Atypical lipomatous tumor: retrospective analysis, prognostic factors and MRI in differential diagnosis

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Summary

***Background*. Authors analyzed retrospectively 98 Atypical Lipomatous Tumor (ALT) treated at a single institution, 96% of which was localized to the extremities and 4% to the trunk, assessing MRI, surgical treatment, local recurrence, follow-up and de-differentiation ability.**
***Methods*. Authors used MRI in order to identify ALT size, site, the presence of septa and contrast enhancement. Surgical margins were divided at final histology in wide/radical, marginal and intralesional.**
***Results*. The most common localization was the lower limb (84% of cases), 52% of cases showed size larger than 10 cm; 80% of cases were deep-seated. MRI revealed thick septa in 83% and contrast enhancement in 78% of the cases. Eleven local recurrences of the disease (11%) were observed, with only surgical margins representing a significant prognostic factor on local recurrence (p = 0.0007). No de-differentiation was reported nor metastatic spread.**
***Conclusions*. The slow growth and the dedifferentiation ability in ALT needs a long follow-up. MRI with contrast is the imaging method of choice. The optimal treatment is wide/radical resection.**

KEY WORDS: ALT; margin recurrence; dedifferentiation; MRI.

Introduction

Lipoma is the most common benign tumor among the soft tissue tumors (1). It generally appears as isolated, slowly growing mass with subcutaneous localization (both to the extremities and the trunk wall), without any symptom or just slight ones. Deep-seated and intramuscular sites are less common and usually show a larger size than subcutaneous lesions (2, 3). Some deep-seated lesions with a large size and histologic atypiae are defined atypical lipomatous tumors (ALT), atypical lipoma or well-differentiated liposarcoma (WDL) (2-5). ALT/WDL are low grade malignant mesenchimal neoplasms, locally aggressive, totally or partially made up of mature adipocytical proliferation with some lipoblasts. Adipocytical and stromal cells show different sizes, nuclear atypias and multivacuolated cytoplasms. They account for 40-45% of all liposarcomas and they are more frequent after the fifth decade of life, with a slight predilection for the male sex (1-3, 6). Cytogenetic molecular analysis highlighted the ability to differentiate between lipoma and ALT/WDL (7, 8). Amplification of the gene MDM2 on chromosome 12 (12q13-15) is a typical feature of ALT/WDL (often associate with co-amplification of various other chromosomal regions), whereas it has never been reported for lipoma (9-13). ALT and WDL are synonyms, with identical morphology, karyotype and biological behavior (3). The use of the terms "atypical lipomatous tumor" and "well-differentiated liposarcoma" dealed in the past mainly with their localization and resectability. The fact that WDL doesn't apparently generate potential metastasis led in the 1970s to the introduction of terms such as atypical lipoma or ALT, especially when referring to lesions affecting the extremities and the trunk wall where wide excision can often be carried out (4). Some Authors believe that diagnosis is based on histology, others on a combination of histology and anatomical location (4, 5, 7, 13). Since retroperitoneal and mediastinal lesions are often difficult to eradicate through wide excision, WDL located in these areas are usually subject to unfavorable prognosis due to a higher percentage of local recurrence and potential tumor dedifferentiation (3, 5, 6). It has been advocated that the term WDL should be used for retroperitoneal localizations while the term ALT for masses localized to the extremities (7). Surgical removal, especially wide excision, should be the treatment of choice for ALT/WDL. Literature data report a significant risk of local recurrence in ALT/WDL after excision if compared to ordinary lipoma (6-8, 14). For such a reason they should be removed surrounded by a layer of normal tissue to reduce the risk of local recurrence (7). This is not always possible, especially when the mass is large-sized and adjacent to major visceral organs, vascular or nerve structures. We analyzed retrospectively 98 ALT/WDL treated at a single institution, 96% of which localized at the extremities and 4% on the trunk, assessing the role of Magnetic Resonance Imaging (MRI), the ideal treatment, the incidence and the factors influencing local recurrence, the follow-up and eventual de-differentiation.

Materials and methods

We identified a consecutive series of 98 patients with ALT/WDL treated between 1994 and 2014, with an average follow-up of 62 months. Twenty-seven patients presented less than 2-years follow-up. There were 61 men and 37 women, with an average age of 60 years (range 19-92). Seventy-six cases were primary localizations, 17 cases were local recurrences and 5 cases were radicalizations of ALT/WD operated on at other institutions not specialized in the treatment of soft tissue tumors and then referred to us. The most common presentation was a slowly growing mass, usually with no symptoms or just slight ones. Tumors were studied previous to surgery with contrast MRI. The examination was useful to exactly identify the lesion extension, dividing them in three size subgroups: less than 5 cm, in between 5 and 10 cm, larger than 10 cm. According to Nagano scoring system, size, site, the presence of septa and contrast enhancement, allowed to distinguish in between ordinary lipoma and ALT/AWD (15). The definitive diagnosis was confirmed by fine-needle biopsy, carried out in 84 cases, whereas in 14 cases of ALT/WD showing dimensions smaller than 5 cm excision was directly performed. In all cases a surgical treatment was performed and histological examination defined the margins in wide/radical, marginal and intralesional. Follow-up was carried on at intervals of 6 months for the first 5 years and once every 12 months from the sixth to the tenth year, alternating MRI with ultrasonography to evaluate the site of deasese to look for the presence of local recurrence, whereas direct computer tomography (CT) scan and conventional X-rays were alternated to investigate the presence of pulmonary metastasis. Statistical analysis was performed with MedCalc software version 16.8.4. Values of $p < 0.05$ were considered statistically significant. All variables were analysed for their impact on overall survival (OS), local recurrence-free survival (LRFS) and metastasis-free survival (MFS). In univariate analysis, OS, LRFS and MFS were calculated according to the method of Kaplan-Meier. The comparison of survival curves was performed by the long-rank test media. The hazard ratios and confidence intervals (95%) were calculated using the Cox hazard test. Only parameters which resulted significant at univariate analysis were included in a multivariate Cox regression model.

Results

The lower limb was the most common localization with 82 cases, 69 of them in the buttock and the thigh muscles and the remaining 9 cases involving the leg. Sixteen cases were localized in the upper limb, with 11 cases in shoulder girdle, 1 case in the arm and 4 cases in the forearm. Four cases were localized in the trunk wall muscles (Table 1). Fifty-nine cases featured size larger than 10 cm, 25 cases size ranging from 5 to 10 cm, 14 cases smaller than 5 cm. Eighty percent of cases were deep-seated, whereas only 20% superficially seated (Table 4). MRI showed thick septa in 83% of the cases, whereas in 17% of ALT/WDL very thin or no septa at all were pointed out. Contrast enhancement was reported in 78% of the cases (Table 4) (Figure 2 A, B). After histological exam 72 cases were classified as WDL and 26 as ALT. No patient showed distant metastasis at onset. Forty-three patients showed wide or radical margins, 51 marginal margins and 4 intralesional margins. We registered 11 local recurrences (11%), in 2 cases after wide/radical excision, in 7 cases after marginal excision, and in 2 cases after intralesional excision. All recurrences were treated with a new excision and no patient developed any metastasis. No patient underwent pre-operative nor post-operative therapies (radiotherapy nor chemotherapy) after index excision. One case with tumor size larger than 10 cm underwent radiotherapy after local recurrence and subsequent amputation since radiation complications, while another case with 5-10 cm tumor size underwent amputation following 4 local recurrences and radiotherapy treatment (12 months, 108 months, 132 months, 144 months after index excision). The average interval between local recurrences was 62 months (range 8-141). No patient with local recurrence showed alteration in grade, nor progression towards de-differentiated forms. No patient died because of ALT/WDL. Statistical analysis highlighted a significant increased incidence of local recurrence at 5 and 10 years after intralesional surgical treatment and an increase of recurrence at 10 years after marginal surgery ($p = 0.0007$) (Table 2) (Figure 1).

Table 1 - Anatomical site of the ALT/WD.

Site	Number
Buttock and thigh	69
Leg	9
Shoulder girdle	11
Arm	1
Forearm	4
Trunk muscle	4
Total	**98**

Table 2 - Scoring for the diagnosis of ALT.

Diameter (cm)	Points	Our results
<10	0	40%
>10	1	60%
Depth		
Superficial	0	20%
Deep	1	80%
Septa (MRI)		
No	0	17%
Yes	2	83%
Enhancement (MRI)		
No	0	22%
Yes	2	78%

Discussion

This study has several limitations: 1) it is a retrospective study, even though performed on a consecutive series of patients treated at a single Institution by the same surgical team; 2) our series included primary ALT/WDL together with local recurrence and radicalization after inadequate surgery performed elsewhere, nevertheless type of presentation did not result to correlate with the outcome (Table 2). In our series of 98 patients with ALT/WDL we noticed 11% of recurrence. Local recurrence is related to intralesional surgery (P=0,0007) at 5 and 10 years follow-ups,

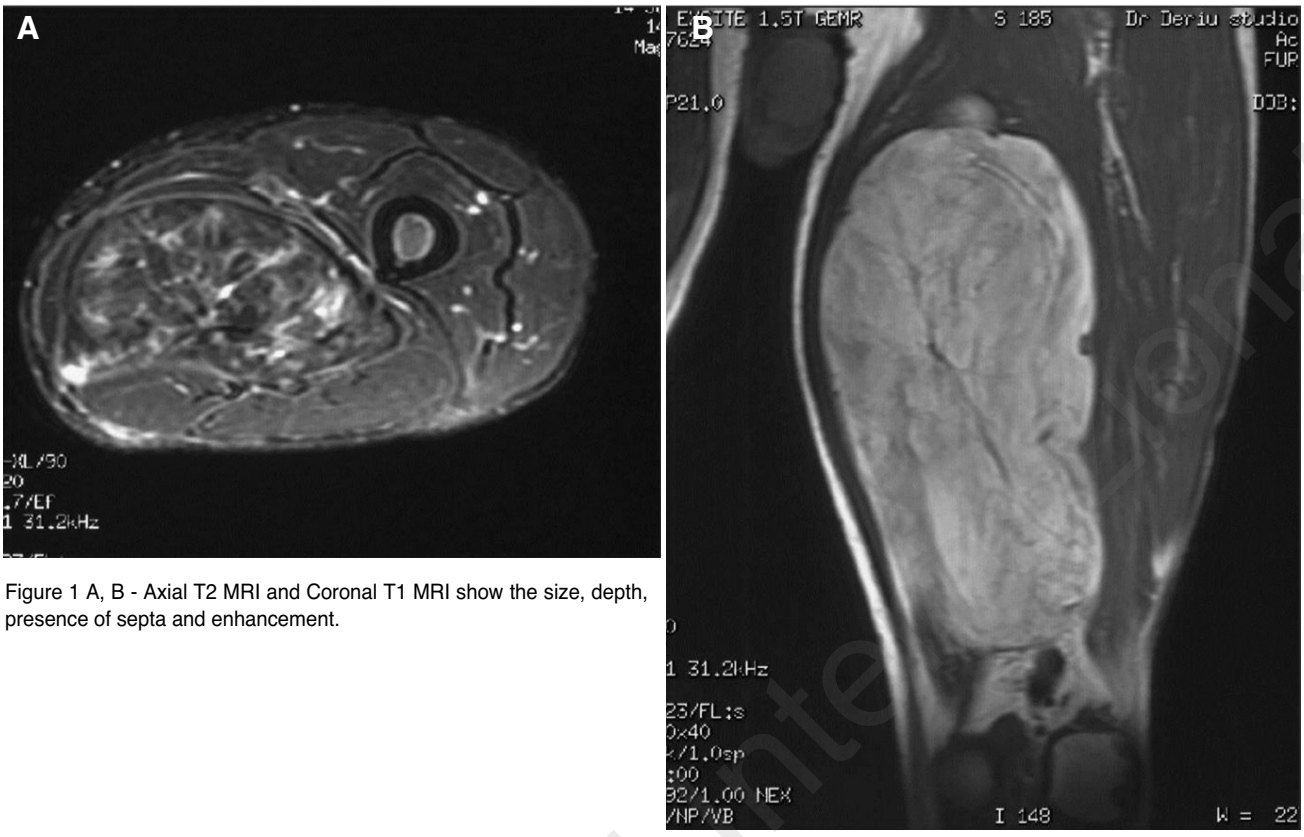

Figure 1 A, B - Axial T2 MRI and Coronal T1 MRI show the size, depth, presence of septa and enhancement.

Table 3 - Local Recurrence Free Survival (LRFS) in ALT/WDL.

Variables		Survival at 5 years (%)	Survival at 10 years (%)	P-Value* (LR Test)
SITE				
	Upper limb	95	94	0,3313
	Lower limb	89	73	
	Trunk	100	100	
SIZE				
	< 5 cm	86	86	0,2994
	5 - 10 cm	94	94	
	> 10 cm	90	73	
MARGIN				
	Wide / Radical	95	95	0,0007
	Marginal	92	71	
	Intralesional	50	50	
PRESENTATION				
	Primitive	96	81	0,6065
	Local Recurrence	82	82	
	Radicalization	67	67	

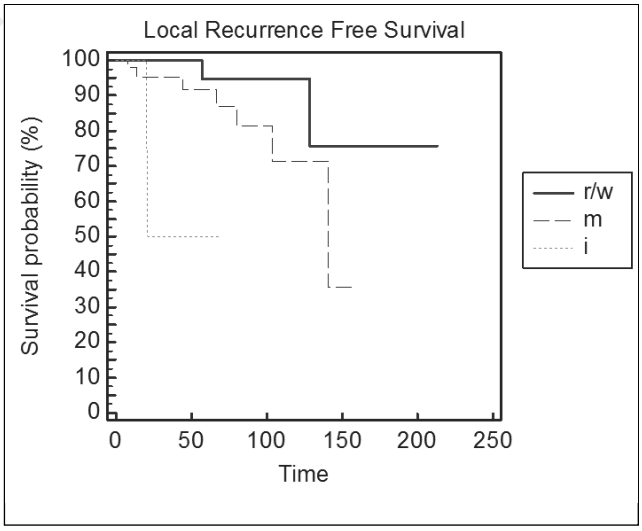

Figure 2 - The margins are prognostic factors for recurrence in ALT/WDL.

while wide/radical excision didn't reveal a significant development of local recurrence. An increasing incidence of local recurrence has been highlighted at 10 years follow-up. Authors reported different percentages of local recurrence and re-recurrence ranging between 8 to 100% (Table 3). Generally longer is the follow-up, higher is the risk of recurrence (2, 4, 7, 8, 14, 16-19). The percentage of recurrence for intrabdominal and retroperitoneal WDL is higher than ALT located at the extremities. Weiss et al., in a study on 92 WDL, found out 91% of local recurrence in retroperitoneal site *vs* 43% of local recurrence for tumors located at the extremities. Within the extremities, ALT didn't show a mortality linked to the disease itself (7). Evans as well pointed out the more frequently recurrence in retroperitoneal WDL (8), with possibility of local complications and transformation of recurrence into de-differentiated liposarcoma likely to lead to metastases (8). Clinical behavior and outcome of WDL are strongly influenced by their site (7, 20). Due to the aggressive character of retroperitoneal lipomatous tumors, Authors claim the

Table 4 - Summary of results of published series of atypical lipomatous tumor.

Author	NoPatients	LR	LRR	De-differentiatin	Mean Follow-up
Billing	38	4 (10%)	0%	0	90
Weiss	46	20 (43%)	60%	3	108
Evans	61	1 (9%)	100%	0	>120
Sommerville	61	5 (8%)	40%	0	50
Lucas	58	14 (24%)	71%	6	112
Rozental	31	16 (52%)	44%	4	84
Basset	51	14 (27%)	35%	1	52
Serpell	11	3 (27%)	00%	0	18
Mavrogenis	67	5 (10.6%)	52%	1	81
Current study	98	11 (11%)	2%	0	62

need to use the terminology "well-differentiated liposarcoma", since the definition "ALT" could be clinically misleading (7). Local recurrence are usually treated with a subsequent excision, even though, especially in retroperitoneal site, resection may be difficult because of the adjacent visceral and neurovascular structures. Despite their tendency to local recurrence, ALT/WDL hardly ever develop metastases. Gerrand et al. only reported one recurrence out of 24 patients affected by WDL, no metastasis and all patients alive at 5 years' follow-up (21). We did not show any metastasis in our series either. The surgical excision with wide margins represents the safest treatment option to reduce any risk of local recurrence. Treatment performed at specialized surgical institutions, supported guarantees the best achievements (22-24). Complete resection of intra-abdominal or retroperitoneal WDL is achieved in varying percentages, ranging from 50 to 95% of patients (22, 25, 26). Marginal and intralesional surgery, even though it should be avoided, is often justified in few selected cases because of the large size of these masses located in the proximity of major visceral, vascular and nervous structures (17, 27). Furthermore, WDL/ALT are often lobulated and tend to form internal hernias that can be misleading for the surgeon, leaving accidentally part of the tumor and unwillingly performing an intralesional surgery (17, 27). Authors supposed that it's appropriate to accept a positive margin of resection for WDL/ALT. Anaya et al. concluded that WDL is the only one sarcoma of the soft tissues that can benefit from debulking, considering its low likelihood to generate metastases (28). Shibata et al. reported surgical debulking can actually improve the symptomatology and extend survival, especially in primitive forms (29). Kubo and Kemp reported good results with no recurrence in case of marginal surgery due to the proximity to nerves, despite their short-term results. ALT/WDL of the extremities didn't lead to metastases even in case of recurrence, and documented mortality rate is close to 0% (30, 31). According with literature data, we also treated ALT/WDL with no wide surgery in 56% of the cases (51 cases of marginal surgery, 4 cases of intralesional surgery) upon their proximity to vasculonervous structures or including those. The low aggressive potential of ALT/WDL, the low percentage of recurrence and the absence of metastases justified our choice. Authors recorded 65% of ALT occurring in the lower limb, against 20% of ordinary lipoma; 83% of ALT measured more than 20 cm against 4% of ordinary lipoma (14, 32). Based on such an evidence, they claimed to differentiate their diagnosis between lipoma and ALT depending on their size and location. Fisher et al. identified some pre-surgical features that support a diagnosis of ALT rather than lipoma: patient's age older than 55 years, tumor's size bigger than 10 cm, the record of previous surgery in the same site (biopsy or previous excision surgery, extremities VS back area) (33). Brisson et al. reported that age older than 60 years, size larger than 10 cm and lower extremities site suggest ALT, even though in their series only size remained the predictive factor to multivariate analysis (34). We also noticed a predilection for the lower limb in 84% of our cases, as well as size larger than 10 cm (identified in 60% of cases) confirmed what had been previously stated,; anyway, we did not found a statistically significant relationship between survival and recurrence related to the site (upper limb, lower limb, trunk wall) or to the tumor size. The painless, slow growth of ALT might justify the large size of such neoplasm at diagnosis. Patients suffering from ALT should undergo accurate imaging to detect the size, location, the proximity to significant structures (neurovascular bundles, bones). MRI constitutes the gold standard imaging exam to assess carefully anatomical compartments and muscular involvement. CT scan is recommended for abdominal and retroperitoneal lesions (35, 36). Fat signal is prevalent in ALT/WDL if compared to de-differentiated forms, where masses appear to be heterogeneous and less lipomatous (13). Various Authors highlighted the relevance of septa in ALT/WDL (37, 38). Gaskin noticed thin septas in lipoma, while ALT usually presents thick septa, often associated with contrast enhancement (39). Nagano created a scoring system to distinguish between lipoma and ALT (15) taking into consideration 4 characteristics: size, depth, presence of septa and contrast enhancement (Table 4). According to Nagano score, 60% of ALT in our series presented size larger than 10 cm, 80% were deep-seated, 83% featured thick septa and 78% showed contrast enhancement. An accurate treatment planning requires necessarily a histological exam. Ultrasound needle-biopsy or incisional biopsy are advisable with large size lesions, whereas small size lesions with typical fat signal at MRI could be treated with direct surgery, avoiding biopsy. It's often difficult at histology to differentiate between lipoma and ALT, and a sample by fine-needle aspiration or needle biopsy does not provide a definite answer and histological ambiguity still remains (40). Literature data also showed a percentage of non-diagnostic biopsies ranging from 6 to 23%

(41, 42). Genetic tests increased the ability to distinguish between ALT and lipoma, but quite often these tests are carried out in non-specialized centers, not equipped with adequate laboratories; moreover, needle biopsy does not guarantee the acquisition of adequate quantities of tissue as needed for genetic analysis.

The effectiveness of radiotherapy on ALT/WDL is still not clear (16, 31). Even though surgery is the preferred treatment, adjuvant radiotherapy may be executed under certain circumstances, specifically in the case of inappropriate excision or in case of recurrence (13, 43). Authors observed theoretically beneficial effects of neoadjuvant radiotherapy as it can sterilize the surgical field and reduce the risk of local recurrence. Neoadjuvant radiotherapy doses are usually 50 Gy (44). Retrospective studies did not demonstrate any benefits with few findings supporting a reduced risk of local recurrence in ALT/WDL (45-47). Some Authors have considered the potential risk of de-differentiation with progression to higher grades in the occurrence of local recurrence of the disease (32). Mavrogenis reported an elevated risk of local re-recurrence, stressing the importance of an extensive primary excision in ALT/WDL, concluding that radiotherapy is not effective to local control, without being able to prove its potential role in a prospective process of de-differentiation (19). ALT/WDL de-differentiation is another issue that requires a long and accurate follow-up (32). The potential of de-differentiation has been reported in literature by various Authors to be as low as 0-13% (2, 6-8, 16, 18, 48). We did not notice any case of de-differentiation, but when it happens there is an increased chance to develop metastases (1, 2, 6, 8, 14, 17, 32, 49). De-differentiation is probably a factor linked to time, not to size (7). Okada et al. re-examined 18 cases of de-differentiated liposarcomas located at the extremities, outlining that 9 of them had originated from the de-differentiation of ALT whose size remained unchanged for long time (50). These results suggested that after the pre-surgical diagnosis of ALT/WDL, surgeons should recommend the tumor's excision before it could de-differentiate, despite the low percentage of its transformation. Some Authors suggest a minimum 5 years' follow-up (19, 27, 32), while others suggest that follow-up might not be carried out at all (2). Our average follow-up was of 62 months. The choice of a long follow-up was due to the slow growth of ALT and to marginal and intralesional surgery (56%) needed to preserve major vascular and nerve structures. Our results highlighted an increase of local recurrence after ten years in marginal and in particular a significant increase of local recurrence at 5-10 years in intralesional surgery (p=0,0007) (Table 2) (Figure 1).

Conclusion

Wide surgical excision is the safest treatment to reduce any risk of local recurrence, whereas marginal and intralesional surgery can be accepted in a few selected cases because of the large size of these masses located in the proximity of major and noble structures. MRI constitutes the gold standard imaging modality to distinguish between lipoma and ALT assessing anatomical compartments, muscular involvement, size, site and depth, the presence of septa and contrast enhancement (15), even if only the detection of MDM2 gene amplification on chromosome 12 (12q13-15) permits differential diagnosis. The choice of a long follow-up is due to the slow growth of ALT and potential ability of de-differentiation.

Conflict of interest

The Authors declare that they have no conflict of interest.

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Ethical approval

This article does not contain any studies with human participants or animals performed by any of the Authors.

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