Atypical Lipomatous Tumor/Well-Differentiated Liposarcoma with Myxoid Stroma in a Hereditary Retinoblastoma Survivor

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Established Facts

- Prognosis and management of liposarcoma is dependent on anatomic location, resectability, and liposarcoma type.
- Atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDL) with myxoid stroma can morphologically resemble myxoid liposarcoma.
- Molecular genetic studies are helpful in distinguishing between ALT/WDL with myxoid stroma and myxoid liposarcoma.

Novel Insights

- Most previously reported orbital myxoid liposarcomas have not been evaluated by molecular genetic methods.
- *DDIT3* amplification, previously documented in dedifferentiated liposarcoma with myxoid stroma can be also observed in ALT/WDL with myxoid stroma.

Keywords

Well-differentiated liposarcoma · Atypical lipomatous tumor · Liposarcoma · Liposarcoma with myxoid stroma · Orbit · Orbital liposarcoma · MDM2 · DDIT3 · RB1 · Retinoblastoma · Myxoid liposarcoma

Abstract

Atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDL) is an indolent, locally aggressive mesenchymal neoplasm, most often confined to the lower extremities and retroperitoneum and rarely identified in the orbit. Diagnosis of ALT/WDL can be challenging due to its frequent morphologic overlap with benign adipose lesions and other more

aggressive liposarcoma subtypes, including myxoid liposarcoma. We describe a 26-year-old female with a history of hereditary retinoblastoma and external-beam radiotherapy to the orbit, who developed orbital liposarcoma. Although initial morphologic assessment raised the consideration of myxoid liposarcoma, subsequent fluorescein in situ hybridization studies demonstrated *MDM2* and *DDIT3* coamplification without *DDIT3* rearrangement, supporting the diagnosis of ALT/WDL with myxoid stroma. The literature review of previously reported orbital myxoid liposarcomas revealed a morphologic overlap of documented tumors with ALT/WDL, dedifferentiated liposarcoma, and pleomorphic liposarcoma with myxoid stroma as well as an absence of immunohistochemical and molecular genetic data supportive of the diagnosis of myxoid liposarcoma. This case emphasizes the potential overlap of ALT/WDL with myxoid liposarcoma and the increasing importance of molecular genetic studies in the diagnosis, prognosis, and management of orbital liposarcoma.

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Introduction

Liposarcoma, the most common soft-tissue sarcoma in adults, is infrequently found in the orbit [1]. Prognosis and management of liposarcoma is dependent on anatomic location, resectability, and subtype [2, 3]. Well-differentiated liposarcoma (WDL), the most common subtype, is characterized by locally aggressive behavior without metastatic potential, unless dedifferentiation occurs. The term “atypical lipomatous tumor (ALT)” has been introduced to emphasize the favorable prognosis of WDL in the head and neck, trunk, and extremities [2, 3]. ALT/WDL may contain abundant myxoid stroma, mimicking other myxoid neoplasms, including myxoid liposarcoma [2–4]. Unlike ALT/WDL, myxoid liposarcoma has well-documented potential for metastasis, particularly in higher-grade lesions. Identification of distinct recurrent molecular genetic alterations in ALT/WDL and myxoid liposarcoma has improved our ability to discriminate between these prognostically different tumors [2–4]. We describe a patient with bilateral hereditary retinoblastoma previously treated with external-beam radiotherapy to the orbits, who developed ALT/WDL with prominent myxoid stroma, initially raising a consideration of myxoid liposarcoma. We discuss the ancillary studies helpful in distinguishing between ALT/WDL and myxoid liposarcoma as well as the prognostic and management implications of accurate diagnosis.

Case Report

A 26-year-old female was found on screening magnetic resonance imaging (MRI) to have a homogeneous, enhancing intraconal mass conforming to the globe and filling the left orbit, initially interpreted as a lymphatic-venous malformation (Fig. 1). The patient’s history revealed germline bilateral retinoblastoma diagnosed at 3 months of age and management with external-beam radiotherapy to both eyes, systemic chemotherapy, and subsequent enucleation of the right eye and iodine-125 (I-125) plaque brachytherapy in the left eye. Three years previously, she was diagnosed with a high-grade postradiation osteosarcoma of the right orbit and paranasal sinuses, which was managed with orbital exenteration and systemic chemotherapy.

On our evaluation, there was notable bilateral orbital hypoplasia and a healed right exenterated socket (Fig. 1). Visual acuity was 20/40 in the left eye and the color plates were normal. Confrontational visual fields were full and there was no limitation of extraocular motility. Hertel exophthalmometry demonstrated mild left proptosis, when compared to previous external examinations. A fine-needle aspiration biopsy of the left orbital mass was nondiagnostic and followed by an open diagnostic biopsy and orbital tumor debulking.

Microscopic evaluation demonstrated soft-tissue fragments containing an infiltrate of spindle-to-ovoid cells in the background of abundant myxoid stroma, fine collagen fibers and delicate, short, focally branching capillaries (Fig. 1). Infiltration of skeletal muscle was present. Occasional lipoblasts and mature-appearing adipocytes were noted. Mitotic figures were not conspicuous (<4 in 10 high-power fields). No significant nuclear pleomorphism or necrosis was identified (Fig. 1). Immunohistochemical stains showed that the neoplastic cells expressed CD34 and S-100 (partial, most prominent in lipoblasts and adipocytes), with a Ki-67 proliferative index of 1–2%. Fluorescein in situ hybridization (FISH) demonstrated *MDM2* (12q15) and *DDIT3* (12q13) coamplification (Fig. 1). There was no evidence of *DDIT3* translocation. The aggregate findings were diagnostic of ALT/WDL with either myxoid stroma or low-grade myxofibrosarcoma-like dedifferentiation. Due to the lack of morphologic features of a low-grade myxofibrosarcoma, such as significant nuclear atypia/pleomorphic cells and the characteristic curvilinear vasculature, we diagnosed this neoplasm as ALT/WDL with myxoid stroma, also known as myxoid ALT/WDL.

Various management options for control of the residual orbital tumor were discussed with the patient. These included orbital exenteration and irradiation, which could potentially compromise her vision due to the proximity of the tumor to the optic nerve. Our monocular patient elected vision-sparing observation. Unfortunately, she developed a recurrent tumor 3 months later, which was morphologically similar to the previously biopsied lesion, and, additionally, contained microscopic foci of high-grade dedifferentiated liposarcoma (DDL), accounting for 5% of the lesion (Fig. 2). FISH studies of the recurrent tumor demonstrated *CDK4* gene amplification. She will follow-up with the Oncology Department for a decision on the definitive treatment of her residual orbital disease, including potential enrollment into clinical trials targeting *CDK4* amplified liposarcoma.

Fig. 1. Clinical, histopathologic, and cytogenetic features of initial biopsy of atypical lipomatous tumor/well-differentiated liposarcoma with myxoid stroma. **a** External photograph demonstrates exenterated right socket and left proptosis. **b** Axial MRI demonstrates absence of the right globe and orbital tissues, compatible with prior right orbital exenteration defect, and a well-circumscribed enhancing left retrobulbar mass. **c** The neoplasm is composed of spindle-to-ovoid cells in a background of abundant myxoid matrix and delicate intervening capillaries (arrow) with focal “pseudo-alveolar” type spaces (asterisk), reminiscent of myxoid liposarcoma. HE. $\times 25$. **d** The neoplastic cells have mildly pleomorphic nuclei with

foci of advanced adipocytic differentiation. HE. $\times 50$. **e** Occasional multinucleated cells with hyperchromatic nuclei and multiple intracytoplasmic vacuoles (arrow) and lipoblasts with indented nuclei and cytoplasmic vacuoles (inset) are present. HE. $\times 500$. **f** Abundant myxoid stroma are highlighted. Alcian blue. $\times 50$. **g** Fluorescence in situ hybridization (FISH) demonstrates amplification of *MDM2* (pink signal) relative to the green *CEP12* centromeric signals (arrows). **h** FISH with breakapart probes for *DDIT3* rearrangement demonstrates multiple closely apposed green and red signals, yielding multiple yellow signals, compatible with *DDIT3* amplification.

Fig. 2. Histopathologic features of a recurrent tumor. **a** Most of the tumor is morphologically similar to the original biopsy, featuring spindle-to-ovoid cells and vacuolated lipoblasts without appreciable nuclear atypia or pleomorphism in a background of abundant myxoid stroma, compatible with atypical lipomatous tumor/well-differentiated liposarcoma. HE. $\times 100$. **b** Foci of highly cellular proliferation with prominent nuclear pleomorphism, hyperchromasia, and atypia, without appreciable adipose differentiation, compatible with high-grade dedifferentiated liposarcoma, are present. HE. $\times 100$.

Table 1. Clinical and pathologic features of ATL/WDL

First author [ref.], year	Pt No.	Age, years/sex	Presenting signs and symptoms	Histopathology	IHC/molecular studies	Management	Recurrence?/ follow-up, months
Cai [7], 2001	1	34/M	proptosis	ATL/WDL, inflammatory	not performed	marginal excision	Yes ($\times 6$)/204
	2	52/F	proptosis	ATL/WDL, spindle cell	not performed	marginal excision	No/53
	3	35/F	orbital pain, proptosis, diplopia	ATL/WDL, lipoma-like and sclerosing	not performed	exenteration	No follow-up
	4	28/M	proptosis, diplopia	ATL/WDL, spindle cell	not performed	exenteration, XRT	No/13
	5	69/M	proptosis	ATL/WDL, lipoma-like	not performed	exenteration	No/108
	6	54/F	proptosis	WDL, lipoma-like and sclerosing with DDL	not performed	exenteration	No follow-up
Stiglmayer [26], 2003	7	55/F	proptosis	WDL/DDL	not performed	XRT prior to biopsy, marginal excision	No follow-up
Rosner [27], 2006	8	24/F	proptosis, extraocular motility restriction	WDL, lipoma-like, inflammatory, sclerosing	CGH: 12q12-22 amplification	marginal excision	Yes ($\times 1$)/24
Jakobiec [28], 2010	9	36/M	proptosis, extraocular motility restriction	WDL, lipoma-like and spindle cell	IHC: MDM2-positive	observation (exenteration, XRT recommended)	No follow-up
Torrado [29], 2011	10	45/M	proptosis, diplopia, mild pain	WDL, lipoma-like	not performed	exenteration, XRT	No/36
Vrcek [30], 2014	11	67/M	proptosis, diplopia, pain	WDL, lipoma-like	IHC: MDM2-positive FISH: MDM2 amplification	marginal excision	No/12
Dworak [31], 2018	12	35/M	proptosis, diplopia, extraocular motility restriction	ATL/WDL	FISH: MDM2 amplification	observation (exenteration recommended)	No follow-up
McKey [5], 2019	13	22/F	diplopia, subconjunctival mass, proptosis	ATL/WDL, lipoma-like	FISH: MDM2 and CDK4 amplification	debulking	Yes ($\times 1$)/108
Our study	14	26/F	proptosis	ATL/WDL with abundant myxoid stroma; recurrent tumor with small foci of DDL	FISH: MDM2, CDK4, and DDIT3 amplification	debulking	Yes ($\times 1$)/3

A summary is provided here of clinically and histopathologically well-documented cases of ATL/WDL (adapted from [5]). Pt, patient; M, male; F, female; IHC, immunohistochemistry; ATL/WDL, atypical lipomatous tumor/well-differentiated liposarcoma; DDL, dedifferentiated liposarcoma; LR, lateral rectus; SR, superior rectus; XRT, external-beam radiotherapy.

Discussion

Liposarcoma is the most common soft-tissue sarcoma in adults, with ALT/WDL comprising 40–45% of all liposarcomas. Approximately 75% of ALT/WDL occurs in the lower extremities and 20% is found in the retroperitoneum [2]. ALT/WDL is uncommon in the orbit with only 20 cases reported in the literature. Similar to the presentation in our patient, orbital ALT/WDL typically manifests with painless, progressive proptosis, induced by an intraconal or extraconal mass which can be circumscribed or infiltrative (Table 1) [5].

Histopathologically, ALT/WDL is characterized by a relatively mature adipocytic proliferation that can resemble lipoma, and, less frequently, may demonstrate spindle/sclerosing and inflammatory morphologic patterns. Focal adipocytic nuclear atypia and hyperchromasia, with frequent multinucleated or large pleomorphic stromal cells, are consistent findings. Lipoblasts in varying numbers can also be seen but are not necessarily diagnostic of liposarcoma, and their absence does not necessarily exclude ALT/WDL [2, 3, 5]. Myxoid stroma can be abundant in ALT/WDL, leading to the consideration of myxoid liposarcoma and other tumors with a myxoid matrix [2–4].

Recognition of distinct recurrent molecular genetic alterations in ALT/WDL, DDL, and myxoid liposarcoma, that involve the *MDM2*, *CDK4*, *HMGA2*, and *DDIT3* genes in the 12q13–15 region that regulate apoptotic, cell-proliferative, and lipogenic pathways, has improved our ability to discriminate between these neoplasms [2–4]. ALT/WDL and DDL harbor consistent amplification of *MDM2* in the 12q13–15 region, corresponding to supernumerary ring and giant marker chromosomes. An *MDM2* immunohistochemical stain can be used as a surrogate marker for *MDM2* amplification. However, molecular genetic studies remain the gold standard of ALT/WDL and DDL diagnosis [2–5].

Myxoid liposarcoma accounts for 15–20% of all liposarcomas and typically occurs in the deep soft tissues of the extremities in young adults. This neoplasm is characteristically composed of uniform, round-to-oval, primitive cells, with variable lipogenic differentiation and a variable number of signet-ring cell lipoblasts in an abundant myxoid stroma with pseudoalveolar pools of mucin and a characteristic branching vascular pattern [2]. Myxoid liposarcoma lacks *MDM2* amplification, and, conversely, demonstrates a rearrangement involving the *DDIT3* gene at 12q13 with either the *FUS* gene on 16p11 in 95% of cases or the *EWSR1* gene on 22q12 in the remaining 5% [2–4]. Interestingly, a recent study demonstrated *DDIT3* amplification,

rather than rearrangement, in 75% of myxoid liposarcoma-like DDL [6]. Although *DDIT3* amplification has, to our knowledge, not yet been specifically identified in ALT/WDL with myxoid stroma, it may have similarly contributed to the myxoid liposarcoma-like morphology of the well-differentiated tumor of our patient. The presence of *MDM2* amplification in this case, a feature not found in myxoid liposarcoma, strongly supports the diagnosis of ALT/WDL and is also compatible with evolution into DDL.

A recent retrospective review of published reports on a total of 37 cases of orbital liposarcoma revealed the histopathologic subtype as myxoid ($n = 21$, 57%), ALT/WDL ($n = 11$, 30%), and pleomorphic ($n = 11$, 11%) [1]. However, critical review of histopathologic descriptions and supporting photomicrographs of previously reported myxoid liposarcoma (Table 2) suggest that some of the presumed orbital myxoid liposarcomas likely represented a myxoid change in ALT/WDL, DDL, or pleomorphic liposarcoma [1, 7–19]. Notably, only 1 previously reported tumor diagnosed as mixed myxoid liposarcoma and WDL was evaluated by molecular methods, and it reportedly lacked the translocations seen in myxoid liposarcoma, suggesting that it was more likely WDL or DDL with variably myxoid stroma [18]. None of the reported cases of orbital myxoid liposarcoma were evaluated with immunohistochemical or molecular genetic studies targeting *MDM2* and *DDIT3* [1, 8–19]. Additionally, 2 patients diagnosed with orbital myxoid liposarcoma were noted to have Li-Fraumeni syndrome caused by mutation in *TP53*, a molecular genetic event that is more commonly seen in ALT/WDL, DDL, and pleomorphic liposarcoma, as opposed to myxoid liposarcoma [2]. These findings underscore the difficulty of accurate morphologic diagnosis of liposarcoma and the need for genetic confirmation in all cases. In fact, one might question the frequency of myxoid liposarcoma in the orbital region.

Accurate differentiation between ALT/WDL and myxoid liposarcoma has important prognostic and therapeutic implications. ALT/WDL is characterized by locally aggressive behavior, with a propensity for recurrence following incomplete excision, and no risk of metastasis unless evolution into DDL occurs. Transformation into DDL occurs in 5–15% of all ALT/WDL cases, generally at 7–8 years following diagnosis, with lower rates in the orbit than in the retroperitoneum and deeper anatomic locations [2, 5]. Recognition of the indolent behavior and favorable prognosis of orbital ALT/WDL has led to a recent trend of globe-sparing resection in favor of traditional orbital exenteration [5]. The role for globe-preserving therapies such as targeted radiotherapy and adjuvant chemotherapy in orbital liposar-

Table 2. Clinical and pathologic features of previously reported orbital myxoid liposarcoma

First author [ref.], year	Pt No.	Age, years/sex	Presenting signs and symptoms	Diagnosis	Histopathology	IHC/ molecular studies	Management	Recurrence?/ follow-up, months
Blodi [9], 1969	1	n.a.	no clinical history provided	myxoid liposarcoma	Spindle or stellate cells loosely or haphazardly arranged among fine collagen fibrils in abundant mucoid ground substance	none	n.a.	n.a.
Naeser [10], 1982	2	58/F	proptosis	myxoid liposarcoma	Predominantly spindle cells with small and dense nuclei in loosely arranged mucoid matrix with rich capillary network	none	exenteration	No/42
Malan [11], 1983	3	15/F	pain, proptosis, diplopia	myxoid liposarcoma	Spindle-shaped prelipoblast cells, large dedifferentiated adipocytes, edematous stroma	none	chemoradiotherapy followed by exenteration and repeated XRT	Yes (×2), fatal at 30 months from diagnosis
Lane [8], 1988	4	22/F	proptosis, diplopia	myxoid liposarcoma	Loose myxoid stroma infiltrated by adipocytes and spindle cells	none	XRT, radical exenteration including adjacent sinuses subtotal excision	No/24
	5	71/F	lower-eyelid swelling	myxoid liposarcoma	Delicate vascular channels, lipoblasts, few mitoses, some giant and pleomorphic cells in myxoid stroma	none		No/24
Jakobiec [12], 1989	6	22/F	proptosis	myxoid liposarcoma	Loose tissue with admixed spindle-shaped cells and inflammatory cells, mostly mast cells	none	radical exenteration including adjacent sinuses	No/48
	7	57/M	subconjunctival mass	myxoid liposarcoma	Prominent capillary proliferation not in classic plexiform pattern, population of spindle cells infiltrating mature lipocytes, stringy pools of mucinous material, scattered mast cells, signet-ring lipoblasts	none	exenteration	No/42
	8	30/F	diplopia	myxoid liposarcoma	Loose watery tissue with lobular pattern created by fibrous subdivisions that provided pseudocapsule, mature lipocytes in myxoid matrix	none	excision of mass and radiation, repeat radiation	Yes (×1) at 23 months, no further recurrence at 41 months
McNab [13], 1990	9	69/F	proptosis	myxoid liposarcoma	Spindle cells in a mucinous matrix, some in signet-ring form, numerous capillaries, nuclear hyperchromatism with scattered enlarged cells	none	exenteration	No/13
Favrot [14], 1994	11	31/F	decreased vision, pain	myxoid liposarcoma	Well-differentiated lipoblasts, capillaries in loose myxoid stroma. Pleomorphic, highly cellular, poorly differentiated areas with multinucleated cells also in myxoid stroma	none	radical orbital exenteration, anterior skull base resection, XRT	No follow-up
Sabb [15], 1996	12	45/F	pain, lower-lid swelling	myxoid liposarcoma	Homogenous spindle-cell tumor with myxoid pattern, small cells with dark nuclei resembling mature adipocytes, prominent vascular pattern in areas, no mitotic activity or necrosis	none	exenteration	No follow-up
Cockerham [16], 1998	13	35/M	proptosis, EOM restriction	myxoid liposarcoma	Lipoblasts, plexiform capillaries, fibrous septa and abundant extracellular myxoid material	none	exenteration, XRT	Yes (×1)/60
Wagle [17], 1999	14	41/M	proptosis	myxoid liposarcoma	Mostly well-differentiated lipocytes resembling normal fat except for increased population of spindle cells in loose myxoid matrix with fibrous tissue septa. Low mitoses, no necrosis	none	exenteration	No
Madge [1], 2010	16	23 F	proptosis, upper-eyelid swelling	myxoid liposarcoma	Heterogenous appearance, some portions of the specimen appearing myxoid and others pleomorphic in nature, of intermediate grade	Li-Fraumeni syndrome	chemotherapy, radiation, exenteration	Yes (×3)/20
	17	38/M	proptosis, diplopia	myxoid liposarcoma	Lipocytes in myxoid stroma	none	excision of mass ×8, chemotherapy, exenteration exenteration, XRT	Yes (×9)/174
	18	40/M	diplopia	myxoid liposarcoma	Lipoblasts in mucoid matrix with capillary network	none		No follow-up
	19	32/F	decreased vision, proptosis, anosmia	myxoid liposarcoma	Gelatinous mucoid tissue with lipoblasts with characteristic scalloped edges, signet-ring appearance, lying in mucoid matrix	Li-Fraumeni syndrome	chemoradiotherapy, exenteration	No/6
Al-Qahtani [18], 2011	20	36/M	proptosis, pain	mixed type liposarcoma, WDL and myxoid	Lobular tumor consisting of proliferating spindle-shaped cells with several lipoblasts suspended within myxoid-rich matrix and complex vascular system; rare mitosis	negative for translocations associated with myxoid liposarcoma	excision of mass, exenteration	Yes (×1)/12
Khurana [19], 2014	22	50/F	proptosis, EOM restriction, decreased vision	myxoid liposarcoma	Delicate vascular channels, characteristic lipoblasts, very few mitoses, some giant and pleomorphic cells	S-100(+)	exenteration	No/24
	23	40/M	pain, proptosis, decreased vision	myxoid liposarcoma	Characteristic lipoblasts in delicate capillary network	none	exenteration	No/48

A summary is provided here of clinically and histopathologically well-documented cases of myxoid liposarcoma. Pt, patient; M, male; F, female; n.a., not available; EOM, extraocular muscle; IHC, immunohistochemistry; XRT, external-beam radiotherapy.

coma is not well-established [1]. Our patient was noted to have small foci of DDL 3 months following the initial debulking surgery. The close temporal relationship between the ALT/WDL and DDL in this case suggests that the DDL component was likely present in the tumor at the onset but perhaps not sampled in the original biopsy.

When compared to ALT/WDL, myxoid liposarcoma has potential for metastasis, which is grade-dependent, ranging from <10% to up to 60%, with patient survival influenced by the completeness of surgical excision [2, 20]. Nonorbital myxoid liposarcoma is typically managed by complete excision with or without radiotherapy [20]. Chemotherapy is generally reserved for patients with unresectable or large tumors (>5 cm) and high-grade tumors [20]. Given the diagnostic controversy surrounding orbital myxoid liposarcoma, the clinical course, prognosis, and optimal management of this neoplasm in the orbital region are not clear.

The improved understanding of molecular genetic events involved in the development of various types of liposarcoma might open doors for targeted therapies, which may be particularly valuable in patients with unresectable or metastatic tumors and in situations when radical surgery may be visually debilitating, as in our monocular patient. Agents targeting *MDM2*, *CDK4*, and the molecular pathways influenced by *DDIT3-FUS* gene fusion are currently being tested in preclinical studies and early clinical trials and may play an increasingly important role in the management of ALT/WDL, DDL, and myxoid liposarcoma in the future [21, 22].

In addition to the complexity of the histopathologic diagnosis of lipomatous tumors, this case illustrates the long-term management challenges of patients with hereditary retinoblastoma. Although the 5-year survival rate for retinoblastoma has increased to 97%, patients with hereditary retinoblastoma have a greatly increased incidence of secondary malignancy, especially sarcoma, including liposarcoma [23]. The propensity for second malignancies is partly due to germline mutations in the *RB1* gene, and is further increased in a dose-dependent fashion by radiotherapy and

chemotherapy with alkylating agents [23]. Recent studies have explored the potential link between specific germline *RB1* mutations and second malignancies. Specifically, the C>T transition nonsense mutation, identified in the *RB1* gene of our patient, has been associated with a higher risk of soft-tissue sarcoma, and may have contributed to the development of bilateral sarcoma [24, 25].

In conclusion, orbital liposarcoma is an uncommon neoplasm which can complicate the clinical course of patients with germline retinoblastoma. Accurate subtype classification is critical in determining prognosis and management. Recent advances in molecular genetics and cytogenetics have greatly improved our ability to distinguish between liposarcoma subtypes and other simulating lesions. Orbital exenteration for ALT/WDL provides the best chance of cure, but debulking and globe preservation may be reasonable in cases where vision is paramount. Patients managed by globe-preserving therapies need to be observed closely for recurrence and the potential evolution into DDL.

Statement of Ethics

Institutional Review Board approval was waved for this retrospective case report study. The study was performed in accordance with HIPAA guidelines and in compliance with the tenets of Declaration of Helsinki.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors contributed to the data acquisition, data analysis, drafting, and final approval of the manuscript.

References

- 1 Madge SN, Tumuluri K, Strianese D, Bonavolonta P, Wilcsek G, Dodd TJ, et al. Primary orbital liposarcoma. *Ophthalmology*. 2010 Mar;117(3):606–14.
- 2 Fletcher CD, Hogendoorn P, Mertens F. *WHO Classification of Tumours of Soft Tissue and Bone*. 4th edition, revised. Lyon: IARC Press; 2013.
- 3 Dei Tos AP. Liposarcomas: diagnostic pitfalls and new insights. *Histopathology*. 2014 Jan; 64(1):38–52.
- 4 Sioletic S, Dal Cin P, Fletcher CD, Hornick JL. Well-differentiated and dedifferentiated liposarcomas with prominent myxoid stroma: analysis of 56 cases. *Histopathology*. 2013 Jan; 62(2):287–93.
- 5 McKey K, Zhang PJ, Shields CL, Lally SE, Eagle RC Jr, Milman T. Orbital Atypical Lipomatous Tumor/Well-Differentiated Liposarcoma Masquerading as Pleomorphic Lipoma: A Diagnostic Challenge. *Ophthalmol Plast Reconstr Surg*. 2019 Mar;35(3):e76–80.

- 6 Mantilla JG, Ricciotti RW, Chen EY, Liu YJ, Hoch BL. Amplification of DNA damage-inducible transcript 3 (DDIT3) is associated with myxoid liposarcoma-like morphology and homologous lipoblastic differentiation in dedifferentiated liposarcoma. *Mod Pathol*. 2019 Apr;32(4):585–92.
- 7 Cai YC, McMenamin ME, Rose G, Sandy CJ, Cree IA, Fletcher CD. Primary liposarcoma of the orbit: a clinicopathologic study of seven cases. *Ann Diagn Pathol*. 2001 Oct;5(5):255–66.
- 8 Lane CM, Wright JE, Garner A. Primary myxoid liposarcoma of the orbit. *Br J Ophthalmol*. 1988 Dec;72(12):912–7.
- 9 Blodi FC. Unusual orbital neoplasms. *Am J Ophthalmol*. 1969 Sep;68(3):407–12.
- 10 Naeser P, Moström U. Liposarcoma of the orbit: a clinicopathological case report. *Br J Ophthalmol*. 1982 Mar;66(3):190–3.
- 11 Malan P, Baldet P, Arnaud B. Primary orbital liposarcoma: clinicopathologic case report and review of the literature. *Orbit*. 1983;2(2):99–105.
- 12 Jakobiec FA, Rini F, Char D, Orcutt J, Rootman J, Baylis H, et al. Primary liposarcoma of the orbit. Problems in the diagnosis and management of five cases. *Ophthalmology*. 1989 Feb;96(2):180–91.
- 13 McNab AA, Moseley I. Primary orbital liposarcoma: clinical and computed tomographic features. *Br J Ophthalmol*. 1990 Jul;74(7):437–9.
- 14 Favrot SR, Ridley MB, Older JJ, Szakacs JE. Orbital liposarcoma. *Otolaryngol Head Neck Surg*. 1994 Jul;111(1):111–5.
- 15 Sabb PC, Syed NA, Sires BS, Lemke BN, Dortzbach RK, Albert DM. Primary orbital myxoid liposarcoma presenting as orbital pain. *Arch Ophthalmol*. 1996 Mar;114(3):353–4.
- 16 Cockerham KP, Kennerdell JS, Celin SE, Fechter HP. Liposarcoma of the orbit: a management challenge. *Ophthalm Plast Reconstr Surg*. 1998 Sep;14(5):370–4.
- 17 Wagle AM, Biswas J, Subramaniam N, Mahesh L. Primary liposarcoma of the orbit: a clinicopathological study. *Orbit*. 1999 Mar;18(1):33–6.
- 18 Al-Qahtani AA, Al-Hussain H, Chaudhry I, El-Khamary S, Alkatan HM. Primary orbital liposarcoma: histopathologic report of two cases. *Middle East Afr J Ophthalmol*. 2011 Oct;18(4):314–6.
- 19 Khurana S, Gupta AK, Sen S, Kashyap S. Primary liposarcoma of the orbit. *Indian J Pathol Microbiol*. 2014 Oct-Dec;57(4):617–9.
- 20 Muratori F, Bettini L, Frenos F, Mondanelli N, Greto D, Livi L, et al. Myxoid Liposarcoma: Prognostic Factors and Metastatic Pattern in a Series of 148 Patients Treated at a Single Institution. *Int J Surg Oncol*. 2018 May;2018:8928706.
- 21 Nassif NA, Tseng W, Borges C, Chen P, Eisenberg B. Recent advances in the management of liposarcoma [version 1; referees: 2 approved]. *F1000 Res*. 2016 Dec;5:2907.
- 22 Trautmann M, Menzel J, Bertling C, Cyra M, Isfort I, Steinestel K, et al. FUS-DDIT3 Fusion Protein-Driven IGF-IR Signaling is a Therapeutic Target in Myxoid Liposarcoma. *Clin Cancer Res*. 2017 Oct;23(20):6227–38.
- 23 Kleinerman RA, Tucker MA, Abramson DH, Seddon JM, Tarone RE, Fraumeni JF Jr. Risk of soft tissue sarcomas by individual subtype in survivors of hereditary retinoblastoma. *J Natl Cancer Inst*. 2007 Jan;99(1):24–31.
- 24 Chaussade A, Millot G, Wells C, Brisse H, Laé M, Savignoni A, et al. Correlation between RB1 germline mutations and second primary malignancies in hereditary retinoblastoma patients treated with external beam radiotherapy. *Eur J Med Genet*. 2019 Mar;62(3):217–23.
- 25 Dommering CJ, Marees T, van der Hout AH, Imhof SM, Meijers-Heijboer H, Ringens PJ, et al. RB1 mutations and second primary malignancies after hereditary retinoblastoma. *Fam Cancer*. 2012 Jun;11(2):225–33.
- 26 Stiglmayer N, Jandrovic S, Miklic P, Hutinec Z. Atypical lipoma: well-differentiated liposarcoma of the orbit with dedifferentiated areas. *Orbit*. 2003 Dec;22(4):311–6.
- 27 Rosner M, Yosepovich A, Paul M, Rosen N, Perelman M. Orbital well-differentiated liposarcoma demonstrating chromosomal imbalances. *Eye (Lond)*. 2006 Jan;20(1):126–8.
- 28 Jakobiec FA, Nguyen J, Bhat P, Fay A. MDM2-positive atypical lipomatous neoplasm/well-differentiated liposarcoma versus spindle cell lipoma of the orbit. *Ophthalm Plast Reconstr Surg*. 2010 Nov-Dec;26(6):413–5.
- 29 Torrado CS, Zaldibar NM, Velasco-Benito V, Fernández-Hermida R. Primary orbital liposarcoma. *J Craniofac Surg*. 2011 May;22(3):1139–41.
- 30 Vrcck I, Hogan RN, Gilliland G. Orbital liposarcoma masquerading as a hemangioma. *Proc Bayl Univ Med Cent*. 2014 Oct;27(4):359–60.
- 31 Dworak DP, Patel SA, Chennuri R, Falco D. Primary Atypical Lipomatous Tumor of the Orbit: A Case Report. *J Ophthalmic Vis Res*. 2018 Jan-Mar;13(1):78–80.