higher risk characteristics previously mentioned, the tumor that was resected contained the following: one mass measuring 8.1 cm, mitotic rate up to 5/10 HPFs, as well as tumor necrosis. It has also been reported that certain immunohistochemistry (IHC) stains can indicate and help differentiate EAML from other malignancies as well. In one retrospective study, it was mentioned that EAML was positive for melanoma cell markers such as HMB45 and smooth muscle cell markers, but negative for epithelial cell markers. In comparison, RCC does not seem to express HMB-45 [1]. The tumor that was resected from our patient was strongly positive for HMB-45, another indicator that this was EAML. Therefore, histological details provide more information as to the potentially aggressive nature of this type of tumor.

Traditionally, treatment has been similar to that of RCC, with surgical resection, which was the modality of treatment utilized in our case where we obtained complete (R0) resection. A multimodal approach has been suggested and should be considered for treating and following EAML including surgery, chemotherapy as well as other molecular targeted therapy. It has been reported that EAML belongs to a group of perivascular epithelioid cell tumors (PEComa), which are typically sensitive to chemotherapy.

It has also been reported that PEComa tumors have activated mTOR cascades that relate to tumor growth and development [1]. Both findings suggest that chemotherapy and molecular targeted therapy, such as mTOR inhibitors, may be of benefit to individuals with EAML. Chemotherapy sensitivity and response have been reported, but further studies are needed to confirm these effects. Local recurrence or distant metastasis typically occurs between 1.5 - 9 years postoperatively [1]. In this case, the recurrence occurred after two years and was detected with close surveillance. Close follow up for cases which met the following criteria has also been recommended: tumor size > 9 cm, tumor thrombus in the vein, epithelioid cells > 70%, atypical cells > 60% and necrosis of the tumor [1].

Conclusion

MREA, unlike commonly benign renal angiomyolipomas, is a highly aggressive lesion. It is imperative for clinicians to identify this lesion early and differentiate this aggressive lesion from RCC. A multimodality treatment approach including resection of the tumor and adjuvant therapy may provide optimum treatment for MREA.

Patient Consent

Patient consent was obtained.

HCA Disclaimer

This research was supported (in whole or in part) by HCA and/or an HCA affiliated entity. The views expressed in this publication represent those of the author(s) do not necessarily represent the official views of HCA or any of its affiliated entities.

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Variables	Asymptomatic (n=13)		Symptomatic (n=15)		
	Mean	Frequency (%)	Mean	Frequency (%)	P*value*
Age (years)	53.92		63.80		0.031

Table2: Difference in between variables among symptomatic vs. asymptomatic pulsion esophageal diverticulum

*p-value were derived using correlation tests; chi square and independent t-test where appropriate; na- not applicable. [+]onset of new symptoms was applicable in case of previous asymptomatic disease; while recurrence of symptoms or failure to control symptoms was applicable to symptomatic individuals only, who had prior documented symptoms

Pulsion Esophageal Diverticulum (PED) is a false diverticulum which forms secondary to out pouching of mucosal +/- sub mucosal layer from inside to outside of the esophageal lumen. In contrast to PED; the traction type esophageal diverticulum results secondary to out pouching of all layers of esophageal wall and often secondary to a pathological process- such as inflammation or tumors, which involve the lumen or outside the lumen of the esophagus [1]. PED develop secondary to imbalance of intraluminal pressure and mucosal wall tension, with absence of an associated mucosal disease. Gastrointestinal (GI) diverticula are commonly seen in large bowel; however, they are infrequently encountered

Type of Diverticulum	Mode of diagnosis	Predominant symptoms	Surgical intervention	Duration of Post operative Hospital stay	Complication	Recurrence of symptoms
1. Zenker's diverticulum	Radiological	Dysphagia	Zenker's Diverticulectomy; left neck incision	1	None	None
2. Zenker's diverticulum	Radiological	Choking/ cough	Zenker'sDiverticulecopexy; endoscopic stapling	1	None	None
3. Zenker's diverticulum	Endoscopic	Dysphagia	Zenker's Diverticulectomy; left neck incision	1	None	None
4. Epiphrenic diverticulum	Endoscopic	Dysphagia	Lateral thoracotomy	4	None	None
5. Epiphrenic diverticulum	Radiological	Dysphagia	Laparotomy with abdominal approach	4	None	Yes

Table 3: Details of patients who underwent surgical interventions

in upper GI tract involving esophagus, duodenum, and other parts of small bowel. Pulsion Esophageal Diverticulum (PED) is also categorized based on the location of the diverticulum in esophagus. Zenker's diverticulum (ZD) and Killian-Jamieson diverticulum occurs below the cricopharyngeus muscle and just above the upper esophageal sphincter (UES) in posterior or antero-lateral wall of hypopharynx respectively. Mid-esophageal diverticulum (MD) occurs in the segment of esophagus starting below the UES and up to 10 cm proximal to gastro esophageal junction (GEJ) [2,3]; and lastly Epiphrenic diverticulum, which occurs just above the lower esophageal sphincter within 10 cm of GEJ [4,5].

Majority of patients with pulsion esophageal diverticulum tend to remain asymptomatic [6-8]. Some patients develop symptoms originating from upper GI tract such as dysphagia, regurgitation, halitosis, and rarely bleeding; while a small number of individuals develop predominantly upper respiratory tract symptoms such as cough, choking, and aspiration [6].

A large number of individuals with PED do not seek a medical advice; receive a treatment; or follow up with the physicians because of their mild intermittent symptoms or completely asymptomatic disease course [7,9-11]. In certain situations however, surgical resection of the diverticulum is necessary due to rapid progression in the size of the diverticulum and/or development of life threatening complications such as aspiration pneumonia [12]. Figure 1 shows the different types of diverticulum diagnosed on

endoscopy and radiological investigations.

Owing to the rarity of the disorder, lack of a standard guideline; the approach to the management of pulsion esophageal diverticulum is largely individualized. Furthermore, the available literature supports different implications while managing patients with symptomatic pulsion esophageal diverticulum; however, implication in terms of management-resection vs. surveillance among patients with asymptomatic pulsion esophageal diverticulum is not well determined [6]. Therefore, in this retrospective observational review of patients, we intend to determine spectrum of presentation of pulsion esophageal diverticulum, as well as determine the approach to the management of patients among asymptomatic and symptomatic patients with pulsion esophageal diverticulum.

Methods

It was a retrospective observational study. The study was conducted in the Department of Medicine, Aga Khan University Hospital Karachi Pakistan. A total of 32 consecutive patients with suspected pulsion esophageal diverticulum were identified from January 2010 to December 2017. After reviewing their clinical, endoscopic and radiological profiles; 4 patients were excluded because of presence of traction type diverticulum-esophageal tuberculosis (n=1) and malignant esophageal ulcer (n=3).

Data from 28 patients with pulsion esophageal diverticulum including demographics; spectrum of symptoms; upper GI endoscopic findings i.e. size and site of diverticulum; radiological findings; frequency of surgical or endoscopic resection; surgical findings; and frequency of post-operative complications were determined. These 28 patients were grouped in to two based on presence or absence of diverticulum related symptoms in to symptomatic vs. asymptomatic individuals. The diverticulum related symptoms were dysphagia, chest pain, regurgitation and heart burn, halitosis, bleeding from diverticulum, cough, choking, and aspiration pneumonia. Patients follow up charts were reviewed in order to determine occurrence of symptoms and/or complications among asymptomatic individuals; while resolution, worsening or recurrence of symptoms among symptomatic individuals who received surgical or non-surgical treatments.

Continuous variables presented as means or median, categorical variable presented as frequencies or proportions. Differences among symptomatic vs. asymptomatic individuals were derived using test of correlations-chi-square test and independent student's t-test where appropriate. P value ≤ 0.05 was considered significant.

Results

A total of 28 patients were found to have pulsion esophageal diverticulum which were encountered during study period (January 2010 to December 2017). Out of 28 patients, 4 patients had Zenker's Diverticulum (ZD), 17 patients had Mid-esophageal Diverticulum (MD), 6 patients had Epiphrenic Diverticulum (ED), and 1 patient had combined MD and ED. Baseline characteristics of 28 patients according to type of pulsion esophageal diverticulum are presented in table1.

Mean age was higher among patients with ED than of those with ZD and MD i.e. 67, 63.5, 54.4 years respectively. Out of 28 subjects, 15 (53.5%) subjects were males. A total of 15 (53.7%) subjects were symptomatic with variables symptoms, predominantly dysphagia and others, as shown in table1.

Baseline characteristics of asymptomatic patients 13 (46.42%) (table1) plus their difference to symptomatic diverticular patients are determined in table 2. All 13 individuals with asymptomatic disease harbor Mid-esophageal diverticulum of small size i.e. ≤1 cm in diameter. These patients were followed for a mean duration of 14 months and none of them reported onset of new symptoms.

Patients with comparatively higher age, Zenker's or Epiphrenic type of pulsion diverticulum, and diameter of 2 to 5 cm or above tend to be symptomatic as shown in table 2.

Out of 15 symptomatic patients, a total of 5 underwent surgical intervention and 10 patients were initially managed with supportive treatment including acid suppression using proton pump inhibitors for reducing heartburn and regurgitation. 5 out of 15 (33.3%) symptomatic patients underwent surgical excision of the diverticulum owing to disabling symptoms, as shown in table 3. Only 1 out of 5 had recurrence of symptoms post surgically. The group of symptomatic patients who received non-surgical therapy (n=10); 5 patients had persistent symptoms despite continuous medical therapy, however; they did not undergo surgical resection because of limitations; and remaining 5 patients had reasonable control of their symptoms with medications.

The limitations for surgical resection among five subjects (ZD

=1, ED=3, MD+ED=1) with persistent symptoms were cardiopulmonary morbidity (n=2), refusal by patient (n=2) and technically difficult position of Zenker's diverticulum (n=1).

Discussion

In concordance with previous published literature, nearly half

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