



## Case report

## Adrenal myelolipoma: Defining the role of surgery. A case report

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## ABSTRACT

**Introduction and importance:** Adrenal myelolipomas (AMLs) are rare, non-functional, benign tumours mostly diagnosed incidentally. They present as small and unilateral masses that are histologically composed of mature adipose tissue with admixed haemopoietic elements. In a small percentage of patients, pressure symptoms, retroperitoneal haemorrhage or tumour rupture may occur. However, indications for surgery in the majority of asymptomatic patients are poorly defined.

**Case presentation:** A 44-year old male patient presented with signs of gastroenteritis. Computed tomography (CT) imaging revealed an encapsulated, sharply delineated mass measuring 87 × 76 × 87 mm displacing the right adrenal gland. Average attenuation was −30 Hounsfield units. Given the pathognomonic features, an AML was suspected. The patient underwent open tumour resection and the diagnosis was histologically confirmed.

**Clinical discussion:** Small (<4 cm), homogeneous, non-hormone secreting incidentalomas with an attenuation of <10 Hounsfield units on non-contrast CT are considered benign requiring neither treatment nor follow-up. Giant AMLs (>10 cm) may cause symptoms or complications and are therefore considered candidates for surgery. The treatment strategy of asymptomatic AMLs ranging from 4 cm to 10 cm, however, is controversial and poorly defined. The role of surgery in this specific subgroup of patients is studied.

**Conclusion:** Surgery is indicated in the presence of a tumour diameter above 6 cm, rapid tumour growth (RECIST 1.1 criteria for progressive disease at 6–12 months follow-up), imaging suspicious of malignancy, radiological signs of local invasion, functioning ipsilateral adrenocortical adenoma, pressure-related symptoms and signs of retroperitoneal bleeding or spontaneous tumour rupture.

## 1. Introduction

Adrenal myelolipomas (AMLs) are benign non-functional tumours of the adrenal cortex composed of mature adipose tissue and varying amounts of myeloid components [1–3]. They represent 3.3 % to 6.5 % of all adrenal masses [1] and rank second in terms of prevalence after adrenocortical adenomas [4]. Although their prevalence is higher in patients with congenital adrenal hyperplasia [5].

Little is known about their etiology and pathogenesis. At the time of diagnosis, most AMLs measure <4 cm in diameter, and display a very slow growth rate. The overwhelming majority of AMLs are unilateral and discovered incidentally during radiological imaging [1]. Indeed, only 5 % of patients are ever symptomatic presenting with local pressure

symptoms [6]. Spontaneous rupture and retroperitoneal haemorrhage are exceedingly rare. The patients are usually diagnosed between their fifth and seventh decade of life and there is an almost even gender distribution [1].

We present the case of an asymptomatic patient with a 9 cm large AML, who was treated at a regional hospital. The treatment algorithms for small (<4 cm) and very large lesions (>10 cm) are well established. However, the role of surgery in the treatment of asymptomatic mid-sized lesions (4–6 cm) is poorly defined. This comprehensive literature review aims to describe the clinical, radiological and histological characteristics of AML as well as to define the indications for surgery.

The work has been reported in line with the SCARE 2020 criteria [7].

**Abbreviations:** AML, adrenal myelolipoma; HU, Hounsfield units; CAH, congenital adrenal hyperplasia; CT, computed tomography; MRI, magnetic resonance imaging.

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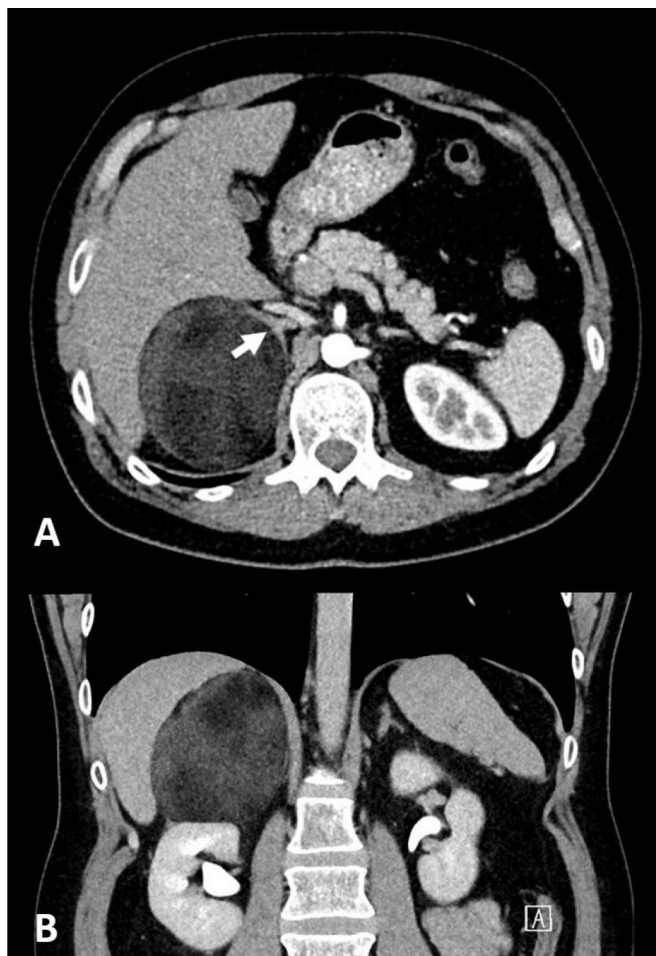
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## 2. Presentation of case

A 44-year old male patient presented to his general practitioner with signs of gastroenteritis. An abdominal ultrasound revealed a 9 cm large adrenal tumour located on the upper pole of the right kidney. The patient's personal and family history was, other than a history of smoking (7 pack-years) uneventful. There were no previous operations or hospitalizations and the patient was on no regular medication. There was no reported weight loss (183 cm, 79 kg, BMI 23.9 kg/m<sup>2</sup>) and blood pressure was normal. Routine laboratory data were within normal range. The patient experienced no pressure related symptoms. A biochemical work-up was not performed.

Computed tomography (CT) revealed an encapsulated, sharply delineated rounded inhomogeneous mass measuring 87 × 76 × 87 mm displacing the right adrenal gland (Fig. 1). The tumour was isodense to fat and displayed no contrast medium uptake. Average attenuation of the tumour was -30 Hounsfield units (HU). In addition, no pathological lymph nodes were detected. Based on these pathognomonic radiological characteristics, the diagnosis of an AML was established. The case was discussed in an interdisciplinary tumour board. Due to the size of the tumour, surgical excision was recommended.

The patient underwent open tumour resection through a right subcostal incision. An en-bloc resection, including the perirenal fat and the adrenal gland, was performed. The procedure was executed by the head of the surgical department.



**Fig. 1.** Computed tomography (arterial phase, A: transversal plane, B: coronal plane): large non-enhancing mass displacing the right adrenal gland. It displays an inhomogeneous cloudy pattern of darker areas representing fat and lighter areas representing myeloid tissue. Y-shaped normal sized enhancing right adrenal gland (white arrowhead).

The postoperative course was uneventful, and the patient was discharged on day 5. The tumour had a weight of 362 g and a maximal diameter of 11 cm (Fig. 2). Histology confirmed the diagnosis of a myelolipoma (Fig. 3). FISH analysis (fluorescence in situ hybridization) for *MDM2* gene (12q15) amplification was negative. Two months later, a follow-up examination was conducted at our endocrinology unit. The patient was in perfect health. The laboratory results for electrolytes, renin, cortisol, aldosterone and adrenocorticotropic hormone were within normal limits. The possibility of a congenital adrenal hyperplasia (CAH) was excluded.

At the time of the radiological diagnosis, the patient initially showed some anxiety and concern with respect to a possible malignant growth. At postoperative follow-up examination, the patient then expressed deep relief about the benign nature of the resected specimen.

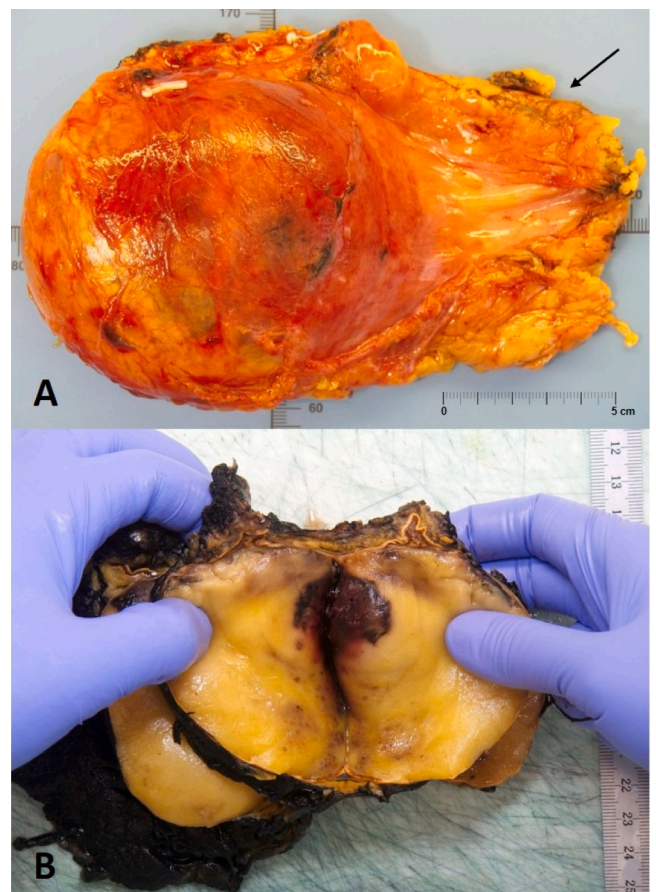
## 3. Discussion

AMLs are benign, slow-growing lesions of the adrenal cortex. About 95 % of AMLs are asymptomatic and therefore classified as incidentalomas.

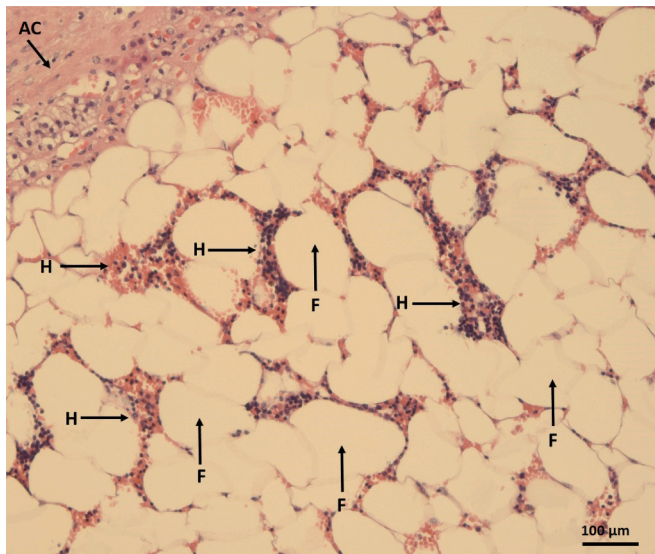
In the present publication, clinical, radiological and histological characteristics of AMLs are described and the role of surgery is discussed.

### 3.1. Definitions

AMLs up to 6 cm are considered small, whereas most authors classify



**Fig. 2.** Macroscopic adrenalectomy specimen (formalin-fixated). A: (surface view). Rounded tumour with adherent perirenal fat and right adrenal gland (black arrowhead). B: (tumour cut open with multiple radial incisions). Yellowish cut surface (adipose tissue) with haemorrhagic spots (myeloid tissue). Surface marked with black ink.



**Fig. 3.** Microscopic image showing mature haematopoietic tissue (arrowheads H) between mature fat cells (arrowheads F) compatible with myelolipoma. In the upper left corner, the transition of the myelolipoma to the adrenal cortex (arrowhead AC) is visible (haematoxylin-eosin staining, overall magnification 100 $\times$ ).

AML with a maximal diameter of  $\geq 6$  cm as large and lesions above 10 cm giant [1,4]. The percentage of large AMLs ranges from 8 % [8] to 14.4 % [6]. Giant AMLs can be found in 3.6 % of cases [6]. In some surgical series, more than a third of all patients may present with giant AMLs, most likely due to selection bias [4].

### 3.2. Prevalence of AML

A large population-based study by Ebbelohj et al. investigated the epidemiology of all adrenal tumours [9]. It showed an overall standardized prevalence of 532/100'000. Upon closer examination, however, this was largely dependent on age, ranging from 13/100'000 in children to up to 1900/100'000 in patients older than 65 years of age [9]. AMLs accounted for approximately 3.3 to 6.5 % of all adrenal tumours [1,6]. In a large retrospective study at a tertiary centre >60'000 CT scans were reviewed. Within this study sample, the overall prevalence for AML amounted to 0.24 % [8]. In patients with CAH, the reported prevalence of AML reached 8.6 % [5].

### 3.3. Laterality

Laterality was studied in a recent comprehensive review of 440 patients with AML [4]. This study showed that AMLs are more frequently reported on the right side (59.2 %) than on the left side (25.3 %). Furthermore, bilateral AMLs are seen in 12.3 % of cases, often in conjunction with CAH [4].

### 3.4. Natural history of AML

AMLs are benign tumours with a low proliferation rate. Most patients remain asymptomatic their entire life. Hamidi et al. observed 163 patients with an AML over a median period of 7.25 years (range: 0.5–20 years) [6]. Overall, median tumour growth was 0 cm, ranging from 1 cm shrinkage to 11.5 cm growth. The median annual tumour growth rate was 0 cm (range:  $-0.6$ – $1.4$  cm). A tumour size above 3.6 cm at the time of diagnosis was considered a risk factor for future tumour growth [6]. Conversely, Campbell et al. followed 69 patients with an AML over a median period of 3.9 years. The median annual tumour growth rate here was 0.16 cm (range: 0.08–0.71). In addition, rather than initial tumour

size, it was a younger age at the time of diagnosis that proved to be a predictor for subsequent tumour growth [8].

### 3.5. Clinical signs and symptoms

The diagnosis of AML is most often made at a median age of 55–65 years [1,6]. Both sexes are affected almost equally [1,4]. A large retrospective study by Hamidi et al., which included 305 patients between 2000 and 2016, showed that about 95 % of AMLs are diagnosed as incidentalomas [6]. The remaining 5 % of patients presented with abdominal fullness due to the mass effect. Symptoms included early satiety, abdominal discomfort, flank and back pain as well as positional shortness of breath [6]. Large radiological referral cohorts reported a median tumour size at the time of diagnosis between 2 and 3 cm [6,8]. Up to 6 % of patients were diagnosed with a concomitant functioning or non-functioning adrenocortical adenoma [6]. Some patients therefore showed symptoms due to hormone excess. Spontaneous tumour rupture or acute retroperitoneal haemorrhage requiring surgery were extremely rare events, occurring in <1 % of cases [6].

### 3.6. Spontaneous rupture and retroperitoneal haemorrhage

Hamidi et al. performed a long-term longitudinal study of the clinical course of AMLs with a median follow-up period of 4.5 years. Radiographic haemorrhagic changes were observed in nine out of 305 patients (3 %) [6]. Acute haemorrhage and/or tumour rupture requiring surgery occurred in three patients within the same study population (1 %) [6]. All of the above named 12 patients presented with an AML larger than 6 cm in diameter [6]. Similarly, Decmann and co-workers published a comprehensive literature review of 440 patients with AML. In this study, the average tumour size was 10.2 cm and tumour rupture was reported in 20 patients (4.5 %) with a median tumour diameter of 12 cm. No rupture occurred in AML smaller than 6 cm [4]. Other studies, such as those by, Campbell et al. reported on 150 patients with 155 radiographically diagnosed AMLs. Here, the median tumour size at diagnosis was 2.1 cm. Sixty-nine patients received a follow-up CT. The mean time interval between both examinations was 3.9 years. No patient presented with tumour rupture or retroperitoneal bleeding, neither at the time of diagnosis nor at follow-up [8]. In summary, retroperitoneal haemorrhage and spontaneous tumour rupture are exceedingly rare events occurring more commonly in tumours measuring >6 cm [4,6].

### 3.7. Radiological diagnosis

The imaging diagnosis of AMLs is in most cases straightforward. CT and magnetic resonance imaging (MRI) reveal the pathognomonic imaging features [1,10]. The adrenal tumour is round, well circumscribed and often presents with a pseudocapsule. AMLs display a cloudy pattern of macroscopic fat without contrast medium uptake due to its poor vascularization and solid strands or islets of contrast enhancing myeloid tissue [1,10]. The proportion of the two components determines the attenuation. With a CT-scan, most AMLs exhibit an attenuation between  $-50$  and  $-20$  HU [1]. The median unenhanced CT attenuation amounts to  $-37.8$  HU [6]. Using an MRI, the macroscopic fat components appear hyperintense on T1 and T2-weighted images, whereas the haematopoietic elements are hypointense on T1- and moderately hyperintense on T2-weighted images [10,11]. Diagnostic difficulties arise if there is an almost even distribution of adipose and myeloid tissue or if the tumour is composed almost exclusively of myeloid tissue. In these instances, differential diagnoses include adrenocortical carcinoma or retroperitoneal liposarcoma [1].

### 3.8. Biochemical work-up and CAH

Patients should be examined for clinical signs and symptoms of hormone excess. A hormonal work-up should be considered and may

include the measurement of potassium and aldosterone concentrations, the renin plasma activity and the performance of a 1 mg overnight dexamethasone suppression test [1].

CAH are a group of autosomal recessive disorders affecting steroid synthesis in the adrenal cortex [1]. The clinical course of CAH can be either severe (classic: salt wasting and non-salt wasting) or mild (non-classic). Routine newborn blood test screening from a heel prick will detect classic CAH. However, the non-classic variant of CAH may remain undetected as it displays residual enzyme activity between 20 and 70 % [1]. A resulting increase in ACTH levels, stimulating the adrenal glands, will lead to bilateral cortical hyperplasia and may promote the development of AMLs [1]. Patients with CAH have a higher prevalence of AMLs that are larger, more often bilateral, and present at a younger age [1,5]. Conversely, CAH should be excluded in patients with large and bilateral AMLs through the measurement of 17-hydroxyprogesterone [5]. In one comprehensive literature review, 10 % (44/440) of patients with AMLs had concomitant CAH [4].

### 3.9. Surgical management

Minimally-invasive resection for AMLs is safe and effective [12]. For giant AMLs, most authors prefer the transperitoneal to the retroperitoneal approach. If malignancy cannot be excluded by imaging, open surgery may be the safer approach [1,4].

Transarterial embolization has been described in the initial treatment of patients with tumour rupture and/or retroperitoneal haemorrhage. It allows for semi-elective surgery after haemodynamic stabilization and correction of coagulation disorders [13,14].

### 3.10. Histological diagnosis

In the majority of patients, radiological imaging is sufficient to establish the diagnosis. Preoperative percutaneous core needle biopsies are performed in patients with ambiguous radiological findings [1,15]. Once resected, pathohistological examination shows a well-demarcated tumour composed of adipose and myeloid tissue [1]. Routine haematoxylin-eosin staining is generally sufficient to confirm the diagnosis [1]. However, in patients with high-grade nuclear changes and an abrupt transition to a spindle cell component, which may be indicative of a liposarcoma, molecular testing for *MDM2* amplification is recommended [1].

### 3.11. Indications for surgery

First, surgery is indicated in symptomatic patients. Symptoms may be due to local pressure (early satiety, abdominal discomfort, flank pain, shortness of breath), retroperitoneal bleeding (anaemia, back pain) or intraperitoneal tumour rupture (haemorrhagic shock). Symptoms may also be due to hormone excess caused by a functioning ipsilateral adrenocortical adenoma.

Secondly, surgery is required in patients presenting with imaging studies suspicious for malignancy or with radiological signs of local invasion. In some instances, core needle biopsy may be considered for diagnosis and, if applicable, define a neoadjuvant treatment strategy.

Furthermore, some authors consider tumour size alone, even in asymptomatic patients, as an indication for surgery [1,5,6,16,17]. The rationale being that preemptive surgery will prevent future complications such as spontaneous tumour rupture [16]. Although there is no agreement as to a clear-cut threshold value, the risk of adverse events increases with tumour size [4,6]. Proposed cut-off values range from 3.5 cm and 5 cm up to 6 cm [5,6,17]. Some authors remain vague and propose surgery for “large” tumours [6], “very large” tumours [1] or on an individual basis [16]. Haemorrhagic complications, however, almost exclusively occur in AMLs with a diameter larger than 6 cm [4,6]. Based on the available data, we would like to propose a cut-off value of 6 cm for elective surgery in asymptomatic patients [4,6].

Eventually, tumour growth rate could be used as a possible indication for surgery. In 2016, the European Society of Endocrinology (ESE) and the European Network for the Study of Adrenal Tumors (ENS@T) published clinical practice guidelines for the management of adrenal incidentalomas [18]. In this surgical series, AMLs represented about 8 % of adrenal masses. In general, small (<4 cm), non-hormone secreting, homogeneous incidentalomas with <10 HU on non-contrast CT are considered benign and need no further imaging [18,19]. Lesions not meeting these criteria should be discussed at a multidisciplinary expert team meeting. Asymptomatic lesions require radiological follow-up. Surgery is indicated if the lesion shows an enlargement of >20 % at 6–12 month follow-up (in addition to at least 5 mm increase in maximum diameter). These criteria correspond to the RECIST (Response Evaluation Criteria In Solid Tumors) 1.1. criteria for tumour progression.

## 4. Conclusion

Indications for surgery in patients with AMLs include tumour diameter above 6 cm, rapid tumour growth according to the RECIST 1.1 criteria for progressive disease at 6–12 months follow-up, imaging suspicious of malignancy, radiological signs of local invasion, functioning ipsilateral adrenocortical adenoma, pressure-related symptoms and signs of retroperitoneal bleeding or spontaneous tumour rupture.

### Provenance and peer review

Not commissioned, externally peer-reviewed.

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### Ethical approval

This case report is exempt from ethical approval in our institution.

### Research registration

Not applicable.

### Consent

Written informed consent was obtained from the patient for publication of this case report and the accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

### Author contribution

Pietro Renzulli treated the patient. Xanthi Steka and Pietro Renzulli wrote the original article. Mariko Melanie Renzulli contributed the radiological images. Bart Vrugt provided the photos of the specimen and the histology slides. Florian Martens and Fabian Hauswirth critically reviewed the first draft. All authors critically reviewed the final version of the manuscript.

### Guarantor

Pietro Renzulli.

### Declaration of competing interest

No conflicts of interest by any of the authors.

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