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Diagnosis and treatment of angiomyolipoma (AML) tumours

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ABSTRACT

Angiomyolipoma (AML) is the most commonly occurring tumour from the PEComa family (PEC tumours; perivascular epithelioid cell tumours), a rare group of neoplasms of mesenchymal origin. AML may occur sporadically or in the course of tuberous sclerosis and lymphangioleiomyomatosis. The sporadic type form is the most common subtype of benign kidney tumours and is four times more frequent in women. Kid ney tumours of the angiomyolipoma type are most commonly detected by chance during an abdominal cavity ultrasound scan, during which they are visible as hyperechogenic tumours, and in most cases they are not a diagnostic problem. AML growth is slow, and complications are rare. The main AML complication can be bleeding to the retroperitoneal space or to the pelvicalyceal system. The typical method of AML care is active surveillance (AS). Asymptomatic tumours with a diameter under 4 cm require control by ultrasound examination every 12 months whereas tumours with a diameter of less than 2 cm are considered not to require control ultrasounds. AML with a diameter of over 4 cm require more frequent ultrasound scans — every six months. The size of the tumour, the presence of symptoms (e.g. pain in a tumour projection, haematuria), planned pregnancy, or suspicion of a malignant tumour are critical in therapeutic decisions. Active treatment options include: embolisation, ablation techniques, nephron-sparing surgery (NSS), and radical nephrectomy. In adult patients with tuberous sclerosis, who require treatment but do not require rapid surgical treatment, everolimus is used. In the case of AML, initially doses of 1 × 10 mg per day should be used (an appropriate dose decrease is required in the case of liver insufficiency), and subsequently treatment may be individualised after determining the lowest effective dose with acceptable adverse effects. A rare epithelioid variety of AML (EAML) shows the potential for a malignant course. The basis of EAML treatment is radical resection, ensuring a high percentage of cures. For non-resectable EAML, chemotherapy, mTOR inhibitors, and VEGFR inhibitors (pazopanib, apatinib) are used, but objective responses have been described only in a very small percentage of patients.

Key words: AML, angiomyolipoma, everolimus

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Introduction

Angiomyolipoma (AML) is the most commonly occurring tumour from the PEComa family (PEC tumours; perivascular epithelioid cell tumours), a rare group of tumours of mesenchymal origin, composed of perivascular epithelioid cells (PEC) [1] (Figure 1). The following are also included in the PEComa group: clear-cell sugar tumour (CCST) — the pulmonary form and the primary extrapulmonary sugar tumour (PEST), lymphangioleiomyomatosis (LAM), clear-cell myomelanocytic tumour (CCMMT), primary cutaneous PEComa, cutaneous clear cell myomelanocytic tumour (CCCMT), and PEComa NOS (not otherwise specified) — a group description of tumours not classified into any of the categories mentioned earlier. Angiomyoli-

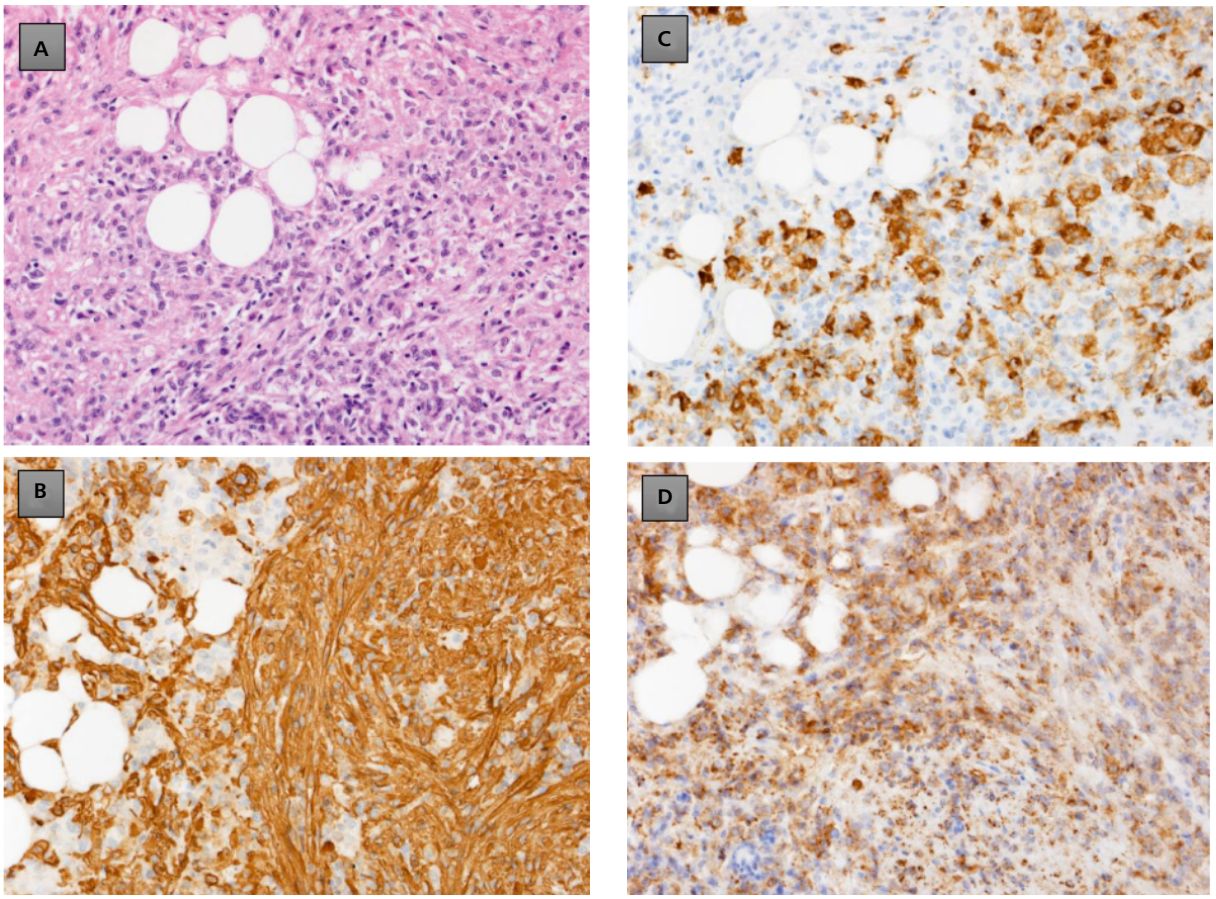

Figure 1. AML containing smooth muscle, fat tissue and blood vessels **A–D** — in order staining HE, SMA, HMB-45, and Cathepsin K [200×]

pomas are most commonly found in the form of a small asymptomatic kidney tumour usually containing a lot of lipid tissue, in a patient without known predisposing factors; this is described as the sporadic form of AML [2]. AML occurrence is also linked to the genetic syndrome caused by germline mutations inactivating the *TSC1* and *TSC2* genes — tuberous sclerosis complex (TSC, Bourneville-Pringle disease), which is characterised by numerous tumours of the hamartoma type, perturbations of the nervous system, including epilepsy, autism, and intellectual disability of various degrees [3]. In this form, AML occurs as large and multiple tumours with a tendency for bleeding, and their presence leads to progressive renal insufficiency [4]. AML is also observed in female patients with lymphangioleiomyomatosis, constituting one of the diagnostic criteria of this disease [5]. In about 8% of AML cases, more commonly in the forms associated with tuberous sclerosis, a predominance of epithelial cells is seen in the tumour, and they may show nuclear atypia [6]. Such tumours are described as the epithelioid subtype of AML (EAML, epithelioid angiomyolipoma), and a small percentage show a tendency to a malignant course, which is atypical for this group [7] (Figure 2).

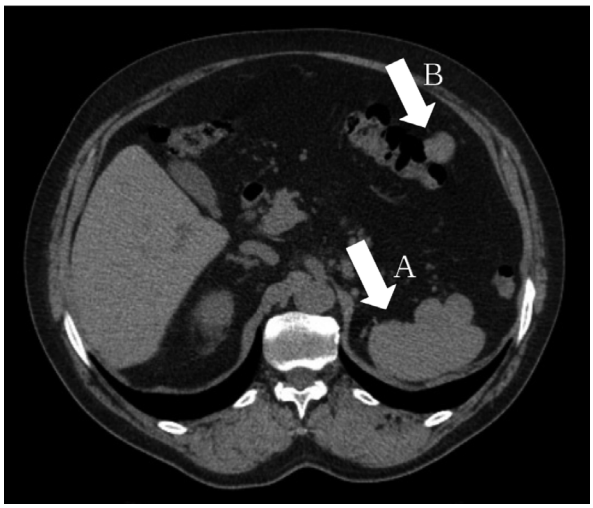

Figure 2. Recurrent (**A**) and disseminated (**B**) EAML after left nephrectomy

Epidemiology

The sporadic form of AML is the most common benign kidney tumour; in a retrospective analysis of 61,389 patients subjected to abdominal cavity ultrasound, this form was found to occur in 0.44% of the general population [2]. In respect to sex, AML occurs 2–4 times more frequently in women [6]. Sporadic forms of AML are observed most frequently in older patients; the average age at diagnosis is about 60 years in both sexes [2]. Sporadic AML in patients younger than 20 years constitutes only about 3.5% of all cases [2]. The AML form associated with tuberous sclerosis occurs very commonly in this group of patients, and its presence is a major criterium for diagnosis of TSC [8, 9]. In the TOSCA trial (TuberOus SClerosis registry to increase disease Awareness), including clinical data from 2216 patients with tuberous sclerosis, AML were present in 51.8%, and among these 88.4% were multiple, and the median age at diagnosis was 12 years [9]. AML associated with tuberous sclerosis are larger than sporadic forms and more often show a tendency to grow [6]. The epithelioid AML subtype (EAML) is characterised by a lower age at diagnosis than the sporadic form, namely approx. 38–41 years [6, 7]. In contrast to the classical AML form, more frequent occurrence in women is not the rule [7]. EAML with atypical epithelioid cells is considered to have a poorer prognosis because of its potential for an unfavourable clinical course [7, 10, 11]. Local recurrences after resection or distant metastases are observed in 18.5–30% of cases [7, 12]. Characteristics indicating a high risk of recurrence or distant metastases have not been unequivocally determined so far because of differing research results and the rarity of this disease entity. The papers available in the literature concerning clinical and pathomorphological characteristics of EAML and factors correlating with a malignant course have been summarised in Table 1.

Anatomic location

Sporadic AML is most commonly localised in the kidney, constituting 0.3–3% of kidney tumours, and is at the same time the most common benign tumour in this anatomical location [18]. AML in general occurs in the form of single sharply delimited asymptomatic tumours, less commonly (5.2%) in multiple forms, and approximately 1.5% occur bilaterally [2, 19]. AML occurs with equal frequency in both kidneys, generally localising in the kidney cortex or in a subcapsular location, and in about 25% of the cases within the kidney capsule and the perirenal fat tissue [2, 20]. In patients with tuberous sclerosis AML localised within kidneys often occur in multiple forms — in one of the analyses, in 76% of patients more than 20 changes were present simultaneously [8]. In such patients they significantly more often show a tendency for growth and in a higher percentage result in complications in the form of intratumoral bleeding, haematuria, or pain [21]. AML, similarly as other tumours of renal origin, can penetrate into the renal veins and the inferior vena cava — a case has even been described of an AML reaching the right atrium of the heart [22]. Fragments of the AML tumour may thus form embolisms [23]. Sporadic extrarenal AML are most commonly localised in the liver [24]. AML localised in the liver also occur in approx. 15% of patients with tuberous sclerosis, with a predominance of the female sex, in the form of asymptomatic tumours several millimetres in size [25]. Single cases of sporadic AML have been described in such locations as: the retroperitoneal space [26], spleen [27], duodenum [28], stomach [29], vagina [30, 31], vulva [32], ovary [33], uterus [34], spermatic cord [35], scrotum [36], palate [37], nasal cavity [38], maxillary sinus [39], cheek mucous membrane [40], auricle [41], parotid salivary gland [42], anterior mediastinum [43, 44], adrenal glands [45], skin [46], tibia [47], or rib [48]. Epithelial AML subtypes, similarly to the classical form, are most commonly localised in the kidney, giving rise to diagnostic difficulties in distinguishing this entity from a poorly differentiated renal cell carcinoma [13]. EAML cases with a malignant course outside the kidney have also been described in the liver [49] and in the retroperitoneal space [50]. There is a description in the literature of an EAML developing inside a classical AML [51].

Diagnosis

Angiomyolipoma most commonly occurs in the form of a small (3–38 mm) asymptomatic tumour with an abundant fat tissue content detected during imaging tests performed for other indications [2]. AML occur with equal frequency in both kidneys localising in general within the kidney capsule or in a subcapsular location [2]. In symptomatic cases the following are most commonly observed: pain (6.1%), hypertension (5.7%), bleeding (5.0%), and renal insufficiency (3.9%) [9, 20]. The imaging technique of choice for AML is computed tomography [52]. Angiomyolipoma detected during abdominal cavity computed tomography is visible as a well-delimited tumour localised in the renal parenchymatous layer, most commonly with a low value of the signal, below –30 Hounsfield units (HU), due to the high fat tissue content [53]. Depending on the fat tissue content AML are divided into three main subtypes differing in values on the Hounsfield scale: fat-rich AML (≤ –10 HU), fat-poor

Table 1. Summary of papers concerning clinical and pathomorphological properties of EAML

Author	Number of cases	F:M	Average age (years)	% TSC	Tumour size, [cm]	% epithelioid cells	% necrosis	Malignant cases	Death due to EAML	Characteristics associated with risk of a malignant course
Aydin et al. [6]	15	6.5:1	38.6	26.7%	8 (1–30)	51% (10–100)	27%	1 — metastasis to LN 2 — infiltration kidney vein	0	–
Faraji et al. [13]	69 (6 own, 63 from the literature)	3:1	44 ± 16	26%	10 ± 6	–	67% (for 6 cases)	6 — LR/metastasis to LN 10 — DM	9	Pronounced cellular atypia, extensive necrosis present, male sex
Brimo et al. [12]	40	1.6:1	50.5 (17–81)	–	7.2 (1.0–17.7)	58% (6–100)	37.5%	9	4	≥ 70% atypical epithelioid cells ≥ 2 fp/ /10 HPF, atypical cell division, extensive necrosis present
Nese et al. [14]	41	1:1	40.7 (14–68)	22%	11.9 (2–37)	100%	73%	6 — LR 16 — DM	11	TSC, AML recurrence, extensive necrosis present, tumour diameter > 7 cm, infiltration of surrounding tissues, tumour growth imitating cancer
Yang et al. [15]	27	1:2.4	42	–	9	–	14.8%	1 — DM	0	–
He et al. [16]	20	1.2:1	49.4 (30–80)	–	8.7 (1–25)	At least 80% in each case	50%	1 — DM	0	–
Lei et al. [17]	52	1:1.4	38.4 (24–76)	–	≤ 4 cm: n = 29; 4–10 cm: n = 11; > 10 cm: n = 3	43.8 ± 22.2	82.7%	3 — infiltration renal vein/inferior vena cava 2 — metastases to LN 2 — DM	2	Large tumour size, high epithelioid cell content, pronounced cellular atypia
Delhorme et al. [10]	5	4:1	54 (45–67)	0%	9 (6.3–21)	–	–	1 — LR 3 — DM	3	–
Tsai et al. [67]	23	2.3:1	42.8	0%	9.5 (1.3–18)	–	57%	4 — infiltration renal vein/inferior vena cava 2 — DM	0	Pronounced nuclear atypia, extensive necrosis present

F:M — ratio of cases in women to men; DM — distant metastases; LN — lymph node; LR — local recurrence; % TSC — frequency of patients with coexisting tuberous sclerosis; necrosis — average necrosis content, % of epithelioid cells — average content of epithelioid cells

Table 2. Diagnostic criteria for tuberous sclerosis, on the basis of [64]

Major symptoms	Minor symptoms
Facial angiofibroma or flat forehead fibromas	Multiple enamel losses
Atraumatic nail fibromas	Anal polyps
> 3 colourless naevi	Bone cysts
Shagreen patches	White brain matter migration foci
Multiple retinal hamartomas	Gum fibromas
Cortical cerebral tumours	Hamartoma with non-kidney localisation
Periventricular subependymal cerebral tumours	Changes in eye retina
Giant cell astrocytoma	Skin changes of the confetti type
Heart rhabdomyoma	Multiple kidney cysts
Pulomonary lymhangioleiomyomatosis	
Renal angiomyolipoma	

Certain diagnosis: occurrence of 2 major symptoms or 1 major and 2 minor
Probable diagnosis: occurrence of 1 major and 1 minor symptom
Possible diagnosis: occurrence of 1 major symptom or ≥ 2 minor symptoms

AML (> –10 HU; tumour:spleen coefficient < 0.71; signal intensity index > 16.5%), and AML with no fat content (fat-invisible) (> –10 HU; tumour:spleen coefficient > 0.71; signal intensity index < 16.5%) [54]. The low-fat form may pose diagnostic difficulties because the low fat tissue content makes it difficult to distinguish from renal cell carcinoma [55]. In one of the analyses, in 4.8% patients who had undergone partial nephrectomy because of a kidney tumour with a diameter of ≤ 4 cm and had a suspicion of renal cell carcinoma, a final diagnosis of low-fat AML was made [56]. Similarly, epithelioid AML subtypes localised in the liver, constituting for approx. 4% of liver AML [57], pose diagnostic difficulties in distinguishing them from hepatocellular carcinoma because both disease entities during analysis using contrast are enhanced in the arterial phase [57, 58]. Currently, many models are being elaborated to distinguish these different entities; for example, the BEARS scale (BEnign Angiomyolipoma Renal Susceptibility), in which female sex, age < 56 years, and tumour diameter < 2 cm suggest a low-fat AML [56] as well as informatic models [59, 60]. In patients with renal insufficiency, magnetic resonance not requiring contrast is to be applied in AML diagnosis where hyperintense foci in T1-dependent images are characteristic without fat tissue suppression and hypointensive with fat tissue suppression [61]. In spite of several reports about the potential utility of the chemical shift in magnetic resonance analysis, this was not confirmed in a meta-analysis encompassing 11 papers concerning this problem [62].

In patients with tuberous sclerosis, because of the common occurrence of low-fat angiomyolipoma, the lack of fat in the tumour mass is not considered as a sufficient factor for performing a biopsy, which should be considered in the case of the presence of calcification, central necrosis, rapid growth, or the presence of a single lesion with a low fat tissue content [63]. Multiple kidney angiomyolipomas are an important element of the clinical picture of patients with tuberous sclerosis (TSC diagnostic criteria are presented in Table 2). In spite of the frequent presence of multiple AML, in over 80% of cases such patients remain asymptomatic [9]. However, because of the increased risk of progression and development of renal insufficiency, their long-term monitoring is necessary. In asymptomatic patients with at least one AML > 4 cm, measurement of creatinine concentrations and TK/MRI are recommended every two years [63]. It is evaluated that in asymptomatic patients without kidney anomalies or AML < 4 cm, monitoring (TK/MRI) and kidney function evaluation may be gradually reduced if the results are stable [63]. The appearance of symptoms indicating kidney complications (pain, feeling of heaviness in the abdominal cavity, haematuria, shock) require immediate TK/MRI imaging [63].

Pathomorphology

A classical angiomyolipoma is a mesenchymal tumour with a non-infiltrating type of growth [1]. It is composed in various proportions of three components: dysmorphic sinuous blood vessels, elongated cells resembling smooth myocytes, and extended epithelioid perivascular cells with abundant lipids, with fat tissue morphology [65]. Depending on the content of lipid-rich cells, an AML fat-poor form is distinguished in which these cells constitute less than 25% of the visual field, and the smooth muscle cell component is dominant [66]. AML localised in the liver are characterised by

the content of a component resembling smooth muscle, which is higher than in classical AML [24]; necrosis and an infiltrating type of growth are more commonly observed [49].

Epithelioid AML (EAML) is characterised by the presence of epithelioid cells with various degrees of nuclear atypia [67]. Giant epithelioid cells, present as groups, may attain a diameter as large as 1 mm, and these are cells with numerous hyperchromatic nuclei with distinct nucleoli [13]. Epithelioid cells are frequently accompanied by the presence of necrosis and the mitotic index of these tumours is generally low — from one to three division figures per 10 large visual fields [13]. Very rarely (approximately 20 known cases) AML with the presence of multiple cysts is observed (angiomyolipoma with epithelial cysts; AMLEC), which indicates a benign course [68] with a cystic morphology [69]. In single cases an extensive infiltration of AML by immune system cells is observed, distinguishing an inflammatory AML subtype (inflammatory angiomyolipoma) [70]. Exceptionally, cases have been described of the occurrence inside AML of other neoplasms: angiosarcoma [71] and renal cell carcinoma (RCC) in a patient with tuberous sclerosis [72].

In immunohistochemical analysis the classical AML subtype shows a strong expression of melanocyte markers: HMB-45 and Melan A in all three tumour components: blood vessels, fat tissue, and smooth muscle, in which at least one of the above-mentioned markers is present in each case [73]. Moreover, frequent expression is observed of NK1-C3 (approx. 2/3 of cases), tyrosinase (in approx. one-half of cases), and KIT (CD117) (from one-half to all cases, depending on the reference) [73, 74]. In the case of epithelioid AML, epithelioid cells typically show co-expression of melanocyte: HMB-45 and Melan A and muscle: SMA and calponin [6] markers. Another melanocyte marker, S-100, characteristic for melanoma cells, most frequently is not expressed in epithelioid cells, but in about 1/3 of cases a cytoplasmic reaction is observed [6]. Moreover, a diffuse expression is observed for: cathepsin K, D2-40 (podoplanin) and progesterone and oestrogen receptors and vimentin [13]. A strong expression of the CD68 marker has also been observed (among others also a macrophage marker), which, because of the lack of its expression in renal cell carcinoma, can be useful in distinguishing these two entities [75]. Cytoplasmic expression of E-cadherin is present both in classical and in epithelioid AML, and in the latter is localised both in the membrane and in the cytoplasm [76]. Stronger diffuse expression of p53 and weaker membrane expression of E-cadherin have been described as characterising cases of malignant EAML, in comparison with other EAML with a benign course [77].

Classical AML with a typical structure composed of muscle tissue, fat tissue, and blood vessels is easy to distinguish from other entities (Figures 1, 3), but its epithelioid subtype may pose diagnostic difficulties (Figure 2).

Differential diagnosis of EAML encompasses poorly differentiated tumours with a frequent localisation within the kidneys or the liver, such as: malignant melanoma metastases, gastrointestinal stromal tumours (GIST), renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), adrenocortical carcinoma (ACC), and kidney oncocytoma [78]. Microscopic and immunohistochemical characteristics distinguishing these entities are summarised in Table 3.

Genetics

AML typically occurs in patients with tuberous sclerosis, a genetic syndrome caused by inactivating germline mutations within the *TSC2* gene at locus 16p13.3 or less frequently *TSC1* at locus 9q34 [81]. These genes encode tuberin and hamartin, respectively, which are proteins forming a complex with GTPase activity, with an inhibitory action on the signalling mTORC1 complex [82]. The lack of suppressor activity caused by their mutations causes excessive activity of the mTOR pathway, stimulating proliferation and in effect neoplasm formation. In the TOSCA trial a difference in AML occurrence was found depending on the mutated gene; AML occurs in 33.3% of patients with the *TSC1* mutation and in 59.2% with the *TSC2* mutation [9]. Correlation between the mutation of a distinct gene and the clinical course is not clear [83]. Somatic deletions in the *TSC2* locus are observed in sporadic cases of angiomyolipomas [84], leading to, similarly as in tuberous sclerosis, an increased activity of the mTORC1 complex [85]. Moreover, 0.3% of patients with AML, lymphangioma, and tuberous sclerosis were found to have a codon 72 (R73) polymorphism of the *TP53* gene, and the presence of this polymorphism was linked to an increased risk of AML development [86]. Moreover, a case has been described of a generally healthy woman with bilateral classical AML and multiple uterine fibroids with a balanced 46,XX,t(11; 12)(p15.4;q15) translocation, whose effect could have been the separation of the promoter and the transcription initiation site from the rest of the *NUP98* gene, which had not earlier been associated with the PEComa family, but its fusions are frequently present in haematological neoplasms [87]. In the case of malignant epithelioid AML, other genetic perturbations are also noted, e.g. in two patients with advanced EAML in metastatic tumours a strong expression of MDM2, a ubiquitin ligase participating in the degradation of p53 suppressor protein, has been described, as

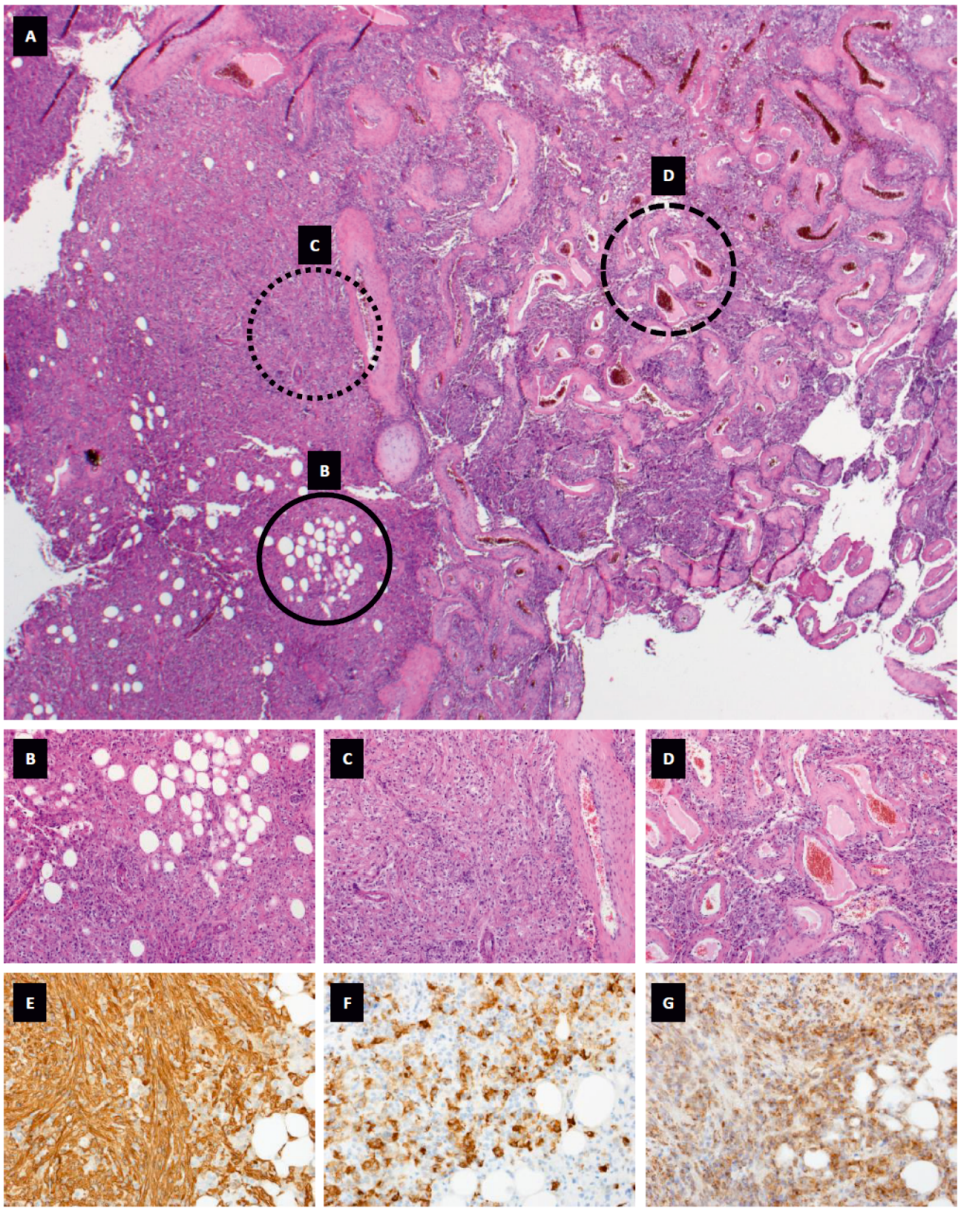

Figure 3. Kidney angiomyolipoma. **A.** According to its name, the tumour contains vessels, smooth muscle, and fat cells [HE, 20×]; **B.** Visible texture of mature fat tissue without atypia characteristics [HE, 200×]; **C.** Solid fragments of the tumour with smooth muscle texture [HE, 200×]; **D.** Sinuous, thick-walled, and partly hyalinised blood vessels [HE, 200×]; **E. F. G.** Panel of characteristic immunochemical staining for angiomyolipomas: successively SMA, HMB-45, and Cathepsin K [HE, 200×]

well as its absence in primary tumours [88, 89]. Further analysis using the FISH method indicated amplification of the *MDM2* gene in part of the cells derived from metastatic tumours, indicating the potential role of *MDM2* in the acquisition of a malignant phenotype by EAML cells. A case of a malignant EAML has been noted with an amplification of the *TFE3* gene, encoding a transcription factor regulated among others by the mTOR kinase, whose fusions and amplifications are frequently observed in malignant PEComa [62].

Classical AML — treatment and prognosis

The majority of sporadic AML are benign and are detected accidentally during imaging tests performed for other indications, remaining asymptomatic and not showing growth [2], thus the treatment of choice is conservative [90]. However, because these tumours can reach large sizes and have a rich blood supply, they may give rise to many complications, the most common being

Table 3. Differential diagnosis of EAML (based on [78–80])

Unit	Microscopic	Immunohistochemical markers						
		HMB-45	Melan-A	S-100	CD-117	Keratins	SMA	Other
EAML	Areas with classical AML morphology, tumour with high cellularity with cells of the histiocyte type; considerable cellular atypia; few divisions. Large nuclei with distinct nucleolus	+	+	±	+	±	±	CD68
ACC	Cells from well differentiated to anaplastic with hyperchromatic, atypical nuclei; considerable mitotic activity with atypical divisions	–	+	±	±	±	–	Inhibin A, calretinin, synaptophysin, SF1, bcl2, p53
RO	Round or polyhedric cells with acidophilic granular cytoplasm. Centrally located nucleus with evenly distributed chromatin	–	–	+	+	+	–	CK8/18, CK14
GIST	Epithelioid and fusiform cells with light, acidophilic cytoplasm without granulosities	–	–	±	+	±	±	DOG1
HCC	Barrel-like distribution of cells with abundant, acidophilic, granular cytoplasm, presence of SINUS vessels	–	–	–	±	+	–	HepPar1, CEA, AFP
RCC	Heterogeneous cell population with differentiated levels of atypia, presence of small cytoplasmic vacuoles; hemosiderin deposits	–	–	±	+	+	–	PAX8, PAX2, CD10, CAIX, RCC, CD63; TF-EB in RCC t(6;11); TFE3 in RCC (X;1p11)/TFE3
M	Cells with many shapes Distinct nucleoli absent	+	+	+	+	±	±	SOX10, BRAF

ACC — adrenocortical carcinoma; HCC — hepatocellular carcinoma; GIST — gastrointestinal stromal tumour; M — melanoma; RCC — renal cell carcinoma; RO — renal oncocytoma

bleeding. Kidney AML are the most common cause of bleeding into the retroperitoneal space not linked to injury [11]. A large size of the tumour (diameter over 3.5–4 cm) is believed to be the main predisposing factor for this complication, significantly increasing the need for invasive procedures [91]. Correlation between the tumour size and the probability of bleeding has, however, been described as unclear in a current, large, systematic review [92]. Other risk factors for bleeding include: the presence of an aneurysm within the tumour, pregnancy, anticoagulation therapy, or injury, even of a low intensity [93]. In sporadic cases independent predictors of tumour growth were shown to be blood group 0 ($p = 0.038$) and De Ritis index (AspAT/AlAT) ≥ 1.24 ($p = 0.047$) [94]. In patients with tuberous sclerosis, the presence of numerous AML taking up most of the parenchyma of both kidneys leads to gradual increase in kidney insufficiency to end-stage insufficiency in as many as 7% of patients [95]. AML progression during successive control visits occurs in about 20% of patients with tuberous sclerosis, and in patients older than 40 years almost one-half require a medical intervention for this reason [9]. This is linked to the need for frequent hospitalisations, in effect lowering the quality of life of these patients [96].

AML — surgical treatment

The most appropriate management method for AML is active surveillance (AS) [97]. Sporadic, asymptomatic tumours with a diameter under 4 cm require an ultrasound control every 12 months (for 2–5 successive years), which in the case of a lack of tumour progression can be limited, whereas tumours with a diameter of under 2 cm are considered in the literature as not requiring controls because of a minimal risk of complications [98]. Asymptomatic sporadic AML with a diameter over 4 cm require more frequent ultrasound controls — every 6 months, because of an increased risk of tumour bleeding and growth [99]. Progression or spontaneous bleeding into the retroperitoneal space is, however, observed only in a small percentage of cases, respectively: 11% and 2% [92]. Of decisive importance for therapeutic decisions

is the tumour size, presence of symptoms (e.g. pain in the tumour projection, haematuria), and a suspicion of malignancy, which correlate with a risk of occurrence of bleeding into the retroperitoneal space [92]. Prophylactic treatment should also be applied in women who are planning a pregnancy, and with AML with a diameter > 4 cm [93]. At the same time, a large tumour size, traditionally taken as a diameter > 4 cm, without other risk factors for bleeding should not determine the need for undertaking prophylactic actions in the form of embolisation or resection [92], because only 1/3 of patients with tumours > 4 cm in diameter will require active therapy [99]. If spontaneous bleeding into the retroperitoneal space or haematuria occur, the presence of a large tumour or clinical symptoms (most commonly pain in the tumour projection) or radiological metastatic characteristics, various therapeutic approaches can be applied: embolisation, ablative techniques, nephron-sparing surgery (NSS), and in selected cases radical nephrectomy is required [90, 92]. If active surveillance has to be interrupted, the treatment of choice is selective arterial embolisation (SAE) [97], as a minimally invasive procedure with optimal maintenance of the function of the affected kidney [100]. Moreover, embolisation, in comparison to resection, is linked to less frequent complications and a reduction in tumour size in most cases, even though in approx. 40–50% of patients the intervention may need to be repeated because of recanalisation or development of new blood vessels [100, 101]. Further AML growth is rarely observed after embolisation; it is linked to the growth of the vascular component of the tumour — these cases require a confirmation of the AML diagnosis [100]. A surgical procedure should only be used in cases where embolisation is not attainable or is technically/anatomically impossible, and it should be as sparing as possible [97]. The use of surgical techniques is linked with frequent occurrence of complications but also with a lower risk of local recurrence [100]. Moreover, partial nephrectomy is considered as a preferred solution in the case of AML of considerable size (> 8 cm diameter) because of their rich vasculature, making embolisation of large tumours complicated and less effective [101], as well as in women with an advanced pregnancy [93].

AML associated with tuberous sclerosis require different procedures because of the frequent tendency of the tumours to grow, spontaneous bleeding into the retroperitoneal space, and the potential development of renal insufficiency. In adult asymptomatic patients with large AML (> 4 cm) it is recommended that the creatinine level be analysed and a control TK/MRI be performed every 1–2 years, whereas asymptomatic patients with smaller tumours can be checked less frequently if their results are stable [63, 102, 103]. The appearance of symptoms indicating kidney complications (pain, feeling of heaviness in the abdominal cavity, haematuria, shock) require immediate imaging diagnosis [63]. Preventive procedures in patients with tuberous sclerosis are recommended in asymptomatic AML with many risk factors for bleeding: size > 8 cm, dominant vascular component, and presence of microaneurysms, and they may be considered in patients with AML > 4 cm when other risk factors are present, e.g. risk of injury in the pelvic area, planned pregnancy, or taking anticoagulants [63]. With increasing frequency for AML associated with tuberous sclerosis, in the scope of bleeding prophylaxis, the use of mTOR inhibitors is recommended as first-line treatment instead of embolisation [104].

AML — systemic treatment

Because of the increased activity of the mTORC1 complex observed in angiomyolipomas, both in cases associated with tuberous sclerosis and with lymphangioleiomyomatosis, over a dozen clinical trials have been performed on the use of mTOR inhibitors in these patients, which have yielded positive results. This led to confirmation by the European Medicines Agency (EMA) in 2011 and the Food and Drug Administration (FDA) in 2012 of everolimus to treat kidney AML in adult patients with tuberous sclerosis, who do not require urgent surgical treatment but are at risk of complications evaluated on the basis of tumour size, the presence of multiple or bilateral tumours, and aneurysms within the tumours. The principles for everolimus use in adult patients with AML in the course of tuberous sclerosis are summarised in Table 4. In the case of impossibility to use a registered drug or the need for therapy of paediatric patients, the use of sirolimus can be considered [63], due to literature references showing its efficacy [105, 106].

One of the first trials of the use of everolimus in patients with tuberous sclerosis was a phase 3 randomised clinical trial EXIST-1 (EXamining everolimus In a Study of Tuberous sclerosis complex 1), encompassing 117 patients with tuberous sclerosis and simultaneous presence of a subependymal giant cell astrocytoma (SEGA) [107]. A decrease in AML volume occurred in 53.3% of patients treated with everolimus, in comparison to 0% of responses in the placebo group. For the largest of the performed trials — a randomised double-blind phase 3 trial EXIST-2 (EXamining everolimus In a Study of Tuberous sclerosis complex 2) — 118 patients with AML with a diameter ≥ 3 cm and tuberous sclerosis or accompanying lymphangioleiomyomatosis were recruited [108]. Seventy-nine patients received everolimus at a dose of 10 mg *p.o.* (median observation time 38 weeks), and treatment response (defined as decrease in tumour mass by at least 50% in relation to the initial size) was observed in 42% of patients receiving everolimus and in none of the patients receiving placebo. Median time until

Table 4. Principles of everolimus therapy in AML in adult patients with tuberous sclerosis (on the basis of [63])

Standard dose		1 × 10 mg/day
With liver insufficiency	A according to Child and Pugh scale	1 × 7.5 mg/day
	B according to Child and Pugh scale	1 × 5 mg/day
	C according to Child and Pugh scale	Max 1 × 2.5 mg/day

- Everolimus is a substrate for the CYP3A4 isoenzyme and glycoprotein P. Inhibitors of CYP3A4 and glycoprotein P may increase its concentration in blood, and inductors may decrease it
- The lowest effective dose should be used with acceptable adverse effects
- Treatment should be continued as long as clinical benefits are observed or until unacceptable toxicity occurs
- Live vaccine use should be avoided
- In the case of simultaneous use of an inhibitor of angiotensin convertase (ACE) — increased risk of angioedema

response to treatment was 2.9 months. After finishing the EXIST-2 trial, on the basis of its promising results, observation of successive patients recruited to the everolimus arm was continued [102]. A decrease in tumour diameter by over a half was observed in 58% of patients, and in 95% some decrease in tumour diameter was seen. Disease progression was observed in 16 patients, among whom in 13 taking of the drug was perturbed because of the occurrence of adverse effects or noncompliance. Retrospective analysis of data from the EXIST-1 and EXIST-2 trials also showed a long-term stabilisation of the glomerular filtration rate during everolimus therapy [109]. In 43.8% of patients who finished treatment after the EXIST-2 trial, AML progression was observed in the form of tumour growth or haemorrhage, but without evidence for increased growth after drug withdrawal [110]. Responses to everolimus treatment, in the form of a decrease in AML size, were also observed in a retrospective analysis of data from the EXIST-1 trial in 33 paediatric patients [111]. In 75.8% (CI: 57.7–88.9%) of patients an objective response was found in the form of a decrease in tumour volume, which was maintained during almost four years of observation. Moreover, in 80% of them the decrease in tumour volume was over 50%. A subsequent nonrandomised, open clinical trial, including 18 patients with TSC, indicated a decrease in AML volume by one-half in 66.67% of cases after a year of receiving everolimus [112]. Similarly as in the EXIST-2 trial, after withdrawal of the drug, a small increase in tumour size was observed — to the value before the beginning of the trial (average tumour volume 12 months after drug withdrawal 77.62 ± 16.66% of the initial value). In a retrospective analysis comparing clinical data of 72 patients with tuberous sclerosis and kidney AML, a significant reduction in size of kidney tumour (85.2% *vs.* 37.9%; p = 0.0003) and a tendency to a lower decrease of the eGFR value were observed (44.4% *vs.* 66.7% of the initial value, p = 0.0840) in 33 patients receiving everolimus in relation to patients only undergoing observation [113]. For better control of adverse effects, due to the need for chronic drug intake, a trial was performed evaluating use of everolimus in an intermittent fashion, in which patients with TSC interrupted the taking of the drug in cases of maintained partial response, and went back on the drug when the size of the tumour reached 70% of the initial value [114]. The average decrease in tumour volume in response to renewal of the treatment was 61% and did not differ significantly from the primary response. There are also reports on long-term, four-year responses to everolimus in a lower dose (2.5–5 mg/d *p.o.*) than is commonly used [115]. The effectiveness of everolimus use was also observed in the case of very large tumours (the largest size over 20 cm in two cases and over 12 cm in a third case) associated with TSC [116]. Moreover, everolimus turned out to be effective as a second-line treatment in the case of AML progression after arterial vessel embolisation [117]. Reduction of tumour volume by over 50% was obtained in 57% of the 14 investigated cases, and the average volume decrease was 53%. It was observed that the rate of reduction of tumour size in response to everolimus depends on its tissue composition — tumours with a rich vasculature and developed smooth muscle shrink over two times faster than tumours composed mainly of fat tissue [118]. This effect is reflected in the change in AML composition during everolimus therapy: the rich vasculature disappears and the relative fat content increases, causing a decrease in the CNR value (contrast to noise ratio) of the tumour image in magnetic resonance [119]. Some nonrandomised open clinical trials have also been conducted on the use of sirolimus in patients with kidney AML and TSC or lymphangioma. In a systematic review including four of these trials [120–123] response to treatment according to RECIST was found in 45.7% patients during one year of therapy and 43.5% in the second year [105]. Among patients who no longer received the drug during the second year of observation, objective response was maintained only in 5%. Excessive activation of the mTORC1 complex, associated, among other things, with somatic mutations inactivating the *TSC2* gene, were also found in sporadic AML, and single reports indicate similar benefits of

using mTOR inhibitors in these patients [85]. However, clinical trials concerning systemic treatment of sporadic AML cases have not been performed.

EAML — treatment and prognosis

The epithelioid AML subtype (EAML) is associated with an uncertain prognosis and the possibility of a malignant clinical course. In rare cases EAML show a tendency for local recurrence or distant metastases, even 12 years after primary tumour resection [124] (Figure 2). In an investigation comparing the clinical course of classical AML and EAML, among 27 patients with EAML, distant metastases occurred in five, and three of them died during the observation. At the same time among 204 patients with classical AML no distant metastases or death due to the disease took place [7]. In another analysis an unfavourable course of the disease (defined as death because of the disease, distant metastases or metastases to local lymph nodes, infiltration of the kidney vein, or local recurrence) was observed in 40% patients with EAML [13]. However, the exact percentage of EAML with a malignant course remains difficult to evaluate, due to the few groups of patients in accessible trials and papers indicating a much smaller scale of the problem, e.g. lack of local recurrence or distant metastases in all analysed EAML cases [6] or the occurrence of distant metastases in only one among 20 patients with EAML [16]. In a systematic review concerning the clinical course of liver EAML, local recurrence after resection was found in 2.4% of cases (6/247), and death due to the disease in 0.8% of cases (2/247) [125]. Factors increasing the probability of finding AML with an epithelioid morphology include a younger age of the patient [6, 7], male sex (OR = 3.33 [7]) and tumour diameter > 4 cm ([OR = 3.8 [7]). EAML diagnosis has been linked with a significantly shorter three-year overall survival (OS) and three-year disease-free survival (DFS) — 50% and 0%, respectively, in comparison to classical AML — OS 100% and DFS 100% [10]. In the same analysis negative prognostic factors for OS were as follows: the EAML subtype, low fat tissue content in the tumour, a broadening of the kidney vein, and insufficient tumour resection. Selection of patients at risk of a malignant course of EAML requires appropriate use of radical surgical treatment and consideration of systemic therapy. However, knowledge concerning the prognosis of a potentially unfavourable disease course is limited. In an investigation including 40 cases of EAML with characteristics of nuclear atypia, it was evaluated that if it fulfils three of four criteria (70% or more atypical epithelial cells, two or more cell divisions in 10 HPF, atypical cell divisions, presence of necrosis), this significantly increases the risk of a malignant course [12]. Another analysis, in which a review of the literature was made (17 EAML cases) and two of the authors' own cases were included, indicated that a significantly increased risk of a malignant character of the tumour is indicated by finding at least five of the following characteristics: diameter ≥ 5 cm, presence of metastases, infiltrating type of growth, the presence of necrosis, at least 50% atypical epithelioid cells, cellular atypia, atypical mitoses, and invasion of vessels [126]. In an analysis of 53 EAML cases, in which in three patients distant metastases occurred, tumours with progression differed from those with a benign course in size — respectively, 10 *vs*. 3.3 cm ($p < 0.001$), epithelioid cell content 83.3 *vs.* 40.9% ($p = 0.001$), and cells with atypia 76.7 *vs*. 24.8 % ($p < 0.001$) [17]. Correlation between tumour size and the number of cell division figures and the ability of EAML to form metastases was, however, not confirmed in another analysis encompassing 23 cases, in which an unfavourable course of the disease was only associated with nuclear atypia and the presence of necrosis [67]. An attempt to classify kidney EAML was made in a trial encompassing 41 patients, dividing tumours into three risk categories on the basis of five characteristics: concomitant tuberous sclerosis, presence of necrosis, renal vein infiltration, infiltrating tumour growth, and tumour diameter > 7 cm [14]. Tumours with more than two characteristics are considered low risk (15% of patients underwent progression), tumours with 2–3 characteristics are considered average risk (64% progression), whereas tumours with four or more characteristics underwent progression in all cases.

EAML treatment

The basis of EAML treatment is radical resection; complete removal of the tumour, even a malignant one, ensures a high percentage of cured cases: from 74% [12] to 100% [6]. In the case of hepatic EAML the most common treatment modality is open surgery [125], although there are reports in the literature of complete removal of hepatic EAML using laparoscopic techniques [57, 127]. Cases of local non-resectable recurrences and distant metastases indicate the need for long-term observation of patients with EAML with malignant properties and of establishing standards of systemic treatment in non-resectable cases. EAML most commonly are resistant to standard chemotherapy with a few exceptions described in the literature, e.g. a stabilisation of the disease lasting several months in response to six cycles of dacarbazine with cisplatin [128]. Similarly as other tumours from this group, epithelioid AML subtypes show an increased activity of the mTORC1 complex and mutations that inactivate *TSC2* [129]. So far, no clinical trials have been performed on the use of mTOR inhibitors in EAML. Over a dozen cases are available in the literature (summarised in Table 5)

Table 5. Cases from the literature of mTOR inhibitor use in systemic therapy

Author	Sex	Age (years)	Localization	Size [cm]	TSC/ /LAM	Somatic mutation	Local recurrence (LR)/ /metastasis (Met)	Radical treatment	Drug	Dose	Best response	Time to progression (months)	Follow-up (months)	Effect
Higa et al. [130]	F	26	Liver	–	LAM	NA	Met: lungs	R	Sirolimus	2 mg/d *p.o.*	PD	4	10	DOD
Wolff et al. [131]	M	24	Kidney	24	TSC	NA	LR	RN	Sirolimus	6 mg/d *p.o.*	PR	NO	12	AWD
	M	72	Kidney	14	–	NA	LR; Met: liver	RN, M	Temsirolimus	–	PR	NO	11	AWD
Shitara et al. [132]	M	52	Kidney	–	TSC	NA	Multiple Met to abdominal cavity	RN	Everolimus	10 mg/d *p.o.*	PR	NO	7	AWD
Kohno et al. [133]	F	50	Kidney	–	–	NA	Met: lungs, liver, pelvis	RN, M	Everolimus	10 mg/d *p.o.*	PR	NO;	6	AWD
											PD	4	4	
									Temsirolimus	–	PR	NO	1	
Faria et al. [134]	M	58	Kidney	5	–	NA	LR	RN	Everolimus	–	PR	NO	4	DOT
Wyluda et al. [135]	F	31	Kidney	–	–	NA	Met: mediastinum	RN	Temsirolimus	–	–	12	17	DOD
Hong et al. [136]	M	58	Kidney	–	–	non. *SMARCB1*	LR; Met: liver, multiple to abdominal cavity	RN, M + RTH	Temsirolimus	25 mg *i.v.* on day 1 and 8/m	PR	8	8	AWD
									Everolimus	7.5 mg *p.o.* for 3 weeks/m	PR	NO	2	
Binyamin et al. [137]	M	56	Kidney	11	–	NA	LR; Met to post-surgery scar, bones	PN	Everolimus	–	PD	2	2	AWD
									Pazopanib	–	SD	6	–	
Anwar et al. [138]	F	27	Adrenal	9	–	NA	–	–	Everolimus	2.5 mg/d	PR	NO	1	AWD
Espinosa et al. [129]	M	34	Kidney	12	–	dup. *TSC2*	Met: liver, lumbar vertebrae	RN, M	Sirolimus	6 mg/d *p.o.*	CR	NO	36	NOD
Hulova et al. [139]	F	28	Kidney	15	–	NA	LR; Met: liver, greater omentum	RN, M	Sunitinib	50 mg/d *p.o.* (1 m + 2 week break)	PD	6	6	DOD
									Everolimus	–	SD	60	76	
Lattanzi et al. [140]	M	38	Kidney	6	–	non.*TP53* and *APC*, frameshift *ATRX*, del. *TSC2*	LR; multiple Met to abdominal cavity	R	Everolimus	–	PR	8	8	AWD
									Nivolumab	3 mg/kg *i.v.* every 2 week	PR	NO	24	
Tayal et al. [141]	F	63	Kidney	–	–	Missense in *KIT, FLT 3, KDR, MET*	Met: lungs, liver, bones, abdominal cavity	R	Imatinib	–	PD	4	4	AWD
									Crizotinib	200 mg/d	PD	4	4	
									Everolimus	5 mg/d *p.o.*	PR	NO	17	

Radical treatment (M — metastasectomy, PN — partial nephrectomy, RN — radical nephrectomy, R — resection, RTH — radiotherapy); NA — not analysed; NO — not reached; somatic mutation (del. — deletion, dup. — duplication, non. — nonsense); CR — complete response; PD — progressive disease; PR — partial response; SD — stable disease; effect: AWD — alive with the disease, DOD — dead due to the disease, DOT — dead from other causes, NOD — no evidence of the disease

of using mTOR inhibitors in systemic therapy of patients with EAML, who had multiple non-resectable recurrences of the disease or developed metastases, sometimes showing long-term partial responses. In some cases, the tumours underwent swift progression in spite of the applied treatment, which indicates that other therapeutic targets must be found. Several cases have been described of responses to treatment with tyrosine kinase inhibitors: a six-month stabilisation of the disease after pazopanib [137] and decrease in the size of EAML metastases to the liver, maintained for over seven months after using apatinib [142]. In the literature there is also a report about a persistent, almost complete response in a patient with recurring and disseminated epithelioid AML after two years of treatment with nivolumab in the second line after therapy with everolimus [140]. Staining of tissues derived from the primary tumour showed a strong expression of PD-L1 (over 50% cells) and the presence of infiltrating T CD8(+) lymphocytes.

Summary

Angiomyolipoma (AML) is a benign mesenchymal tumour, which may occur sporadically or in the frame of tuberous sclerosis and lymphangioleiomyomatosis. The sporadic form is the most common form of benign kidney tumour and occurs four times more frequently in women. Renal tumours of the AML type are most commonly detected during abdominal ultrasound scans, computed tomography, or magnetic resonance. In abdominal cavity ultrasound scans they are visible as hyperechogenic tumours and in most cases do not pose a diagnostic problem. The most important diagnostic method in the case of AML is computed tomography, which is performed in patients with the suspicion of a tumour on the basis of an abdominal cavity ultrasound scan. AML growth is slow and complications are rare. The main AML complication may be bleeding to the retroperitoneal space or the pelvicalyceal system. Only the epithelioid AML variant has a malignant potential. The most appropriate management method of AML is active surveillance (AS). Asymptomatic tumours with a diameter below 4 cm require an ultrasound control every 12 months, whereas tumours with a diameter of under 2 cm are considered in the literature as not requiring controls. Asymptomatic sporadic AML with a diameter over 4 cm require more frequent ultrasound controls — every six months. Of decisive importance for therapeutic decisions is the tumour size, the presence of symptoms (e.g. pain in the tumour projection, haematuria), planned pregnancy, and a suspicion of malignancy. Options for active treatment include: embolisation, ablation techniques, nephron-sparing surgery (NSS), and radical nephrectomy. In adult patients with tuberous sclerosis, who require treatment but do not require rapid surgical treatment, everolimus is used. In the case of AML, initially doses of 1 × 10 mg per day should be used (an appropriate dose decrease is required in the case of liver insufficiency). The treatment should be individualised by determining the lowest effective dose with acceptable adverse effects. In the case of AML subtypes with a malignant course attempts are made to use classical chemotherapy, mTOR inhibitors, or VEGFR inhibitors (pazopanib, apatinib), obtaining objective responses only in some of the patients.

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