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## **Lipomatous tumours in adrenal gland: WHO updates and clinical implications**

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**ABSTRACT**

Adrenal lipomatous tumour is a group of adrenal tumours with a significant component of adipose tissue. According to the current World Health Organization (WHO) classification of tumours of endocrine organs, adrenal myelolipoma is the only entity amongst the group of tumours being described. In the literature, other more recently documented adrenal lipomatous tumours included 24 lipomas, 32 teratomas and 16 angiomyolipomas. Rare fatty tumours of the adrenal gland comprised liposarcoma, hibernoma, adrenocortical tumours with fat component and rare adrenal tumours with fat component. Myelolipoma comprises approximately 3% of primary adrenal tumour. It is noted more common in females and the right adrenal gland. Approximately 40 bilateral myelolipomas were reported. The tumour is most frequently recorded in patients between fifth and seventh decades of life. Adrenal lipomas often seen in males and in the right adrenal gland. They were commonly noted in patients in the sixth decade of life. The diagnosis could only be possible on examination of the surgical removed specimen. Adrenal teratomas were more common in females and with a bimodal age distribution. Slightly over 60% of the patients with adrenal teratoma are symptomatic. Adrenal angiomyolipomas were often symptomatic, more common in females and in the fifth decades of life. To conclude, adrenal lipomatous tumour is uncommon. They are often benign and non-functional. It is important to recognize the features of this group of lipomatous tumours in the adrenal gland as they are being detected on increasing incidence as a result of the wide-spread use of modern imaging modalities.

## **INTRODUCTION**

Adrenal lipomatous tumour is defined as a group of adrenal tumours with a significant proportion of adipose tissue. Only two large series of adrenal lipomatous tumours were noted in the literature (Lam & Lo 2001; Zhao *et al.* 2014). In the past, adrenal lipomatous tumours were often detected at autopsy. In the recent years, they were detected as fat containing adrenal incidentaloma by ultrasonography, computerized tomography (CT) or magnetic resonance imaging (MRI) as well as functional imaging such as positron emission tomography (PET).

Myelolipoma is the most common type of adrenal lipomatous tumours. In the 4<sup>th</sup> edition of World Health Organization (WHO) Classification of tumours of endocrine organs, adrenal myelolipoma is the only entity amongst the group of tumours being described (Lam *et al.* 2017). Apart from adrenal myelolipomas, there is lack of information of the other adrenal lipomatous tumours. These adrenal lipomatous tumours were often reported as case reports in the literature. They are relatively recently described in the literature when compared to myelolipoma. To date, there is no review in literature on this group of adrenal tumours in the literature. In this review, the currently available data on the epidemiological, clinical and pathological aspects of this group of adrenal disease were presented. Particular emphases were put on the adrenal lipomatous tumours other than myelolipomas as they have not been covered in the current WHO classification.

## **MYELOLIPOMA**

The most well-known adrenal lipomatous tumour is adrenal myelolipoma. Myelolipoma is the second most common adrenocortical tumour and the most common adrenal lipomatous tumour (Lam 1992; Lam & Lo 2001). It is a benign tumour in the adrenal cortex composed of mixture of adipose tissue and bone marrow (haematopoietic) elements.

In large series, adrenal myelolipoma comprises approximately 3% to 4% of primary adrenal tumour (Lam & Lo 2001, Kulis *et al.* 2012, Shenoy *et al.* 2015).

In 2017's edition of World Health Organization (WHO) Classification of Tumours of Endocrine Organs, adrenal myelolipoma is classified as mesenchymal and stroma tumour in the adrenal cortex (Lam *et al.* 2017). In this edition, when compared to the previous edition, the epidemiology, localization, clinical features, macroscopy, histopathology, genetic profile, prognostic and predictive factors of the tumour were updated. These updates were included in the following sections.

In the literature, Arnold recorded the earliest documented case of adrenal myelolipoma as "adrenal lipoma" in German literature in 1866 (Arnold 1986). Then, Edgar von Gierke, a German pathologist, reported the fatty component and myeloid component in 1905 (Gierke 1905). The name "myelolipoma" was first coined by 1929 by a French pathologist - Charles Oberling (Oberling 1929).

The fat component of adrenal myelolipoma was postulated to be derived by the mesenchymal stem cells of stromal fat of adrenal cortex (Feng *et al.* 2013). The mature adipocytes then stimulate factors to recruit circulating hematopoietic elements to the site. The metaplasia occurs in response to stress related to stimuli such as necrosis, infection, stress or trauma. The stress may be related to prolonged increased of endogenous adrenocorticotropic hormone (ACTH) stimulation (Shenoy *et al.* 2015). Myelolipoma has been reported to be associated with many diseases as it was commonly being detected incidentally during workup for other diseases. In some adrenal myelolipomas, they were detected in patients with chronic diseases such as cancers and diabetes mellitus. In these conditions, endogenous ACTH could be elevated. It is of interest that some adrenal myelolipomas were associated with haematological diseases in which haemolytic anaemia or ineffective erythropoiesis is present (Au *et al.* 2000; Motta *et al.* 2016). These

haematological conditions could contribute to the presence of extramedullary haematopoiesis that was postulated to trigger the myeloid component in adrenal myelolipoma.

More than 1200 cases of adrenal myelolipomas were reported in the literature with more than 75% of the cases reported after 2000 (Shenoy *et al.* 2015). The increase in incidence of reporting the entity in the recent years is assumed to be due to the increase use of imaging modalities. Adrenal myelolipomas have been reported in a few larger series (Table 1) (Lam & Lo 2001; Castillo *et al.* 2007; Gershuni *et al.* 2014; Yin *et al.* 2014; Zhao *et al.* 2014). The tumour is more commonly reported in females (Table 1) (Yin *et al.* 2014; Zhao *et al.* 2014). It is most often noted in patients between fifth and seventh decades of life with an average age at presentation in the sixth decade of life. There is a wide age range at presentation from 16 months to 84 years (Lam & Lo 2001; Hsu *et al.* 2012; Barman *et al.* 2014). Also, it is twice more frequently seen in right adrenal gland as compared to the left (Table 1).

In the English literature, approximately 40 cases of bilateral myelolipomas were noted (Jung *et al.* 2007; Yang *et al.* 2015; Zattoni *et al.* 2015; Chakraborty *et al.* 2016; Kale *et al.* 2016, Soved *et al.* 2016). Shenoy and colleagues analysed the literature and reported that 12% of cases reported in the literature are bilateral (Shenoy *et al.* 2015). This may be related to the bias in reporting cases of bilateral myelolipomas. From the pooled results of some large series in the literature, approximately 1% of adrenal myelolipomas were bilateral (Table 1). Recently, Zattoni and colleagues have reviewed the literature of bilateral adrenal myelolipomas (Zattoni *et al.* 2015). The authors noted that the average age of the 19 patients with bilateral adrenal myelolipomas was 46 years (range 24 to 69) with an equal sex ratio (9 males and 10 females). Bilateral adrenal myelolipomas often associated with hormonal dysfunctions such as in congenital adrenal hyperplasia, Cushing disease (with

pituitary adenoma) and hyperaldosteronism (Jung *et al.* 2007; Chakraborty *et al.* 2016; Kale *et al.* 2016; Soveid & Rais-Jalali 2016).

On review of the literature, Shenoy and colleagues reported that adrenal myelolipoma comprised 6% of adrenal incidentaloma detected on radiological examination (Shenoy *et al.* 2015). For the symptomatic cases, the symptoms reported are often abdominal pain or discomfort. Occasionally, adrenal myelolipoma may present with symptoms and signs of acute abdomen as a consequence of complications (e.g. haemorrhage, rupture and abscess) (Kumar *et al.* 2015).

Biochemically, majority of the adrenal myelolipomas were non-functional. In the literature, endocrine dysfunction was noted in 7% of adrenal myelolipoma (Shenoy *et al.* 2015). A couple of cases were associated with hormonal manifestations such as excessive steroid (Cushing's syndrome), aldosterone (Conn's syndrome), sex hormones and catecholamines secretions (Tamidari *et al.* 2006; Udupa *et al.* 2012; Su *et al.* 2014; Shenoy *et al.* 2015). The hormonal manifestations disappeared after resection of these myelolipomas. The cause of the hypersecretion is largely unknown but may be due to mechanical irritation of the adrenal myelolipoma. Also, hyperthyroidism was noted in 51-year-old woman with adrenal myelolipoma (Ide *et al.* 2007). In this case, the cells in the myelolipoma expressed thyroid hormone receptor. In addition, many cases have been shown in cases with congenital adrenal hyperplasia has been reported (Soveid & Rais-Jalali 2016). The condition accounted for nearly half of the adrenal myelolipomas with endocrine dysfunction (Shenoy *et al.* 2015). The aetiology could be secondary to chronic stimulation of the adrenals by adrenocorticotrophic hormone (ACTH).

Radiological examination of adrenal myelolipoma reveals a hypodense mass consistent with the presence of adipose tissue (Figure 1A). Pre-operative diagnosis could be obtained by fine needle aspiration. The presence of cells of myeloid series with interspersed

adipocytes in fine needle aspiration could make a tentative diagnosis of myelolipoma (Settakorn *et al.* 1999; Hasan *et al.* 2008).

Adrenal myelolipoma is a well demarcated cortical tumour which is yellow to red depending of the relative proportion of the fat and hematopoietic components. The mean maximum dimension of the adrenal myelolipoma in the large ranges from 40 to 60 mm (Lam & Lo 2001; Zhao *et al.* 2014). From the pooled data of some large series in the literature, the mean maximum dimension of the tumour was 63mm (Table 1). The tumour could be very big. The largest adrenal myelolipoma was reported by Lamont and colleagues in the right adrenal gland of a 50-year-old man which is 400 mm in diameter and having a weight of 4254 grams (Lamont *et al.* 2002). Also, the case reported by Akamatu and colleagues in the left adrenal gland of a 51-year-old man weighed 6,000g (310 mm) which is the heaviest adrenal myelolipoma reported (Akamatu *et al.* 2004)

On histological examination, myelolipoma is composed of mature adipocytes and bone marrow (haematopoietic elements) (Figure 1B). The latter means may consist of different cells of myeloid (white blood cell forming), erythroid (red blood cell forming) and megakaryocytic (platelet forming) lines. Calcification was noted in 30% of adrenal myelolipoma (Kenney *et al.* 1998). Heterotopic bones have been reported in a few adrenal myelolipoma (Mitsui *et al.* 2014). Differential diagnoses include other less common lipomatous lesions.

Adrenal myelolipoma could occur together with adrenal adenoma as collision tumour in the adrenal gland. This is not surprising as these tumours are common tumours in adrenal gland. In the literature, approximately 20 cases have been documented (Caliumi *et al.* 2004; Ong *et al.* 2007; Lu *et al.* 2008; Yamada *et al.* 2011). Lu and colleagues analysed 17 cases reported in the literature and noted they were often noted in females (male to female ratio = 1:3) and in the left adrenal gland (Lu *et al.* 2008). The myelolipomas noted in this setting



was often small and with diameter ranged from 5mm to 30 mm (Caliumi *et al.* 2004; Lu *et al.* 2008). Many of these are non-functional adenomas. There are some other lesions reported that could co-exist with adrenal myelolipoma such as ganglioneuroma, pheochromocytoma, hibernoma, etc. (Schwartz & Wasson 2003; Shenoy *et al.* 2015).

The genetic profile of adrenal myelolipoma is rarely mentioned. Chang and colleagues reported an adrenal myelolipoma with a chromosomal translocation (3; 21)(q25;p11) (Chang *et al.* 2002). Similar change is noted in hematopoietic neoplasm reflecting that myelolipoma could derive from misplaced haematopoietic cells. Also, Bishop and colleagues have reported that eight of the 11 myelolipomas from female patients had non-random X-chromosome inactivation. These findings suggest clonal origin of myelolipoma (Bishop *et al.* 2006).

No malignant progression of adrenal myelolipoma has been reported. In the literature, the longest clinical follow-up reported in the literature was 12 years (Lam & Lo 2001). Managements of the large/symptomatic tumours are by surgery as large myelolipomas (such as measuring more than 60 mm) are prone to spontaneous rupture. Most of the centres worldwide do not operate for asymptomatic adrenal myelolipoma less than 40mm in diameter (Shenoy *et al.* 2015)

## **ADRENAL LIPOMA**

There are 24 well documented cases of adrenal lipomas in the English literature (Table 2) (Lange 1966; Prinz *et al.* 1982; Avinoach *et al.* 1989; Lam *et al.* 1997; Lam & Lo 2001; Ghavamian *et al.* 1998; Sharma *et al.* 1998; Büttner 1999; Milathianakis *et al.* 2002; Rodríguez-Calvo *et al.* 2007; Shumaker *et al.* 2008; Gupta *et al.* 2009; Shah *et al.* 2009; Singaporewalla *et al.* 2009; Goldenberg *et al.* 2011; Gunay *et al.* 2011; Kapetanakis *et al.* 2011; Patel *et al.* 2011; Jain *et al.* 2012; Zhao *et al.* 2014). The first case in the English

literature was reported by Lange in 1966 (Lange 1996). It appears that many adrenal lipomas were reported in the Asian population as two third (16 of 24) of the reported cases were noted in the Asian population. The prevalence of the tumour is low and there is no large series of adrenal lipoma in the literature. In 2001, Lam and Lo reported 3 cases in a 30-year period and adrenal lipoma accounted for 0.7% of the primary adrenal tumours (Lam & Lo 2001). In a more recent series, Zhao and colleagues reported 3 cases of adrenal lipoma in a 31-year period. They reported that the tumour accounted for 4% of all adrenal lipomatous tumours (Zhao *et al.* 2014).

In contrast to other adrenal lipomatous lesions, adrenal lipoma is more common in males. The female to male ratio is 0.7 to 1 (10 males and 14 females). Also, adrenal lipoma was found in patients in the sixth decade of life (mean age = 54; age range = 35 to 78). One third of the reported cases was in this age group.

All the adrenal lipomas noted in the literature are non-functional. It is not surprising that majority of the cases were incidental findings either at autopsy or at radiological examination. There were 9 symptomatic cases as a result of the mechanic effect of the tumours. The case reported by Lange in 1966 showed paroxysmal hypertension which is assumed to be due to mechanical irritation of the adrenal medulla to produce catecholamines. The symptomatic patients with adrenal lipoma presented with pain (Lange 1966).

Adrenal lipoma is more frequently noted on in the right adrenal gland (17 on the right; 7 on the left; right to left ratio= 2.4 to 1). In the literature, Milathianakis and colleagues reported a giant adrenal lipoma of 200 mm in dimension and 2900g (Milathianakis *et al.* 2002). The mean maximum dimension of adrenal lipomas was 75mm (range, 10mm to 200 mm). Slightly over half (54%; 13/24) of the tumours noted in the literature were larger than 60 mm. Also, the mean weight of the adrenal gland with the tumour was 417g (range, 7 to

2900 grams). Apart from the giant adrenal lipoma reported by Milathianakis and colleagues, the other adrenal lipomas were less than 1000 gram (Milathianakis *et al.* 2002).

Apart from detected at autopsy, the adrenal lipomas were often detected as incidentalomas on radiological examination. Ultrasonography of the abdomen showed a hyperechoic mass in the region of adrenal gland (Lam & Lo 1997; Sharma *et al.* 1998; Milathianakis *et al.* 2002; Patel *et al.* 2011). Recently, Puri and colleagues have reported the use of endoscopic ultrasound guided fine aspiration on a patient with adrenal lipoma (Puri *et al.* 2015). However, no detail information was reported in the case. Most often, adrenal lipoma was detected by computed tomography scan which demonstrated a well circumscribed, non-enhancing supra-renal mass of adipose tissue density. Magnetic resonance imaging was not often performed and showed similar findings to those in computed tomography scan (Shumaker *et al.* 2008; Patel *et al.* 2011). Nevertheless, the diagnosis of adrenal lipoma could only be made on histological examination.

On macroscopic examination, the tumour is well demarcated and composed of yellow adipose tissue (Figure 2A). Most of the tumours are yellow with homogenous and soft cut sections. However, patches of haemorrhages could be seen (Lam 1997; Kapetanakis *et al.* 2001; Singaporewalla *et al.* 2009; Jain *et al.* 2012). In one case, the bleeding from the vessels in the lipoma resulted in retroperitoneal bleeding (Singaporewalla *et al.* 2009).

On microscopic examination, adrenal lipoma is composed of mature adipose tissue (Figure 2B). Calcification was noted in 3 of the reported cases (Ghavamian 1998; Milathianakis *et al.* 2002; Lam & Lo 2001). Chronic inflammatory cells (Kapetanakis *et al.* 2011) were found in a case having symptoms for 10 years. Also, a case had active inflammation and abscess as a result of adjacent infection as a result of percutaneous nephrolithotomy (Gupta *et al.* 2009). In addition, a case had necrosis which is related to co-existing tuberculosis (Ghavamian *et al.* 1998).

The main differential diagnosis of adrenal lipoma is myelolipoma which is much more common in incidence. The only feature that differentiates lipoma from myelolipoma is the absence of myeloid elements in the adrenal lipoma. Thus, adequate tissue blocks should be sampled from non-fatty areas such as haemorrhagic region or calcified areas to rule out the presence of myeloid elements.

Of the 24 adrenal lipomas in the literature, 6 were detected at autopsy and 18 were detected at examination of surgical resected specimens. In the latter group, 5 were operated by laparoscopic approach and 13 by open surgery. Adrenal lipoma is a benign tumour. In the literature, clinical follow up was identified in 39% (7 of the 18) of the patients underwent surgery. The longest clinical follow-up of the lesion documented was 7 years (Lam & Lo 2001). None of the tumours had local recurrence or signs of malignancy on clinical follow-up.

In summary, adrenal lipoma is rare. The diagnosis could only be possible on surgical removed specimen. It is a benign lesion. However, it could be symptomatic and presented with pain as a result of complications.

## **ADRENAL TERATOMA**

In the English literature, 32 adrenal teratomas with well documented features were reported (Table 3) (Lam & Lo 1999; Kaneko *et al.* 2000; Khong *et al.* 2002; Bedri *et al.* 2002; Hui *et al.* 2004; Polo *et al.* 2004; Castillo *et al.* 2006; James *et al.* 2009; Oguzkurt *et al.* 2009; Shrestha *et al.* 2010; Ersoz *et al.* 2011; Kim *et al.* 2011; Li *et al.* 2011; Bhatti *et al.* 2013; Ciftci *et al.* 2013; Tang *et al.* 2014; Zhao *et al.* 2014; Li *et al.* 2015a; Li *et al.* 2015b; Mardi *et al.* 2015; Nadeem *et al.* 2015; Ratkal *et al.* 2015; Bhatia *et al.* 2016; Narla *et al.* 2016). Adrenal teratoma was first reported by Lam & Lo in 1999 (Lam & Lo 1999). In a 30-year study period, the authors have reported 3 adrenal teratomas. The adrenal teratomas

accounted for 1.3% of the surgical resected primary adrenal tumours and 0.7% of all primary adrenal tumours (Lam & Lo 2001). In 2014, Zhou and colleagues in their 31-year-study showed 2 adrenal teratomas which comprised 2.7% of adrenal lipomatous tumours (Zhao *et al.* 2014). The other large series was by Li and colleagues who reported 5 adrenal teratomas and the prevalence of the lesion in adrenal diseases in a 5-year period is 0.13% (Li *et al.* 2015b).

The majority of the adrenal teratomas were reported in Asian populations. Other than these, a few cases were reported in United States of America (USA) (n=3), Chile (n=2) and Spain (n=1). In the cases noted in Asian populations, half of the reported cases (48%; 15/31) were reported from Chinese patients from Hong Kong or China. The other patients were from India (n=4), Nepal (n=1), Pakistan (n=1), South Korea (n=1) and Japan (n=1). Also, there are three cases reported from Turkey and one case from Saudi Arabia.

Adrenal teratoma was more common in females with female to male ratio = 1.9 to 1 (21 females; 11 males). From the pooled data in literature, adrenal teratoma occurs in a wide age range with the median age at presentation at 23. There is bimodal age distribution for the cases (Figure 3A). The tumours are common in the first decade as well as the third decade of life. There is no gender difference in the age distribution.

Slightly over 60% (20 of 32; 62.5%) of the patients with adrenal teratoma were symptomatic. The most common symptom is abdominal pain (n=14). Other clinical presentations noted include abdominal distention and hypertension. A case was noted in a newborn boy in respiratory distress (James *et al.* 2009). Bhatia and colleagues reported an adrenal teratoma complicated by extension through diaphragm and involving the lung giving the symptom of coughing (Bhatia *et al.* 2016). All the cases are non-functional on biochemical investigations. Oguzkurt and colleagues have reported an adrenal teratoma with

increase serum alpha fetoprotein level in a 45-day-old infant (Oguzkurt *et al.* 2009).

However, no immature element was noted on histology.

All the adrenal teratomas reported in the literature had either CT or MRI done. The examination showed mainly a fatty mass as in other adrenal lipomatous tumours. However, when compared to other adrenal lipomatous tumours, adrenal teratomas were often cystic, heterogeneous and commonly having calcification (Figure 3B). From the pooled data in literature with detailed descriptions, 90% (26 of 29) of adrenal teratomas were cystic and 76% (22 of 29) showed calcification. The typical radiological features of adrenal teratoma are heterogeneous mass in the adrenal region containing fluid, adipose tissue and/or serum in the form of a fat-fluid level and with calcification. Pre-operative diagnosis of adrenal teratoma was made in four (13%) adrenal teratomas (Li *et al.* 2015a; Mardi *et al.* 2015; Nadeem *et al.*, 2015)

Adrenal teratoma has no side preponderance (right =17; left =15). From the pooled data in the literature, the mean maximum dimension of the tumour is 99 mm (range, 24mm to 380 mm). Eighty-four per cent (27 of 32) of the reported cases were of diameter 60mm or above. A giant adrenal teratoma was reported by Polo and colleagues which weighed 10 kg (Polo *et al.* 2004). The other tumours weighed between 48.5g to 1620g. On cut sections, adrenal teratoma was often cystic. Greasy sebaceous material, skin and hair are commonly noted. In addition, it may compose of large mass of adipose tissue mimicking other fatty tumours such as myelolipoma and lipoma (Lam & Lo 1999) (Figure 3C). In some instance, cartilage, bone and teeth as well as mucinous substance could be noted on macroscopic examination (Shrestha & Lalchan 2010; Nadeem *et al.* 2015).

On histological examination, all cases were mature teratoma. Characteristically, they are mostly cystic and contain tissues from 3 germ layers (Figure 3D). Mardi and colleagues noted a case with complete layers of colon wall (Mardi *et al.* 2015). No evidence of

immature elements or malignancy noted. Erosoz described a case in an 8-year-old boy with co-existing neurocytoma (Erosoz *et al.* 2011). Also, Narla and colleagues noted an adrenal teratoma associated with carcinoid in a 2-year-old girl (Narla *et al.* 2016).

Teratomas are result of abnormal development of pluripotent cells: embryonic cells or germ cells. Teratomas of embryonic origin are congenital. For instance, 3 adrenal teratomas occurred in young infants; one antenatal, one at birth and one at 3 months of age (James *et al.* 2009; Oguzkurt *et al.* 2009; Ciftci *et al.* 2013). Teratomas of germ cell origin could be congenital or in adult. The close anatomic association of adrenal cortex with the urogenital apparatus and its embryological development from coelomic epithelium make it a possible site of development of teratoma.

The main differential diagnosis of adrenal teratoma was to differentiate from retroperitoneal teratoma. It is often difficult and many of the cases reported in the literature actually mentioned clearly that it is not possible to differentiate the teratoma arising in these two sites. The finding of normal adrenal cortex encasing the tumour could be the most important sign of adrenal teratoma. The other possible differential diagnosis is metastatic malignant teratoma. A case of malignant teratoma presented with adrenal mass has been reported (McMillan & Horwich 1987).

In the literature, 19 of the 32 cases had follow-up information. The clinical follow-up of patients with adrenal teratoma ranged from half a year to 8 years (mean= 2.7 years). None of the patients had recurrent or malignant change.

## **ADRENAL ANGIOMYOLIPOMA**

Angiomyolipoma is a member of the family of neoplasms that derive from perivascular epitheloid cells (PEC) (PEComa family) (Thway & Fisher 2015). It could occur in the settings of tuberous sclerosis complex. Lymphangoleiomyomatosis (LAM) is as an

infrequent symptomatic pulmonary complication in tuberous sclerosis (Hancock *et al.* 2002). It also belongs to the PEComa family. Angiomyolipoma is a tumour composed of blood vessels, smooth muscle (myo) cells and fat cells. The tumour is positive for melanocytic (HMB-45 and melan-A) and smooth muscle marker (smooth muscle actin). It most often occurs in the kidney or liver.

Adrenal angiomyolipoma is very rare. Because of the anatomical location, it is difficult to distinguish between primary renal and primary adrenal angiomyolipoma on radiological examination. A total of 16 well documented cases have been noted in the literature (Table 4) (Lam & Lo 2001; Elsayes *et al.* 2005; Godara *et al.* 2007; Sutter *et al.* 2007; D'Antonio *et al.* 2009; Chee Kong *et al.* 2010; Yener *et al.* 2011; Hu & Xi 2012; Hafeez Bhatti *et al.* 2013; Sazuka *et al.* 2013; Goswami *et al.* 2014; Zhao *et al.* 2014; Li *et al.* 2015; Kwazneski Li *et al.* 2016). Most of the cases (12 of 16 ;75%) were reported in Asia.

Lam and Lo first documented the histology of 2 adrenal angiomyolipoma in the literature in 2001 (Lam & Lo, 2011). Both cases were asymptomatic. In the report, angiomyolipoma accounted for 0.5% and 0.8% of the primary and surgical resected primary adrenal tumours respectively. On the other hand, most of the reported cases in the literature were symptomatic (69%; n=11) and presented with abdominal pain.

By analysing the features of well documented cases in the English literature, adrenal angiomyolipoma was more common in females (11 females, 5 males; female to male ratio = 2.2: 1). The tumours were noted in a wide age range from 20 to 72. The mean age at presentation was 51 with 43% (n=7) of the cases first noted in the fifth decades of life. It has no site predilection (8 on the right side and 8 on the left side).

In a study of 209 patients with renal angiomyolipomas, 11% (n=24) had tuberous sclerosis (likely or definite) (Lane *et al.* 2008). Similarly, of the 16 adrenal angiomyolipomas noted in the literature, 2 had tuberous sclerosis and 1 had lymphangioliomyomatosis; giving



a 19% prevalence of syndrome complex in adrenal angiomyolipomas. There is an additional case of adrenal angiomyolipoma noted in a series of extra-thoracic lymphangioliomyomatosis (Maziak *et al.* 1996). However, no detail information was given about the case and thus this case was not counted in the current analysis.

Radiologically, the tumour appeared heterogeneous with fat and haemorrhagic component mimicking myelolipoma (Sazuka *et al.* 2013). It can also be misdiagnosed as adrenocortical tumour (Godara *et al.* 2007; Yener *et al.* 2011; Hu & Xi 2012).

On pathological examination, the dimension of the tumours ranges from 2mm to 160mm (mean = 88 mm) and the weight of the tumours range from 3 to 626 grams (mean = 168 gram). The histological features of most of the tumours noted in the literature are classical with mixture of the 3 components – vessels, muscles and adipose tissue (Figure 4). Calcification was documented in 2 cases (Hafeez Bhatti *et al.* 2013; Kwazneski Ii *et al.* 2016). Also, one of the cases has epitheloid morphology (D'Antonio *et al.* 2009).

All the cases reported to date are benign on morphological examination. Over a short mean follow-up period of 3.3 years, all the cases showed no tumour recurrence or metastases.

## **OTHER ADRENAL LIPOMATOUS TUMOURS**

The other lipomatous tumours in the adrenal gland are rare. They could be divided into 3 groups; rare primary adrenal lipomatous tumours, adrenocortical tumours with fat component and adrenal tumours with fat component (Table 5).

### *Rare primary lipomatous tumours*

The rare primary adrenal lipomatous tumours are liposarcoma and hibernoma.

Liposarcoma is the most common retroperitoneal sarcoma. There are four major liposarcoma subtypes: atypical lipomatous tumour/well-differentiated liposarcoma,

dedifferentiated liposarcoma, myxoid/round cell liposarcoma, and pleomorphic liposarcoma (Matthyssens *et al.* 2015). It is very difficult to differentiate whether the liposarcoma is primary in the adrenal or in the soft tissue in the peritoneum. In the literature, two adrenal liposarcomas have been reported (Lam & Lo 2001; Zhao *et al.* 2014). They were noted in female patients in the fourth decade of life. Also, both adrenal liposarcomas were myxoid (round cell) liposarcoma. It is worth noting that retroperitoneal liposarcoma are most often of well-differentiated subtype or dedifferentiated liposarcoma (Matthyssens *et al.* 2015).

Hibernoma is a tumour composed of brown fat. Histologically, the tumour is composed of primitive embryonal fat characterized by multi-vacuolated fat cells containing phosphatides in the cytoplasm and eccentrically placed nuclei. Two cases of adrenal hibernomas were reported in the English literature. The first case of adrenal hibernoma was reported by Schwartz and Wasson in 2003 (Schwartz & Wasson 2003). The tumour was associated with myelolipoma. The other case was reported by Val-Bernal and colleagues in 2013 (Val-Bernal *et al.* 2013). The patient also had a cortical adenoma producing primary hyperaldosteronism. Both are small tumours (11 mm and 17 mm respectively), asymptomatic and detected in associated with other benign adrenal tumours.

#### *Adrenocortical tumours with fat component*

Adrenal cortical adenoma is the most common tumour in the adrenal gland (Lam 1992). Myelolipomatous changes are common. On the other hand, lipomatous changes without bone marrow component are not frequently reported. Seven adrenal cortical adenomas with extensive area of adipose tissue have been described in the literature. They have been labelled as adrenal cortical adenoma with fat component (Sato *et al.* 1995), adenoma with lipomatous metaplasia (Papotti *et al.* 1996), adrenal cortical extensive fat cell metaplasia (Feldberg *et al.* 1996), lipoadenoma (Uriev *et al.* 2014; Mylarappa *et al.* 2014; Luo

*et al.* 2015). In addition, Montone and colleagues have reported 2 cases of adrenocortical neoplasm with uncertain malignant potential having separate areas of myelolipomatous and lipomatous metaplasia (Montone *et al.* 2009). Similar to conventional adenomas, majority of these tumours were reported in female patients; only 2 cases were reported in male patients

Adrenal oncocytoma is an adrenal cortical tumour consists entirely or predominately of cells with dense eosinophilic cytoplasm. Four cases have been reported to contain fat. They were benign on clinical follow-up (Lin *et al.* 1998; Rosenkrantz *et al.* 2010). Two of these cases were asymptomatic and two presented with abdominal pain.

There are 3 adrenocortical carcinoma reported to be having a component of adipose tissue (Izumi *et al.* 2003; Heye *et al.* 2005; Egbert *et al.* 2010). The tumours were noted in left adrenal, functional and in male patients. One of them is a myxoid variant of adrenocortical carcinoma (Izumi *et al.* 2003)

#### *Other primary adrenal tumours with fat component*

Fat have been reported in cavernous hemangioma (Tremote *et al.* 2007) and pheochromocytoma (Ramsay *et al.* 1987)

## **CONCLUSION**

Adrenal lipomatous tumour is uncommon. Myelolipomas is the predominant type but various types of lipomatous adrenal gland tumours such as lipomas, teratoma, angiomyolipoma, etc. are increasing being reported. This group of tumours are often benign and non-functional. Table 6 presented the key features of the common adrenal lipomatous tumours showing that there are subtle differences between them. Surgery is recommended for tumours that are symptomatic, hormonally active and presenting with complications. It is important to recognize the features of this group of lipomatous tumours in the adrenal gland

as they are being detected on increasing incidence as a result of the wide-spread use of modern imaging modalities.

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## Figure Legends

### Figure 1. Adrenal myelolipoma

1A. CT scan showing a well demarcated hypodense mass (cross arrows) in the right adrenal region.

1B. Microscopic features of myelolipoma showing the presence of adipose tissue mixed with bone marrow cells of red blood cell and white blood cell lineages noted. Calcification is noted fibrous stroma (haematoxylin and eosin x 40)

### Figure 2. Adrenal lipoma

2A. Adrenal lipoma composed of yellow homogenous fatty tissue encased by adrenal cortex. Note the adrenal gland at one end of the tumour

2B. Microscopic appearance of the adrenal lipoma showing that it is composed of mature adipose tissue with no bone marrow elements (haematoxylin and eosin x 1)

### Figure 3. Adrenal teratoma

A. The age distribution of adrenal mature teratoma showing the tumour is more common in the age groups (0 to 9) as well (20-29).

B. CT scan showing a well demarcated heterogeneous mass in the left adrenal region.

C. Macroscopic appearance showing the tumour is composed large amount of fatty tissue.

D. Microscopic appearance showing the presence of cartilage as well as adipose tissue (haematoxylin and eosin x 20)

### Figure 4. Adrenal angiomyolipoma.

Microscopic appearance of the adrenal angiomyolipoma showing the presence of blood vessels and myoid cells in additional to the adipose tissue (haematoxylin and eosin x 20).