Adrenal myelolipomas

Jan Calissendorff, Carl Christofer Juhlin, Anders Sundin, Irina Bancos, Henrik Falhammar

Adrenal myelolipomas are benign, lipomatous tumours with elements of myeloid cells, most of which present as adrenal incidentalomas and comprise 3·3–6·5% of all adrenal masses. Adrenal myelolipomas are usually unilateral (in 95% of cases), variable in size, most often found during midlife, and affect both sexes almost equally. On imaging, adrenal myelolipomas show pathognomonic imaging features consistent with the presence of macroscopic fat. Large adrenal myelolipomas can cause symptoms of mass effect, and can occasionally be complicated by haemorrhage. In the event of a concomitant adrenal cortical adenoma or hyperplasia, adrenal hormone excess might be detected in patients with adrenal myelolipoma. Patients with congenital adrenal hyperplasia exhibit a higher prevalence of adrenal myelolipomas than other patient groups, and are at risk of developing large and bilateral lesions. This Review discusses the pathogenesis, clinical presentation, and management of adrenal myelolipomas

Lancet Diabetes Endocrinol 2021; 9: 767–75

Published Online August 24, 2021 https://doi.org/10.1016/S2213-8587(21)00178-9

Department of Endocrinology (J Calissendorff PhD, H Falhammar PhD) **and Department of Pathology and Cytology** (C C Juhlin PhD), **Karolinska University Hospital, Stockholm, Sweden; Department of Oncology-Pathology** (C C Juhlin) **and Department of Molecular Medicine and Surgery** (J Calissendorff, H Falhammar), **Karolinska Institutet, Stockholm, Sweden; Department of Surgical Sciences, Radiology and Molecular Imaging, Uppsala University, Uppsala, Sweden** (Prof A Sundin PhD)**; Division of Endocrinology, Diabetes, Metabolism, and Nutrition, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA** (I Bancos MD)

Correspondence to: Dr Jan Calissendorff, Department of Molecular Medicine and Surgery, Karolinska Institutet SE-171 76 Stockholm, Sweden **jan.calissendorff@sll.se**

Introduction

Myelolipomas were first described in 1905 as an adrenal tumour composed of mature fat mixed with myeloid and erythroid cells.[1] Adrenal myelolipomas are the second most common benign type of tumour in the adrenals, following after adrenocortical adenomas.[2,3] On imaging, adrenal myelolipomas appear as rounded tumours containing macroscopic fat and varying amounts of myeloid components.[4] Most myelolipomas are slow-growing tumours, which might occasionally cause pressure symptoms.[5,6] Seldomly, patients might present to the emergency room due to haemorrhage or rupture of myelolipomas.

Despite being so common, the entity is still unfamiliar for many physicians, and there is therefore a need to make the condition better known. This Review discusses the pathogenesis, epidemiology, clinical presentation, association with congenital adrenal hyperplasia, histology, differential diagnosis, radiological features, as well as management and outcome of adrenal myelolipoma, and additionally addresses clinically important questions on follow-up and gaps of knowledge.

Pathogenesis

Adrenal myelolipomas consist of adipose tissue and haematopoietic cells arising in patients with a healthy bone marrow. In the fetus, this extramedullary haematopoiesis is a physiological process until the bone marrow matures, and erythropoietin receptors are expressed in the adrenal cortex.[7] Extramedullary haematopoiesis also occurs in adult life, secondary to defective haemoglobin synthesis.[8] In rare instances, patients with adrenal myelolipoma might have a concomitant haematological disease, such as thalassaemia.[9] In patients with chronic anaemia, increased concentrations of erythropoietin can stimulate the development of adrenal myelolipoma, similarly to the reported bilateral large myelolipomas that are secondary to erythropoietin administration.[10]

Most scientific data suggest an association between increased adrenocorticotropic hormone (ACTH) concentrations and an increased risk of developing adrenal myelolipomas, given that these lesions are frequently reported in patients with Cushing's syndrome or congenital adrenal hyperplasia.[11–13] Although the concentrations of ACTH can be very high in primary adrenal insufficiency (eg, Addison's disease), to our knowledge, adrenal myelolipomas have not been reported in these patients. In Thomas Addison's original paper from 1855, one of the 11 patients had tuberculosis deposits to the adrenals, but also "opaque matter exhibited a copious amount of fatty matters, but no nucleated cells".[14] This finding might have been a first description of adrenal myelolipoma driven by high ACTH concentration in a patient with primary adrenal insufficiency. Sufficient amounts of remaining adrenocortical tissue in patients with autoimmune Addison's disease could make them susceptible to developing myelolipomas. However, autoimmune Addison's disease causes atrophy and fibrotic derangement of the adrenal glands, which might explain why adrenal myelolipomas have not been reported in this setting, despite chronically increased ACTH concentrations.

Pituitary extracts injected in rat adrenals have been shown to give rise to a myeloid phenotype, thereby possibly suggesting that ACTH could influence the development of myelolipomas.[15] However, the few available studies regarding ACTH receptor expression in adrenal myelolipomas are not consistent, with some studies reporting overexpression and others a complete absence of ACTH receptor immunoreactivity.[16–18] However, most patients with myelolipoma have normal concentrations of ACTH, indicating other drivers of myelolipoma development.

Other postulated mechanisms include metaplasia of reticuloendothelial cells in the adrenal glands due to stress, infection, or trauma, or via embolism of bone marrow cells.[19] Speculations suggest that myelolipomas result from adrenocortical adipocytes derived from mesenchymal stem cells and circulating bone marrow released and recruited by granulocyte stimulating factor.[20]

Molecular and genetic characteristics

Apart from the potential physiological association of ACTH and erythropoietin with myelolipoma development, little is known about the underlying molecular events driving the formation of an adrenal myelolipoma. To our

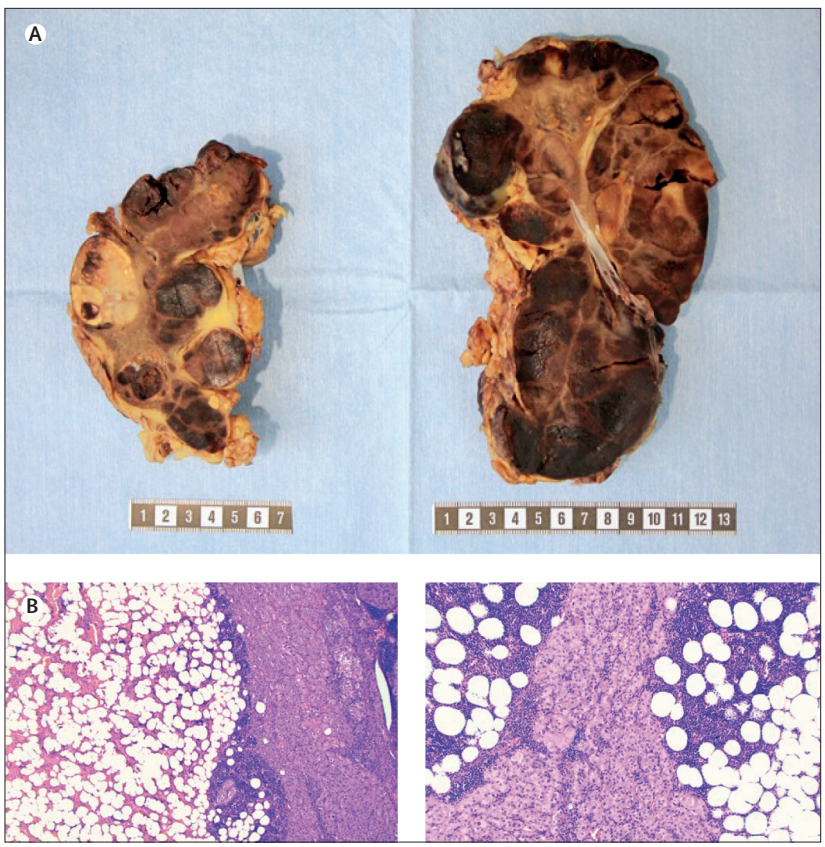

Figure 1: **Macroscopic and histological attributes of a bilateral adrenalectomy specimen in a patient with congenital adrenal hyperplasia**
(A) Gross image of the resected adrenals showing multiple foci of adrenal myelolipoma (dark brown-red areas) intermingled with hyperplastic adrenal cortical tissue (bright yellow). Metric ruler is depicted for size estimations. (B) Representative photomicrographs of sections stained with haematoxylin and eosin from each adrenal specimen (magnified ×40 and ×100, respectively) showing myelolipoma and hyperplastic cortical tissue.

knowledge, studies of next-generation DNA sequencing on these tumours have yet to be published; therefore, most genetic information is based on targeted gene sequencing analyses. The first somatic genetic aberrancy associated with adrenal myelolipoma was the finding of a balanced translocation between chromosomes 3q25 and 21p11 in a single patient, thereby providing the earliest genetic evidence for a tumoural origin.[21] Another suggested mechanism could be non-random X chromosome inactivation in haematopoietic cells and fat cells, which could suggest a clonal origin.[22] Moreover, initial molecular studies involved the investigation of a potential menin 1 (Multiple Endocrine Neoplasis type 1, *MEN1*) gene dysregulation, a theory based on the fact that a subset of adrenal myelolipomas could have hormonal activity, and were also reported in conjunction with other endocrine tumours in the same patient.[23–26] However, no *MEN1* gene mutations or *MEN1* loss of heterozygosity were noted in that patient.[27] Additionally, an miRNA signature for adrenal myelolipoma was identified, in comparison with adrenocortical tumours.[28] Specifically, *hsa-miR-451a*, *hsa-miR-486–5p*, *hsa-miR-363–3p*, and *hsa-miR-150–5p* were overexpressed in myelolipomas, of which *hsa-miR-451a* overexpression was also reproduced in the plasma of patients with myelolipomas. The observed miRNA dysregulation suggests that one or several of the aberrantly expressed miRNAs could influence myelolipoma development through translational regulation of various mRNAs.[28] These biomarkers need further validation and might be useful in making a non-invasive diagnosis of adrenal myelolipoma.

Histopathological aspects

Adrenal myelolipomas are characterised by a yellow-to-brown red cut surface, representing adipose tissue with scattered areas of haemorrhage reflecting the dispersed marrow tissue. Histologically, adrenal myelolipomas are well circumscribed and heterogenous, with variable amounts of mature adipose tissue admixed with an extramedullary trilinear haematopoiesis with full maturation (figure 1). Therefore, pathologists should be able to identify megakaryocytes as markers of thrombocytopoiesis, various erythroid cells as evidence of erythropoiesis, and granulocytic cells as part of the myeloid lineage. Occasionally, areas of degeneration (haemorrhage and calcifications) are observed. Immunohistochemical verification of the diagnosis of adrenal myelolipoma is usually not required because the histological appearance is straightforward on routine haematoxylin and eosin staining, but rare differentials with lipomatous appearances of clinical importance, such as liposarcoma, myxoid liposarcoma, and myofibrosarcoma, should not be overlooked.[29–31] In these instances, the identification of high-grade nuclear changes and increased mitotic activity are indications to the diagnosis, although well-differentiated liposarcomas might be devoid of lipoblasts and only show adipocytes with scarce amounts of nuclear atypia. Because immunohistochemical analyses are of little value in differentiating between sarcomas and myelolipomas, molecular testing for *MDM2* and *CDK4* amplifications (liposarcomas) or *DDIT3* gene fusions (myxoid liposarcomas) could be considered.[32–35] Other fatty adrenal tumours, such as lipomas, teratomas, and angiomyolipomas, are also potential confounders; however, these tumours are associated with a favourable prognosis and are not alarming in the same sense as sarcomas if misclassified.[29,36] Notably, an angiomyolipoma is a triphasic tumour consisting of dysmorphic blood vessels, smooth muscle elements admixed with mature adipose tissue, and positive for smooth muscle actin, and to differentiate the cases, a desmin immunostaining could be useful for the diagnosis.[29] Moreover, subsets of adrenocortical tumours can also exhibit myelolipomatous change and should not be confused with bona fide adrenal myelolipomas.[37,38]

Epidemiology

Most adrenal myelolipomas are identified incidentally and comprise 3·3–3·6% of all adrenal tumours in a population, and in up to 6·0–6·5% of all adrenal tumours reported in

endocrine clinics.[2,3,13,39–41] In published cohorts undergoing adrenalectomy, the prevalence of myelolipomas was 4–10% overall, and represented 15–20% in tumours larger than 4 cm in size (table).[3,13,29,42–51] Prevalence of myelolipomas in 62 279 patients receiving CT at a tertiary centre was 0·24%,[6] but a 2020 analysis has shown that, in the general population (at 40 years of age), the prevalence of myelolipomas has been estimated to be 0·32%.[11] Notably, patients with congenital adrenal hyperplasia present with a much higher prevalence (8·6%) of adrenal myelolipomas.[11]

Clinical presentation

Adrenal myelolipomas are usually diagnosed in adults, at a median age of 55–65 years, and affect both sexes almost equally (table).[2,3,6,13,42,47,49] Most adrenal myelolipomas (85–90%) are incidentalomas, diagnosed on imaging done for reasons other than adrenal disease, or during cancer staging (5–10%).[2,6,13,39,46] Symptoms of adrenal mass effect with abdominal discomfort leads to eventual detection of a myelolipoma in 5% of cases.[13,47] Rarely, symptoms of overt hormone excess, due to concomitant primary aldosteronism or Cushing's syndrome, can lead to detection of an adrenal myelolipoma along with an adrenal cortical adenoma.[13] Notably, 6% of patients with adrenal myelolipomas have a concomitant functioning or non-functioning adrenal cortical adenoma.[13] Only few patients with adrenal myelolipomas undergo work-up with dexamethasone suppression testing; therefore, the true prevalence of autonomous cortisol secretion in these patients is unknown.

At the time of initial diagnosis, patients usually present with a unilateral adrenal myelolipoma (in 95% of cases), with a median tumour size of 2·0–2·5 cm; however, the size ranges widely (between 0·5 cm and >10 cm).[3,6,47] In comparison with patients who have smaller tumours, those with large adrenal myelolipomas (>6·0 cm) are more likely to present with bilateral disease (3% *vs* 21%) and report symptoms of mass effect (0% *vs* 32%).[13] Symptoms of mass effect include abdominal, back and flank pain, and positional shortness of breath.[13] Additionally, acute haemorrhage necessitating surgery was reported only in patients with large adrenal myelolipomas, occurring in 6·8% of cases.[13] Rupture of adrenal myelolipoma is exceedingly rare, described to occur mainly in tumours larger than 8 cm to 10 cm in size.[52–54]

Association with congenital adrenal hyperplasia

Congenital adrenal hyperplasia is a group of autosomal recessive disorders affecting the steroid synthesis in the adrenal cortex.[55] As a response to this hormone deficiency, increased ACTH secretion from the pituitary gland ensues due to a reduction in negative feedback. Congenital adrenal hyperplasia can be classified as classic, including the salt-wasting and simple virilising phenotype, and the non-classic phenotype.[56] Since the introduction of neonatal screening of congenital adrenal hyperplasia in many countries during the past few decades, almost all classic cases are diagnosed in the neonatal period.[57,58] The non-classic phenotype has 20–70% residual enzyme activity and, therefore, has less symptoms and signs than classic congenital adrenal hyperplasia.[59] Because non-classic congenital adrenal hyperplasia often is not detected at neonatal screening, most patients are probably never diagnosed.[59]

ACTH as an adrenal growth stimulating factor can result in large adrenals (adrenal cortical hyperplasia) in untreated or poorly managed patients with congenital adrenal hyperplasia. Whether continuous high concentrations of ACTH also can cause tumour growth is less clear. In a 2020 meta-analysis of adrenal tumours in patients with congenital adrenal hyperplasia, 63 (29·3%) of 215 patients were affected with adrenal tumours, and when only patients with genetically confirmed congenital adrenal hyperplasia were included, 41 (23·6%) of 174 patients were affected (table).[11] Moreover, in another meta-analysis, undiagnosed congenital adrenal hyperplasia was the cause of adrenal incidentalomas in 58 (5·9%) of 990 patients when only

	Population-based or nationwide cohorts[2,3]	Endocrine clinic and radiology referral cohort[13,39-41]	Adrenalectomy cohort[3,13,29,42-51]	Congenital adrenal hyperplasia cohort[11]
Proportion of all adrenal tumours	3·3–3·6%	1·8–6·5%	4–10% of all adrenal tumours; 15–20% of large adrenal tumours (>4 cm)	25·4% (all congenital adrenal hyperplasia) 36·6% (genetically verified congenital adrenal hyperplasia)
Proportion of benign adrenal tumours	3·7%	..	..	25·4% (all congenital adrenal hyperplasia) 36·6% (genetically verified congenital adrenal hyperplasia)
Median age at diagnosis, years	..	60–65	50–55	44
Female sex	..	45%	35–75%	35·7%
Mode of discovery				
Incidental	95%	86%	35–70%	Almost all occur due to poor hormonal control with either incidental discovery, or based on symptoms of mass
Symptoms of mass effect	0%	5%	20–50%	Almost all occur due to poor hormonal control with either incidental discovery, or based on symptoms of mass
Other	5%	9%	2–5%	Almost all occur due to poor hormonal control with either incidental discovery, or based on symptoms of mass effect
Median tumour size at diagnosis	..	2–4 cm	5–7 cm	10·2 cm
Bilateral myelolipomas	..	5%	5–10%	59·6%
Unilateral myelolipomas	..	95%	90–95%	40·4%

Table: **Epidemiology and clinical presentation of patients with adrenal myelolipomas**

biochemical diagnosis with 17-hydroxyprogesterone (17-OHP) was made, and in two (0·8%) of 252 patients if genetic confirmation had been done.[61,62] When analysing patients with already diagnosed congenital adrenal hyperplasia and subsequent adrenal tumours, 16 (25·4%) of 63 patients harboured adrenal myelolipomas, which changed to 15 (36·6%) of 41 patients when only studies with genetically confirmed congenital adrenal hyperplasia were included (table).[11] Of the patients with congenital adrenal hyperplasia and concomitant adrenal myelolipoma, 26 (46%) of 57 patients were asymptomatic and 19 (33%) of 57 patients had abdominal pain or flank pain.[11] Patients with congenital adrenal hyperplasia and adrenal myelolipomas were older than those with congenital adrenal hyperplasia and a non-myelolipoma adrenal tumour (44 years *vs* 33 years), the adrenal tumours were larger (10·2 cm *vs* 1·0 cm) and were more frequently bilateral (59·6% *vs* 10·7%). Most (93·5%) patients with adrenal myelolipomas had been diagnosed late with congenital adrenal hyperplasia or had been poorly managed,[11] further indicating that prolonged periods of increased ACTH concentration probably have a role in the development of adrenal myelolipomas.

In a review of literature that included 440 patients with adrenal myelolipomas, 44 (10%) had concomitant congenital adrenal hyperplasia.[9] Whether congenital adrenal hyperplasia should be screened for with 17-OHP in all patients with a myelolipoma is, however, unclear. The Endocrine Society guidelines do not recommend routine screening for adrenal masses, including myelolipomas, in the case of congenital adrenal hyperplasia.[57]

See Online for appendix

Association with adrenal hormone excess

In a single-centre study of 126 patients with adrenal myelolipomas who were evaluated for adrenal hormone excess, autonomous cortisol secretion was diagnosed in three (3%) of 92 patients and primary aldosteronism was diagnosed in nine (12%) of 74 patients.[13]In another study of 65 patients with a surgically treated adrenal myelolipoma, adrenal hormone excess was reported in 4·6% of patients, although the diagnostic work-up was incompletely described.[47] Another study of 150 patients with adrenal myelolipoma, in which only 20 patients were tested for endocrine dysfunction, reported three patients with autonomous cortisol secretion and one patient with primary aldosteronism.[6] A small case series of concomitant aldosterone, cortisol, or androgen excess in patients with myelolipomas has shown adrenal cortical hyperplasia on pathology.[54] Adrenal myelolipoma has also been reported in Carney complex.[63,64] Other very rare reported coincidental associations with adrenal myelolipoma include an aldosterone-secreting adrenocortical carcinoma,[65] pheochromocytoma,[66,67] and also adrenal medullary hyperplasia.[68]

Association with other disorders

Adrenal myelolipomas associated with haematologic diseases have sometimes been reported, and these patients often have chronic anaemia. Patients with various forms of thalassaemia and myelolipoma have been described,[69] as well as those with hereditary spherocytosis[70,71] and sickle cell disease.[72] In 27 patients with thalassaemia, sickle cell anaemia, or myelofibrosis, myelolipomas were reported in five (19%) patients.[73] Lin and colleagues[74] reported that two (9%) of 23 patients had plasma cell myeloma within myelolipomas.[74] These adrenal myelolipomas contained huge aggregates of dysplastic plasma cells in individuals who previously did not have a myeloma diagnosis.

Diagnosis of adrenal myelolipoma

A diagnosis of myelolipoma is established on imaging, either on CT or MRI with or without contrast enhancement, by identifying the macroscopic fat components. The typical CT or MRI appearance of an adrenal myelolipoma is a rounded tumour mainly comprising macroscopic fat (figure 2A),[4] but also with a higher quantity of attenuating myeloid components, either appearing as a cloudy pattern (figure 2B), as solid strands (figure 2C), or forming a separate solid nodule within the fat (figure 2D).[75] However, there is huge variation in the proportions of fat and myeloid tissue between myelolipomas. In myelolipomas almost totally comprising macroscopic fat, the CT attenuation is very low (pure fat: –100 Hounsfield units) and appear dark on CT and white on T1-weighted and T2-weighted MRI (appendix p 1).[75] With increasing myeloid components (figure 2D), the CT attenuation increases and many myelolipomas measure between –50 Hounsfield units and –20 Hounsfield units.[46] Sometimes, the myeloid and fat components are distinctly separated and are of approximately similar proportions (figure 2E), and in other myelolipomas the myeloid components can be very dominating, with merely one or a few small islands of macroscopic fat (appendix p 2) in an otherwise solid myeloid tumour. Sometimes, the fat components are very small to non-existent in quantity and do not allow for supporting the CT or MRI diagnosis of myelolipoma by attenuation measurement of the fat components. The solid myeloid components are typically contrast-enhancing (figure 2H, appendix p 3).[76] The myelolipomas are generally clearly demarcated, which is facilitated by the fairly frequent appearance of a pseudocapsule.[77] Adrenal myelolipomas can be bilateral, typically when they are large (figure 2I). Sometimes, calcifications (usually small in size) are found within the myelolipoma (figure 2J).[78] Differential diagnoses constitute adrenocortical carcinomas with macroscopic fat or retroperitoneal liposarcoma,[9,79,80] both of which are extremely unusual.

Notably, adrenal biopsy (either fine-needle aspiration biopsy or core needle biopsy) is not recommended in the diagnostic work-up of adrenal myelolipoma, mainly due to the high accuracy of imaging.

Adrenalectomy is usually reserved for a minority of patients with adrenal myelolipomas and is more common in patients with large tumours, those with tumour growth, acute haemorrhage, symptoms of abdominal mass effect, or uncontrolled congenital adrenal hyperplasia.[13,47,49] In several case series of surgically treated myelolipomas, the median tumour size was around 5–8 cm.[13,45,47–49] Adrenalectomy has also been the treatment of choice in patients with ipsilateral concomitant adrenal hormone excess.[13,44,54] In a series of 305 patients with adrenal myelolipomas, surgery was done on 37 (12%) patients because of increasing tumour size in a large myelolipoma, symptoms of mass effect, ipsilateral adenoma with adrenal hormone excess, acute haemorrhage, or concomitant resection for other reasons, and to confirm a questionable diagnosis on imaging.[13] Patients undergoing adrenalectomy were younger, had larger tumours with accelerated tumour growth, and a higher likelihood of haemorrhagic changes on imaging than those who were managed conservatively.[13]

Long-term outcomes

Most patients with myelolipomas are asymptomatic and do not exhibit tumour growth or develop adrenal malignancy. In a series of 163 patients with myelolipomas followed up with imaging over a median of 7 years (range 0·5–20 years), the overall median tumour growth was 0 cm, ranging from 1 cm tumour shrinkage to 11 cm tumour growth.[13] The maximum tumour growth per year was 1·4 cm. Only 26 (16%) of 163 patients had an overall tumour growth of at least 1 cm.[13] A tumour larger than 3·6 cm at diagnosis was reported to be a risk factor for future tumour growth. In another study of 69 patients with adrenal myelolipomas followed up for a median of

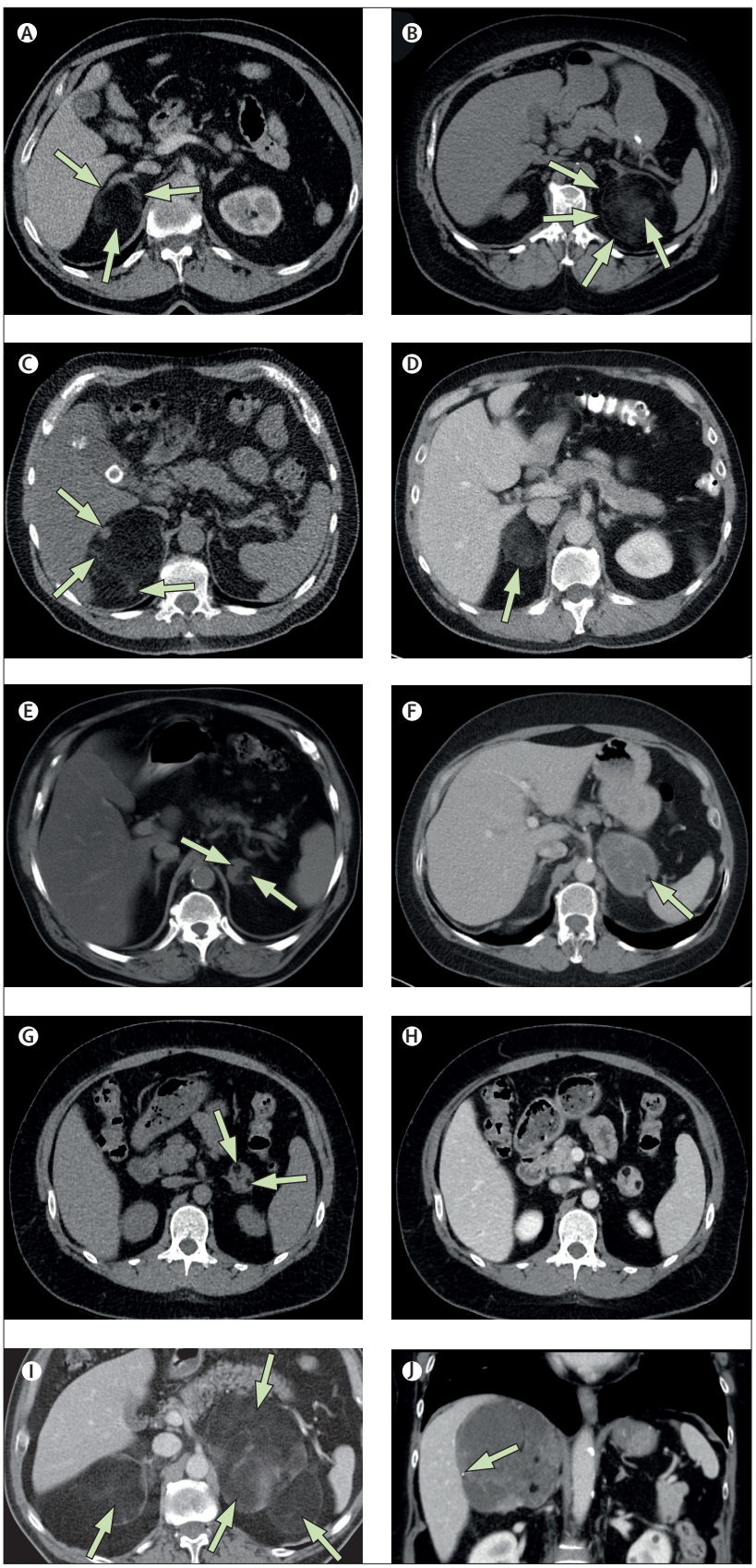

Figure 2: **Transversal CT images and coronal CT image of myelolipoma**
(A–I) Transverse CT images, (J) coronal CT image. (A) Typical myelolipoma in the right adrenal gland (long arrow), comprising almost exclusively macroscopic fat, spreading the lateral and medial adrenal limbs apart (short arrows), extending posteriorly but demarcated from the periadrenal fat by a thin capsule. (B) The myelolipoma in the left adrenal gland is dislocating the lateral adrenal limb ventrally and extends laterally to the spleen. The capsule is clearly shown (short arrows), and the myeloid components have a cloudy appearance (long arrow). (C) In the myelolipoma in the right adrenal gland, the myeloid components are shown as a nodule (long arrow) in the ventromedial part of the tumour and as strands (small arrows) in its posterior aspects. (D) In this myelolipoma in the right adrenal gland (arrow), the myeloid and fat components are mixed and are evenly spread throughout the whole tumour. (E) By contrast, in this myelolipoma in the left adrenal gland, the myeloid (short arrow) and fat components (long arrow) are distinctly separated and are located in the medial and lateral part of the tumour, respectively. (F) The myelolipoma in the left adrenal gland comprises almost exclusively myeloid tissue, in which there is a small island of macroscopic fat in the posterolateral aspect of the tumour (arrow). (G) CT without intravenous contrast enhancement. In this myelolipoma in the left adrenal gland, with a similar appearance as that in (F), there are two small fatty islands (short arrows). (H) CT with intravenous contrast enhancement in the venous phase shows in the same tumour shown in (G) contrast enhancement of the myeloid components, similar to that of the liver and spleen. (I) Myelolipomas are sometimes bilateral, especially when large in size (arrows). (J) Sometimes, calcifications are observed in myelolipomas, which are usually small (arrow).

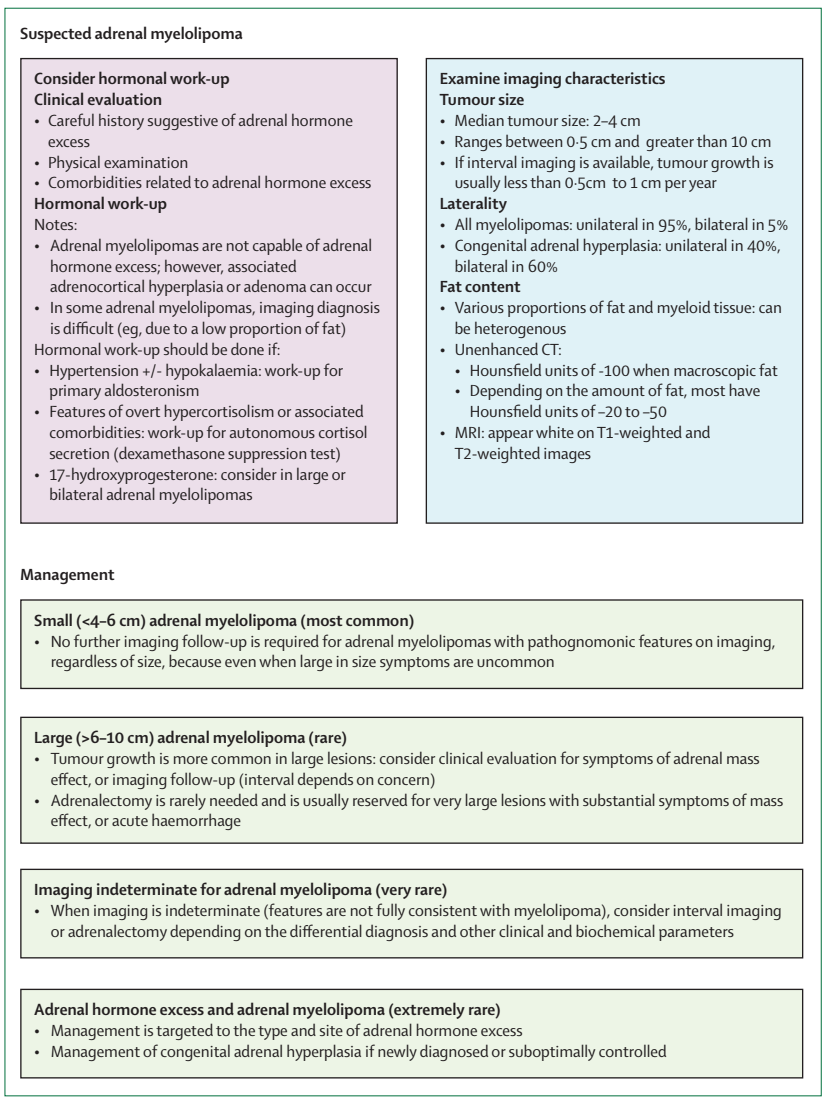

Figure 3: **An algorithm on imaging characteristics, investigations, and management of adrenal myelolipomas**

3·9 years, 11 (16%) patients had a median tumour growth of 1·1 cm (range 0·6–8·4 cm), a median growth per year of 0·16 cm (range 0·08–0·71 cm).[6] In this study, younger age and duration of follow-up, but not the initial tumour size, were associated with tumour growth.[6] In another series of 15 patients followed up for an average of 3·2 years (0·3–10·8 years), 13 (87%) remained asymptomatic and two (13%) continued to have some abdominal discomfort during follow-up.[44] Imaging follow-up showed a minor increase in tumour size in six (40%) of 15 patients.[44] Patients with large myelolipomas might develop new onset symptoms of mass effect when tumour growth continues. Acute haemorrhage and tumour rupture are very rare events, which almost always occur in very large myelolipomas (usually >8 cm to 10 cm). When adrenalectomy is done, it is a definite treatment for myelolipoma, with no recurrence reported.[13,29,46]

Management

Any patient with a newly identified adrenal mass needs to undergo a parallel work-up to determine the cause of the adrenal mass and the presence of hormonal excess. Due to scarcity of original literature regarding the management of myelolipomas, guidance is mostly based on expert opinion.

After determining the likelihood of myelolipoma on the basis of the imaging characteristics (most with pathognomonic features), we also recommend considering hormonal work-up informed by the clinical presentation (figure 3). Patients with suspected hormone excess should be investigated with a 1-mg overnight dexamethasone suppression test as well as measurements of aldosterone concentrations, renin plasma activity, and potassium concentrations (figure 3). In very rare situations of diagnosed adrenal hormone excess, management should be targeted to the type and site of adrenal hormone excess, which could be ipsilateral or contralateral to the myelolipoma (figure 3).

Patients with large or bilateral myelolipomas, or both, should be investigated for a possibility of congenital adrenal hyperplasia, with measurement of 17OHP concentrations. Bilateral adrenalectomy is occasionally used in poorly controlled congenital adrenal hyperplasia,[81] sometimes with concomitant bilateral adrenal myelolipomas. ACTH concentrations usually increase after the procedure, which might stimulate the growth of ectopic adrenal rest tumours.[82] Since adrenal rest tumours, especially in the testicles, might impair fertility,[83] surgical removal of adrenal myelolipomas in congenital adrenal hyperplasia should only be done after careful consideration.

In most patients with adrenal myelolipoma, imaging diagnosis is clear and no further imaging follow-up or adrenalectomy is required (figure 3). In rare selected cases of very large myelolipomas, clinical or imaging follow-up could be considered. However, adrenalectomy in these cases is usually reserved only if symptoms of mass effect or acute haemorrhage is present (figure 3). In other rare instances when imaging is not completely typical of myelolipoma, such as tumours with a high abundance of calcifications, or when identification of macroscopic fat is difficult, management should be discussed at a multidisciplinary meeting with options, including imaging follow-up, another type of imaging (eg, ^{18}F-fluorodeoxyglucose-PET), or adrenalectomy. Given that most myelolipomas are discovered as incidentalomas, in the occasional instances of atypical imaging findings, myelolipomas are frequently managed as such, whereby the patient might be discharged when the tumour size and appearance is unchanged on follow-up imaging at 6 months (or in comparison to imaging ≥6 months previously).

Gaps in knowledge

Most adrenal myelolipomas are small, non-functioning, and asymptomatic. A minority of myelolipomas might grow, and rarely cause symptoms of mass effect.

Search strategy and selection criteria

Source references for this Review were identified through PubMed searches of articles published between Jan 1, 1985, and May 1, 2021, using the term "adrenal myelolipoma", with the addition of "incidentaloma", "congenital adrenal hyperplasia", "hyperaldosteronism", "Cushing", "pheochromocytoma", "Addison's disease", "hypertension", "bilateral", "hematologic disease", and "radiology" when more specific information was searched for. The reference lists of the articles retrieved in these searches were also reviewed and included when appropriate. The first search was done Dec 28, 2020, and repeated May 5, 2021. Only publications in English language were used.

However, the predictors of growth or development of haemorrhage are not clear and therefore management should be individualised. The adequate duration and interval of monitoring via imaging in patients with atypical imaging features are unknown. Future studies should clarify the approach to hormonal assessment in patients with myelolipomas. The pathogenic drivers of myelolipoma development and growth are not known, but there is an association between myelolipoma development and increased ACTH concentration and possibly of erythropoietin concentration, but other paracrine drivers could be identified in the future. Adrenal tumours might occasionally exhibit local ACTH secretion,[62,84] causing Cushing's syndrome and potentially myelolipomas. Genetic explanations might also be identified, as well as differently expressed mRNAs.

Conclusion

Adrenal myelolipomas are indolent tumours that are usually discovered incidentally. Imaging presents a tumour with fat and myeloid components. Patients with adrenal myelolipoma might seldom exhibit adrenal hormone excess due to concomitant adrenocortical adenoma or hyperplasia, and decision by a physician on hormonal work-up should be individualised. Association with congenital adrenal hyperplasia needs to be considered in any patient with adrenal myelolipoma, but especially in patients with large and bilateral lesions. Large lesions might warrant follow-up because growth could develop, which might cause mass effect symptoms, although this outcome is rare. In tumours with atypical appearance on imaging (ie, low fat content), repeated imaging should be considered. Adrenalectomy might very rarely be discussed in selected patients.

Contributors

All authors contributed equally to the bibliographical search, the drafting, and the final writing of the Review. All authors approved the final submitted version.

Declaration of interests

IB is supported by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health (NIH) USA under award K23DK121888. The views expressed are those of the authors and not necessarily those of the National Institutes of Health. IB reports consulting with Strongbridge, HRA Pharma, Corcept, CinCor, and Sparrow Pharmaceutics, and serves on the data safety board for Adrenas Therapeutics. HF has consulted for Neurocrine Biosciences, Diurnal, Roche Diagnostics International, and Adrenas Therapeutics. The other authors declare no competing interests.

References

1 Gierke E. Über Knochenmarksgewebe in der Nebenniere. *Zeiglers Beitr Pathol Anat* 1905; **7:** 311–24.
2 Ebbehoj A, Li D, Kaur RJ, et al. Epidemiology of adrenal tumours in Olmsted County, Minnesota, USA: a population-based cohort study. *Lancet Diabetes Endocrinol* 2020; **8:** 894–902.
3 Ichijo T, Ueshiba H, Nawata H, Yanase T. A nationwide survey of adrenal incidentalomas in Japan: the first report of clinical and epidemiological features. *Endocr J* 2020; **67:** 141–52.
4 Reginelli A, Vacca G, Belfiore M, et al. Pitfalls and differential diagnosis on adrenal lesions: current concepts in CT/MR imaging: a narrative review. *Gland Surg* 2020; **9:** 2331–42.
5 Daneshmand S, Quek ML. Adrenal myelolipoma: diagnosis and management. *Urol J* 2006; **3:** 71–74.
6 Campbell MJ, Obasi M, Wu B, Corwin MT, Fananapazir G. The radiographically diagnosed adrenal myelolipoma: what do we really know? *Endocrine* 2017; **58:** 289–94.
7 Juul SE, Yachnis AT, Christensen RD. Tissue distribution of erythropoietin and erythropoietin receptor in the developing human fetus. *Early Hum Dev* 1998; **52:** 235–49.
8 Taher A, Vichinsky E, Musallam K, Cappellini MD, Viprakasit V. Guidelines for the Management of Non Transfusion Dependent Thalassaemia. Weatherall D, ed. Nicosia: NTDT, 2013.
9 Decmann Á, Perge P, Tőth M, Igaz P. Adrenal myelolipoma: a comprehensive review. *Endocrine* 2018; **59:** 7–15.
10 Civrilli K, Damry N, Steppé R, Efira A, Mathieu J. Bilateral adrenal myelolipomas. *JBR-BTR* 2008; **91:** 90–91.
11 Nermoen I, Falhammar H. Prevalence and characteristics of adrenal tumors and myelolipomas in congenital adrenal hyperplasia: a systematic review and meta-analysis. *Endocr Pract* 2020; **26:** 1351–65.
12 Boudreaux D, Waisman J, Skinner DG, Low R. Giant adrenal myelolipoma and testicular interstitial cell tumor in a man with congenital 21-hydroxylase deficiency. *Am J Surg Pathol* 1979; **3:** 109–23.
13 Hamidi O, Raman R, Lazik N, et al. Clinical course of adrenal myelolipoma: a long-term longitudinal follow-up study. *Clin Endocrinol (Oxf)* 2020; **93:** 11–18.
14 Addison T. On the constitutional and local effects of disease of the suprarenal capsule. London: Samuel Highley, 1855.
15 Selye H, Stone H. Hormonally induced transformation of adrenal into myeloid tissue. *Am J Pathol* 1950; **26:** 211–33.
16 Hagiwara H, Usui T, Kimura T, et al. Lack of ACTH and androgen receptor expression in a giant adrenal myelolipoma associated with 21-hydroxylase deficiency. *Endocr Pathol* 2008; **19:** 122–27.
17 Larose S, Bondaz L, Mermejo LM, et al. Coexistence of myelolipoma and primary bilateral macronodular adrenal hyperplasia with GIP-dependent Cushing's syndrome. *Front Endocrinol (Lausanne)* 2019; **10:** 618.
18 Almeida MQ, Kaupert LC, Brito LP, et al. Increased expression of ACTH (MC2R) and androgen (AR) receptors in giant bilateral myelolipomas from patients with congenital adrenal hyperplasia. *BMC Endocr Disord* 2014; **14:** 42.
19 Shenoy VG, Thota A, Shankar R, Desai MG. Adrenal myelolipoma: controversies in its management. *Indian J Urol* 2015; **31:** 94–101.
20 Feng C, Jiang H, Ding Q, Wen H. Adrenal myelolipoma: a mingle of progenitor cells? *Med Hypotheses* 2013; **80:** 819–22.
21 Chang KC, Chen PI, Huang ZH, Lin YM, Kuo PL. Adrenal myelolipoma with translocation (3;21)(q25;p11). *Cancer Genet Cytogenet* 2002; **134:** 77–80.
22 Yildiz L, Akpolat I, Erzurumlu K, Aydin O, Kandemir B. Giant adrenal myelolipoma: case report and review of the literature. *Pathol Int* 2000; **50:** 502–04.
23 Banik S, Hasleton PS, Lyon RL. An unusual variant of multiple endocrine neoplasia syndrome: a case report. *Histopathology* 1984; **8:** 135–44.

24 Saunders RN, Koch CA, Brown KB, et al. Bilateral adrenal myelolipomas in a woman with chronic anticoagulation, postmenopausal uterine bleeding, primary hyperparathyroidism and hyperthyroidism. *Am J Med Sci* 2013; **346:** 82–85.

25 Hegstrom JL, Kircher T. Alimentary tract ganglioneuromatosis-lipomatosis, adrenal myelolipomas, pancreatic telangiectasias, and multinodular thyroid goiter. A possible neuroendocrine syndrome. *Am J Clin Pathol* 1985; **83:** 744–47.

26 Yoshioka M, Fujimori K, Wakasugi M, et al. Cushing's disease associated with adrenal myelolipoma, adrenal calcification and thyroid cancer. *Endocr J* 1994; **41:** 461–66.

27 Schulte KM, Heinze M, Mengel M, Scheuring S, Köhrer K, Röher HD. Complete sequencing and mRNA expression analysis of the MEN-I gene in adrenal myelolipoma. *Horm Metab Res* 2000; **32:** 169–73.

28 Decmann A, Perge P, Nyíro G, et al. MicroRNA expression profiling in adrenal myelolipoma. *J Clin Endocrinol Metab* 2018; **103:** 3522–30.

29 Lam KY, Lo CY. Adrenal lipomatous tumours: a 30 year clinicopathological experience at a single institution. *J Clin Pathol* 2001; **54:** 707–12.

30 Cho J, Kinsey D, Kimchi ET, et al. Retroperitoneal extra-adrenal myelolipoma misdiagnosed as liposarcoma: a case report. *Radiol Case Rep* 2020; **16:** 364–68.

31 McLaughlin SA, Schmitt TM, Huguet KL, Menke DM, Nguyen JH. Myofibrosarcoma of the adrenal gland. *Am Surg* 2005; **71:** 191–93.

32 Dei Tos AP, Doglioni C, Piccinin S, et al. Coordinated expression and amplification of the MDM2, CDK4, and HMGI-C genes in atypical lipomatous tumours. *J Pathol* 2000; **190:** 531–36.

33 Sirvent N, Coindre JM, Maire G, et al. Detection of MDM2-CDK4 amplification by fluorescence in situ hybridization in 200 paraffin-embedded tumor samples: utility in diagnosing adipocytic lesions and comparison with immunohistochemistry and real-time PCR. *Am J Surg Pathol* 2007; **31:** 1476–89.

34 Rabbitts TH, Forster A, Larson R, Nathan P. Fusion of the dominant negative transcription regulator CHOP with a novel gene *FUS* by translocation t(12;16) in malignant liposarcoma. *Nat Genet* 1993; **4:** 175–80.

35 Crozat A, Aman P, Mandahl N, Ron D. Fusion of CHOP to a novel RNA-binding protein in human myxoid liposarcoma. *Nature* 1993; **363:** 640–44.

36 Zhou L, Pan X, He T, et al. Primary adrenal teratoma: a case series and review of the literature. *Mol Clin Oncol* 2018; **9:** 437–42.

37 Perna V, Taylor NF, Dworakowska D, et al. Adrenocortical adenomas with regression and myelolipomatous changes: urinary steroid profiling supports a distinctive benign neoplasm. *Clin Endocrinol (Oxf)* 2014; **81:** 343–49.

38 Stenman A, Shabo I, Ramstrom A, Zedenius J, Juhlin CC. Synchronous aldosterone- and cortisol-producing adrenocortical adenomas diagnosed using CYP11B immunohistochemistry. *SAGE Open Med Case Rep* 2019; **7:** 1–4.

39 Song JH, Chaudhry FS, Mayo-Smith WW. The incidental adrenal mass on CT: prevalence of adrenal disease in 1,049 consecutive adrenal masses in patients with no known malignancy. *AJR Am J Roentgenol* 2008; **190:** 1163–68.

40 Yeomans H, Calissendorff J, Volpe C, Falhammar H, Mannheimer B. Limited value of long-term biochemical follow-up in patients with adrenal incidentalomas—a retrospective cohort study. *BMC Endocr Disord* 2015; **15:** 6.

41 Patrova J, Jarocka I, Wahrenberg H, Falhammar H. Clinical outcomes in adrenal incidentaloma: experience from one center. *Endocr Pract* 2015; **21:** 870–77.

42 Bezjak M, Sesar P, Ulamec M, et al. Adrenal myelolipoma—report of 15 patients. *Acta Med Croatica* 2013; **67:** 255–58 (in Croatian).

43 Bin X, Qing Y, Linhui W, Li G, Yinghao S. Adrenal incidentalomas: experience from a retrospective study in a Chinese population. *Urol Oncol* 2011; **29:** 270–74.

44 Han M, Burnett AL, Fishman EK, Marshall FF. The natural history and treatment of adrenal myelolipoma. *J Urol* 1997; **157:** 1213–16.

45 Mantero F, Terzolo M, Arnaldi G, et al. A survey on adrenal incidentaloma in Italy. *J Clin Endocrinol Metab* 2000; **85:** 637–44.

46 Gadelkareem RA, Moeen AM, Khalil M, et al. Experience of a tertiary-level urology center in clinical urological events of rare and very rare incidence. V. Urological tumors: 1. adrenal myelolipoma. *Curr Urol* 2020; **14:** 85–91.

47 Zhao J, Sun F, Jing X, et al. The diagnosis and treatment of primary adrenal lipomatous tumours in Chinese patients: a 31-year follow-up study. *Can Urol Assoc J* 2014; **8:** e132–36.

48 Gershuni VM, Bittner JG 4th, Moley JF, Brunt LM. Adrenal myelolipoma: operative indications and outcomes. *J Laparoendosc Adv Surg Tech A* 2014; **24:** 8–12.

49 Yin L, Teng J, Zhou Q, et al. A 10-year single-center experience with surgical management of adrenal myelolipoma. *J Endourol* 2014; **28:** 252–55.

50 Ahn SH, Kim JH, Baek SH, et al. Characteristics of adrenal incidentalomas in a large, prospective computed tomography-based multicenter study: the COAR study in Korea. *Yonsei Med J* 2018; **59:** 501–10.

51 Iñiguez-Ariza NM, Kohlenberg JD, Delivanis DA, et al. Clinical, biochemical, and radiological characteristics of a single-center retrospective cohort of 705 large adrenal tumors. *Mayo Clin Proc Innov Qual Outcomes* 2017; **2:** 30–39.

52 Amano T, Takemae K, Niikura S, Kouno M, Amano M. Retroperitoneal hemorrhage due to spontaneous rupture of adrenal myelolipoma. *Int J Urol* 1999; **6:** 585–88.

53 Machuca Santa-Cruz F, Pérez Rodríguez D, Julve Villalta E, et al. Spontaneous retroperitoneal hematoma secondary to the rupture of suprarenal myelolipoma. *Arch Esp Urol* 2000; **53:** 724–25 (in Spanish).

54 Su HC, Huang X, Zhou WL, et al. Pathologic analysis, diagnosis and treatment of adrenal myelolipoma. *Can Urol Assoc J* 2014; **8:** E637–40.

55 Merke DP, Auchus RJ. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *N Engl J Med* 2020; **383:** 1248–61.

56 Nordenström A, Lajic S, Falhammar H. Clinical outcomes in 21-hydroxylase deficiency. *Curr Opin Endocrinol Diabetes Obes* 2021; **28:** 318–24.

57 Speiser PW, Arlt W, Auchus RJ, et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2018; **103:** 4043–88.

58 Zetterström RH, Karlsson L, Falhammar H, Lajic S, Nordenström A. Update on the Swedish newborn screening for congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Int J Neonatal Screen* 2020; **6:** 71.

59 Nordenstrom A, Falhammar H. Management of endocrine disease: diagnosis and management of the patient with non-classic CAH due to 21-hydroxylase deficiency. *Eur J Endocrinol* 2019; **180:** R127–45.

60 Falhammar H, Wedell A, Nordenström A. Biochemical and genetic diagnosis of 21-hydroxylase deficiency. *Endocrine* 2015; **50:** 306–14.

61 Falhammar H. Non-functioning adrenal incidentalomas caused by 21-hydroxylase deficiency or carrier status? *Endocrine* 2014; **47:** 308–14.

62 Falhammar H, Torpy DJ. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency presenting as adrenal incidentaloma: a systematic review and meta-analysis. *Endocr Pract* 2016; **22:** 736–52.

63 Lowe KM, Young WF Jr, Lyssikatos C, Stratakis CA, Carney JA. Cushing Syndrome in Carney complex: clinical, pathologic, and molecular genetic findings in the 17 affected Mayo Clinic patients. *Am J Surg Pathol* 2017; **41:** 171–81.

64 Reza-Albarran AA, Gomez-Perez FJ, Lopez JC, et al. Myelolipoma: a new adrenal finding in Carney's complex? *Endocr Pathol* 1999; **10:** 251–57.

65 Sun X, Ayala A, Castro CY. Adrenocortical carcinoma with concomitant myelolipoma in a patient with hyperaldosteronism. *Arch Pathol Lab Med* 2005; **129:** e144–47.

66 Ukimura O, Inui E, Ochiai A, Kojima M, Watanabe H. Combined adrenal myelolipoma and pheochromocytoma. *J Urol* 1995; **154:** 1470.

67 Jakka N, Venkateshwarlu J, Satyavani N, Neelaveni K, Ramesh J. Functioning adrenal myelolipoma: a rare cause of hypertension. *Indian J Endocrinol Metab* 2013; **17** (suppl 1)**:** S249–51.

68 Ishay A, Dharan M, Luboshitzky R. Combined adrenal myelolipoma and medullary hyperplasia. *Horm Res* 2004; **62:** 23–26.

69 Gamberini MR, Prandini N, Chiodi E, Farneti C, Garani MC. Adrenal incidentaloma in thalassemia: a case report and literature review. *Pediatr Endocrinol Rev* 2011; **8** (suppl 2)**:** 324–30.

70 Calhoun SK, Murphy RC, Shariati N, Jacir N, Bergman K. Extramedullary hematopoiesis in a child with hereditary spherocytosis: an uncommon cause of an adrenal mass. *Pediatr Radiol* 2001; **31:** 879–81.

71 Salemme M, Rodella R, Fisogni S, Facchetti F. Nodular extramedullary hematopoiesis involving the adrenal gland. An uncommon cause of adrenal "incidentaloma". *Pathologica* 2011; **103:** 46–49.

72 Gamss C, Chia F, Chernyak V, Rozenblit A. Giant hemorrhagic myelolipoma in a patient with sickle cell disease. *Emerg Radiol* 2009; **16:** 319–22.

73 Papavasiliou C, Gouliamos A, Deligiorgi E, Vlahos L, Cambouris T. Masses of myeloadipose tissue: radiological and clinical considerations. *Int J Radiat Oncol Biol Phys* 1990; **19:** 985–93.

74 Lin CY, Levy D, Higgins JPT, Kunder CA, Kao CS. Adrenal myelolipomas involved by plasma cell myeloma. *Am J Clin Pathol* 2018; **150:** 406–14.

75 d'Amuri FV, Maestroni U, Pagnini F, et al. Magnetic resonance imaging of adrenal gland: state of the art. *Gland Surg* 2019; **8** (suppl 3)**:** S223–32.

76 Bokhari MR, Zulfiqar H, Garla VV. Adrenal myelolipoma. Treasure Island, FL: StatPearls, 2021.

77 Shaaban AM, Rezvani M, Tubay M, Elsayes KM, Woodward PJ, Menias CO. Fat-containing retroperitoneal lesions: imaging characteristics, localization, and differential diagnosis. *Radiographics* 2016; **36:** 710–34.

78 Low G, Dhliwayo H, Lomas DJ. Adrenal neoplasms. *Clin Radiol* 2012; **67:** 988–1000.

79 Craig WD, Fanburg-Smith JC, Henry LR, Guerrero R, Barton JH. Fat-containing lesions of the retroperitoneum: radiologic-pathologic correlation. *Radiographics* 2009; **29:** 261–90.

80 Ferrozzi F, Bova D. CT and MR demonstration of fat within an adrenal cortical carcinoma. *Abdom Imaging* 1995; **20:** 272–74.

81 MacKay D, Nordenström A, Falhammar H. Bilateral adrenalectomy in congenital adrenal hyperplasia: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2018; **103:** 1767–78.

82 Burman P, Falhammar H, Waldenström E, Sundin A, Bitzén U. 11C-metomidate PET/CT detected multiple ectopic adrenal rest tumors in a woman with congenital adrenal hyperplasia. *J Clin Endocrinol Metab* 2021; **106:** e675–79.

83 Claahsen-van der Grinten HL, Stikkelbroeck N, Falhammar H, Reisch N. Management of endocrine disease: gonadal dysfunction in congenital adrenal hyperplasia. *Eur J Endocrinol* 2021; **184:** R85–97.

84 Saeger W. Pathology of adrenal neoplasms. *Minerva Endocrinol* 1995; **20:** 1–8.