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Renal angiomyolipoma: Clinico-pathologic study of 17 cases with emphasis on the epithelioid histology and p53 gene abnormalities

Ons Boudaouara[a,*], Rim Kallel[a], Dhouha Dhieb[b], Walid Smaoui[c], Houda Ben Ayed[d], Leila Keskes[b], Tahya Sellami Boudawara[a]

[a] Department of Pathology, Sfax University Medical Center, Sfax 3029, Tunisia
[b] Department of Genetics, Sfax University Medical Center, Sfax 3029, Tunisia
[c] Department of Urology, Sfax University Medical Center, Sfax 3029, Tunisia
[d] Community Health and Epidemiology Department, Sfax University Medical Center, Sfax 3029, Tunisia

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ABSTRACT

Background: Epithelioid angiomyolipoma (EAML) is a rare potentially malignant variant of renal angiomyolipoma (RAML).

This study aims to determine whether RAML clinico-pathologic and molecular features (i.e. p53 gene abnormalities) differ significantly with regards to its histologic variant or to the presence of an epithelioid component within it.

Methods: Consecutively resected RAML were reviewed, tumours comprising at least 80% of epithelioid cells were considered as EAML according to the 2016 World Health Organization classification of tumours of the kidney. P53 gene abnormalities were investigated using both immunohistochemical and molecular analysis.

Results: A total of 3 EAML among 17 RAML were identified, accounting for 3.9% of the total AML cases. Fatty aspect on imaging was more observed within tumours devoid of an epithelioid component. EAML showed a higher mitotic rate and a stronger p53 staining, no renal poles involvement and was not treated by nephron sparing surgeries. RAML comprising an epithelioid component demonstrated severer nuclear atypia as well as stronger p53 staining. P53 gene sequencing revealed a missense mutation (c.747G > C) in one classic AML harbouring a strong labelling with p53.

Conclusions: Strong p53 staining in a RAML, even in the absence of gene mutation, may suggest the presence of an epithelioid component or of a truly EAML. To the best of our knowledge, c.747G > C p53 gene mutation is being reported for the first time in a RAML, although its role in AML pathogenesis is still unknown.

1. Introduction

Renal angiomyolipoma (RAML) is a mesenchymal neoplasm belonging to the perivascular epithelioid cell tumour family (PEComa) [1-4]. It occurs mostly sporadically (80% of all cases) although it may be associated with genetic alterations of tuberous sclerosis complex (TSC), an autosomal dominant congenital disease [5,6]. Classic AML (CAML) has a triphasic histology and contains variable amounts of abnormal thick-walled blood vessels, spindle and epithelioid smooth muscle cells and adipose tissue [7]. Epithelioid AML (EAML) has been defined as a rare variant of AML comprising at least 80% of epithelioid cells according to the 2016 World Health Organization (WHO) classification of tumours of the kidney [7]. In contrast to the classic variant which is benign, EAML might demonstrate poorer outcomes with possible recurrences and metastasis [3,4,7-9]. Hitherto, the pathogenesis of renal EAML (REAML) remains poorly understood because of the scarcity of this neoplasm. Clinico-pathologic features of RAML with regards to its histologic subtype (HS) or to the presence of an epithelioid component within the tumour were rarely documented in the literature [1,5]. P53 gene abnormalities are one of the key genetic steps in several tumours including RAML [8]. P53 gene mutations and epigenetic alterations frequently lead to accumulation of abnormal protein within tumour cells and may be detected by immunohistochemical analysis [8]. Yet, p53 expression seems to be stronger within EAML when compared with CAML and may suggest the tumour's malignant behaviour [8].

Through the present study, we tried to establish the incidence of REAML based on all consecutively resected RAML at our institution.

* Corresponding author at: Department of Pathology, Sfax University Medical Center, Ain's Street km 0.5, Sfax 3029, Tunisia.
E-mail address: annoussa1988@hotmail.com (O. Boudaouara).

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Furthermore, we investigated the clinico-pathologic features that might be associated with RAML HS or with the presence of an epithelioid component within it. Finally, we explored p53 immunohistochemical and mutation analysis in EAML and RAML containing an epithelioid component in comparison with otherwise typical triphasic RAML.

2. Materials and methods

2.1. Patients, inclusion and exclusion criteria

Pathology files at our institution were retrospectively searched for RAML in the period between January 2004 and December 2016. The pathological diagnosis was primarily made on the basis of morphologic analysis and confirmed in all cases by immunohistochemistry (positivity of tumour cells to a melanocytic marker (HMB-45)). Cases of perirenal AML without renal involvement, as well as tumours resected elsewhere addressed at our institution for further opinion were excluded.

2.2. Methods

In all eligible cases, we recorded clinical features—namely, age, gender, symptoms and medical history of TSC; imaging tumour characteristics (i.e. site, size, multiplicity, side and fatty aspect); surgical treatment patterns and follow-up data. Haematoxylin-eosin (HE) and immunostain slides were reviewed in each case. Pathological attributes that were retrieved comprised HS, haemorrhage, necrosis, degree of nuclear atypia, mitotic activity and perinephric fat infiltration. RAML HS was categorized as classic or epithelioid. The latter was assigned according to the 2016 WHO criteria defining it as a proliferation of predominantly polygonal or spindle cells with abundant clear to eosinophilic cytoplasm involving more than 80% of the tumour area. Detailed analysis of epithelioid component on HE slides recognized, when applicable, two architectural growth patterns: carcinoma-like pattern (designated as pattern A) comprising large cells arranged as cohesive nests, broad alveoli and compartmentalized sheets and diffuse pattern (known as pattern B) composed of epithelioid to plump spindled cells arranged in diffuse sheets. Immunohistochemical and molecular studies were accomplished on cases with available formalin-fixed, paraffin-embedded (FFPE) tissues (14 cases). Immunohistochemistry was performed using monoclonal antibodies against HMB-45 (Leica, HMB-45, country: Denmark, city: Glostrup) and p53 (DO-1, Dako, country: Deutschland, city: Wetzlar). The degree of immuno-staining with p53 was assessed semi quantitatively according to the score adopted by Li et al. [8] based on staining intensity and positive tumour cells proportion (Appendix A). The staining intensity was graded as follows: 0 (no staining), 1 (light yellow), 2 (yellowish brown) and 3 (brown). The positive cells were graded according to the percentage of positive cells as follows: 0 (no positive tumour cells), 1 (< 10% positive tumour cells), 2 (11–50% positive tumour cells), 3 (51–80% positive tumour cells) and 4 (> 80% positive tumour cells). The percentage of positive cells and the staining intensity were then multiplied to generate the immunoreactivity score. Based on this score, p53 immunostaining was divided into 3 groups: negative (score = 0), low (score between 1 and 4), and strong (score > 4). P53 mutational status was determined using genomic DNA extracted from FFPE tumour tissue. DNA was extracted via the QIAamp DNA FFPE Tissue kit (Catalogue No 56,404, Qiagen, Germany). Amplification of p53 gene Hotspot region (exons 5 to 9) was performed in optimal PCR conditions. Exons 5 and 8 were subdivided into two overlapping fragments to simplify their amplification. Primers were listed in Appendix B. The sequencing was done using an ABI PRISM 3100-Avant automated DNA sequencer with the BigDye Terminator Cycle Sequencing reaction kit v1.1. (ABI PRISM/Biosystems).

2.3. Statistical analysis

Statistical analyses were carried out using IBM SPSS Statistics version 21 software. Categorical variables were compared using the Chi-square test in independent samples or the Fischer's exact test. Student's *t*-test on the equality of means was used to compare continuous variables if their distribution had been Gaussian; if not Mann-Whitney *U* test was used. P-values of < 0.05 were deemed statistically significant.

3. Results

3.1. Descriptive analysis

Seventeen patients (3.9%) out of 435 patients, who were consecutively operated for renal masses in our institution, had RAML and fulfilled eligibility criteria for this study.

Mean age at diagnosis was 46 ± 10.7 years and female to male ratio was 3.25:1. Tumours were discovered incidentally in 3 cases (18%) while clinical symptoms were present in the majority of cases (14 cases, 82%). Lumbar pain was the most common symptom (14 cases, 82%) followed by haematuria (6 cases, 35.3%). One RAML occurred in a patient with TSC. Average tumour size at the time of resection was 7.8 ± 4.9 cm. Multiple RAML were evidenced in 3 cases (17.6%). Three patients (17.6%) had multiple RAML, 2 among them had 2 tumour masses involving only the right kidney. The remainder presented 5 bilateral RAMLs. Otherwise, tumours were single and located either in the right or the left kidney in 7 cases each (41.1%). Fatty content on imaging was observed in 10 cases (66.7%). Eleven patients (64.7%) underwent nephron sparing surgery whereas radical nephrectomy was performed in 6 cases (35.3%).

Histologic distribution revealed that tumours were mainly of classic

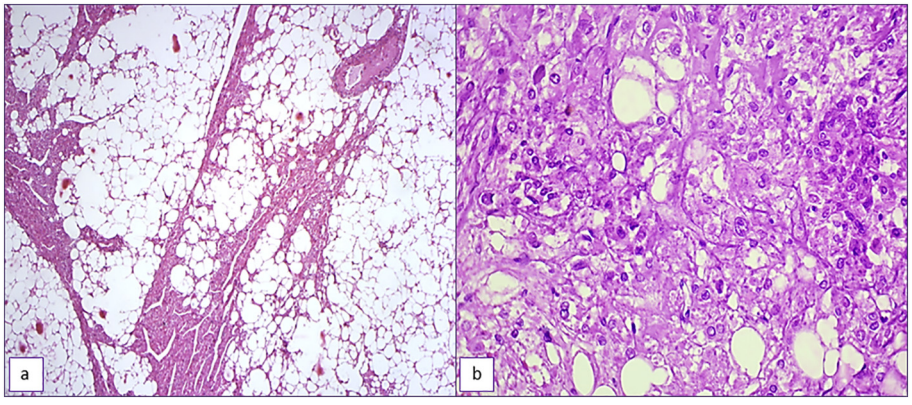

Fig. 1. Histologic subtypes of renal angiomyolipomas: (A) classic variant with triphasic histology, HE x 40; (B) epithelioid variant, HE x 200.

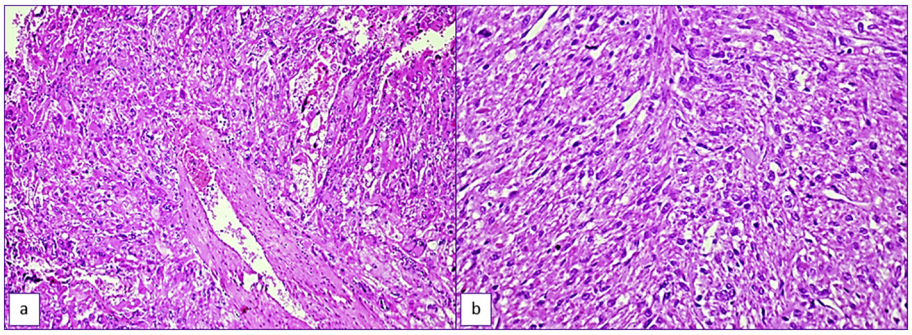

Fig. 2. Spectrum of morphologic features of renal epithelioid angiomyolipomas: (A) carcinoma-like growth pattern with moderate nuclear atypia; (B) diffuse growth pattern with mild nuclear atypia, HE x 200. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

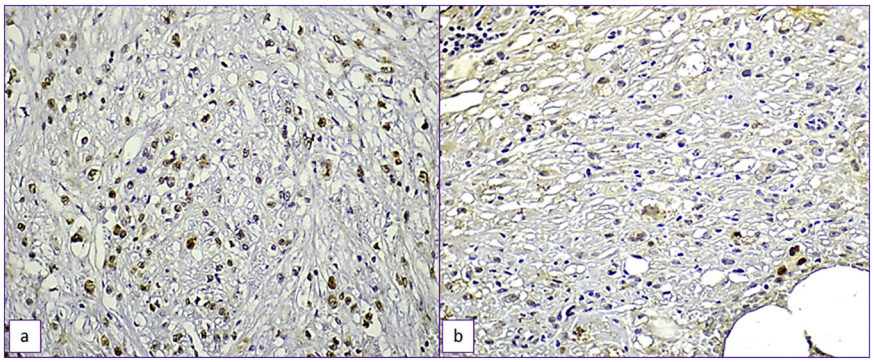

Fig. 3. P53 protein expression in renal angiomyolipomas: (A) strong immuno-staining (p53 score = 8); (B) low immuno-staining (p53 score = 2), x400.

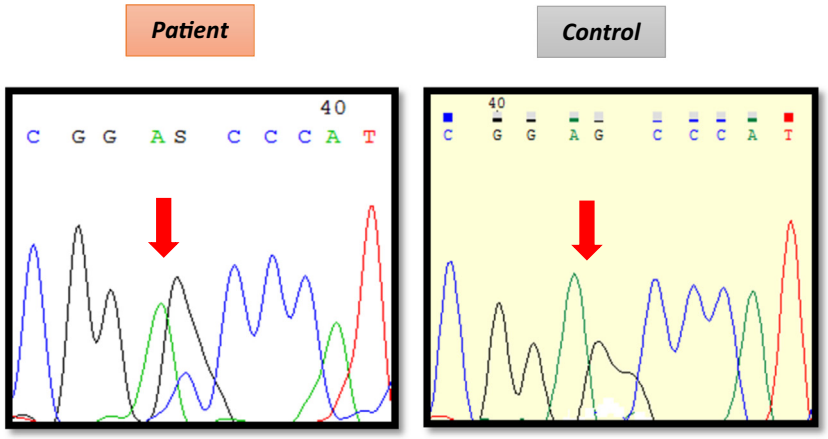

Fig. 4. Detection of c.747G > C mutation in exon 7 of p53 gene in a renal angiomyolipoma.

HS (14 cases, 82.4%); the diagnosis of REAML was retained in only 3 cases (17.6%) (Fig. 1). Pathological slides review objectified an epithelioid component within 10 AML including the 3 aforementioned EAML (58.8%), this component presented a diffuse growth pattern in 9 cases and a carcinoma-like growth pattern in only one case (Fig. 2). Areas of haemorrhage and necrosis were evidenced in 9 (52.9%) and 6 cases (35.3%) respectively. Four AMLs (23.5%) exhibited both haemorrhage and necrosis. Nuclear atypia was graded as mild in 6 cases (35.3%) and as moderate or severe in 11 cases (64.7%) (Fig. 2). Mitotic rate outreached one mitosis per ten high power field (HPF) in 3 cases (17.6%). Perinephric fat infiltration was present in 4 cases (23.5%).

FFPE were available for further immunohistochemical and molecular analysis in 14 cases (82.4%). In 5 out of the 14 cases (35.7%), immuno-staining with p53 was assessed as strong while labelling was assigned as absent or low in 9 cases (64.2%) (Fig. 3). Median p53 immuno-staining score was valued at 2 (range: 0–12). P53 mutation analysis identified a point missense mutation (c.747G > C) in exon 7 (Fig. 4), this mutation was found in one renal CAML harbouring a strong immuno-reactivity with p53 (score = 12).

The median follow-up time was 12 months (range: 2–72 months). Although eight patients were lost to follow-up, the remainder including the 3 REAML (9 patients, 52.9%) showed no evidence of recurrence or metastasis.

3.2. Comparison of renal angiomyolipomas' features on the basis of their histologic subtype or the presence of an epithelioid component within the tumour

RAML characteristics with regards to its HS or to the presence of an epithelioid component within the tumour were summarized in Tables 1 and 2 respectively. Compared with the classic variant of RAML, the epithelioid HS showed an increased mitotic rate (one or more than one mitosis pen ten HPF) (17.6% VS 0%; P = 0.001), no renal poles involvement (0% VS 64.7%; P = 0.02) and was not subsequently treated

Table 1
Clinico-pathologic features of renal angiomyolipomas by their histologic subtype.

Variable	All cases (N = 17)	CAML (N = 14)	EAML (N = 3)	P-value
Age[a] (years)	46,29 ± 10,7	47,86 ± 9,8	39 ± 14,2	0,39
Gender				
Male	4 (23,5)	3 (17,6)	1 (5,8)	1
Female	13 (76,4)	11 (64,7)	2 (11,7)	
Tuberous sclerosis complex				0,17
Yes	1 (5,8)	0 (0)	1 (5,8)	
No	16 (94,1)	14 (82,3)	2 (11,7)	
Symptoms				
Yes	14 (82,3)	12 (70,5)	2 (11,7)	0,46
No	3 (17,6)	2 (11,7)	1 (5,8)	
Size[a] (cm)	7,84 ± 4,9	7,2 ± 4,7	10,83 ± 5,8	0,39
Tumour number				
Single	14 (82,3)	13 (76,4)	1 (5,8)	0,06
Multiple	3 (17,6)	1 (5,8)	2 (11,7)	
Location within the kidney				**0,02**
Polar	11 (64,7)	11 (64,7)	0 (0)	
Non polar	6 (35,3)	3 (17,6)	3 (17,6)	
Fatty content on imaging[b]				0,24
Yes	10 (66,7)	9 (60)	1 (6,7)	
No	5 (33,3)	3 (20)	2 (13,3)	
Treatment				
Radical nephrectomy	6 (35,3)	3 (17,6)	3 (17,6)	**0,02**
Other[c]	11 (64,7)	11 (64,7)	0 (0)	
Nuclear atypia				
Mild-none	6 (35,3)	6 (35,3)	0 (0)	0,51
Moderate-severe	11 (64,7)	8 (47)	3 (17,6)	
Mitosis				
Absent	14 (82,3)	14 (82,3)	0 (0)	**0,001**
> 1/10HPFs	3 (17,6)	0 (0)	3 (17,6)	
Necrosis				
Yes	6 (35,3)	4 (23,5)	2 (11,7)	0,51
No	11 (64,7)	10 (58,8)	1 (5,8)	
p53 immuno-staining[d]				
None-low	9 (64,3)	9 (64,3)	0 (0)	**0,02**
Strong	5 (35,7)	2(14,3)	3 (21,4)	
p53 immuno-staining score[d, e]	2	1	12	**0,02**
p53 gene mutation[d]				1
Yes	1 (7,1)	1 (7,1)	0 (0)	
No	13 (92,9)	10 (71,4)	3 (21,4)	

Abbreviations: CAML, classic angiomyolipoma; EAML, epithelioid angiomyolipoma; HPFs, high power fields.
[a] Means ± standard deviations are shown for the continuous variables: "age", "size".
[b] Computed tomography or magnetic resonance imaging was realized in 15 cases.
[c] Partial nephrectomy (n = 5), tumorectomy (n = 6).
[d] immunohistochemical and molecular analysis were performed in 14 cases.
[e] Medians are shown for the continuous variable: "p53 immuno-staining score".

by a nephron sparing surgery (0% VS 64.7%; P = 0.02). Furthermore, a stronger p53 labelling (21.4% VS 14.3%; P = 0.02) and a higher immuno-staining score (P = 0.02) were noticed in EAML in comparison with CAML. However, there were no further associations between tumour HS and the other clinico-pathologic features.

According to the current study, the presence of an epithelioid component was significantly associated to the severity of nuclear atypia within RAML (58.8% VS 0%; P = 0.001). Moreover, tumours comprising an epithelioid component evidenced a stronger p53 labelling

Table 2
Clinico-pathologic features of renal angiomyolipomas by the presence of an epithelioid component within the tumour.

Variable	All cases (N = 17)	Presence of epithelioid component (N = 10)	Absence of epithelioid component (N = 7)	P-value
Age[a] (years)	46,29 ± 10,7	74,50 ± 12,57	44,57 ± 8,08	0,56
Gender				
Male	4 (23,5)	3 (17,6)	1 (5,9)	0,60
Female	13 (76,4)	7 (41,2)	6 (35,3)	
Tuberous sclerosis complex				1
Yes	1 (5,9)	1 (5,9)	0 (0)	
No	16 (94,1)	9 (52,9)	7 (41,2)	
Symptoms				
Yes	14 (82,3)	7 (41,2)	7 (41,2)	0,22
No	3 (17,6)	3 (17,6)	0 (0)	
Size[a] (cm)	7,84 ± 4,9	6,62 ± 4,73	9,60 ± 5,11	0,24
Tumour number				
Single	14 (82,3)	7 (41,2)	7 (41,2)	0,22
Multiple	3 (17,6)	3 (17,6)	0 (0)	
Location within the kidney				1
Polar	11 (64,7)	6 (35,3)	5 (29,4)	
Non polar	6 (35,3)	4 (23,5)	2 (11,8)	
Fatty content on imaging[b]				**0,04**
Yes	10 (66,7)	4 (26,7)	6 (40)	
No	5 (33,3)	5 (33,3)	0 (0)	
Treatment (N, %)				0,13
Radical nephrectomy	6 (35,3)	4 (23,5)	2 (11,8)	
Other[c]	11 (64,7)	6 (35,3)	5 (29,4)	
Nuclear atypia				
Mild-none	6 (35,3)	0 (0)	6 (35,3)	
Moderate-severe	11 (64,7)	10 (58,8)	1 (5,9)	**0,001**
Mitosis				
Absent	14 (82,4)	7 (41,2)	7 (41,2)	0,22
> 1/10HPFs	3 (17,6)	3 (17,6)	0 (0)	
Necrosis				
Yes	6 (35,3)	2 (11,8)	4 (23,5)	0,16
No	11 (64,7)	8 (47)	3 (17,6)	
p53 immuno-staining[d]				**0,03**
None-low	9 (64,2)	3 (21,4)	6 (42,8)	
Strong	5 (35,7)	5 (35,7)	0 (0)	
p53 immuno-staining score[d, e]	2	8,5	1	**0,04**
p53 gene mutation[d]				1
Yes	1 (7,1)	1 (7,1)	0 (0)	
No	13 (92,9)	7 (50)	6 (42,8)	

Abbreviations: HPFs, high power fields.
[a] Means ± standard deviations are shown for the continuous variables: "age", "size".
[b] Computed tomography or magnetic resonance imaging was realized in 15 cases.
[c] Partial nephrectomy (n = 5), tumorectomy (n = 6).
[d] Immunohistochemical and molecular analysis were performed in 14 cases.
[e] Medians are shown for the continuous variable: "p53 immuno-staining score".

(35.7% VS 0%; P = 0.03) and a higher immuno-staining score (P = 0.04). Yet, the absence of an epithelioid component was more significantly noticed within RAML exhibiting a fatty aspect on imaging (40% VS 0%; P = 0.04). Besides, no additional associations were noticed between the existence of an epithelioid component and the other clinico-pathologic features.

4. Discussion

As in previous reports [1,5,6,9-14], AML represented in our study an uncommon renal neoplasm and accounted for 3.9% of all consecutively resected renal tumours. Nevertheless, our series had higher rates of REAML in comparison with prior studies (17.6% VS 4.6 to 7.7% of resected RAML) [1,3,4,14-16]. This finding may be explained by the opportunity of our institution to receive more atypical RAML cases i.e. epithelioid ones.

In our study as well as for Li et al. [8], increased mitotic rate was more frequently observed within EAML. Inconsistently, Park et al. [1] did not find any significant association between these two parameters. Additionally, our data found no polar location and no nephron sparing surgery in ERAML cases. The relationship between HS and tumour site within the kidney was not investigated formerly through the literature, whereas Delhorme et al. [5] did not evidence any association between HS and surgical treatment pattern.

For several decades, the extent of the epithelioid component warranted to designate a renal neoplasm as an EAML has been poorly defined [17]. In fact, authors used different thresholds varying from 5% to 100% of epithelioid cells in a given tumour to consider it as an EAML [1-3,17-19]. These divergences in diagnostic criteria may lead to gathering heterogeneous samples during studies, potentially resulting in various prognoses based on the threshold applied [1]. Recently, the 2016 WHO classification of tumours of the kidney established a cut-off of 80% of epithelioid cells to define REAML [16].

Since epithelioid histology seems to be a reliable feature that predicts aggressive clinical course of RAML, we investigated the clinicopathological features suggesting the presence of an epithelioid component within RAML. Our analysis revealed that RAML containing an epithelioid component demonstrated severer nuclear atypia on histologic examination. Prior studies did not explore this relationship, even though the degree of nuclear atypia was found to be significantly associated to epithelioid HS of RAML, particularly in those having a carcinoma-like growth pattern (pattern A) [1,8,14].

Our data affirmed that the absence of an epithelioid component was more noticed within RAML exhibiting a fatty aspect on imaging. Inconsistently, Lane et al. [19] found that this relationship was devoid of statistical significance; whereas Delhorme et al. [5] and Guo et al. [20] affirmed that REAML was more associated to poor and non-fatty aspects.

The protein produced of the normal p53 gene has a very short half-life whereas the product of the mutant gene is more stable and can be easily detected immunohistochemically [8,21]. In accordance with previous reports [1,22], p53 staining was much stronger in EAML cases than that in CAML, even though this strong immuno-staining was rarely linked to p53 gene abnormalities. Similarly, several studies reported high levels of p53 protein in RAML cases lacking p53 gene mutation [15,23]. In fact, elevated p53 protein expression evidenced in a number of RAML in previous studies, as well as in the current study, may be attributed to different epigenetic mechanisms other than direct p53 gene mutation [23,24]. Additionally, in our study, labelling with p53 was more pronounced within RAML comprising an epithelioid component in comparison with otherwise typical ones. This relationship was not formerly investigated through previous studies. Further studies are required to explore these mutational and epigenetic events that might be involved in AML tumorigenesis and particularly in its epithelioid variant.

According to the literature, p53 gene sequencing in REAML identified 5 point mutations, two were silent mutations concerning codon 154 [22] and 218 [22], and three were missense mutations, two involving codon 249 [25] and one involving codon 281 [26]. Yet, Li et al. [8] find no point mutations in p53 gene except a single nucleotide polymorphism at codon 72 (P72R). In our study, we identified one point missense mutation (c.747G > C) in exon 7 in a CAML harbouring a strong immuno-reactivity with p53 (score = 12). According to clinvar and rs28934571 database [27], this mutation has been only described in Li-Fraumeni syndrome. To the best of our knowledge, c.747G > C mutation is being reported for the first time in a RAML. Thus, its exact role in AML pathogenesis needs to be clearly investigated.

5. Conclusion

RAML display two different entities with different outcomes. According to this study, EAML, the less common variant, involves rarely renal poles and is uncommonly treated by a nephron sparing approach. Mitosis, nuclear atypia as well as strong p53 staining in RAML may suggest the presence of an epithelioid component or of a truly EAML.

This elevated p53 protein content is, however, rarely linked to p53 gene mutation and might be attributed to different epigenetic events. In our study, we report for the first time a missense p53 gene mutation (c.747G > C) in a RAML, although its role in AML pathogenesis is still unknown.

Authors contribution

Ons Boudaouara, Douha Dhieb, Tahya Sellami-Boudawara: Conceptualization, Methodology, Visualization. Walid Smaoui, Ons Boudaouara: Data curation. Ons Boudaouara, Dhouha Dhieb, Houda Ben Ayed: Investigation, Formal analysis, Software, Writing- Original draft preparation. Tahya Sellami-Boudawara, Rim Kallel, Leila Keskes: Supervision, Validation. Ons Boudaouara, Rim Kallel, Walid Smaoui: Writing- Reviewing and Editing.

Declaration of competing interest

None.

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