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Cerebral Oligodendroglial Tumor Coexisting With Adrenal Ganglioneuroma; A Case Report

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Abstract

Purpose: Multiple primary neoplasms are defined as two or more synchronously or metachronously occurring tumors of separate origins in the same individual. Either cerebral oligodendroglioma or adrenal ganglioneuroma have been diagnosed as constituents of multiple primary neoplasms in several patients. However, there is no report of concurrent occurrence of these two tumors in a single patient.

Case presentation: A 5-year girl underwent surgery for a supratentorial brain tumor, diagnosed as oligodendroglioma. Emerging from anesthesia and during the postoperative period, she developed systolic hypertension. Systemic workup was performed and an abdominal heterogeneous calcified mass was detected in the left paraaortic site which was later found to be an adrenal ganglioneuroma. In this case-study different aspects of such a concurrence were discussed.

Discussion: Based on the literature review, oligodendroglioma has been reported to simultaneously occur with juvenile pilocytic astrocytoma, gemistocytic astrocytoma, vestibular schwannoma, dysembryoplastic neuroepithelial tumor, and some extraneural tumors like breast cancer and thymoma. Ganglioneuromas have been concurrently found with schwannomas, thyroid carcinoma, gastric carcinoma, Wilms tumor and other neuroendocrine–neuroblastic tumors like pheochromocytoma. The patients were mostly stable after the appropriate treatment.

Conclusions: In case of multiple primary neoplasms, each tumor should be managed in the standard fashion, and the concurrent occurrence would not worsen the prognosis of neither coexisting neoplasm. Though it is possible that a potential germline mutation would have caused both tumors, no evidence could be found in favor of this theory. The condition is more likely to be a coincidence.

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Introduction

Multiple primary neoplasms are defined as two or more concurrently occurring tumors of separate origins in the same individual [1-2]. These conditions are further categorized into two groups, namely; synchronous neoplasms which are diagnosed simultaneously or within two months apart, and metachronous lesions which have at least a two-month interval between their appearance [2].

Ganglioneuromas are one of the main categories of neoplasms, originating from the neural crest cells [3-4]. Adrenal ganglioneuromas are uncommon tumors and tend to be found incidentally [4]. These tumors would be associated with extra-adrenal neuroblastic tumors, or rarely occur synchronously with other neoplasms [5]. Oligodendrogliomas are relatively infrequent tumors which are rarely associated with synchronous or metachronous tumors [6].

According to the authors' literature review, no report of concurrent occurrence of these two tumors in a single patient has been ever recorded. The current case-study presents an oligodendroglioma occurring synchronously with a ganglioneuroma tumor of the adrenal.

Case description

A 5-year girl was admitted to the emergency department with a history of headache and vomiting for two weeks. The patient was the firstborn of healthy non-consanguineous parents, with normal development and uneventful past medical history. The family history was negative for any hereditary cancer syndrome. On admission, she had left hemiparesis and bilateral papilledema with no other neurological deficit. Brain Magnetic Resonance Imaging (MRI) revealed a massive heterogenous multi-cystic enhancing lesion in the right temporoparietal area with extensive vasogenic edema and mass effect upon the midbrain **(Figure 1-A)**.

She underwent craniotomy and tumor gross total resection. The frozen section micromorphological examination of the tumor upon the intraoperative request was compatible with a glial tumor **(Figure 2-A)**.

Emerging from anesthesia and during postoperative care, the patient developed systolic hypertension which was managed with intravenous labetalol. While systemic workup for renal function and cardiologic assessments were unremarkable, abdominal ultrasound detected a heterogeneous calcified mass in the left paraaortic site. Abdominal Computed Tomography (CT) scan revealed a calcified mass arising from the left adrenal **(Figure 1-B)**. Blood and urine catecholamine tests, Vanillylmandelic Acid (VMA), were in the normal range. The patient was scheduled for laparotomy and tumor resection two weeks after craniotomy.

Although it was initially assumed that the brain lesion would be secondary to the adrenal mass, the histopathological examination of the surgical specimens showed other results. The Hematoxylin and eosin-stained sections of the brain mass revealed a neoplastic proliferation of glioneuronal cells with oligodendroglial features including perinuclear halos, chicken-wire vasculature, and microscopic calcifications **(Figure 2-B)**. Parenchymal infiltration and perivascular aggregation of tumor cells were noted. Evidence of hypercellularity and microvascular proliferation **(Figure 2-c)** was present, but no significant mitosis or necrosis was appreciated. Immunohistochemistry (IHC) study showed negative immunoreactivity for IDH1/2, P53, and GFAP, while OLIG2 immunomarkers was positive. The Ki67 was positive in 1-2% of tumor cells. Molecular studies using Fluorescence in Situ Hybridization (FISH) demonstrated 1p/1q ratio of 0.98 and 19q/19p ratio of 0.97, translating as no 1p/19q codeletion. Morphologic histopathological assessments of the adrenal mass showed a neoplastic proliferation of admixed ganglion cells and Schwann cells. The ganglion cells were mature with compact, eosinophilic cytoplasm with distinct cell borders, single eccentric nucleus, and prominent nucleolus, which was compatible with ganglioneuroma **(Figure 2-D)**.

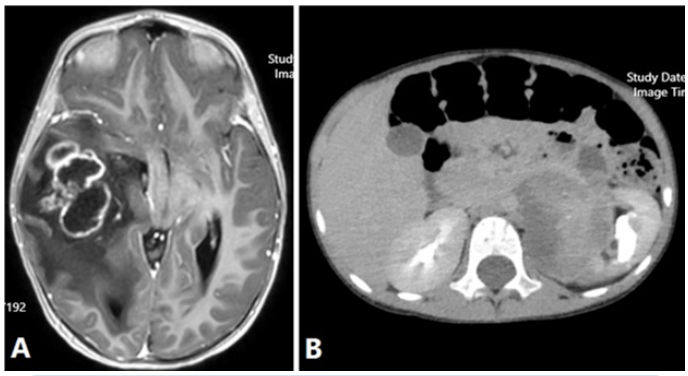

Figure 1: **(A)** MRI showed a multicystic mass of the right parietotemporal lobe measuring 60*41*38mm with peripheral wall enhancement and peripheral angiogenic edema. **(B)** Abdominal computed tomography (CT) scan detected a calcified mass arising from the left adrenal.

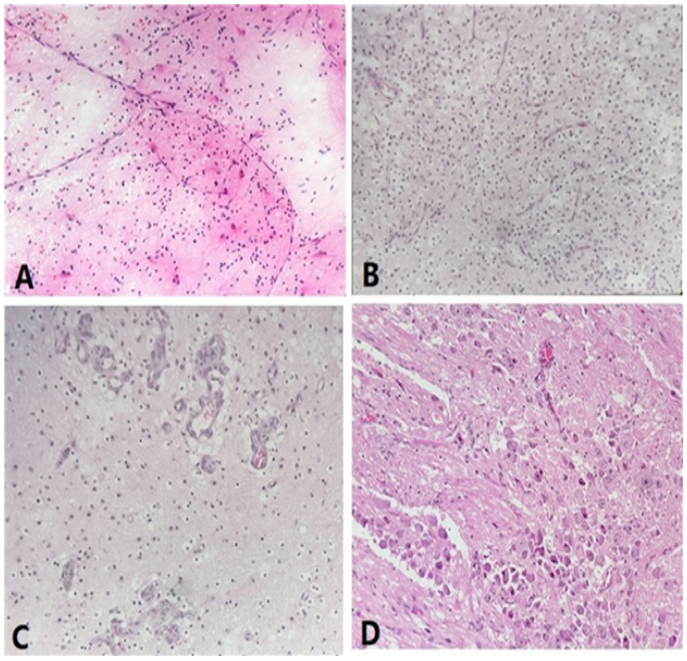

Figure 2: **(A)** Touch smear preparation of the biopsied material from temporoparietal mass upon intraoperative consultation shows fibrillary background and branching fine vasculature, (Hematoxylin and eosin x400). **(B)** Microscopic view of the temporoparietal mass with a neoplastic proliferation of glioneuronal cells, mostly with oligodendroglial features including perinuclear halos and chicken-wire vasculature, (Hematoxylin and eosin x200). **(C)** Microscopic view of the microvascular proliferation (Hematoxylin and eosin x200). (D) Morphologic histopathological assessments of the adrenal mass showed a neoplastic proliferation of admixed ganglion cells and Schwann cells. (Hematoxylin and eosin x200).

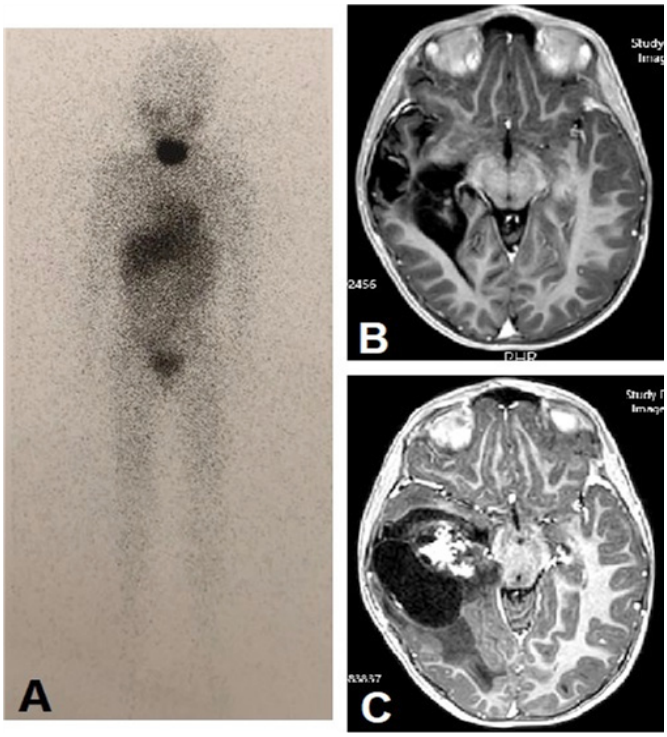

Figure 3: **(A)** Postoperative nuclear scan using iodine-131 meta-iodobenzylguanidine (MIBG scan) demonstrated normal radiotracer uptake throughout the body. **(B)** Postoperative brain MRI showed no tumor remnant. **(C)** Brain tumor recurrence was detected on follow-up MRI one year after surgery.

The patient was discharged home after recovery and was referred to the oncology department for further management. Nuclear scan using iodine-131 Meta-Iodobenzylguanidine (MIBG scan) detected no abnormal radiotracer uptake throughout the body **(Figure 3-A)**. Postoperative brain MRI showed no tumor remnant **(Figure 3-B)**. Considering the low-grade features, the patient received no adjuvant therapy for brain tumor, and underwent close follow-up. Moreover, because of the normal distribution of MIBG through the body in postsurgical examination, chemotherapy was not administered for adrenal ganglioneuroma. The patient underwent surveillance for both tumors, and after 6 months, no clinical or radiologic relapse was detected. Nonetheless, brain tumor recurrence was detected on follow-up MRI one year after surgery **(Figure 3-C)**. Tumor resection was performed, and the result of histopathology testing was the same as the previous oligodendroglial tumor with no anaplastic feature. This time the patient underwent adjuvant Radiation Therapy (RT) and chemotherapy. The treatment is still ongoing, and the patient's condition is stable.

Discussion

Oligodendroglioma is a primary intracranial neoplasm originating from the oligodendrocytes of the cerebral hemispheres, thalamus, or lateral ventricles [6-8]. Accounting for 5% of all neuroepithelial tumors [9,10], oligodendrogliomas are relatively slow-growing, diffusely infiltrating gliomas graded based on their phenotype and genotype [6,7]. A large retrospective analysis conducted by Goel and colleagues found that pediatric oligodendroglioma differs from adult oligodendroglioma in terms of demographic factors, as well as tumor size, location, and grade [8]. Ganglioneuroma is also a relatively scarce subtype of neuroblastic tumors, constituting only 6.4% of this group of neoplasms [5,11]. Regarding the rare incidence of each of these tumors, it is quite unlikely for a patient to present with co-occurrence of oligodendrogliomas and ganglioneuromas.

Either oligodendrogliomas or ganglioneuromas were diagnosed as constituents of multiple primary neoplasms in several patients. Oligodendrogliomas have been found with Juvenile Pilocytic Astrocytoma (JPA), gemistocytic astrocytoma, vestibular schwannoma, Dysembryoplastic Neuroepithelial Tumor (DNET), and some extra-neural tumors like breast cancer and thymoma **(Table 1)** [12-18]. Moreover, a single case of synchronous supratentorial and infratentorial oligodendrogliomas in a young man has been reported [6]. Ganglioneuromas have been concurrently reported with schwannomas, thyroid carcinoma, gastric carcinoma, Wilms tumor, and other neuroendocrine–neuroblastic tumors like pheochromocytoma **(Table 2)** [19-29]. Even so, adrenal ganglioneuroma was not reported to occur with neither oligodendroglioma nor other types of ganglioneural tumors.

Table 1: Characteristics of case reports of multiple primary neoplasms including an oligodendroglioma

Postoperative outcomes	Age/ Sex Location	Tumors	Clinical presentation	Intervention(s)	Long-term outcomes
Extraneural					
[12]	53/ F, Iran	An anaplasticoligodendroglioma, A B2 thymoma	Nausea, Chest pain, Headache, HTN	Craniotomy and total GTR + adjuvant XRT + adjuvant chemotherapy, CT-guided biopsy of a mediastinal mass, Median sternotomy three mo. after craniotomy	Last F/U: no new symptoms
[13]	45/ F, India	An anaplastic oligodendroglioma, A moderately differentiated SCC of tongue	Headache, Generalized tonic-clonic seizure, Pain in the Lt. side of the tongue, Referred pain in the lt. ear	Rt frontal craniotomy and GTR of brain lesion + adjuvant RT (59.4Gy), Palliative XRT to tongue and neck lymph nodes	Last F/U: no neurological deficit, Partial response in the tongue lesion
[14]	61/ F, Taiwan	An anaplastic oligodendroglioma, An invasive ductal carcinoma (T2N2M0, A ductal carcinoma in situ	Progressive recent and remote memory impairment, Cognitive dysfunction, Mild weakness (4+/5) of the Rt. upper and lower limbs, KPS = 60%	Craniotomy and GTR of the largest brain lesion + adjuvant XRT + TMZ, Rt-side modified radical mastectomy and Lt-side total mastectomy + adjuvant XRT + chemotherapy	Progression-free, KPS = 70%
Intraneural					
[15]	43/ F, Italy	A low-grade oligodendroglioma, A vestibular schwannoma	Progressive Lt.-sided hearing loss, Tinnitus, Disequilibrium, Partial motor seizures No signs of phacomatosis	Surgical near-total resection via retrosigmoid approach, Surgical resection by transsylvian approach + adjuvant XRT + TMZ	Last F/U: No seizures (on levetiracetam), KPS=100, no regrowth on MRI

[16]	49 / M, USA	An oligodendroglioma, A gemistocytic astrocytoma	N/A	N/A	N/A
[17]	43/ M, USA	An oligodendroglioma, A juvenile pilocytic astrocytoma	Headaches, Nausea, Vomiting, Decline in visual acuity, Disequilibrium	Rt frontotemporal craniotomy, Suboccipital craniectomy and C-1 laminectomy + TMZ	Neurologically/ radiographically stable
[18]	29 / M, USA	An oligodendroglioma, A DNET	A new-onset generalized seizure	Rt frontal craniotomy and GTR of both tumors	Recurrence at the site of oligodendroglioma after 4y
[6]	23/ M, USA	A supratentorial grade2 oligodendroglioma, An anaplastic pontine oligodendroglioma	Intermittent diplopia, tinnitus and persistent headache	Partial resection of Rt. precentral tumor, Biopsy of pontine tumor, adjuvant XRT + TMZ+ PCV	Stable precentral tumor, Progression of pontine tumor followed by partial response

GTR: Gross Total Resection; XRT: Radiotherapy; F/U: Follow-Up; HTN: Hypertension; TMZ: Temozolomide. PCV: Procarbazine-Ccnu-Vincristine; D: Day(S); DNET: Dysembryoplastic Neuroepithelial Tumor; SCC: Squamous Cell Carcinoma; KPS: Karnofsky Performance Status; Nl: Normal; RT: Right; LT: Left; MO: Month(S); Y: Year(S).

Table 2: Characteristics of case reports of multiple primary neoplasms including a ganglioneuroma.

Investigator	Age/ Sex Location	Tumors	Clinical presentation	Intervention(s)	Long-term outcomes
Extraneural					
[19]	41 / F, Italy	A GNB, A PCC-GN, A PGL A PCC	Paroxysmal HTN, Headache, Sweating, Watery diarrhea	Surgical excision + chemotherapy + XRT + immunotherapy (GNB), Surgery (PCC-GN), Surgery (PGL), Surgery (PCC)	No metastasis or recurrence
[20]	4 / F, Turkey	A ganglioneuroma, A Wilms' tumor	Flank pain, Asymmetrical abdominal distention, A firm rt upper quadrant mass	Percutaneous renal biopsy + pre-op chemotherapy, Rt radical nephrectomy, Lt.sided mass resection, Radiotherapy + chemotherapy	Stable
[21]	3.5 / M, UK	A ganglioneuroma A Wilms' tumor	Generalized malaise, poor appetite, Swelling of the Lt. side of the abdomen	Bilateral biopsies + pre-op chemotherapy, Total Rt. nephrectomy Bilateral partial nephrectomy + adjuvant chemotherapy	Complete remission
[22]	35 / M, Canada	A ganglioneuroma, A Seminoma (pT1)	Rt testicular discomfort and swelling	Radical rt orchidectomy + chemotherapy, CT-guided FNA + open surgical biopsy	Relapse-free
[23]	4 / F, USA	A ganglioneuroma, Extradural ganglioneuroma, A Wilms' tumor	Abdominal distension, Weight loss, Palpitation, HTN, Decreased Lt-sided patellar reflexes	Open biopsy + Partial resection of the lumbar mass, Chemotherapy, CT-guided core biopsy, Complete Rt. nephrectomy	No evidence of disease recurrence or neurologic deficits, Stable extradural ganglioneuroma
[24]	73 / M, Canada	Multiple ganglioneuromas, Two gastric adenocarcinomas, A hand fibroma,	Upper and lower GI polyposis, Multiple hyperpigmented macules on lip, Multiple mucosal swellings on inner lip, Multiple skin tags, Painless Rt..side abdominal mass	GI biopsy + total gastrectomy, Omentectomy, Cholecystectomy, Thyroid FNA + total thyroidectomy	Multinodular goiter detected in F/U, No limitation in daily activities
[25]	52 / F, Japan	A ganglioneuroma, A PCC	Referred for surgical treatment of a mediastinal tumor	Thoracoscopic excision of mediastinal tumor, Laparoscopic excision of retroperitoneal tumor	N/A
Intraneural					
[26]	60 / M, Taiwan	A Rt. adrenal ganglioneuroma, A paratesticular ganglioneuroma, An optic nerve meningioma, A papillary thyroid carcinoma,	Progressive enlargement of rt hemiscrotum, HTN	Adrenalectomy and simple nephrectomy, Total thyroidectomy and radical neck dissection, Orchiectomy	Nl chest CT, Nl thyroid U/S, No visual impairment or proptosis
[27]	17 / F, Greece	A schwannoma A ganglioneuroma	A slow-growing neck mass on the Lt. side	Surgical excision	N/A
[28]	41 / F, China	A ganglioneuroma A schwannoma	A left cervical palpable hard painless mass	Surgical resection	No recurrence/metastasis during the 4y of F/U
[29]	54 / M, China	Ganglioneuromatosis Multiple schwannomas	Intermittent bloody stools and abdominal pain, Intestinal intussusception due to a polyp	Partial colectomy	No recurrence

HTN: Hypertension; Pre-op: Preoperative; FNA: Fine Needle Aspiration; GI: Gastrointestinal; F/U: Follow-up; PCC: Pheochromocytoma; GNB: Ganglioneuroblastoma; PCC-GN: Composite Pheochromocytoma-Ganglioneuroma; PGL: Paraganglioma; XRT: Radiotherapy; Nl: Normal; Rt: Right; Y: Year(s).

Clinical presentation

Patients with supratentorial glial/neuroglial tumors, including oligodendrogliomas, typically present with various symptoms based on the size and location of the tumor. These symptoms may include seizure, headache, impairments in cognition, focal weakness with or without sensory deficits, and problems with balance and movement [10].

On the other hand, adrenal ganglioneuromas are often discovered incidentally upon imaging exams. Since ganglioneuromas are often clinically silent and result in neither hormonal excess nor clinical manifestations, therefore patients are mostly asymptomatic.[5] Concurrent tumors generally show typical presentations. In concurrent cases, ganglioneuromas are presented as either painless or painful abdominal mass along with other neoplasia **(Table 2)**. Both synchronous [20,22,27,28,29] and metachronous [19,21,23,24-26] presentations of these tumors with other neoplasms were reported with classic symptoms of each tumor, with a time-span of five weeks to 18 years between the presentation of the symptoms of respective tumors.

Diagnosis and genetics

Clinically, intracranial mass lesions can be diagnosed via neuroimaging studies, including brain CT and MRI. Postoperative histopathological assessments can confirm the diagnosis and WHO grade. Of note, studies have shown that patients suffering from oligodendroglioma present with isocitrate dehydrogenase (IDH) 1/2 gene mutation and chromosome 1p/19q codeletion, as the two most commonly observed mutations [30]. Additionally, other molecular mechanisms and markers for oligodendroglioma are methylation of the O6-methylguanine-DNA-methyltransferase (MGMT) gene promoter, capicua (CIC) and Far-Upstream Binding Protein 1 (FUBP1) gene mutations, telomerase reverse transcriptase (TERT) mutations, and amplification of the Epidermal Growth Factor Receptor (EGFR) gene [31]. Nonetheless, genetic abnormalities observed in adult versus pediatric oligodendroglioma have been seen to be different. Indeed, the hallmarks observed in adult oligodendroglioma, mutations in IDH1 or IDH2 with 1p19q codeletion, are seldom seen in pediatric patients [5,32]. Moreover, BRAF- KIAA1549 fusion which is typically observed in younger patients with pilocytic astrocytoma, have also been noted in pediatric oligodendrogliomas [31,33]. Additionally, one particular pathway that has garnered interest in playing a key role in the formation of oligodendroglial tumors is the PI3K/AKT/mTOR pathway, which promotes malignant transformation [34].

Neuroblastomas, ganglioneuroblastomas, and ganglioneuromas are classified as tumors originating from neural crest cells, with ganglioneuromas being the most mature member of this family [35]. Most cases of ganglioneuromas occur in the retroperitoneal space or the posterior mediastinum, with fewer cases noted in the cervical region [5]. Patients with adrenal ganglioneuromas are often in their 40s and 50s. In contrast, ganglioneuromas are rare in pediatric patients and typically present in retroperitoneum and posterior mediastinum locations [5]. Various molecular markers have been observed in ganglioneuromas. For example, a study conducted by Wilzén et al. found the upregulation of the tyrosine kinase receptor ERBB3, a member of the EGFR family, as a marker for ganglioneuroblastoma/ganglioneuroma-like expression profile in neuroblastic tumors [36]. Furthermore, recent studies have shown ganglioneuromas to be driven by activated AKT pathway, and proposed therapeutically targeting the tumor cells with mTOR inhibitors [37,38]. Moreover, mutations in the PIK3CA or MAX genes have also been observed as other possible risk factors for developing ganglioneuromas [39,40].

Theoretically, it would be assumed that a single molecular pathway, such as the PI3K/AKT/mTOR pathway, may play a contributing role in developing both tumors. Nonetheless, this theory is hard to be proven, and it is most likely that these two tumors have been incidentally co-occurred.

Management

Surgical resection is the mainstay of care for pediatric patients with oligodendroglial tumors. However, standard care of adjuvant treatment for these tumors remains controversial. Although a clear distinction of grades II and III is not always possible, adjuvant therapies are mostly planned for cases with oligodendrogliomas grade III (anaplastic) and recurrent cases [9]. Postoperative radiotherapy is recommended plus chemotherapy with procarbazine, lomustine (CCNU), and vincristine (PCV) for patients harboring tumors with 1p19q co-deletions, and temozolomide (TMZ) for those lacking this co-deletion [9]. Generally, tumors with 1p19q co-deletions are more chemosensitive and the patients have better prognosis. The patient presented in this case-study had a grade II oligodendroglial tumor without 1p19q co-deletions. She did not receive adjuvant therapy after the first surgical resection, but underwent radiation therapy plus chemotherapy after the resection of recurrent tumor.

The usual treatment for adrenal ganglioneuroma has been minimally invasive adrenalectomy. Wide excision is not indicated because of infrequent recurrences or metastases among ganglioneuromas [4,41]. Adjuvant chemotherapy such as intraoperative cyclophosphamide would be considered alongside surgical resection in case of rare, metastatic tumors [42]. Accordingly, no adjuvant therapy was recommended for the adrenal ganglioneuroma in the current patient.

Prognosis and outcomes

Most cases identified as oligodendroglioma displayed a relatively favorable clinical course and outcome. Specifically, chromosome 1p/19q codeletion has shown a protective effect on prognosis of patients with grade II/III oligodendrogliomas [30].

Unlike neuroblastomas and ganglioneuroblastomas, ganglioneuromas seldom metastasize and hence are considered the most benign of the three.[35] They often have a benign clinical course, with surgical resection resulting in excellent prognosis [4,11,42].

As a component of multiple primary neoplasms, no adverse outcomes were reported in the cases of ganglioneuromas accompanied with other tumors. Adrenal ganglioneuroma were concurrently reported with Wilms tumors in 3 pediatric patients, and with other extra-neural tumors in 3 adult patients [19-25]. All of these patients were well-controlled after separate interventions for the resection of ganglioneuromas and the concurrently occurring lesions. Furthermore, our literature review found 4 adult patients with coexisting ganglioneuromas and intraneural tumors, including 3 cases of schwannomas and

1 case of optic nerve meningioma [26-29]. Treatment was curative in these patients, and no recurrence or metastasis was found in 3 cases with available follow-up **(Table 2)** [19-29].

Cases with multiple primary neoplasms including an oligodendroglioma consisted of three adult patients with anaplastic oligodendrogliomas coexisting with extra-neural tumors, all of them were successfully managed with surgery and adjuvant radiotherapy and chemotherapy [12,14].

Four other cases of oligodendrogliomas were reported in adult patients simultaneously with intracranial tumors, including a vestibular schwannoma, a gemistocytic astrocytoma, a juvenile pilocytic astrocytoma, and a DNET [15-18]. Moreover, a case of synchronous supratentorial grade-2 and infratentorial grade-3 oligodendrogliomas in a young man has been reported [6]. All reported cases received separate treatments for each of coexisting tumors, and from 7 patients with available follow-up, 6 cases had stable course after treatment. The patient with concurrent DNET and oligodendroglioma experienced recurrence at the site of oligodendroglioma 4 years after surgery. The current case also had a relatively early recurrence of oligodendroglioma, which was managed with surgical resection followed by RT and adjuvant chemotherapy.

Conclusions

While rare, a diagnosis of multiple primary neoplasms should be considered when confronting patients with several respective masses. In this instance, each tumor should be managed in the standard fashion. As inferred from the current case and our literature review, the concurrent occurrence would not worsen the prognosis of neither coexisting neoplasms. Though it is possible that a potential germline mutation would have caused both tumors in the current case, no evidence could be found in favor of this theory and the condition is more likely to be a coincidence.

Declarations

The authors report no conflict of interest and no funding or financial support.

The study was approved by the institutional ethical committee.

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