

RAS/MAPK Pathway Alteration in Pediatric Low-Grade Glioma Complicated with Ventriculo-Peritoneal Shunt Related Ascites

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Abstract

Introduction: Ventriculo-Peritoneal Shunt (VPS) related ascites is a rare complication of pediatric Low Grade Gliomas (pLGG). Physiopathology of this complication is not fully understood and there is paucity of data regarding the molecular profile of pLGG gliomas complicating with ascites and the optimal management of this unusual event.

Methods: International multi-institutional retrospective analysis of patients diagnosed with BRAF altered pLGG and ascites arising as a complication of VPS. Demographics, tumor characteristics, therapeutic approaches and outcomes were recorded.

Results: Nineteen patients were identified. Median age at diagnosis was 14 months (IQR:7-16). Most patients (16;84.2%) presented with lesions involving the optic pathway. Mean tumor standard volume was 34.8 cm² (range:12.5-85.4). Pilocytic Astrocytoma was the most frequent histological diagnosis (14;73.7%). Eight (42.1%) tumors harbored BRAF V600E mutation and seven (36.8%) KIAA1549 fusion. The onset of ascites was documented at a median time of 5 months following VPS insertion. Four (21%) patients were managed with paracentesis only, 7(36.8%) required both paracentesis and shunt diversion, 7(36.8%) required only a shunt diversion and 1 (5.2%) patient was managed conservatively. Ascites was the indication to change chemotherapy regimen in 10 patients. Eight patients received targeted therapy (4 dabrafenib/4 trametinib) and 5 were radiated. Eleven patients were alive at the time of this report with a median OS of 69 months (range:3-144).

Conclusions: Ascites is an early feature in the course of pLGG irrespective of alterations in the RAS/MAPK pathway with high mortality rate and should be considered as an adverse prognostic risk factor in pLGG.

Introduction

Low-Grade gliomas (LGG) are characterized by alterations in the RAS-mitogen-activated protein kinase (RAS/MAPK) pathway [1–4]. LGGs are the most common pediatric brain tumors accounting for 10-15% of intracranial tumors in children (5) and frequently present in the optic pathway track (OPG), hypothalamus and thalamus. Due to their location, these tumors can lead to obstructive hydrocephalus requiring a ventriculo-peritoneal shunt (VPS) insertion for cerebrospinal fluid (CSF) diversion.

Ascites is a rare complication from a VPS and only twenty-one cases have been described in the literature as single case reports or small case series (Table 1). Several etiologies have been suggested, and it is likely that multiple factors contribute to its formation [6–9]. Nevertheless, the mechanisms by which ascites can occur in this subset of patients remains to be elucidated. To date, there is paucity of meaningful data to understand the clinical significance of ascites in pediatric patients with LGG. Furthermore, there is no standard of care for patients with ascites and the current therapeutic approaches usually include repetitive paracentesis or alternative CSF diversions [9–11].

Table 1
 Ascites complicating Ventriculo-Peritoneal Shunt in Pediatric Low Grade Glioma
 (Literature Review) [6–11, 17]

Total (n)	21
Age at tumour diagnosis	9
Median months	21 (6-108)
Gender	13
Male	6
Female	7
Location	21
Optic Pathway	21
Histology	12
Pilocytic Astrocytoma	12
MEK/BRAF status	1
BRAF V600E M	1
Lines of chemotherapy	8
Median	1(1-3)
Radiation	8
YES/NO	2/6
Surgery	9
Biopsy	6
Subtotal Resection (STR) [#]	3
Time from Shunt to Ascites	15
Median months	5(0.25-31)
Alternative Shunt Site	21
NO	4
YES*	17
Ventriculo Atrial	13
Ventriculo Gallbladder	4
Ventriculo Yugular	1
Ventriculo Pleural	1
CSF Protein g/L	16
Median	31(6.3-171)
Ascites Protein g/L	14
Median	130 (10-720)
Ascites outcome	21
Resolution	21
Overall Survival	10
Months	27(2-60)
Survival Status	18
Alive	16
Dead	2
Abbreviations: CSF: Cerebro Spinal Fluid. Symbols: [#] 2 patients had 2 x STR.	
*2 Patients had two alternative shunt reinsertions sites.	

Importantly, emerging targeted therapies for pLGG have shown promising results and might represent a tool to avoid the development of serious complications during the course of the disease [12–15]. Thus, understanding the correlation between particular molecular alterations seen in pLGG and the risk of developing this unusual occurrence is of utmost importance. Moreover, it's important to elucidate whether ascites itself could be an independent adverse prognostic in pLGG.

In this study, we aim to define the clinical and molecular characteristics of this unique subset of pediatric gliomas to address these unanswered questions. We assembled a large cohort of children with molecularly-characterized LGG who developed ascites following a VPS insertion.

Material And Methods

An international multi-institutional collaboration was established among six pediatric oncology institutions in Canada, Spain, Jordan and Argentina to retrospectively identify children and adolescents diagnosed with LGG who required a VPS and developed ascites during the course of their disease.

Ethics Board approval was obtained by each participant institution. Only patients with histologically proven diagnosis of low-grade glioma were included. BRAF V600E mutation status was performed by Immunohistochemistry and further confirmed by real-time Polymerase Chain Reaction (PCR) when available. In samples not harboring BRAF V600E mutation, tandem duplication KIAA1549 was performed by FISH or RNA sequencing. Ascites was clinically suspected and further confirmed by abdominal ultrasound or Abdominal Computerized Tomography scan. Demographics and clinical data was retrospectively collected and included. Tumor histology, size and location, BRAF status, treatment modalities received (chemotherapy, surgery, radiation and/or targeted therapy) biochemistry of ascites fluid, clinical and surgical management and outcome of ascites and survival status.

Results

A total of nineteen children (10 girls) were identified and included in the study (Table 2). Median age at diagnosis of LGG was fourteen months (IQR:7-36) and 14/19 patients were younger than 24 months of age at the time of diagnosis.

The great majority of patients had tumors located in the optic pathway with three exceptions: two patients were diagnosed with a thalamic and one with a hemispheric pilocytic astrocytoma. All tumors were non metastatic at presentation, two patients had documented diencephalic syndrome (#4 and #19). No patient presented with stigmata of NF-1. Mean tumor standard volume at the time of ascites by using the product of the largest 2 MRI lengths from transverse, anterior-posterior, and cranio-caudal dimensions was 34.8 cm² (range:12.5-85.4) The most common histological diagnosis was pilocytic astrocytoma (n=14;73.3%), followed by Pilocyoid Astrocytoma (n=3;15.8%), ganglioglioma (n=1;5.2%), and LGG NOS (n=1;5.2%). Eight (42.1%) tumors harbored V600E mutation; KIAA 1549 fusion was detected in seven (36.8%), while in four further BRAF-negative samples (21%) there was not enough tissue remaining to perform further molecular analyses.

Characteristics and Management of ascites (Table 2)

Following obstructive hydrocephalus, insertion of a VPS was required at a median time of 3.5 months (IQR 0-21.7) from tumor diagnosis, and ascites was diagnosed as a complication at a median of 5 months (IQR 3-13) after the procedure. Ascites required active management and was eventually solved in all patients, however only one patient could be successfully managed conservatively with diuretics. Interestingly, this patient was also the only who received targeted therapy prior to the onset of ascites (4 months) and has continued on dabrafenib as single agent with good tumor control. Therapeutic paracentesis was performed in eleven patients, being the definitive treatment in four, while the remaining seven required a shunt diversion. Fourteen patients required a shunt conversion to successfully divert ascites fluid. The preferred modality of alternative shunt was ventriculo-atrial in thirteen and ventriculo-gallbladder in one. Seven patients had a ventriculo-atrial shunt upfront as first treatment option with no previous therapeutic paracentesis performed.

Table 2 Demographics, Tumor characteristics and Ascites management

#	Gender	Age at Diagnosis (months)	Location	Tumor size (mm)	Histology	BRAF Alteration	Time from VPS insertion to ascites (m)	Protein Level (g/l)		Paracentesis	Alternative Shunt Site	Survival status
								Ascites	CSF			
1	M	12	OPW	48 x 50	PA	V600E	2	N/A	N/A	NO	NO	A
2	F	10	OPW	42 x 43	GG	V600E	0.5	N/A	12	NO	VAS	A
3	F	16	OPW	34 x 37	PMA	KIAA1549	106	N/A	28	YES	VAS	A
4	F	2	OPW	72 x 81	LGG NOS	V600E	0.2	6	N/A	YES	NO	A
5	F	100	OPW	47 x 52	PA	V600E	3	3.5	7.5	YES	VGBS	A
6	M	7	OPW	43 x 41	PMA	KIAA1549	4	33	19.5	NO	VAS	A
7	F	48	OPW	72 x 41	PA	KIAA1549	1	N/A	5	YES	NO	A
8	M	7	OPW	44 x 34	PA	V600E	2	3.8	9.9	YES	VAS	A
9	M	132	Thalamic	59 x 52	PA	Negative	36	0.17	10.2	NO	VAS	A
10	M	15	OPW	52 x 74	PA	KIAA1549	11	42.5	N/A	YES	VAS	A
11	F	72	OPW	38 x 53	PMA	Negative	4	12.38	N/A	NO	VAS	A
12	M	24	OPW	34 x 63	PA	KIAA1549	7	19	5	NO	VAS	D
13	F	23	OPW	55 x 75	PA	KIAA1549	13	8,5	17	NO	VAS	D
14	M	6	OPW	50 x 65	PA	KIAA1549	5	12	N/A	YES	VAS	D
15	F	9	Hemispheric	77 x 111	PA	V600E	13	18	12	YES	VAS	D
16	M	3	OPW	N/A	PA	Negative	5	8	17	YES	NO	D
17	F	2	OPW	N/A	PA	V600E	7	N/A	4	YES	NO	D
18	M	144	Thalamic	64 x 73	PA	Negative	17	1.05	23.5	YES	VAS	D
19	F	21	OPW	101 x 76	PA	V600E	1	3.25	N/A	NO	VAS	D

Abbreviations:OPWG:Optic Pathway Glioma, M:Male, F:Female, VPS:Ventriculo-Peritoneal Shunt, PA:Pilocytic Astrocytoma, GG:Ganglioglioma, PMA:Piloxyoid Astrocytoma, LGG:Low Grade Glioma, NOS:Not Otherwise Specified, VAS:Ventriculo-Atrial Shunt, VGBS:Ventriculo-Gallbladder Shunt, CSF:Cerebro Spinal Fluid, A: Alive, D:Dead, N/A: Not Available

Protein level in ascites fluid was available for twelve patients ranging from 4 to 28 g/L with a median of 12 g/L. Level of protein in paired CSF samples was also elevated with a median value of 7 g/L (range:0.17-42.5). Patients who required a shunt diversion displayed higher level of protein in the ascites fluid than those who were managed only with paracentesis, with median values of 18 and 7 g/L respectively. Tumor cells were not identified by cytology in CSF or ascites fluid in any of the patients.

Before the event "ascites" was registered, 18/19 patients had received different tumor treatment strategies including surgery, chemotherapy and/or radiation. We here present the surgical and medical management provided in relation to the time of ascites (Table 3).

Table 3 Tumor Treatment Related to Onset of Ascites and Survival Outcomes

#	Tumor treatment prior to Ascites				Tumor treatment post Ascites				Survival Outcomes	
	Surgery	Chemotherapy	Radiation	Targeted Therapy	Surgery	Chemotherapy	Radiation	Targeted Therapy	OS (m)	Status
1	Bx/STR	VCR-CARBO/VBL/TPCV	NO	Dabrafenib	NO	NO	NO	Dabrafenib	66	A
2	NO	NO	NO	NO	Bx	VCR-CARBO	NO	NO	52	A
3	Bx/STR	VBL/TPCV/VCR-CARBO/VNR	NO	NO	NO	NO	NO	Trametinib	133	A
4	Bx	VBL	NO	NO	NO	NO	NO	Dabrafenib	54	A
5	Bx/STR	NO	YES	NO	STR	NO	NO	Dabrafenib	115	A
6	Bx/STR	VCR-CARBO	NO	NO	NO	BVZ + metronomic [#]	NO	Trametinib	72	A
7	Bx/STR	IRI-CDDP	NO	NO	NO	VCR-CARBO/VBL/IRI-BVZ/metronomic [#] -BVZ/VBL-BVZ	NO	Trametinib	144	A
8	Bx	IRI-CDDP	NO	NO	NO	VBL	NO	NO	115	A
9	Bx/STR	VBL / BVZ	NO	NO	NO	NO	NO	NO	60	A
10	Bx	VCR-CF-CDDP-ETOP/VCR-CARBO	NO	NO	NO	VCR-CARBO	NO	NO	16	A
11	Bx	VCR-CARBO	NO	NO	NO	VBL/VBL-BVZ	YES	Trametinib	69	A
12	Bx	VCR-CARBO	NO	NO	STR	VBL/TPCV	NO	NO	24	D
13	Bx/STR	VCR-CARBO/VBL/TPCV/VCR-CARBO	NO	NO	NO	BVZ/VBL-BVZ	YES	NO	70	D
14	2 x STR	NO	NO	NO	NO	VCR-CARBO	NO	NO	106	D
15	NO	VCR-CARBO/VBL	NO	NO	Bx	IRI-BVZ	NO	NO	69	D
16	Bx	VCR-CARBO/TMZ	NO	NO	NO	NO	NO	NO	16	D
17	Bx	VCR-CARBO/VCR-Cyclo-ETOP	NO	NO	NO	TMZ	YES	NO	72	D
18	Bx x 2/STR	IRINO-CDDP/IRINO-TMZ/VBL-BVZ-Imatinib	YES	NO	NO	NO	NO	NO	24	D
19	Bx	VBL	NO	NO	NO	NO	NO	Dabrafenib	3	D

Abbreviations: VCR-CARBO:Vincristine-Carboplatin, VBL:Vinblastine, VNR:Vinorelbine, TPCV: Thioguanine, Procarbazine, Carmustine, Vincristine, BVZ:Bevacizumab, IRI:Irinotecan, CDDP:Cisplatin, Cyclo:Cyclophosphamide, ETOP:Etoposide, TMZ:Temozolomide. Bx: Biopsy, STR:Sub Total Resection, OS:Overall Survival, D:Dead. A: Alive.

[#]Oral metronomic chemotherapy containing Fenofibrate, Celecoxib,Thalidomide, Cyclophosphamide, Etoposide. "/" Indicates treatments or procedures are sequential in time.

Tumor Management and Outcomes (Fig. 1)

Surgery

A diagnostic biopsy of the tumor was performed in eighteen patients and only one underwent a subtotal resection (STR) upfront. All but two biopsies were performed prior to the development of ascites. Following tumor progression and before the onset of ascites, surgical approach was attempted in nine patients; two of them were further receipts of two consecutive partial resections. STR or tumor debulking due to tumor regrowth was performed only in two patients following ascites.

Chemotherapy

Eighteen children received chemotherapy as part of the treatment at some point during the course of the disease with a median of three different lines per patient (range:0-6). Vincristine and carboplatin was the preferred chemotherapy regimen, received by thirteen patients, being the first-line option in eleven. Only patient #5 did not receive chemotherapy and was managed with radiation prior to the onset of ascites, consecutive surgical resections and dabrafenib (Fig. 2).

Sixteen patients received a median of two (range:1-4) lines of treatment prior to ascites being detected. The complication was diagnosed at a median of 7 months from initiation of chemotherapy and five of the patients presented ascites within the first three months of therapy.

After the onset of ascites, different chemotherapy strategies were adopted by the treating physician in ten cases and only one patient continued on the same drug regimen. Eight patients were not treated with further chemotherapy after the complication, five of whom were treated with targeted therapy trametinib or dabrafenib.

Targeted Therapy

A total of eight patients received targeted therapy at some point as part of the treatment. Out of the four patients treated with BRAF inhibitor dabrafenib, only patient #1 developed ascites while on dabrafenib, following two previous lines of chemotherapy; the ascites was successfully managed conservatively and he remained in targeted therapy at the time of the analysis. Patients #4, #5 and #19 were started on dabrafenib at 1, 52 and 1 months respectively following the diagnosis of ascites; patient #4 was two months old at diagnosis of a V600E mutant OPG with a severe diencephalic syndrome [17]; she developed ascites one month after diagnosis and was switched from vinblastine to dabrafenib in a critical condition with a spectacular clinical and radiological response; no VPS diversion was required and she had remained on dabrafenib for sixty months at the time of the analysis. Patient #5 described above in whom dabrafenib was discontinued due to intra tumoral hemorrhage and tumor growth and patient #19, a twenty-one months old infant who presented with severe neurological deterioration and diencephalic syndrome, initially treated with vinblastine and switched to dabrafenib, who died of sepsis in the context of disease progression one month later.

Patients #3, #6, #7 and #11 received MEK inhibitor trametinib at 16, 22, 48, and 56 months from diagnosis of ascites respectively. Patients #3 and #6 remained stable on trametinib at the time of the analysis at 36 and 48 months respectively while patients #7 and #11 presented further tumor progression and received chemotherapy and focal proton therapy respectively. All four patients were alive at the time of the analysis.

Outcomes

There were eleven survivors with a median follow-up of sixty-nine months (range:16-144 months); five of them carried the V600E mutation in the BRAF pathway and in four KIIA 1549 fusion was detected. Three survivors did not require a shunt conversion, two of them managed with paracentesis and targeted therapy and one with targeted therapy only. Only two survivors were receipts of radiation as part of the treatment.

Eight patients died with a median time from tumor diagnosis and from development of ascites to death of 46.5 months (range:3-106) and 22.5 months (range:0-69) respectively. Five of them had a glioma harboring V600E mutation, six required diversion to a ventriculo-atrial shunt to manage ascites and four were receipts of radiation. Only patient #19 who showed a very poor clinical status at diagnosis received targeted therapy dabrafenib for one month with rapid deterioration and succumbed to disease 3 months from initial diagnosis. Ascites was associated with tumor progression in all but one case (#9), who did not require further oncology treatment after the shunt diversion. Patients #16 and #18 died at five and two months respectively after the onset of ascites and did not receive oncology treatment afterwards due to poor clinical condition. All deaths were due to disease progression except patient 13# who died with stable disease due to severe endocrine comorbidities. Median Overall Survival for the entire cohort was 69 months (Range:3-144). Median age at diagnosis for both groups of survivors and deceased patients was 15 months.

Discussion

Optic Pathway Gliomas are commonly complicated by hydrocephalus, which may require CSF diversion. Because of the large size and location of these tumors, third ventriculostomy is usually not feasible and insertion of a ventricular-peritoneal shunt is the common management option for optic/hypothalamic LGG-associated hydrocephalus.

CSF ascites is a rare complication of ventriculo-peritoneal shunts and has been anecdotally reported in children with optic gliomas. [6–11, 16–19]. Although the existing literature describes the event to affect to a young population, patients in our series were diagnosed with a LGG at a younger median age than the previously reported cases (14 vs 21 months); with most of our patients being infants younger than twenty four months of age at diagnosis. Young age itself represents a known contributing factor of adverse prognosis for pediatric gliomas [21]; based on our observations, infant gliomas could be considered as a risk factor to develop ascites. Z.Gil et al [7] reported on 22 children diagnosed with chiasmatic-hypothalamic LGG, 12 underwent shunt placement and 4 developed VPS-associated ascites, all of them were affected by a tumor located in the chiasm or the visual pathway. By contrast, they did not find any cases of ascites as a result of VPS placement among the five children suffering from hypothalamic glioma. In our case series of 19 patients, 16 had a OPG, while 2 had a thalamic lesion and one an hemispheric LGG.

Existing literature suggests ascites as an early event and our cohort confirms these findings with a median time of five months between VPS insertion and onset of ascites. Seven patients developed ascites one year or later after VPS insertion, demonstrating that ascites may also present as a late complication in the course of this disease.

The etiology of ascites in this context is multifactorial and complex and several possible mechanisms have been proposed [6–9]. It is thought to be the result of an imbalance between CSF production and absorption in presence of a patent VP shunt. West et al [10] described three children with OPG who developed ascites following VPS; they suggested that because the tumor is widely exposed to the cerebral spinal fluid, protein exuded by the tumor into the subarachnoid space would cause an elevated CSF protein concentration. We observed high protein level in both CSF and ascites fluid when performed. In our retrospective series, no differential analysis of protein was performed in the CSF and/or ascites hence we could not evaluate the respective characteristics of each fluid. However, this suggests that the high protein level in the CSF is a common factor among patients presenting this complication.

The management of ascites was successful in all cases, but the specific role of chemotherapy, radiotherapy or targeted therapy in the outcome is biased by the surgical interventions performed, since eighteen patients underwent shunt diversion and/or paracentesis and only one patient was exclusively managed medically; this patient had an excellent tumor control with dabrafenib only.

We chronologically analyzed the treatment approaches in our cohort in order to explore a potential correlation between clinical and radiological tumor course and the development of ascites. Eighteen patients received at least one modality of treatment prior to the complication including two patients who were irradiated. Overall our cohort was heavily treated prior and after ascites, demonstrating an aggressive course of the disease with high mortality rate.

The fact that ascites was detected at a median of three months following initiation of treatment and in six patients earlier than two months, could also suggest ascites as a result of tumor burden. This hypothesis would also be supported by the large tumor volume in the MRI scan performed at the time of the complication, in keeping with existing data of tumor measurement in surgically unresectable pLGG in functionally crucial locations [20, 21].

The onset of ascites was subsequently followed by a change in treatment in the majority of our patients at median of three months, supporting the hypothesis that ascites occurs as a consequence of tumor regrowth, thus reflecting the need for change or initiation of therapy. However, our data are limited to statistically confirm these premises and a larger cohort would be needed to better establish the role of ascites as a negative prognostic risk factor in pLGG.

KIAA1549-BRAF is known to be the most frequent molecular alteration in non-NF1 pLGG (60%), followed by BRAF V600E mutation (25%) [2–4]; Our cohort does not reproduce this proportion, with 8/19 tumors harboring BRAF V600E mutation; amongst twenty-one cases of ascites in patients with low grade glioma reported in the literature, only two had documented analysis of the RAS/MAPK pathway, both harboring BRAF V600E mutation. Of note, six BRAF mutated LGG in our series are Pilocytic Astrocytomas in contrast with known data that BRAF fusion is significantly enriched in this histology. Interestingly there were no patients with NF1 in our cohort neither in the existing literature. This support the known fact that gliomas related to NF1 are less likely to behave aggressively and ascites might also represent a complication exclusively related to sporadic hypothalamic gliomas.

Our data support that ascites is an unfavorable event in the course of a LGG, irrespective of alterations in the RAS/MEK pathway. The high mortality rate of 8/19 in our cohort may reflect the seriousness of the ascites as a complication in the course of pLGG and therefore ascites should be considered as an additional adverse prognostic risk factor to the previously identified diencephalic syndrome and disseminated disease [22–24]. Of note, none of our patients had disseminated disease, and diencephalic syndrome was specifically reported only in two patients. This mortality rate is higher than other case series on ascites complicating VPS in LGG, with only 2/21 deaths. However, the follow-up in these reports was shorter with a median follow-up time of only 27 months while we here report a longer follow-up with a median overall follow-up time of 69 months.

Eight patients in our cohort received targeted therapy as part of their treatment strategy (4 dabrafenib/4 trametinib), following different lines of chemotherapy and/or radiation. One patient with poor performance status was treated with dabrafenib and succumbed due to disease progression soon after diagnosis. All other patients treated with targeted therapy alone or as part of the treatment survived. This may suggest a role for targeted therapies in the management of this serious complication.

Limitations to our study are represented by its retrospective nature, the lack of uniform criteria for the management of both tumor and complications among different participating institutions and the long time period of collection, which has a reflection in the treatment modality delivered, with targeted therapies being only available in recent years and not uniformly across institutions. Moreover, only limited molecular analysis could be performed in the tumor samples with lack of data regarding further molecular alterations that could worsen the prognosis of these tumors such as CDKN2A deletion [25].

In summary, we here report a case series of nineteen molecularly-characterized pLGG enriched in BRAF mutation that presented with ascites as an unusual but serious complication with a high mortality rate. Consequently, we suggest to consider ascites as an additional adverse prognostic risk factor in pLGG. The potential role of targeted therapy in the course of this complication as well as the understanding of the pathogenesis of ascites requires further prospective studies, including molecular characterization of tumor tissue and ascites fluid.

Declarations

Competing Interests:

Authors disclose non-financial funding directly or indirectly related to the work submitted for publication.

Ethics approval

This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of the participant Institutions approved this study.

Statement of Availability of data and materials:

All data analysed and generated during this study are included in this published article.

Code availability:

Not applicable.

Importance of the study:

Our cooperative multi institutional work describes to our best knowledge the largest case series of a extremely rare complication in the course of pediatric Low Grade Glioma (pLGG): Ascites related to Ventriculo-Peritoneal Shunt; and provides with a molecular characterization of this subset of gliomas which are enriched in BRAF V600E mutation. We suggest this serious event as an additional adverse prognostic factor in pLGG.

Author contributions:

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by [Palma Solano-Páez]. The first draft of the manuscript was written by [Palma Solano-Páez] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. This manuscript is not under consideration at any other publication.

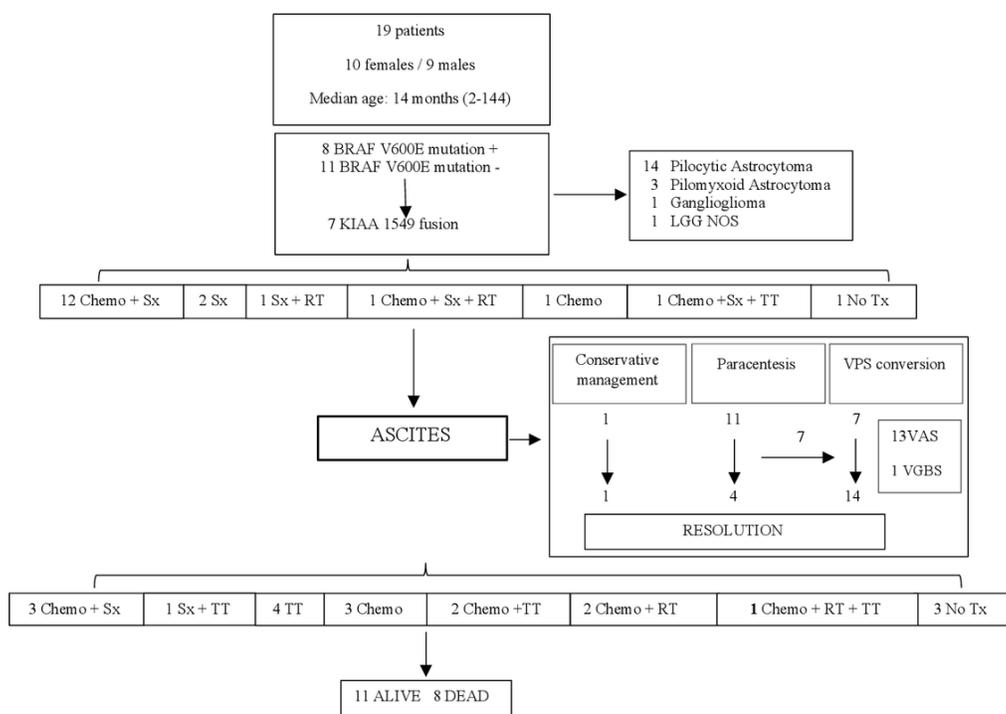
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Figures

Fig. 1



Abbreviations: VPS:Ventriculo-Peritoneal Shunt, VAS:Ventriculo-Atrial Shunt, VGBS:Ventriculo-Gallblader Shunt, LGG: Low Grade Glioma, NOS: Not Otherwise Specified, Chemo: Chemotherapy, Sx: Surgery, RT: Radiotherapy, TT: Targeted therapy, Tx: Treatment.

Figure 1

Pediatric Low Grade Glioma Complicated with Ventriculo-Peritoneal Shunt Related Ascites: Consort Figure.

Fig.2

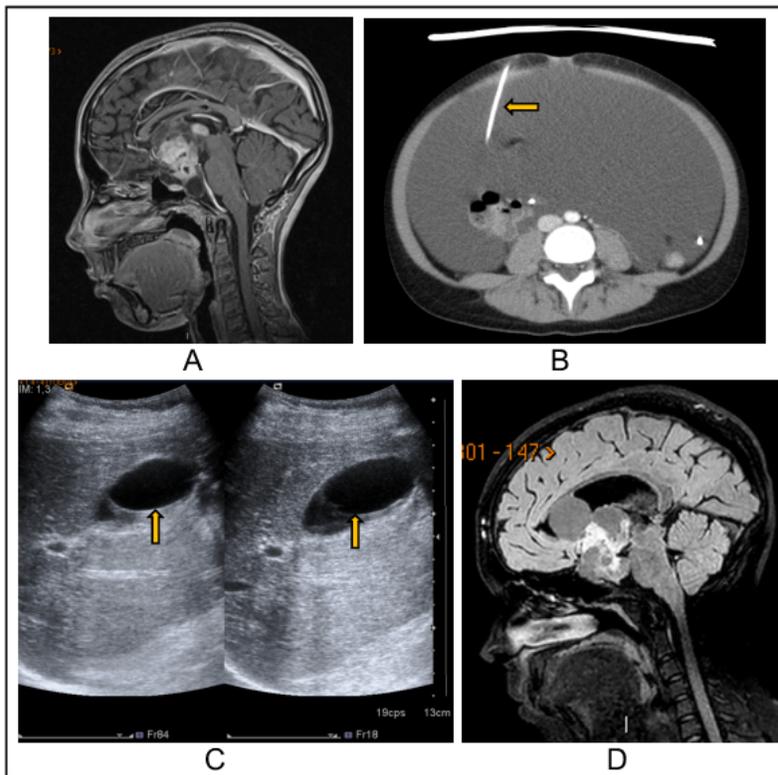


Figure 2

Clinical course of patient #5: BRAF-V600E mutant LGG and ascites treated with Ventriculo Gallbladder Shunt diversion. Eight years old girl who presented with central precocious puberty and was diagnosed with an Optic Pathway Pilocytic Astrocytoma harboring BRAF-V600E mutation (no CDK2NA deletion). The tumor remained stable off-therapy for sixteen months. No visual deficit. A: MRI Brain Sagittal post contrast sequence revealed tumor progression and obstructive hydrocephalus. A VPS was inserted and focal radiation was delivered. B: Abdominal CT scan demonstrated massive ascites with patent distal intraperitoneal catheter (arrow). C: Ascites was successfully managed with paracentesis and VPS conversion to a ventriculo-gallbladder shunt, seen in abdominal ultrasound (arrow). Further tumor progression occurred one year post radiation and a surgical subtotal resection was performed. D: MRI Brain Sagittal FLAIR sequence: Tumor regrowth four years post radiation. Targeted therapy with BRAF inhibitor dabrafenib was started. Dabrafenib was eventually discontinued due to an acute intra-tumoral hemorrhage and tumor regrowth 14 months after its initiation. The OPG has remained stable with no further oncology therapy. The patient is legally blind with central panhypopituitarism eleven years from initial diagnosis