Clinical Case Report

Medicine®

OPEN

Ganglioglioma of the adenohypophysis mimicking pituitary adenoma

A case report and review of the literature

Yuan Hong, MD[a], Yuanjian Fang, MD[a], Qun Wu, MD[a], Jianmin Zhang, MD, PhD[a,b,c], Yongjie Wang, MD[a,*]

Abstract

Introduction: Ganglioglioma is a generally benign tumor, mostly occurring in patients <30 years old. Temporal lobe is most frequently involved. Up to now, only 3 cases were reported of ganglioglioma in the pituitary gland, all being confined to the neurohypophysis. Here, we are the first to report an adenohypophysis ganglioglioma.

Case presentation: A 43-year-old woman presented with chronic headache was referred to our hospital. Magnetic resonance imaging (MRI) indicated pituitary adenoma. Endoscopic transnasal transsphenoidal surgery was performed. The tumor was rich in blood supply, with tough texture, therefore only subtotal resection was conducted. Pathology analysis revealed an adenohypophysial tumor composed of dysplastic ganglion cells and neoplastic glial cells collided with nonspecific hyperplasia of pituitary cells. Immunohistochemistry revealed positive staining of synaptophysin, glial-fibrillary acidic protein, and CD34. The results were consistent with the diagnosis of ganglioglioma. After the surgery the patient recovered well except developing cerebrospinal fluid rhinorrhea, which was controlled by lumbar drainage. MRI 6 months later did not show any sign of progression.

Conclusion: According to the findings of our case, concerns should be raised considering ganglioglioma as a differential diagnosis of mass located in the sellar region. Furthermore, an ideal management strategy for pituitary ganglioglioma is not known; therefore, more cases and long-term follow-up are needed to enrich our knowledge of the diagnosis, treatment, and prognosis of this rare intracranial lesion.

Abbreviations: ACTH = triiodothyronine, thyroxine, adrenocorticotropin, ADH = anti-diuretic hormone, FSH = follicle-stimulating hormone, GFAP = glial-fibrillary acidic protein, GH = growth hormone, GTR = gross total resection, IHC = immunohistochemistry, LH = plasma cortisol, luteinizing hormone, MRI = magnetic resonance imaging, NFP = neurofilament protein, NSE = neuron-specific enolase, PRL = prolactin, STR = subtotal resection, TSH = thyroid-stimulating hormone.

Keywords: adenohypophysis, ganglioglioma, hyperplasia of pituitary cells, subtotal resection

1. Introduction

Gangliogliomas can occur at any age, but mostly involve patients <30, with equal distribution among pediatric and adult populations.[1,2] Men own the predominance in gangliogliomas.[3] Most gangliogliomas are confined to temporal lobe,[1,2,4] and are the most common neuroepithelial tumors leading to long-term epilepsy.[5] The patients tend to benefit higher seizure free rates from lesionectomy.[5] Ganglioglioma in other region such as brain stem, intraventricle, spinal cord, and sellar region was rare.[6–9] The only reported suprasellar ganglioglioma was located in neurohypophysis.[7] Up to now, there has been no adenohypophysial ganglioglioma reported. Here, we describe such a rare case mimicking pituitary adenoma and finally confirmed by pathological analysis.

2. Case presentation

A 43-year-old woman was referred to our hospital complaining of a 4-year history of headache. She denied nausea, vomiting, seizure, and blurred vision. Magnetic resonance imaging (MRI) at outside hospital revealed a lesion in the sellar region displaying hypointense signal on T1 weighted image, partial hyperintense signal on T2 weighted image, and capsule enhancement on contrast image (Fig. 1A–D). Pituitary adenoma was suspected. Her past medical history was unremarkable except being allergic to penicillin. Vital signs were stable. Neurological examination was intact. Labtest revealed an elevated level of prolactin (PRL) at 744.0 mIU/L (reference value: 40.3–530 mIU/L). Other hormones such as growth hormone (GH), thyroid-stimulating hormone (TSH), triiodothyronine, thyroxine, adrenocorticotropin (ACTH), plasma cortisol, luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, estrodiol, and progesterone were all within normal range. An endoscopic transnasal transsphenoidal surgery was performed. After opening the dura

Editor: N/A.

Source of Funding: None.

The work was partially supported by grants from the National Natural Science Foundationof China (81502139), Natural Science Foundation of Zhejiang province (Y17H090036), Zhejiang provincial science and Technology Program (2015C33192).

Informed consent: Informed consent was obtained from all individual participants included in the study.

The authors declare that they have no conflict of interest.

[a] Department of Neurosurgery, The Second Affiliated Hospital, School of Medicine, [b] Brain Research Institute, [c] Collaborative Innovation Center for Brain Science, Zhejiang University, Hangzhou, Zhejiang, P.R. China.

[*] Correspondence: Yongjie Wang, Department of Neurosurgery, The Second Affiliated Hospital, School of Medicine, Zhejiang University, NO.88 Jiefang Rd, 310009, Hangzhou, P.R. China (e-mail: 11018196@zju.edu.cn).

Medicine (2018) 97:30(e11583)

Received: 28 March 2018 / Accepted: 20 June 2018

http://dx.doi.org/10.1097/MD.0000000000011583

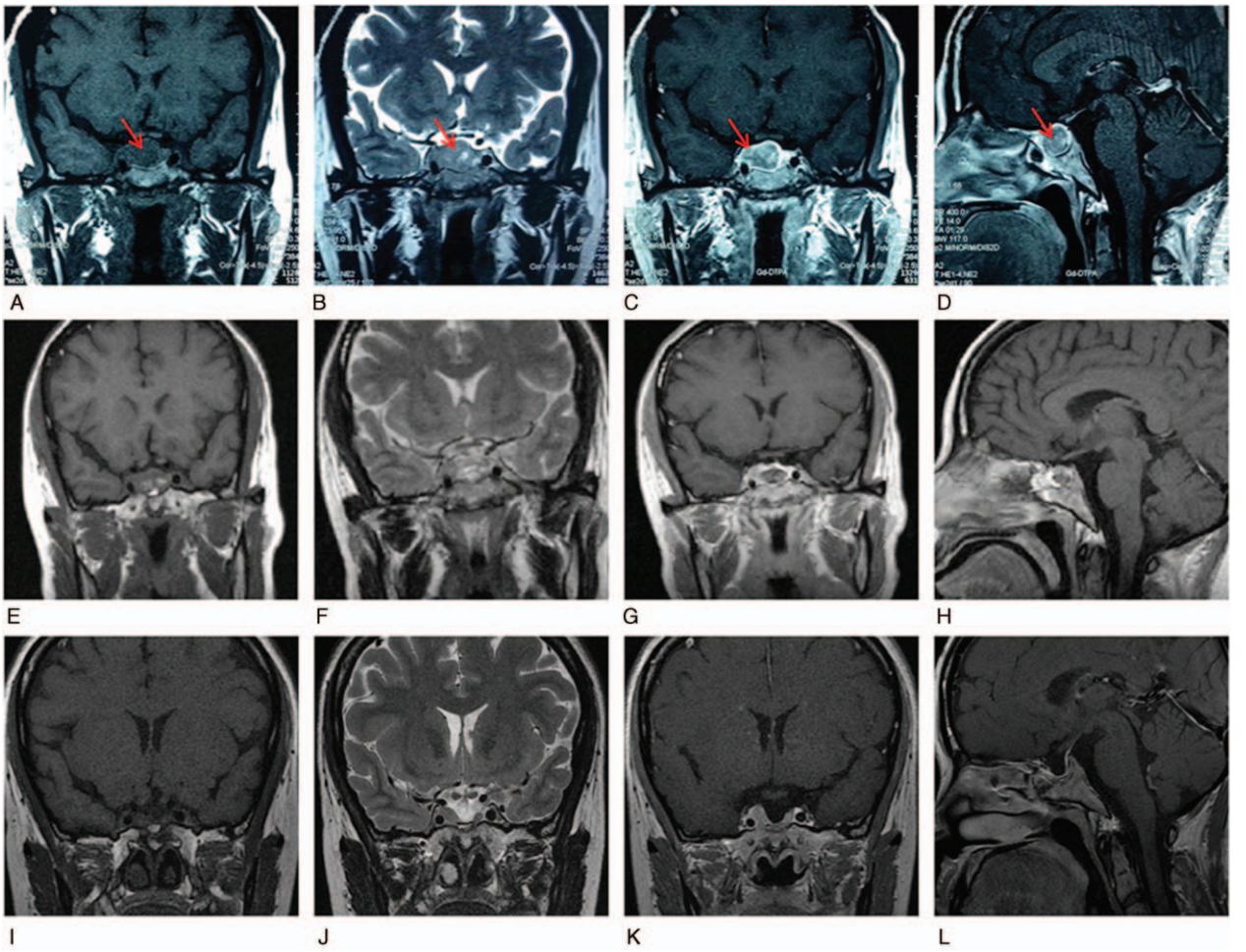

Figure 1. MRI scans of the patient with ganglioglioma. A–D, MRI scan before surgery. T1 weighted image (A) revealed a lesion (arrow head) in the sellar region with hypointense signal; T2 weighted image (B) displayed inhomogeneous hyperintense signal (arrow head); contrast image of coronal plane (C) and sagittal plane (D) showed capsule enhancement (arrow head). E–H, MRI scan within 48 hours after surgery revealed a residual hyperintense signal in sellaturcica without enhancement. I–L, Displayed an empty sella with compressed pituitary devoid of mass and abnormal enhancement. E and I for T1 weighted image; F and J for T2 weighted image; G and K for contrast image of coronal plane; H and L for contrast image of sagittal plane. MRI = magnetic resonance imaging.

of sellar turcica, a dark red mass with firm texture and rich blood supply was found, adhering closely to sellar diaphragm. Subtotal resection was conducted because of the highly vascularized nature of the tumor. Cerebrospinal fluid leakage occurred during surgery. Reconstruction of sellar turcica was performed with fat graft and gelatin spongy.

Two days after surgery, the hyperprolactinemia was resolved (192.0 mIU/L) and postoperative MRI revealed a residual hyperintense signal in sellar turcica without enhancement (Fig. 1E–G). Histological examination demonstrated an adenohypophysial tumor composed of dysplastic ganglion cells with vesicular hypochromatic nuclei and prominent nucleolus, neoplastic glial cells with small and irregular oval nuclei, and hyperplasic pituitary cells (Fig. 2A). Immunohistochemistry (IHC) showed positive staining of synaptophysinin ganglion cells, and positiveglial-fibrillary acidic protein (GFAP) in glial

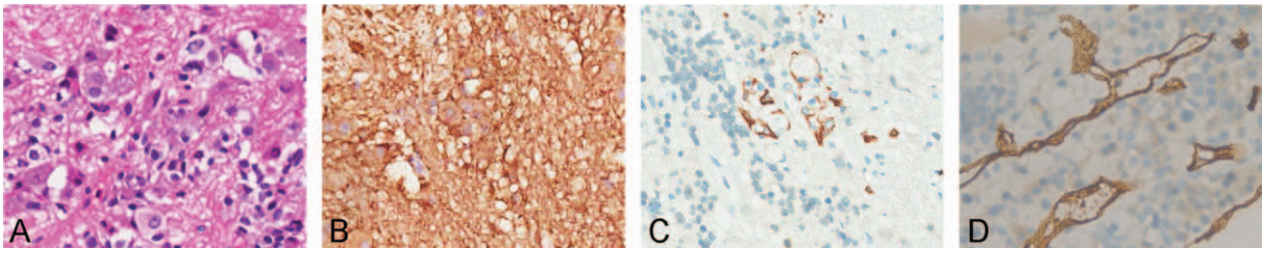

Figure 2. Hematoxylin and eosin (HE) staining and IHC of the resected pituitary ganglioglioma. (A) (HE stain, ×200) showed dysplastic ganglion cells with vesicular hypochromatic nuclei containing prominent nucleolus. IHC showed positive staining of synaptophysin in ganglion cells (B), GFAP in glial cells (C), and CD34 around blood vessels (D). GFAP = glial-fibrillary acidic protein; IHC = immunohistochemistry.

cells (Fig. 2B and C). Interestingly, staining of CD34 was positive around blood vessels (Fig. 2D). Other trivial findings included positive ACTH, FSH, TSH, GH, LH, and PRL in pituitary cells, and <2% of Ki-67 labeling index. No anti-diuretic hormone (ADH) and oxytocin were found, indicating that the tumor was derived from adenohypophysis rather than neurohypophysis. The sepathological findings were consistent with ganglioglioma in adenohypophysis.

After surgery the patient developed cerebrospinal fluid rhinorrhea. The symptom was resolved after lumbar drainage and the patient was discharged. Follow-up 6 months later with MRI showed on tumor progression (Fig. 1J–L).

3. Discussion

Gangliogliomas are rare slow-growing primary benign tumor according to WHO classification, representing 0.4% to 7.6% of pediatric brain tumors, and up to 1.3% in adults.[10] The most frequently affected site is the temporal lobe, but no regions are spared.[2,3] Sellar region is rarely involved and very few cases have been reported (Table 1).[5]

The pathogenesis of ganglioglioma is still unclear, possibly from pluripotent progenitor cells or as a malformative neuronal lesion with glial component representing a transformed hamartomatous element.[4,15] Compared with other regions of the central nervous system, pituitary gland normally has no mature ganglion cells,[15] implying an even more complicated pathogenic process. From the studies of gangliocytomas mixed with pituitary adenomas, several hypothesis were raised concerning the origination of ganglion cells within adenohypophysis: unrelated development of pituitary adenoma in a preexisting neuronal choristoma derived by abnormal migration of hypothalamic neurons; the presence of hypophysiotropic hormones from gangliocytoma stimulates and promotes the formation of pituitary adenoma; origination of the neuronal component from transdifferentiation of a preexisting pituitary adenoma; common origination of neuronal and adenoma cells from uncommitted progenitor cells.[16–18] Patients with gangliogliomas usually present with long-term history of seizure. And it has a predilection for men and young adults.[8] Besides temporal lobe, it also has been reported in pineal gland, hypothalamus, optic pathway, brainstem, spinal cord, and ventricular system.[19] However, ganglioglioma was rarely reported. Meanwhile, neuronal lesions of pituitary region are extremely rare, including neuronal ectopia, choristoma, gangliocytoma, and ganglioglioma.[20–22] Intrasellar gangliocytoma is commonly associated with the adenohypophysis, which is the anterior lobe of the pituitary gland and secretes TSH, ACTH, GH, LH, FSH, and prolactin.[16] Ganglioglioma, as reported in the literature, seemed to be restricted to the neurohypophysis, which locates posteriorly and is responsible for ADH and oxytocin.[23,11,12] Fehn described a 66-year-old man with neurohypophysial gangliolgioma secreting ADH, who developed the syndrome of inappropriate antiduretic hormone secretion.[11] A similar case was described by Saeger et al.[23] Scheithauer et al[21,12] reported a non-ADH-producing ganglioglioma in the neurohypophysis discovered incidentally at autopsy of an 89-year-old female with Alzheimer's disease.

Ganglioglioma is characterized as cystic or solid tumors with enhancement and calcification.[2] MRI found 57% lesions containing cystic component and 43% lesions as entirely solid with hyperintense signal on proton density images, mild hyperintense signal on T2 weighted images and mainly isointense on T1 weighted images.[10] It was the mass effects caused by cystic components that might lead to seizures.[24] On CT 59% of gangliogliomas were reflected as hypodense lesions, followed by 41% as calcification and 36% as enhanced lesions.[10] Based on these findings it was suggested that a relatively large cystic mass or a poorly defined solid mass as described above should raise the concern of ganglioglioma, especially when large area of calcification was noted.[1,24] All these were concluded from supratentorial gangliolgiomas. The images of our patient and other similar cases in the sellar region, however, were not indicative, which makes the diagnosis of pituitary ganglioglioma extremely difficult and relies solely on pathology.[11,21,23]

Histologically, the ganglioglioma is characterized by a mixture of atypical ganglion cells and neoplastic glial cells.[10] The neural component is usually separated by reticulin frameworks into perivascular clusters. The glial component is usually of astrocytes in nature, less commonly with an oligodendroglial appearance.[25] Haematoxylin and eosin staining has the drawback of misinterpreting neoplastic ganglion cells as trapped native cells or as peculiar astrocytes. Occasionally, it may be difficult to differentiate ganglion cell tumors from an infiltrating glioma with entrapped neurons. Immunostaining of specific neural marker such as synaptophysin, chromogranin A, NFP, and GFAP can help with the diagnosis.[4,15] GFAP is critical to diagnose glial component of ganglioglioma.[26,27] CD34, a stem-cell epitope not present in neural cells of the adult brain, is consistently expressed in 70% to 80% of gangliogliomas and can help differentiate gangliogliomas from dysembryoplastic neuroepithelial tumors, oligodentrogliomas, gangliocytomas, and astrocytomas.[11,28,29] In our case, positive staining of synaptophysin and GFAP in ganglion cells was found. Also staining of CD34 was positive around blood vessels. All these findings pointed to the diagnosis of ganglioglioma in the adenohypophysis. Ki-67 and P53 labeling indices were positively

Table 1

Reported gangliogliomas in the sellar region.

No.	Year	Author	Age	Sex	Symptom	Origin region	Hormonal disorders	Resection
1	1998	Fehn et al[11]	66	Male	Headache, nausea and confusion	Neurohypophysis	ADH	TR
2	2008	Scheithauer et al[12]	89	Female	NA	Neurohypophysis	No	NA
3	2008	Jalali et al[7]	7	Female	Dimnution of vision	Optic pathway	No	GTR
4	2015	Matyja et al[13]	26	Male	Headache and dizziness	Pituitary	GH, ACTH, TSH, PRL, FSH, LH	STR
5	2016	Jukes et al[14]	54	Female	Acromegaly progressing	Pituitary	GH	TR
6		Present case	43	Female	Headache	Adenohypophysis	PRL	TR

ACTH = adreno-cortico-tropic-hormone, ADH = antidiuretic hormone, FSH = follicle-stimulating hormone, GH = growth hormone, GTR = gross total resection, LH = luteinizing hormone, NA = not available, PRL = prolactin, STR = subtotal total resection, TR = total resection, TSH = thyroid stimulating hormone.

related to tumor recurrence.[4] Recurrent tumor, however, may not show malignant transformation.[30] Rate of malignant degeneration of ganglioglioma varies between 4% and 32%.[15]

The unique finding of the present case is the distinct location of the ganglioglioma in adenohypophysis, collided with nonspecific hyperplasia of adenohypophysis cells, which was specifically consisted with adenohypophyseal hormones. Unlike ganglioglioma located in other areas, tumors in sellar region are often associated with endocrinological disorder. In this specific case, an elevated prolactin was detected, possibly due to the compression on the pituitary. The pathological findings in our case support the theory of hypophysiotropic ganglioglioma originated from progenitor cells. The embryogenesis-related nature of CD34 and co-localization with traditional neuronal markers in ganglioglioma may reflect an origin from a bipotent precursor that undergoes an early migrational disorder and abnormal glioneuronal development.[31] The observations that CD34 was not in parallel with Ki-67 antigen and anaplastic ganglioglioma displayed significantly less CD34-positive staining may indicate its role in pathogenesis rather than tumor progression.[30] In addition to CD34, a nonspecific hyperplasia of pituitary cells instead of pituitary adenoma was manifested by multiple positive hormone stainings in our patient, which support the stimulatory effect of ganglioglioma on the proliferation of pituitary cells. Considering the proximity, together with the specific histological composition and physiological function, the hypothalamus was probably the source of progenitor cells.[17]

Ganglioglioma follows a relatively benign natural history. Data from Mayo clinics revealed a 15-year overall survival rate of 94%.[2] The 5-year survival rate of patients with anaplastic gangliogliomas, however, was 63% and the median overall survival was 28.5 months.[32] Gross total resection (GTR) is generally the treatment of first choice.[2,4] With GTR, Michael reported a recurrence rate of 7%,[33] and Julia reported a 7.5 year recurrence free survival rate of 97%.[2] Abundant blood supply and unfavorable location restricted the extent of resection, as described in our case.[2] Compared with GTR, subtotal resection (STR) was significantly inferior in local control (LC) (89% after GTR vs 52% after STR, $P < .001$), overall survival (OS) (95% after GTR vs 62% after STR, $P < .001$) and median time to recurrence (16.7 years after GTR vs 1.8 years after STR).[2,29] Other unfavorable prognosis factors include male sex, >40 years, an extratemporal tumor and symptoms other than epilepsy.[5,33,34]

After STR, adjuvant radiotherapy between 40 and 60 Gy, although controversial, has been recommended.[35,36] It prolonged the recurrent time insignificantly to 5.6 years, but did not improve overall survival.[2,32] At the same time, it has the potential hazard of accelerating malignant transformation of ganglioglioma. Andrew reported a case of ganglioglioma deteriorating to neuroblastoma 7 years after initial radiotherapy.[25] Rumana and Valadka[37] reported 4 cases of malignant degeneration of benign gangliogliomas after postsurgical radiotherapy. It has been postulated that radiotherapy may stimulate the dedifferentiation of low-grade glial component and finally result in malignant degeneration of benign ganglioglioma.[37] Considering age and treatment, our patient belongs to the high risk population of recurrence. After weighing the advantages and disadvantages of radiotherapy, together with patient's own intention, a close follow-up was selected. Fortunately up to now the patient did not show any sign of recurrence.

4. Conclusions

In conclusion, adenohypophysial ganglioglioma is an extremely rare and easily misdiagnosed lesion. Here, we were the first to report such a case. Preoperative diagnosis may be impossible due to nonspecific clinical manifestation and imaging characteristics, thus confirmed diagnosis can only be made postoperatively based on histopathological and immunohistochemical analysis. The purpose of presenting this case is to raise awareness among clinicians to consider this clinical entity as a differential diagnosis. Furthermore, ideal management strategy still remains unknown. Gross total surgical resection is the treatment of first choice. The role of radiotherapy, however, is controversial. Therefore, more cases are needed to expand our knowledge of the diagnosis, treatment, and prognosis of this rare intracranial lesion.

Author contributions

Conceptualization: Yongjie Wang.
Data curation: Yongjie Wang.
Funding acquisition: Qun Wu.
Investigation: Qun Wu.
Supervision: Jianmin Zhang.
Validation: Jianmin Zhang.
Writing – original draft: Yuan Hong.
Writing – review and editing: Yuanjian Fang.

References

[1] Castillo M, Davis PC, Takei Y, et al. Intracranial ganglioglioma: MR, CT, and clinical findings in 18 patients. AJR Am J Roentgenol 1990; 154:607–12.
[2] Compton JJ, Laack NN, Eckel LJ, et al. Long-term outcomes for low-grade intracranial ganglioglioma: 30-year experience from the Mayo Clinic. J Neurosurg 2012;117:825–30.
[3] Becker AJ, Lobach M, Klein H, et al. Mutational analysis of TSC1 and TSC2 genes in gangliogliomas. Neuropathol Appl Neurobiol 2001; 27:105–14.
[4] Hirose T, Scheithauer BW, Lopes MB, et al. Ganglioglioma: an ultrastructural and immunohistochemical study. Cancer 1997;79:989–1003.
[5] Luyken C, Blumcke I, Fimmers R, et al. Supratentorial gangliogliomas: histopathologic grading and tumor recurrence in 184 patients with a median follow-up of 8 years. Cancer 2004;101:146–55.
[6] Lagares A, Gomez PA, Lobato RD, et al. Ganglioglioma of the brainstem: report of three cases and review of the literature. Surg Neurol 2001; 56:315–22. discussion 322-4.
[7] Jalali R, Deopujari CE, Bhutani R, et al. Suprasellar ganglioglioma with unusual diffuse involvement of the entire optico-chiasmal hypothalamic pathway. J Cancer Res Ther 2008;4:140–3.
[8] Hauck EF, Vu L, Campbell GA, et al. Intraventricular ganglioglioma. J Clin Neurosci 2008;15:1291–3.
[9] Lotfinia I, Vahedi P. 'Intramedullary cervical spinal cord ganglioglioma, review of the literature and therapeutic controversies'. Spinal Cord 2009;47:87–90.
[10] Zentner J, Wolf HK, Ostertun B, et al. Gangliogliomas: clinical, radiological, and histopathological findings in 51 patients. J Neurol Neurosurg Psychiatry 1994;57:1497–502.
[11] Fehn M, Lohmann F, Ludecke DK, et al. Ganglioglioma of the neurohypophysis with secretion of vasopressin. Exp Clin Endocrinol Diabetes 1998;106:425–30.
[12] Scheithauer BW, Silva AI, Parisi JE, et al. Ganglioglioma of the neurohypophysis. Endocr Pathol 2008;19:112–6.
[13] Matyja E, Maksymowicz M, Grajkowska W, et al. Ganglion cell tumours in the sella turcica in close morphological connection with pituitary adenomas. Folia Neuropathol 2015;53:203–18.
[14] Jukes A, Allan R, Rawson R, et al. Growth hormone secreting pituitary adenoma with admixed gangliocytoma and ganglioglioma. J Clin Neurosci 2016;31:202–4.
[15] Miller DC, Lang FF, Epstein FJ. Central nervous system gangliogliomas. Part 1: Pathology. J Neurosurg 1993;79:859–66.

[16] Koutourousiou M, Kontogeorgos G, Wesseling P, et al. Collision sellar lesions: experience with eight cases and review of the literature. Pituitary 2010;13:8–17.
[17] Kontogeorgos G, Mourouti G, Kyrodimou E, et al. Ganglion cell containing pituitary adenomas: signs of neuronal differentiation in adenoma cells. Acta Neuropathol 2006;112:21–8.
[18] Horvath E, Kovacs K, Scheithauer BW, et al. Pituitary adenoma with neuronal choristoma (PANCH): composite lesion or lineage infidelity? Ultrastruct Pathol 1994;18:565–74.
[19] Prasad GL, Kumar R, Kurwale N, et al. Intraventricular gangliogliomas: a review. World Neurosurg 2016;87:39–44.
[20] Horvath E, Kovacs K, Tran A, et al. Ganglion cells in the posterior pituitary: result of ectopia or transdifferentiation? Acta Neuropathol 2000;100:106–10.
[21] Scheithauer BW, Kovacs K, Randall RV, et al. Hypothalamic neuronal hamartoma and adenohypophyseal neuronal choristoma: their association with growth hormone adenoma of the pituitary gland. J Neuropathol Exp Neurol 1983;42:648–63.
[22] Cossu G, Daniel RT, Messerer M. Gangliocytomas of the sellar region: a challenging diagnosis. Clin Neurol Neurosurg 2016;149:122–35.
[23] Saeger W, Ludecke DK, Losa M. [Combined neuronal and endocrine tumors of the sellar region]. Pathologe 1997;18:419–24.
[24] Adachi Y, Yagishita A. Gangliogliomas: characteristic imaging findings and role in the temporal lobe epilepsy. Neuroradiology 2008;50:829–34.
[25] Tarnaris A, O'Brien C, Redfern RM. Ganglioglioma with anaplastic recurrence of the neuronal element following radiotherapy. Clin Neurol Neurosurg 2006;108:761–7.
[26] Liberski PP, Fiks T. [Gangliocytoma, ganglioglioma and anaplastic oligodendroglioma]. Pol J Pathol 2001;52(4 suppl):71–85.
[27] Wierzba-Bobrowicz T, Schmidt-Sidor B, Gwiazda E, et al. The significance of immunocytochemical markers, synaptophysin and neurofilaments in diagnosis of ganglioglioma. Folia Neuropathol 1999;37:157–61.
[28] Deb P, Sharma MC, Tripathi M, et al. Expression of CD34 as a novel marker for glioneuronal lesions associated with chronic intractable epilepsy. Neuropathol Appl Neurobiol 2006;32:461–8.
[29] Blumcke I, Giencke K, Wardelmann E, et al. The CD34 epitope is expressed in neoplastic and malformative lesions associated with chronic, focal epilepsies. Acta Neuropathol 1999;97:481–90.
[30] Blumcke I, Wiestler OD. Gangliogliomas: an intriguing tumor entity associated with focal epilepsies. J Neuropathol Exp Neurol 2002;61: 575–84.
[31] Blumcke I, Lobach M, Wolf HK, et al. Evidence for developmental precursor lesions in epilepsy-associated glioneuronal tumors. Microsc Res Tech 1999;46:53–8.
[32] Selvanathan SK, Hammouche S, Salminen HJ, et al. Outcome and prognostic features in anaplastic ganglioglioma: analysis of cases from the SEER database. J Neurooncol 2011;105:539–45.
[33] Majores M, von Lehe M, Fassunke J, et al. Tumor recurrence and malignant progression of gangliogliomas. Cancer 2008;113:3355–63.
[34] Gelebert-Gonzalez M, Serramito-Garcia R. The role of postoperative radiotherapy for the treatment of gangliogliomas. Cancer 2010;116: 3071author reply 3071-2.
[35] Im SH, Chung CK, Cho BK, et al. Intracranial ganglioglioma: preoperative characteristics and oncologic outcome after surgery. J Neurooncol 2002;59:173–83.
[36] Liauw SL, Byer JE, Yachnis AT, et al. Radiotherapy after subtotally resected or recurrent ganglioglioma. Int J Radiat Oncol Biol Phys 2007;67:244–7.
[37] Rumana CS, Valadka AB. Radiation therapy and malignant degeneration of benign supratentorial gangliogliomas. Neurosurgery 1998; 42:1038–43.