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Review Article

Recurrent liponeurocytoma: A case report and systematic review of the literature

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ABSTRACT

Background: Liponeurocytomas are rare neurocytic neoplasms that most often arise in the posterior fossa and affect individuals in the third and fifth decades of life. Most reported cases of this unique tumor in the literature have described a favorable clinical prognosis without recurrence. However, increasing reports of recurrent cases prompted the World Health Organization, in 2016, to recategorize the tumor from Grade I to the less favorable Grade II classification. We conducted a systematic review to identify recurrent cases of this unique tumor and to summarize differences between the primary and recurrent cases of liponeurocytoma.

Methods: A systematic review exploring recurrent liponeurocytoma cases was conducted by searching the PubMed, Google Scholar, and Scopus databases for articles in English. Abstracts from articles were read and selected for full-text review according to a priori criteria. Relevant full-text articles were analyzed for symptoms, imaging, location, histological, pathological, treatment, and recurrence-free time between the primary and recurrent cases.

Results: Of 4392 articles, 15 articles accounting for 18 patients were included (level of evidence: IV) in the study. Recurrence-free time decreased from an average of 82 months between the primary tumor resection to first recurrence to 31.3 months between the first and second recurrence. Recurrent tumors demonstrated increased pleomorphic neural cells, necrosis, vascular proliferation, and MIB-1 index when compared to the primary tumor. Several cases also demonstrated decreased lipidizing components when compared to the primary tumor, further indicating increased dedifferentiation. The primary treatment for this tumor was surgical resection with occasional adjunctive radiotherapy.

Conclusion: Recurrent cases of liponeurocytoma have features of increased malignant proliferation compared to the primary cases. The standard treatment for these primary and recurrent tumors is gross total resection. The role of adjunctive radiotherapy remains a matter of debate.

Keywords: Liponeurocytoma, Neurocytic neoplasm, Recurrent, Systematic review

INTRODUCTION

Liponeurocytomas are rare and slow-growing tumors of neuroectodermal origin first described by Bechtel *et al.* in 1978 who, on histological examination, reported mixed mesenchymal and neuroectodermal composition.[3] Given this juxtaposition of features, this tumor has

often been mistaken for several other CNS tumors, most prominently, medulloblastoma. Prior reports have described liponeurocytomas as "lipomatous or lipidized medulloblastoma," "medullocytoma," and "lipomatous glioneurocytoma."

In response to increasing reports of this unique pathology, in 2000, the World Health Organization (WHO) described liponeurocytoma as a separate mixed neuronal and glial tumor and categorized it as WHO Grade I, reflecting its favorable prognosis. However, as reports of recurrence after resection mounted, in 2016, the tumor was recategorized as the WHO Grade II.[20]

Over 80 cases of liponeurocytomas have been reported in the literature. Of those, 18 cases demonstrate recurrence following resection of the primary tumor.[1,2,6-8,10,11,14-17,19,21,22,24,25] Only seven cases thus far have reported a second tumor recurrence.[1,2,11,14,21,22]

Here, we report a case of liponeurocytoma which recurred following two gross total resections (GTRs), along with a review of the 18 previously reported cases of recurrent liponeurocytoma with the hope of improving understanding of histopathological changes that occur with recurrence as well as guiding treatment and surgical decision-making in the treatment of this rare but intransigent entity.

MATERIALS AND METHODS

Case description

A 55-year-old man with a history of a left cerebellar liponeurocytoma resected at an outside facility 9 years prior was subsequently lost to follow-up. He presented to our institution's emergency center with 2 months of severe bifrontal and occipital headaches as well as loss of balance with a predilection to falling toward his left. The patient's physical examination was notable for mild dysmetria on finger-to-nose test (L>R) as well as mild ataxia with heel to shin (L>R).

Magnetic resonance imaging (MRI) revealed a mixed solid and cystic mass in the left cerebellum measuring 4.4 × 2.6 × 3.2 cm with surrounding vasogenic edema and associated mass effect with partial effacement of the fourth ventricle. The mass was T1 iso-to-hypointense and heterogeneously hyperintense on T2 [Figure 1]. Given the patient's neurologic decline, severe headaches, and radiographic findings of partial effacement of the fourth ventricle, the patient was offered surgical resection. A left retrosigmoid craniotomy was performed and extended to the sigmoid and transverse sinuses. The tumor was identified at the pial surface of the cerebellum and subsequently debulked internally. GTR was

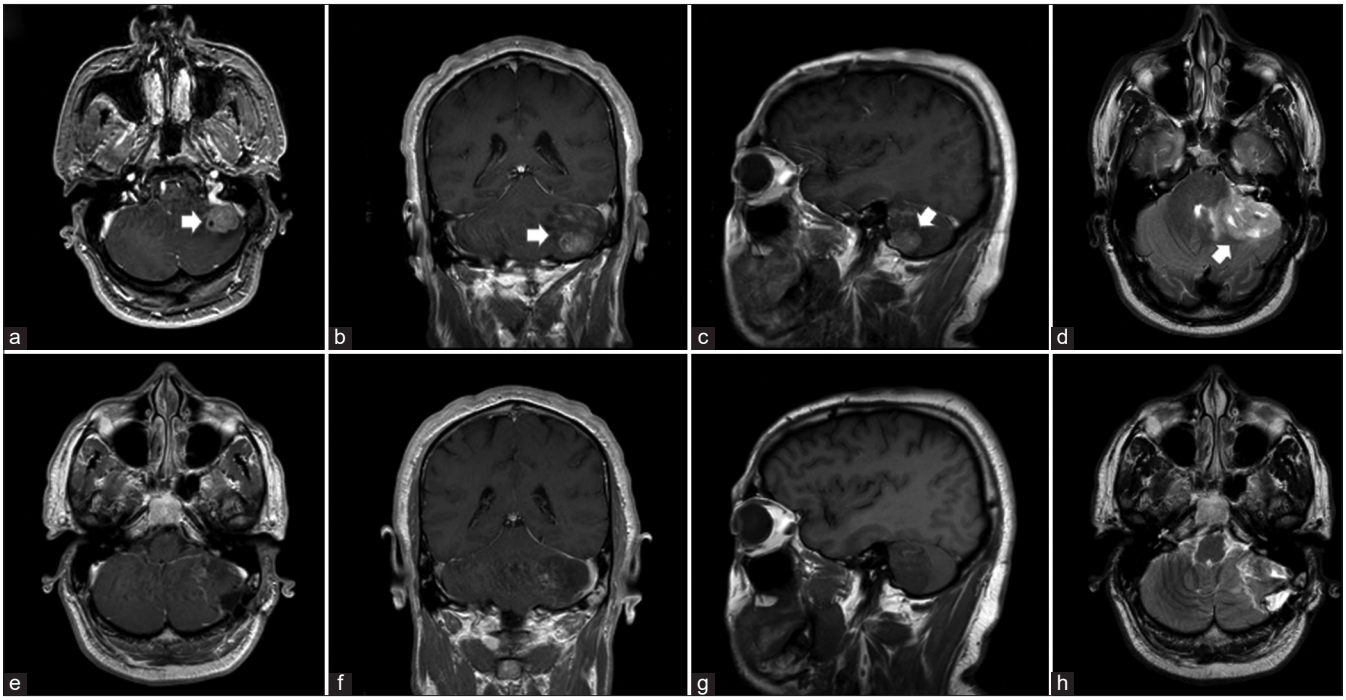

Figure 1: Magnetic resonance imaging demonstrates (a-d) presumptive recurrent liponeurocytoma (white arrow) as a heterogeneous solid and cystic mass in the left cerebellum abutting the left sigmoid sinus. (a-c) On axial, coronal, and sagittal T1-weighted imaging the lesion was isointense to the cortex with areas of hypointensity (not shown) with heterogeneous enhancement. The tumor was well marginated with minimal edema and without obstructive hydrocephalus. (d) Axial T2-weighted imaging shows heterogeneous hyperintensity of the tumor. Postoperative T1 axial, coronal, and sagittal (e-g); and T2 axial (h) images show complete resection of the mass.

achieved. The patient tolerated the procedure well and had an unremarkable postoperative course. At a 2-week follow-up, the patient had recovered well with normalization of finger-to-nose and heel-to-shin tests, though he did have a Romberg test notable for mild left-sided sway.

Pathologic analysis revealed monotonous neurocyte-like cell proliferation, vague rosetting, and focal vascular proliferation. Multifocal fat droplets with adipocyte formation were also seen. No necrosis or mitotic activity was identified [Figure 2]. The tumor stained positive for S100, CD56, and synaptophysin. Immunoperoxidase stains for p53, EMA, GFAP, and IDH-1, on the other hand, were negative in the tumor. MIB-1 proliferation index was 2.8%.

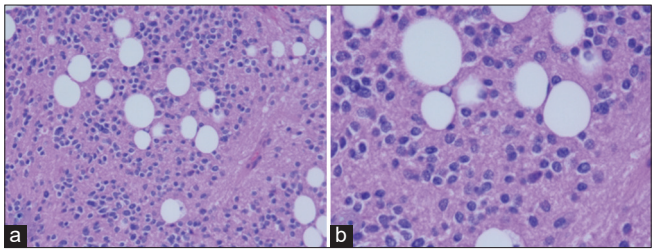

Figure 2: Histopathologic slides of the first recurrent liponeurocytoma. (a) Low magnification of the specimen shows large multifocal fat droplets intermixed with neurocytic cells and focal vascular proliferation. (b) High magnification shows detail of the monotonous nature of the neurocytic cells.

Three years postoperatively, routine surveillance MRI revealed a recurrent tumor measuring 2.1 × 2.0 × 2.9 cm in the left cerebellar hemisphere accompanied with mass effect on the left inferior sigmoid sinus, with associated loss of flow void in the distal left transverse sinus, proximal sigmoid sinus, and left jugular bulb. The mass was hyperintense on T1 and isointense on T2 [Figure 3]. On further questioning, the patient reported severe headaches, intermittent diplopia, neck pain, and difficulty maintaining balance. Physical examination revealed no focal neurologic deficits, however.

Given that the patient was symptomatic, the patient was once again offered surgical resection. He underwent a redo left retrosigmoid craniotomy for resection of his tumor. At surgery, we found a largely well-encapsulated tumor. The tumor was initially internally debulked and then removed in piecemeal fashion. The patient had an unremarkable postoperative period. Postoperative MRI showed no evidence of residual tumor.

Pathologic analysis of the recurrent tumor demonstrated reduced lipomatous components compared to the prior pathology. Moreover, focal necrosis of the tumor, increased vascular proliferation, and increased cellularity were all noted on these tissue specimens, and the MIB-1 proliferation index had increased to 7.4%. Immunohistochemical marker phenotype remained unchanged [Figure 4]. On a 2-week

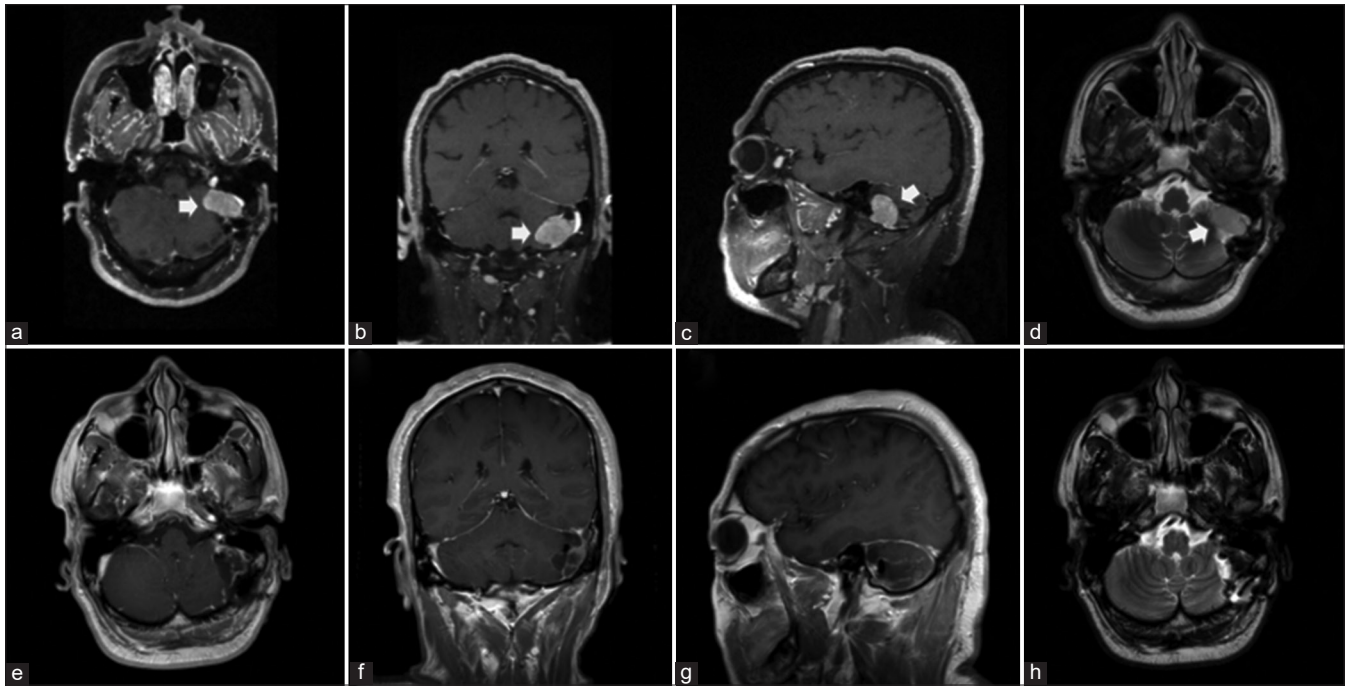

Figure 3: Magnetic resonance imaging (MRI) demonstrates (a-d) recurrence of the liponeurocytoma (white arrow) occupying the left cerebellum. (a-c) On axial, coronal, and sagittal T1-weighted imaging, the lesion was hyperintense compared with the cortex. The tumor was well marginated without edema or obstructive hydrocephalus. (d) Axial T2-weighted imaging of the tumor is isointense to the cortex (not shown), with increased heterogeneous enhancement as compared to the initial recurrence. Postoperative T1 axial, coronal, and sagittal (e-g); and T2 axial (h) MRI images demonstrate no radiographic evidence of residual disease.

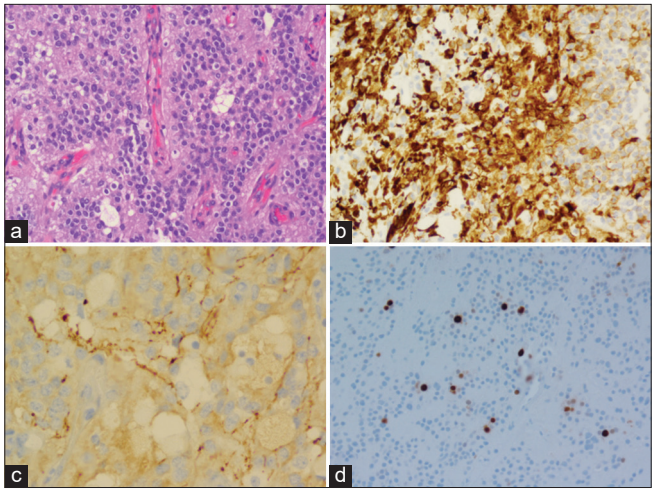

Figure 4: Histopathologic slides of the second recurrent liponeurocytoma (a) show small, microscopic collections of fat with increased vascularity and cellularity compared to the first recurrent tumor. (b) Small tumor cells with mixed lipomatous differentiated neoplastic cells express synaptophysin. (c) Axons of the surrounding central nervous system tissue express neurofilament. (d) The Ki-67 proliferation index (as determined by MIB-1 staining) is 7.4%.

follow-up, the patient has continued to do well with no focal deficits noted on the physical examination.

Literature search

We performed a systematic review of recurrent liponeurocytoma following the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines [Figure 5].[18] On November 3, 2021, the PubMed MEDLINE (National Library of Medicine), Scopus (Elsevier), and Google Scholar (Google) databases were queried for relevant articles by key words "liponeurocytoma," "neurolipocytoma," "lipomatous medulloblastoma," "lipidized medulloblastoma," "medullocytoma," and "lipomatous glioneurocytoma." These key words were combined with "recurrent," "cerebellar," and "central" using the "AND" operator. We did not restrict our search based on date of publication, article type, or language.

Duplicated records were excluded once the search was completed. Studies were subsequently screened based on title and abstract. The remaining articles were screened by a full-text review for final inclusion. Studies were selected for final review based on the following inclusion criteria: case report or peer-reviewed original research detailing a cohort of patients who underwent treatment for liponeurocytoma more than once (demonstrating recurrence), English language, and full-text availability. Studies other than full-length articles such as abstracts, posters, and editorials were excluded from the study. Two reviewers (D.S. and P.P) independently screened all articles and disagreements were reconciled by discussion.

Data extraction was performed by two reviewers (D.S. and C.E.) based on prespecified criteria. Data of interest included identifying demographic characteristics and symptoms of individuals with recurrent liponeurocytoma; findings on imaging, pathology, and immunohistochemistry in the primary and recurrent tumors; treatment of primary and recurrent tumors; and time between the primary tumor and recurrence and between recurrences.

RESULTS

Our literature search identified 18 previously reported cases of recurrent liponeurocytoma [Table 1]. There was a slight male predominance (55.5%). Age at which the primary tumor was diagnosed ranged from 4 to 74 years with an average age of 46 years. The most common location for the primary tumor was the cerebellum (13 cases or 72.2%) followed by the lateral and fourth ventricles (two cases or 11.1% each). One case was reported in the frontal lobe. Given the predominance of the cerebellum as the site for tumor localization, the most reported presenting symptoms of the primary and recurrent tumors included headaches, gait disturbance, vertigo, and difficulty with ambulation. GTR of the primary tumor was performed in 15 cases (83.3%) and subtotal resection (STR) was performed in 3 cases (16.7%). Two patients with the primary tumors underwent postoperative radiation therapy.

The time between the primary tumor removal and detection of recurrence ranged from 8 months to 15 years with an average time for recurrence of 82 months. GTR of the recurrent tumor was performed in 13 cases (72.2%) and STR was performed in 5 cases (27.8%). Radiotherapy was employed in three cases for the treatment of the recurrent tumor. Seven of the previously reported patients, like our patient, experienced a second recurrence of their liponeurocytoma. Four of these patients had undergone complete resection of the first recurrence; three had undergone STR of the first recurrence. A second recurrence was not seen in patients who had been treated with radiotherapy.

The time between the first and second recurrence ranged from 3 months to 5 years with an average time for recurrence of 31.3 months. Five patients (71.4%) with a second recurrence were treated with a GTR of the tumor, 1 patient (14.3%) was treated with a STR supplemented with a standard medulloblastoma chemotherapy regimen, and 1 (14.3%) patient was treated with Gamma-Knife surgery. No more than 2 recurrences of the tumor have been reported in the literature.

Histological examination of the tumor was, for the most part, consistent between the primary tumor and the recurrent tumors. In six recurrent tumors (three from the first recurrence and three from the second recurrence),

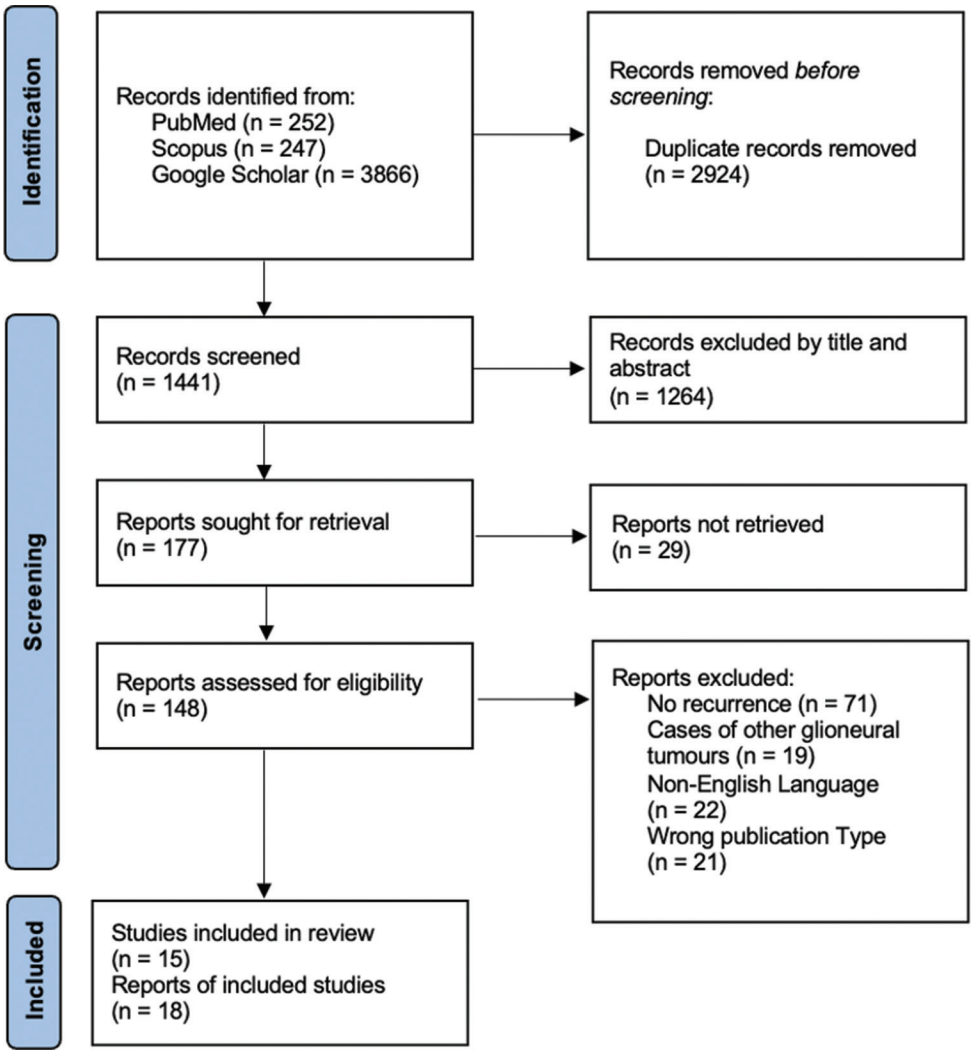

Figure 5: PRISMA flowchart. This flowchart delineates the search and review process used to identify and select articles for inclusion in this study.

histological examination showed increased pleomorphic neural cells and decreased lipidized areas when compared to the primary tumor. In three recurrent tumors (one from the first recurrence and two from the second recurrence), histological examination showed increased lipidized areas when compared to the primary tumor. No necrosis or vascular proliferation was seen in the primary tumor. Necrosis and vascular proliferation were increased in six recurrent tumors (five from the first recurrence and one from the second recurrence). Increased mitosis from the primary tumor was described in five recurrent tumors (three from the first recurrence and two from the second recurrence). The Ki-67/MIB-1 proliferation index was described in 12 primary tumor cases with a mean of 5.08%. The Ki-67/MIB-1 proliferation index was reported after the first tumor recurrence in 10 cases with a mean of 9.08%. The Ki-67/MIB-1 proliferation index was reported after the second tumor recurrence in four cases with a mean of 8.25%.

DISCUSSION

Liponeurocytomas are rare neurocytic neoplasms that most frequently arise in the posterior fossa and affect individuals in the third and fifth decades of life, and mostly demonstrate favorable clinical prognosis.[9] However, due to increased evidence of recurrent cases, the WHO, in 2016, updated the tumor from a Grade I classification to a Grade II classification.[20] In 2018, Gembruch *et al.* completed a systematic review of all liponeurocytomas, including recurrent cases, reported in the literature.[9] We report an additional case and provide a more focused look at the radiological and histological differences between the primary and recurrent tumors. We also seek to highlight key differences between singly and multiply recurrent cases to provide guidance in the identification of and treatment approach for more aggressive variants of liponeurocytoma.

Table 1: Reported cases of recurrent liponeurocytoma in the literature.

References•	Age (years)/ sex	First tumor					Second tumor					Third tumor				
		Location	Sx	Imaging	Size, pathology, IHC	Tx	RFS (Months)	Sx	Imaging	Size, pathology, IHC	Tx	RFS (Months)	Sx	Imaging	Size, pathology, IHC	Tx
Giangaspero *et al.*, 1996[11]	37/M	Left cerebellar hemisphere	Headache and gait disturbance	NA	7 cm High cellularity with small nuclei and chromatin-speckled nuclei, oligodendrocyte-like perinuclear halo, cytoplasmic lipid accumulation, Rosenthal fibers, laminated calcifications, rare mitosis and absent vascular proliferation and necrosis MIB-1<1% Synaptophysin+, GFAP+, NF–	GTR	120	NA	NA	Slightly more pleomorphic cell nuclei with irregular contours. Increased vascular proliferation and necrosis, mitosis present, less prominent lipidized areas; otherwise, similar MIB-1=5% Synaptophysin+, GFAP+, NF–	GTR	12	NA	NA	Slightly more pleomorphic cell nuclei with irregular contours. increased vascular proliferation and necrosis, mitosis present, less prominent lipidized areas; otherwise, similar MIB=5%	GTR
	36/M	Left cerebellar hemisphere	Headache and gait disturbance	NA	High cellularity with small nuclei and chromatin-speckled nuclei, oligodendrocyte-like perinuclear halo, cytoplasmic lipid accumulation, rare mitosis and absent vascular proliferation and necrosis MIB-1<1% Synaptophysin+, GFAP+, NF–	GTR	120	NA	NA	Slightly more pleomorphic cell nuclei with irregular contours. Increased vascular proliferation and necrosis, mitosis present, less prominent lipidized areas; otherwise, similar MIB-1=5% Synaptophysin+, GFAP+, NF–	GTR	60	NA	NA	Slightly more pleomorphic cell nuclei with irregular contours. increased vascular proliferation and necrosis, mitosis present, less prominent lipidized areas; otherwise, similar MIB=5%	GTR
Soylemezoglu *et al.*, 1996[25]	53/M	Left CPA	Headache, vertigo, gait disturbance, and left-sided hearing loss	Enhancing lesion on CT	Small, poorly differentiated cells with hyperchromatic nuclei, numerous oligodendrocyte-like perinuclear halo, lipid-filled cells intermingled with tumor cells, low mitotic activity absent necrosis MIB-1<5% NSE+, Synaptophysin+, MAP–2+, GFAP+, vimentin+, S-100+, NFP–, Lu-5–, EMA–, desmin–, p53–	GTR	132	Headache, vertigo, gait disturbance, left-sided hearing loss, nystagmus, dysarthria, and + Romberg	Enhancing lesion on CT scan	NA	GTR					
George and Scheithauer, 2001[10]	59/M	Left frontal lobe	Difficulty walking, decreased memory, and cold sensation in the right arm and leg	Intrahomogenous enhancing lesion on CT scan	Moderately cellular with uniform small cells with round nuclei and scant cytoplasm, lipid-filled cells scattered in clusters throughout the tumor, mitosis present (3 per 10 high-power units MIB-1=5% NSE+, Synaptophysin+, S-100+, GFP–	STR	67	NA	NA	Histologically identical to original tumor, rare mitosis present MIB-1=5.8% Immunohistochemistry was identical EMA–, NF –	GTR					
Alkadhi *et al.*, 2001[1]	53/M	Left cerebellar hemisphere and CPA	Headaches, vertigo, gait disturbance, left-sided hearing loss and tinnitus, right-sided facial paralysis, and+ Romberg	Hypointense with diffuse hyperintense streaks on T1, hyperintense on T2	Small poorly differentiated closely packed cells with intermixed lipid-filled cells, no necrosis of vascular proliferation MIB-1=Low Synaptophysin+, GFAP+	GTR	144	Headaches, gait imbalance, and vertigo, left-sided hearing loss, nystagmus, dysarthria, and + Romberg	NA	NA	STR	48	NA	NA	NA	GTR
Jenkinson *et al.*, 2003[14]	51/F	Right cerebellar hemisphere	Headaches, vomiting, gait imbalance, nystagmus, dysarthria, ataxia	Hyperintense lesion on T1 MRI	Small poorly differentiated closely packed cells with intermixed lipid-filled cells, occasional mitosis, absent vascular proliferation, and necrosis. MIB-1<3% NSE+, Synaptophysin+, MAP2C+, S100+, GFAP+	STR+Radiation (54 Gy)	12	Headaches	Hyperintense lesion on T1 MRI	Similar histological examination increased lipomatous portion MIB-1<3% Same IHC	STR	3	NA	Hyperintense lesion on T1 MRI	Increased lipomatous component with decreased neurocytic elements MIB <3% Same IHC	STR+ Chemotherapy
Buccoliero *et al.*, 2005[6]	61/M	Right cerebellar hemisphere	NA	NA	3 cm Small poorly differentiated closely packed cells with intermixed lipid-filled cells, occasional mitosis MIB-1=15%	GTR	42	None	Nodular homogenous enhancing lesion on CT scan	2 cm Same proportion of small poorly differentiated closely packed cells with intermixed lipid-filled cells, perinuclear halo, diffuse homer-wright rosettes and scattered pseudo rosettes, rare necrosis and microhemorrhage, moderate vascular hyperplasia, focal areas of high mitosis MIB-1=20% NSE+, NF+, GFAP+, SY+, S100–	GTR+Radiotherapy (15.4 Gy)					

(*Contd...*)

Table 1: (*Continued*).

References	Age (years)/ sex	First tumor					Second tumor					Third tumor				
		Location	Sx	Imaging	Size, pathology, IHC	Tx	RFS (Months)	Sx	Imaging	Size, pathology, IHC	Tx	RFS (Months)	Sx	Imaging	Size, pathology, IHC	Tx
Jouvet *et al.*, 2005[15]	4/F	Fourth ventricle	Headache, intracranial hypertension, nausea, vomiting	Hypointense lesion on T1 and hyperintense on T2	3×2×5 cm Small poorly differentiated cells with intermixed lipid-filled cells, perinuclear halo, absent vascular proliferation and necrosis, rare mitosis MIB-1=15% Synaptophysin+, NF+, GFAP+, Vimentin+, S100+, EMA+, Cytokeratin−	GTR	14	Headache	Hypointense lesion on T1 MRI, Isointense on T2	Two homogenous nodules in the fourth ventricle: 3×1.5×2 cm and 1.2×8 cm Fewer adipose-like cells, endocrine architecture, rosette-like arrangement of tumor cells around thin vessels MIB-1=30% Similar IHC. cytokeratin+	GTR					
Limaiem *et al.*, 2009[19]	42/M	Left cerebellar hemisphere and vermis	Headache, vertigo, visual disturbance, gait disturbance,+ Romberg	Heterogeneous with discrete hyperintensity on T1, hyperintense on T2	5×4 cm Small poorly differentiated cells with intermixed lipid-filled cells, occasional mitosis, absent vascular proliferation, and necrosis MIB-1=2% NSE+, Synaptophysin+, GFAP+	GTR	120	Headache and vertigo	NA	Similar histological examination with absent vascular proliferation and necrosis. MIB-1=3%	GTR					
Chakraborti *et al.*, 2011[7]	36/M	Both lateral ventricles	Headache and blurred vision	Mixed density on CT scan	Small poorly differentiated cells with intermixed adipose cells. Absent mitosis. No necrosis and vascular proliferation. MIB-1<1% Synaptophysin+, Chg A+, NF+, MAP-2+, GFAP+, S100+, P53−	GTR	112	NA	Nonenhancing lesion with mixed iso to hyperintense areas on T1, isointense on T2	Similar histological examination increased lipomatous portion. Present necrosis and vascular proliferation. MIB-1=4% Same IHC	GTR, Radiotherapy					
Cohen-Inbar *et al.*, 2011[8]	74/M	Right cerebellar hemisphere	Headache and vertigo		Small poorly differentiated and closely packed cells with intermixed adipose cells	GTR	156	Mild vertigo	Nonenhancing lesion on CT	Similar histological examination MIB-1<5% Synaptophysin+	GTR					
Anghileri *et al.*, 2012[2]	40/F	Vermis and right paravermian region	Dizziness, gait disturbance, postural tremor	Hypodense on CT	Small poorly differentiated cells with intermixed lipid-filled cells. MIB-1=Low NSE+, Synaptophysin+, MAP-2+, GFAP+, NF−	GTR	96	None	Hyperintense lesion on MRI	Similar histological examination MIB-1=Low Same IHC	GTR					
	59/F	Vermis	Headache, vertigo, neck pain, and walking impairment	NA	NA	STR	15	Gait imbalance, ataxia, and+ Romberg	Heterogeneous intensity on MRI	Small poorly differentiated cells with intermixed lipid-filled cells. MIB-1=Low NSE+, Synaptophysin+, MAP-2+, GFAP+, NF−	STR	48	Dizziness and gait instability	NA	Similar histological examination, increased lipomatous portion MIB-1=Low Same IHC	Gama-Knife surgery
Pelz *et al.*, 2013[21]	54/F	Fourth ventricle	Headaches and neck pain	Hypointense and hyperintense components on T1 MRI, Hyperintense on FLAIR	Small poorly differentiated cells with intermixed lipid-filled cells, perinuclear halo. No mitosis. Absent vascular proliferation MIB-1=Low Synaptophysin+, NeuN+ and GFAP−	GTR	24	NA	NA	NA	GTR	24	NA	NA	NA	GTR (Radiation offered but declined)
Konovalov *et al.*, 2015[17]	49/M	Vermis	Ataxia, gain disturbance, neck pain	Heterogeneous with areas of hyperintensity on T1 MRI	MIB-1=5% Synaptophysin+, GFAP+	GTR radiotherapy (36 Gy)	108	Ataxia and diplopia	NA	NA	STR					
Radke *et al.*, 2015[22]	59/F	Left cerebellar hemisphere	NA	NA	Small poorly differentiated cells with intermixed lipid-filled cells, perinuclear halo, perivascular pseudorosettes, rare mitosis MIB-1=3% Synaptophysin+, MAP2+, GFAP+	GTR	180	NA	Heterogeneous lesion on MRI, hyperintense on T2	Similar histological examination with increased mitotic figures, Increased vascular proliferation with absent necrosis MIB-1=10% Synaptophysin+, GFAP+, S100+, NeuN+, Cytokeratin−	GTR	24	NA	NA	Increased features of anaplasia and cellularity, nuclear atypia, and increased mitotic activity, complete loss of lipomatous component MIB-1=20% Same Immunohistochemistry, P53−	GTR
Khatri *et al.*, 2018[16]	36/F	Left cerebellar hemisphere	Headache and difficulty walking	Heterodense lesion with heterogeneous contrast enhancement on CT, iso- to hypointense on T1 and hyperintense on T2 with heterogeneous enhancement	3.5×4×5.5 cm Small poorly differentiated cells with intermixed lipid-filled cells, no mitosis, absent necrosis MIB-1=Low Synaptophysin+, GFAP+, Vimentin+	GTR	8	NA	Hyperintense lesion on T2 MRI in the right cerebellar hemisphere	1.2×1.5×0.8 cm	GTR+ Radiotherapy					
Shen *et al.*, 2021[24]	29/F	Both lateral ventricles	Headache	Hypodense lesion on head CT, hyperintense with patchy areas of isointense on T1	7.1×4.5×5.1 cm Small poorly differentiated cells with intermixed lipid-filled cells, oligodendrocyte-like perinuclear halo MIB-1=5% NSE+, Synaptophysin+, GFAP+, P53+, Olig−, EMA−, NF−	GTR	12	NA	NA	NA	STR					

Sx: Symptoms; Tx: Treatment; IHC: Immunohistochemistry; RFS: Recurrence-free survival; GTR: Gross total resection; STR: Subtotal resection

Radiologically, liponeurocytoma share features seen in other cystic and neurocytic neoplasms of the central nervous system. They are usually described, like our first recurrence, as iso-to-hypointense on T1-weighting imaging and hyperintense on T2-weighted imaging.[23] Lesions that are hyperintense on T1 and isointense on T2, like the second recurrent tumor in our patient, have been described in the literature less frequently.[14] This unique imaging finding is associated with lesions with an abundance of lipidized tissue.[12] To the best of our knowledge, this represents the first recorded case of liponeurocytoma where an inversion of T1 and T2 sequence intensity occurred between recurrent lesions. Moreover, histological evaluation of the second recurrent tumor found a decreased lipomatous component compared to the first recurrent tumor, highlighting a different mechanism for the imaging changes in the second recurrence. Possible causes of increased intensity on T1 and decreased intensity on T2 between the recurrent tumors include increased intratumor areas of hemorrhage or protein concentration.[5]

Histologically, liponeurocytomas are characterized by small and poorly differentiated neurocytic cells with focal areas of intermixed neuroepithelial cells with lipid accumulation. The tumor cells are usually described as round to oval.[13] However, spindle-shaped and more multinuclear bizarre-shaped cells have also been reported in the literature. Other common histological features of this tumor include sharp demarcation from the surrounding brain tissue, cell-free fibrillary neutrophils, vessel hyalinization, calcification, and neural rosettes and pseudorosettes.[27] While the primary tumors, for the most part, showcase these benign features, the recurrent tumors have been shown to demonstrate more atypical features. In our patient, for example, the second recurrent tumor showed necrosis, vascular proliferation, and increased mitosis and atypia, features not present in the first recurrent tumor. Similarly, in six of the 25 (including the first and second recurrence) recurrent tumors found in the literature, increased necrosis and vascular proliferation were seen when compared to the primary tumor or prior recurrent tumor. Moreover, in our patient, the MIB-1 proliferation index increased by 5.4% between the first and second recurrent lesions. As shown earlier, this trend of increasing MIB-1-positive cells between the primary and recurrent lesions and between recurrences has been well documented in the literature and seems to indicate malignant progression and different grade of neuronal differentiation between the primary lesions as compared to the recurrent lesions. The reduced lipomatous components seen with recurrence in our case and others documented in the literature can be interpreted further as a sign of progression and dedifferentiation with recurrence.

Recurrence in liponeurocytoma is rare. In a systematic review of 73 patients with liponeurocytoma, Gembruch *et al*. found that 14 or 28.6% had a primary tumor recurrence. Moreover, they found that six or 8.2% of patients experienced a second tumor recurrence.[9] In our patient, recurrence-free survival (RFS) time decreased with each recurrence. This pattern follows the trends seen in other cases with multiple recurrences. Our review found the RFS decreased from an average of 82 months between the primary tumor resection and first recurrence to an average of 31.3 months between the first and second recurrence. Increasing cellularity and dedifferentiation along with increased malignant progression and proliferation may also explain this phenomenon. Moreover, several studies have proposed a possible genetic cause of liponeurocytoma formation and recurrence. Particularly, transcription factors NEUROG1 and fatty acid-binding protein-4 are enhanced in liponeurocytoma. It is possible that the interactions between these genes and others explain the molecular mechanisms that decrease RFS time between recurrences.[2,26]

Complete surgical resection has been described as the preferred treatment for patients with liponeurocytoma. Despite this, Gembruch *et al*. found that of the 49 patients in their cohort that received complete surgical resection of the tumor, six experienced tumor recurrence. Radiotherapy has been discussed as a viable adjunctive therapy in patients with liponeurocytoma. Gembruch *et al*. found no recurrence in eight patients who received adjunctive radiotherapy paired with complete resection and only found one case of recurrence in six patients who received adjunctive radiotherapy paired with incomplete resection.[9] However, given the extensive side effect profile of cranial radiation, the debate remains whether there is enough evidence for this to become the standard of care for all primary liponeurocytomas.[4] In a limited sample size, our systematic review showed effective management of recurrent tumor without a second recurrence in the three patients who received adjunctive radiotherapy for treatment of a recurrent tumor. This may indicate adjunctive radiotherapy as an appropriate treatment option for patients with recurrent disease and tumors with aggressive histological features including reduced lipomatous components, increased necrosis and vascular proliferation, and increased MIB-1 proliferation index.

Limitations

There are several limitations to this study. Although our research relied on three main databases, PubMed, Google Scholar, and Scopus, yielding over 4365 articles, there is a chance that the literature search is not entirely complete. This is especially true for this topic as liponeurocytoma was not established as a separate glioneuronal tumor until 2000. Thus, while our search accounted for other names used to describe this pathology, it is still likely that the results were not comprehensive. Moreover, only studies in English were

included in the study, potentially excluding other regions where this pathology may be more common. In addition, because of the nature of this review, any errors in diagnosis, radiological examination, or pathological examination related to the included cases would bias our conclusions. Furthermore, the quality of evidence was moderate to low, as all the studies used in the review were case reports with a level of evidence of V and no randomized trials or cohort and case–control studies were identified. Another limitation of this study is the heterogeneity of the data collected in the case reports and case series. For instance, many cases did not have specific information on tumor imaging, size, pathology, or immunohistochemistry in the primary and recurrent tumors.

CONCLUSION

The present case is the 19th reported case of recurrent liponeurocytoma and only the eighth case with more than 1 recurrence following treatment. This paper highlights the noted radiological and histological differences between the primary and recurrent tumors and points to a trend of increased malignant proliferation between primary and recurrent tumors. The standard treatment for these tumors is complete resection. The role of adjunctive radiotherapy remains an area of investigation, but the data thus far indicate that at least in the case of histologically aggressive appearing tumors, adjunctive radiation treatment is likely warranted.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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