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Clinicopathological analysis of Adrenal Myelolipoma and predicting Complications Based on Histology: An experience from a tertiary care center

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Abstract

Introduction: Adrenal myelolipoma (AML) is a benign tumor that histologically comprises a variable admixture of hematopoietic cells and adipose tissue. Most of these tumors are nonfunctional and asymptomatic but can sometimes pose challenges in differential diagnosis. We present a cohort of 115 cases of AML, emphasizing their clinicoradiological and pathological features, associated adrenal lesions, and tumor variables inferring the complications.

Materials and Methods: All proven cases of AML who underwent adrenalectomy from 2003 to 2023 were included. Data on patient demography, radiological details, follow-up, and complete pathological examination of the tumor were studied.

Results: Out of 115 patients with AML, 54 were males aged 17-73. Radiological diagnosis could correctly be made in 80% of patients (92/115). Intratumoral calcifications and necrosis were noted in tumors exceeding 6 cm in size and were present in 4.3% and 6.9% of the tumors, respectively, whereas intratumoral hemorrhage is commonly observed (80%). Statistically, a significant correlation was noted between the frequency of tumor complications and tumor weight (p value <0.001) and dimensions (p value <0.001). All patients were managed surgically with either open adrenalectomy (52.2%) or laparoscopy converted to open surgery (11.3% patients). A significant correlation was observed between tumor size and type of surgery needed (p value=0.001), with open surgery needed when tumor size exceeded 6 cm.

Conclusion: Tumor variables, i.e., size, weight, and fat-to-myeloid proportion (>1) may predict tumor complications and guide the type of surgery needed.

Keywords: Histopathology; Adrenal; Giant; Complication; Myelolipoma; Myeloid; Fat

Introduction

Adrenal myelolipoma (AML) is a rare, benign mesenchymal tumor of the adrenal cortex enlisted in the category of mesenchymal and stromal tumors in the latest WHO classification of adrenal cortex tumors [1]. Following adrenocortical adenomas, which are the most common adrenal incidentalomas (~60-70%), AML constitutes the second most frequent adrenal incidentaloma (6-16% of all primary adrenal incidentalomas) [2-4]. They histologically comprise a variable admixture of hematopoietic cells and mature adipose tissue. Clinically, a great majority of these tumors are nonfunctional and

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asymptomatic. Earlier, most cases were incidentally detected in autopsies or during laparotomies performed for other reasons. However, recently, increased detection of AML has been attributed to the widespread use of imaging modalities such as ultrasonography (USG), computed tomography (CT) and magnetic resonance imaging (MRI) of the abdomen in various conditions. Much of the data on this rare tumor is through case reports and a few small case series. As most of these are incidentally detected during workup for other conditions and as radiological diagnosis may not be very straightforward in all cases, histopathological evaluation of nonfunctioning adrenal cortical tumors assumes a crucial role in distinguishing this entity from other nonfunctioning adrenal cortical tumors such as cortical adenoma. Although they exhibit a benign disease course, it is necessary to be aware of their diagnostic features, as AML could sometimes pose significant challenges in differential diagnosis from other benign and malignant adrenal tumors. Herein, we present a cohort of 115 histologically confirmed cases of adrenal myelolipoma, emphasizing whether complications in adrenal myelolipomas are related to tumor size and tumoral myeloid/fat percentage. To our knowledge, this is the largest cohort of AML cases reported to date.

Materials and Methods

This was a retrospective observational study at SGPGI, a tertiary care medical center in Lucknow, India. All histologically proven cases of adrenal myelolipoma who underwent adrenalectomy over 21 years from 2000 to 2021 were included in the study. Data on patient demography, radiological details and follow-up were retrieved from the medical records department. Complete pathological examinations were studied for all cases, including gross and microscopy of the tumor. The following tumor details were evaluated:

1. On gross examination based on the tumor dimensions, the tumor was divided into the following three categories:
   a. <6 cm
   b. 6.1-10 cm
   c. >10 cm (giant adrenal myelolipoma)
2. Quantitative scoring (percentage and number/hpf) of the following tumor components in the total tissue volume examined:
   a. Adipose tissue (%)
   b. Myeloid (%)
   c. Megakaryocytes (number/hpf)
3. Hematoxylin and eosin-stained slides of all cases were evaluated for the presence or absence of
   a. Hemorrhage
   b. Calcification
   c. Necrosis

A correlation, if any, was analyzed between the following parameters:

1. Tumor dimensions, weight, and laterality
2. Patient characteristics (age, sex, clinical features)
3. Cellular composition of the tumor (myeloid and fat percentage, number of megakaryocytes per hpf)
4. Tumor necrosis, hemorrhage, and calcification

Aims and Objectives

1. To describe the demographic, radiological, associated adrenal lesions, and histological characteristics of adrenal myelolipoma
2. To assess whether there is any correlation of complications (intractable pain, acute abdomen, hemorrhage, rupture, hematemesis) in adrenal myelolipoma with tumor variables, including tumor dimensions, tumor weight, tumor laterality, and proportion of myeloid to fat component in the tumor.

Statistical analysis

Independent samples t test, Mann–Whitney U test and P value were used to assess whether there was any relationship between the various tumor variables and complications. The AUROC curve was used to demonstrate the diagnostic accuracy of the weight and largest tumor dimensions to detect complications. The Spearman rank correlation coefficient was used to test the linear relationship between variables.

Results

Study population characteristics

One hundred fifteen patients with adrenal myelolipoma were evaluated, of which fifty-four were males and sixty-one were females (M:F ratio= 0.88:1). The age of the patients ranged from seventeen to seventy-three years (mean 46 years).

Clinical, radiological, and laboratory characteristics of AML

Clinical characterstics

During clinical evaluation, twenty-one patients (18.3%) were asymptomatic at presentation. The remaining patients presented with ambiguous complaints of abdominal pain and discomfort (53%), followed by headache (5.2%). In 27.5% of the patients, AML was detected incidentally due to complaints pertaining to other organ systems [urinary tract infection (5.1% patients), menstrual irregularities (5.1% patients), lower urinary tract obstructive symptoms (3.4% patients),

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respiratory tract symptoms (2.5% patients), musculoskeletal complaints such as back pain (1.7% patients)], generalized weakness (0.8% patients) or during routine health screening. Features of adrenal gland dysfunction, manifesting as cushingoid features, were observed in six patients.

Radiological details

During radiological evaluation, AML was incidentally detected in most of our patients (92.2%). Clinico-radiological diagnosis of adrenal myelolipoma could correctly be made in 80% of patients (92/115 patients). Other clinical-radiological diagnoses that were offered were angiomyolipoma (11 patients), adenoma (4 patients), pheochromocytoma (4 patients), myolipoma/lipomatous lesion (2 patients) and adrenal cortical carcinoma (2 patients). **Figure 1** shows various tumor characteristics of AML on CECT imaging.

Laboratory characteristics

As part of evaluation of adrenal gland tumor, 24-hour urinary metanephrine/nor-metanephrine excretion and serum cortisol levels were evaluated in 106 patients. Elevated urinary catecholamine levels were seen in 18.3% of our patients, while hypercortisolism was seen in 4.7%. Of the patients who had hypercortisolism, three had another associated adrenal lesion (adrenal cortical hyperplasia, bilateral adrenal oncocytoma and bilateral adrenocortical adenoma). **Figure 2** shows AML with associated adrenocortical hyperplasia, adrenocortical adenoma and oncocytic neoplasm.

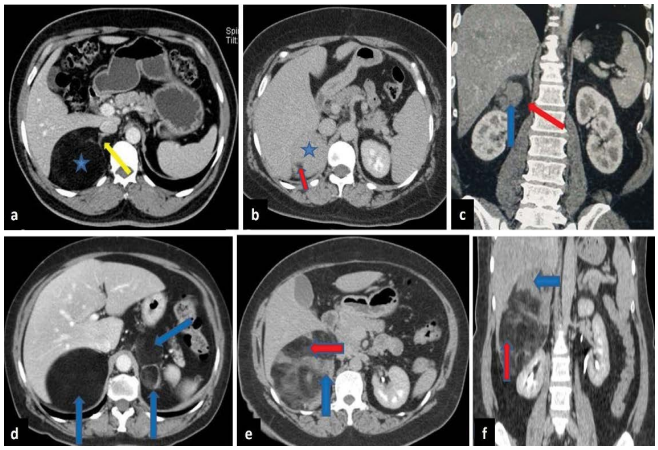

Figure 1: Axial CECT images show (A) a well-circumscribed, predominantly fat-containing mass lesion (asterisk) with intralesional wisps of higher attenuation (less dark areas, yellow arrow) involving the right adrenal gland. Axial and coronal images (B&C) show a right suprarenal mass lesion with a predominant soft tissue component (blue asterisk/arrow) and a subtle fat component (red arrow). D: shows bilateral adrenal masses with a predominant fat component (blue arrows). Axial and coronal (E&F) images show giant myelolipoma in the right suprarenal region with unevenly distributed soft tissue components (blue arrow) intermixed with fat components (red arrow)

AML with associated endocrine and nonendocrine diseases

An associated endocrine or nonendocrine disease was identified in a few patients. Associated adrenal endocrine/ non-endocrine tumors noted were adrenal gland hyperplasia (1 patient), oncocytoma (1 patient) bilateral adrenal oncocytoma (1 patient), adrenocortical adenoma (2 patients) and schwannoma (1 patient) (overall 6/115 patients; 5.2% patients); Other endocrine diseases whose co-occurrence was seen were hypothyroidism (5.1% patients) and diabetes mellitus (18.1% patients). Non endocrine diseases namely carcinoma/metastatic carcinoma, neurofibroma, thalassemia, renal angiomyolipoma, cirrhosis, Crohn's disease and acute pancreatitis were seen in 14 patients (12.1%) the occurrence of which most likely is coincidental.

Histolopathological characteristics of the study population

Tumor characterstics and gross features

On the macroscopic and microscopic evaluation of the tumor, the weight and size of the tumor ranged from 13 grams-8000 grams (average weight: 379.9 gm) and 3 cm-43 cm (mean tumor dimension-9 cm), respectively. Nearly half (47.8%) of the tumors measured 6.1-10 cm in size, while 30.4% of the tumors were identified as giant AML (defined as AML>10 cm in maximum dimension). A total of 80.8% of patients presented with right-sided AML, 13.9% had left-sided AML, and bilateral AML was noted in six patients (5.2%).

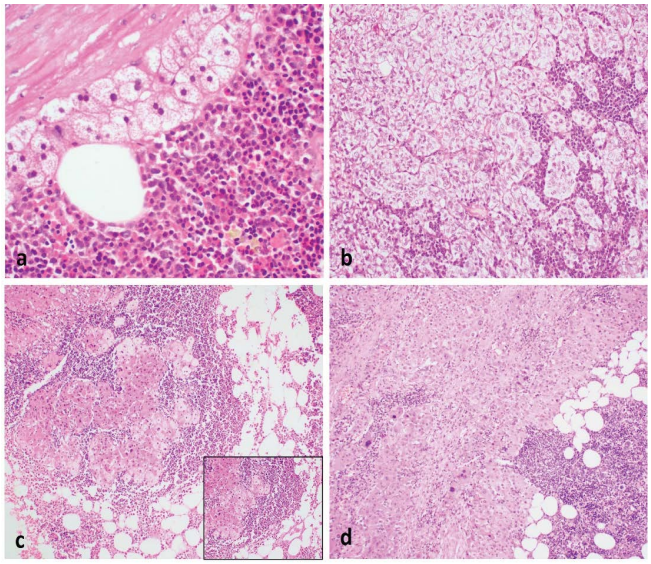

Figure 2: Adrenal tissue is noted at the periphery, beneath which is noted a mass comprising of adipose tissue admixed with hematopoietic elements in variable proportions (A: H&E stain; 100x). Associated adrenocortical hyperplasia (B: H&E stain; 200x), adrenocortical adenoma (C: H&E stain; 100x, inset; 200x) and oncocytic adrenocortical neoplasm (D: H&E stain; 100x) are also noted.

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Histopathological characterstics

On histopathological evaluation, hematoxylin and eosin-stained sections from representative areas of the tumor showed a variable admixture of lipomatous components and hematopoietic elements from all three lineages, i.e., myeloid cells, erythroid cells and megakaryocytes **(Figure 3).**

Table 1 shows a correlation between tumor size and patient characteristics (age, sex, clinical features, type of surgery required) and tumor variables (cellular composition, tumor necrosis, hemorrhage). A positive correlation was noted between the weight of the tumor with the largest tumor dimension and fat component, while the myeloid component showed a negative correlation with the weight and largest dimension of the tumor and shown in **table 2.**

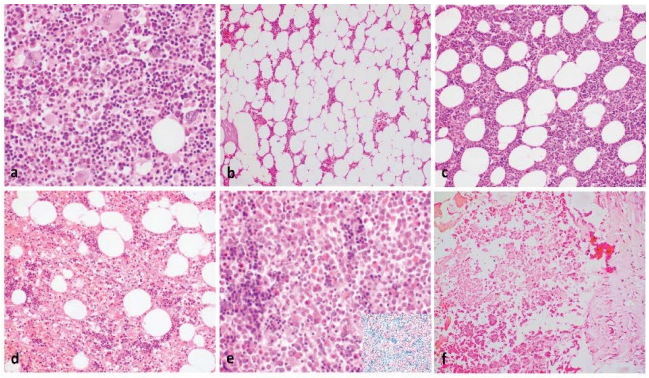

Figure 3: Histopathology of myelolipoma comprising varying proportions of adipose tissue mixed with areas of hematopoietic tissue containing erythroid, myeloid and megakaryocytic elements (A, B, C; H&E stain; 200x, B; 100x). Complicated cases show internal hemorrhage (D; H&E stain; 100×) along with the presence of hemosiderin-laden macrophages (E; H&E stain; 200×, inset; Perl's stain showing hemosiderin, 200×) and necrosis (F; H&E stain; 100×)

Tumor variables associated with complications

Complications such as tumoral hemorrhage were noted in ninety-two (80%) cases. Intratumoral calcifications and necrosis were noted only in tumors exceeding 6 cm and were present in 4.3% and 6.9% of the tumors, respectively.

Table 3 shows the correlation between complications and tumor characteristics such as laterality, weight, dimensions and composition (fat vs. myeloid component). A statistically significant correlation was noted between the frequency of tumor complications and tumor weight (p value<0.001, sensitivity 91.7%, specificity 67%) and dimensions (p value<0.001, sensitivity 83.3%, specificity 66%). In contrast, tumor laterality and proportion of fat/myeloid component in the tumor did not have a significant effect **(Table 4 and Figure 4).**

Management of AML

All patients were managed surgically with either open adrenalectomy (60 patients; 52.2%), laparoscopic adrenalectomy (42 patients; 36.5%) or laparoscopy converted to open surgery (11.3% of patients). A significant correlation was observed between tumor size and type of surgery needed (p value=0.001), with open surgery needed when tumor size exceeded 6 cm.

Discussion

Adrenal myelolipoma was first described by Gierke et al. in 1905 as an adrenal gland mass lesion formed from a variable admixture of myeloid and erythroid cells with mature fat [5]. The term "formations myelolipomatoses" was subsequently coined in 1929 by Obering [6]. There are varying theories of the origin of these tumors. The hematopoietic component of these tumors is postulated to be derived from

Table 1: Correlation between tumor size, patient characteristics, and other tumor variables.

Size	Age	Sex	Lat	Wt	Fat	Myeloid	Meg	Hm	Cal	Nec	Pain abd	HTN	Open surgery
(cm)	mean±SD	(M:F)	(R/L/ BL)	(gms)	(%mean±SD)	(%mean±SD)	(/hpf)						
≤6 (N=25)	45.68±9.2	09:16	20,3,2	82.5	66.4±22.1	33.6±22.1	4.4	14 15.2%)	0	0	12	13	6
6.1-10 (N=55)	45.3±12.5	24:31:00	46,7,2	144.9	72.1±23.3	27.9±23.3	4.5	45 (48.9%)	2	4	31	21	37
>10 (N=35)	47.17±12.3	21:14	27,6,2	978.3	77.0±15.6	23.0±15.6	4.7	33 (35.9%)	3	4	18	5	30
Comparison between groups	0.761			**0**	0.16	0.16	0.938	**0**	0.087	**0.05**	**0.034**	0.087	**0.001**

Lat: Laterality, Wt.: Weight, Meg: Megakaryocyte, Hm: Hemorrhage, Cal: Calcification, Nec: Necrosis, HTN: Hypertension

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Table 2: Spearman rank correlation coefficient to test the linear relationship between tumor variables

			Wt (gm)	Largest dimension	Fat	Myeloid
Spearman's rho	Wt_(gm)	Correlation Coefficient	1	**0.855****	0.288**	-.288**
		Sig. (2-tailed)	.	**<0.001**	0.002	0.002
		N	115	115	115	115
	Largest dimension	Correlation Coefficient	.855**	1	.194*	-.194*
		Sig. (2-tailed)	0	.	0.038	0.038
		N	115	115	115	115
	Fat	Correlation Coefficient	.288**	.194*	1	-1.000**
		Sig. (2-tailed)	0.002	0.038	.	.
		N	115	115	115	115
	Myeloid	Correlation Coefficient	-.288**	-.194*	-1.000**	1
		Sig. (2-tailed)	0.002	0.038	.	.
		N	115	115	115	115

**. Correlation is significant at the 0.01 level (2-tailed), *. Correlation is significant at the 0.05 level (2-tailed).

Table 3: Correlation between complications and tumor characteristics like laterality, weight, dimensions and composition (fat vs. myeloid component).

Variable's	Complications	No Complications	P value
Left-sided (n=16)	1 (6.3%)	15 (93.4%)	0.551
Right-sided (n=93)	11 (11.8%)	82 (88.2%)	
Bilateral (n=6)	0	6 (100%)	
Weight (gm)	1448.83±2185.95	261.06±365.55	**<0.001#**
	[455, 264-1891]	[128, 60-270]	
Largest dimension	16.92±9.88	8.83±3.94	**<0.001 #**
	[15, 10-20]	[7.5, 6.4-10.5]	
Fat	81.67±7.18	71.26±22.04	0.108
	[82.5, 76.3-88.8]	[80, 60-90]	
Myeloid	18.33±7.18	28.74±22.04	0.108 #
	[17.5, 11.3-23.8]	[20, 10-40]	

Independent samples t-test/# Mann–Whitney U test. P value <0.05 significant.

Table 4: Sensitivity and specificity of weight and largest dimensions of the tumors to detect the complications.

Variable´s	AUROC (95% CI) [P value]	Cutoff	Sensitivity	Specificity
Weight (gms)	85.9% (77.5%, 94.4%)	198.5	100%	64.10%
	[p value <0.001]	223.5	91.70%	67%
		290	75%	76.70%
Largest dimension	82.4% (70.9%, 94%)	8.5	91.70%	61.20%
	[p value <0.001]	9.5	83.30%	66%
		10.7	66.70%	75.70%

CI: Confidence Interval, AUROC: Area under the Receiver Operating characteristics curve. P<0.05 significant

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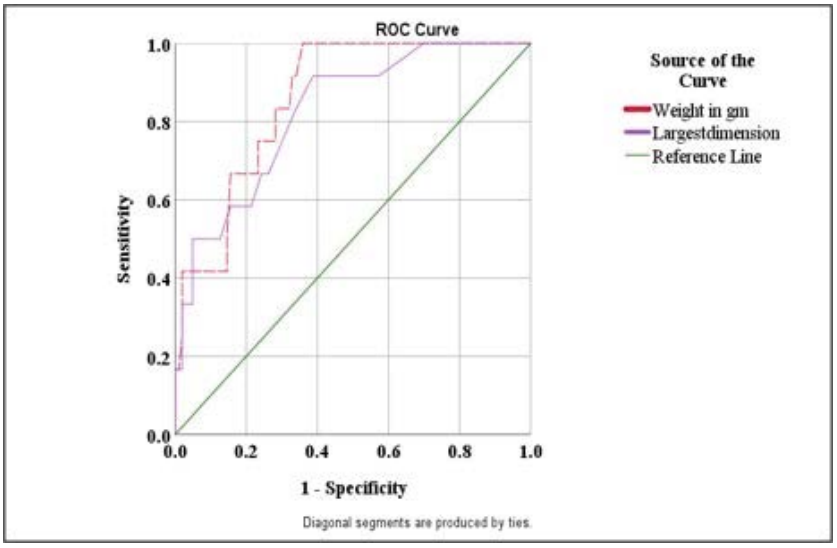

Figure 4: AUROC curve showing the diagnostic accuracy of the weight and largest dimensions of the tumors for the detection of complications

ectopic myeloid tissue, bone marrow emboli, hamartosis, metaplasia, and proliferation of reticuloendothelial cells of blood capillaries[7,8]. The adipose tissue component is hypothesized to develop from mesenchymal stem cells residing in the periadrenal adipose tissue [9]. A few theories also incriminate the roles of hormonal pathways in the development of AML. There is a tendency for a few untreated cases of congenital adrenal hyperplasia (CAH), which have elevated ACTH levels, to develop into myelolipoma, suggesting that chronic ACTH stimulation on the adrenal may be responsible for tumor development [10]. The development of AML in patients with ineffective erythropoiesis suggests the role of high erythropoietin and, hence, extramedullary hematopoiesis in tumor growth [11]. Demonstration of nonrandom X chromosome inactivation in most of these tumors by Bishop et al. suggests that AML has a clonal origin [12].

AML occurs in the 5th -7th decades of life with an average age of 51 years[1,13-15]. In our study, the patients' ages ranged from 17 to 73 years (mean age 46). Most studies have reported equal occurrence of AML in both sexes, whereas certain studies have reported a slight female predilection. [(1)] The present study also noted a mild female preponderance.

Most AML cases are asymptomatic; hence, obtaining the exact clinical prevalence of AML is difficult. The incidence of AML is estimated to be 0.08% to 0.25% [16,17]. In symptomatic patients, presenting features vary from most commonly abdominal discomfort/pain to less commonly dyspepsia, palpable abdominal mass, nausea and vomiting, lower extremity paresthesia, paralysis, and rarely back pain, weight loss, and virilization [13]. Similar to other studies, in our study, AML was incidentally detected in most patients (92.2%). Symptomatic patients presented most with pain in the abdomen. None of our patients showed features of androgen excess/virilization.

AML is biochemically mostly nonfunctional and shows no diagnostic abnormalities during laboratory investigations. Although myelolipomas occur mostly as isolated adrenal lesions, endocrine disorders, including congenital adrenal hyperplasia, hypercortisolism, primary hyperaldosteronism, concomitant adrenocortical adenoma, hypogonadism, ganglioneuroma, primary hyperparathyroidism and pheochromocytoma, are the most prevalent associated diseases in patients with myelolipoma [18-22]. In the present study too, concomitant endocrine diseases that were noted were adrenal gland hyperplasia, unilateral and bilateral adrenal oncocytoma and adrenocortical adenoma (5.2%) . One case each in the present study showed an associated adrenal cortical adenoma with Cushing's syndrome and a coexisting schwannoma respectively . Associated non endocrine diseases like cancers, thalassemia and liver diseases were noted in around 12.1% patients in our study. Decmann Á et al also reported similar incidence of associated non-endocrine lesions in myelolipoma patients, of which majority had thalassemia and various cancers [13]. Of the various associations, development of AML in one of our patients with thalassemia supports the role of extramedullary hematopoiesis in tumor growth.

Radiological investigations such as ultrasound (USG), computed tomography (CT) scan and magnetic resonance imaging (MRI) play a crucial part in the detection and diagnosis of AML[23-24]. Of these,CT scans are considered the most sensitive radiological modality [24]. Myelolipomas appear as well-delineated heterogeneous masses with low-density mature fat (less than -30 Hounsfield Units [HU]) interspersed with more dense myeloid tissue [25].

AML has been reported roughly twice as frequently in the right adrenal gland as in the left side [1,7]. Approximately 54 cases of bilateral AML have been reported in the literature [13]. A marked preponderance of right-sided AML was noted in our patients (five times more common than left-sided AML).

On pathologic evaluation, the size of the tumor may vary from a few mm to more than 40 cm, with an average of 10.2 cm [13]. Tumors larger than 10 cm are termed giant myelolipomas [7]. In the detailed review by Abel Decman et al., who analyzed 420 cases of AML reported over 50 years (1957-2017), 35.7% of cases were found to be giant AML [13]. Almost similar results were observed in the current study, with a mean dimension of the tumor being 9 cm. A total of 30.4% of the tumors were identified as giant AML. Tumor size is an essential parameter in deciding tumor behavior. Complications such as rupture, retroperitoneal hemorrhage and rarely hemorrhagic shock are more likely to occur in tumors larger than 10 cm (giant AML) [26]. Abel Decman et al. reported tumor rupture in 20 out of 400 AML cases (4.5%) [13]. The diameter of the ruptured tumors was 12 cm, and the smallest tumor that bleed was 6.5 cm [15]. A significant association between tumor dimensions and weight with the detection of tumoral hemorrhage was evident in our study, indicating that tumor size can be a significant predictor for the likelihood of developing complications such as hemorrhage.

Grossly, AML presents as a well-demarcated tumor surrounded by a pseudocapsule formed by the zona glomerulosa and zona fasciculata. Color may vary from yellowish to red–brown depending on the relative proportions of fat and hematopoietic tissue. Microscopically, it comprises two constant elements: mature adipose tissue and trilineage hematopoietic cells, with abundant granulocytic and erythroid lineages and plenty of megakaryocytes. In the present study, we did not find any significant association between the proportion of tumor elements and tumor size or the occurrence of complications such as hemorrhage or tumor rupture.

The primary differential diagnoses, which mainly include other adrenal tumors with lipomatous components such as adrenal lipoma, adrenal cortical adenoma, adrenal cortical carcinoma, retroperitoneal liposarcoma, teratoma and exophytic renal angiomyolipoma, can be ruled out with certainty on histopathological evaluation. As AML is composed of trilineage hematopoietic cells, at times, they can be confused with foci of extramedullary hematopoiesis, which develops either physiologically during fetal life or pathologically in certain hematological diseases, such as hemoglobinopathies and myeloproliferative disorders. However, these are distinct entities and differ from the normal trilineage hematopoiesis in bone marrow by a lack of reticular sinusoids. In AML, there is usually a well-demarcated lesion, normal bone marrow and a prominent mature adipose tissue component [27]. In contrast, EMH usually does not form a well-defined lesion and is associated with hematological disease, and fat is not needed [28].

There are no formally approved guidelines for managing AML, and treatment varies from case to case. Incidentally detected small asymptomatic AML cases do not require intervention and may be left as such. Surgical removal is the mainstay of therapeutic intervention for symptomatic cases due to significant tumor size, functional tumors with hormonal activity and/or tumor-related complications such as rupture or hemorrhage.

Conclusion

Myelolipomas are rare benign adrenal tumors commonly associated with other endocrine disorders. CT scan plays a pivotal role in its diagnosis but may show indeterminate findings in a few cases. In these cases, histopathological evaluation helps differentiate it from its other mimics. Most tumors are small, asymptomatic, incidentally detected AML and do not require intervention. Tumors with significant size, functionality with hormonal activity and/or tumor-related complications require surgical removal. Tumor size, tumor weight, and fat-to-myeloid proportion (>1) may predict tumor complications and guide the surgery needed.

Author contributions

(I) Conception and design: Dr Neha Nigam, Dr Sabaretnam Mayilvaganan (II) Administrative support: Dr Vinita Agrawal (III) Provision of study materials or patients: Dr Neha Nigam, Dr Sabaretnam Mayilvaganan (IV) Collection and assembly of data: Dr Neha Nigam, Dr Neha Kumari, Dr Anil Kumar Singh, Dr Prabhakar Mishra, Dr Pallavi Prasad, Dr Nandita Chaudhary (V) Data analysis and interpretation: Dr Neha Nigam, Dr Neha Kumari, Dr Prabhakar Mishra (VI) Manuscript writing: Dr Neha Nigam, Dr Neha Kumari, Dr Amit Rastogi (VII) Final approval of manuscript: All authors

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