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Original Article

Extraventricular neurocytoma of the sellar region: report of two cases and literature review

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Abstract: Extraventricular neurocytoma (EVN) of the sellar region is a rare occurrence. To date, merely two reports concerning this tumor have been reported. In this report, we present two cases of EVN that occurred in the sellar region, and reviewed the pathological characteristics and treatment strategies for this disease. Two patients were admitted to our hospital for impaired vision. MRI scans indicated an enhanced invasive mass in the sellar region. One patient was treated via the subfrontal approach, and partial removal was achieved. The other patient was treated via the transsphenoidal approach by microscopy, and subtotal removal was achieved. Histologically, the tumor demonstrated typical features of neurocytoma, which presented nests, islands and strands of neuropil background. Immunohistochemistry (IHC) revealed diffuse Synaptophysin, MAP-2 and neurofilament positivity. Patients were diagnosed with EVN (WHO grade II) and adjuvant radiotherapy was given. In the present report, no loss of 1p/19q or atypical pathological feature was found. Furthermore, some of the molecular pathological characteristics of EVN were explored by literature review. Through these two cases, we confirm that EVN of the sellar region shares similar clinical pathological features with EVN of the other regions. Immunohistochemical examination is an effective method for the diagnosis of EVN. The preferred treatment for EVN of the sellar region is total removal by surgical approaches. Postoperative radiotherapy should be performed for tumors with atypical pathological features or when complete removal is not achieved.

Keywords: Extraventricular neurocytoma, sellar region, pituitary adenoma

Introduction

Extraventricular neurocytoma (EVN) is a rare brain tumor, which shares the same histological features with central neurocytoma (CN). Thus far, merely 85 cases of intracranial EVN have been reported [1]. In 2007, the World Health Organization (WHO) has described EVN as a distinct neuropathological entity of neuronal tumors [2]. EVN can occur to any nervous tissue outside the ventricles. However, most EVN cases have been described within the cerebral hemispheres, followed by localization in the spinal cord, cerebellum, skull base and brain stem. Furthermore, merely two cases of EVN of the sellar region have been reported in the world [3]. In the present case report, we describe two cases of EVN of the sellar region, who were treated and followed up in our hospital. In this report, pathogenesis, clinical features, treatment strategies and prognostic factors were presented and discussed.

Case report

Case 1

A 50-year-old woman presented with decreasing vision in the left eye and diplopia over a two-month period. Her visual acuity was 0.6 in the left eye and 0.1 in the right eye, and no abnormality was found in the visual field or fundus. MRI revealed cystic-solid lesions with well-defined periphery located within the sella and at the suprasellar region (**Figure 1A**). The subsided floor of the sella turcica, enlarged sella turcica, and invasion of the left cavernous sinus were also found. The optic chiasm was compressed and lifted out of its normal position. T1- and T2-weighted images revealed equisignal intensity and prominent enhancement.

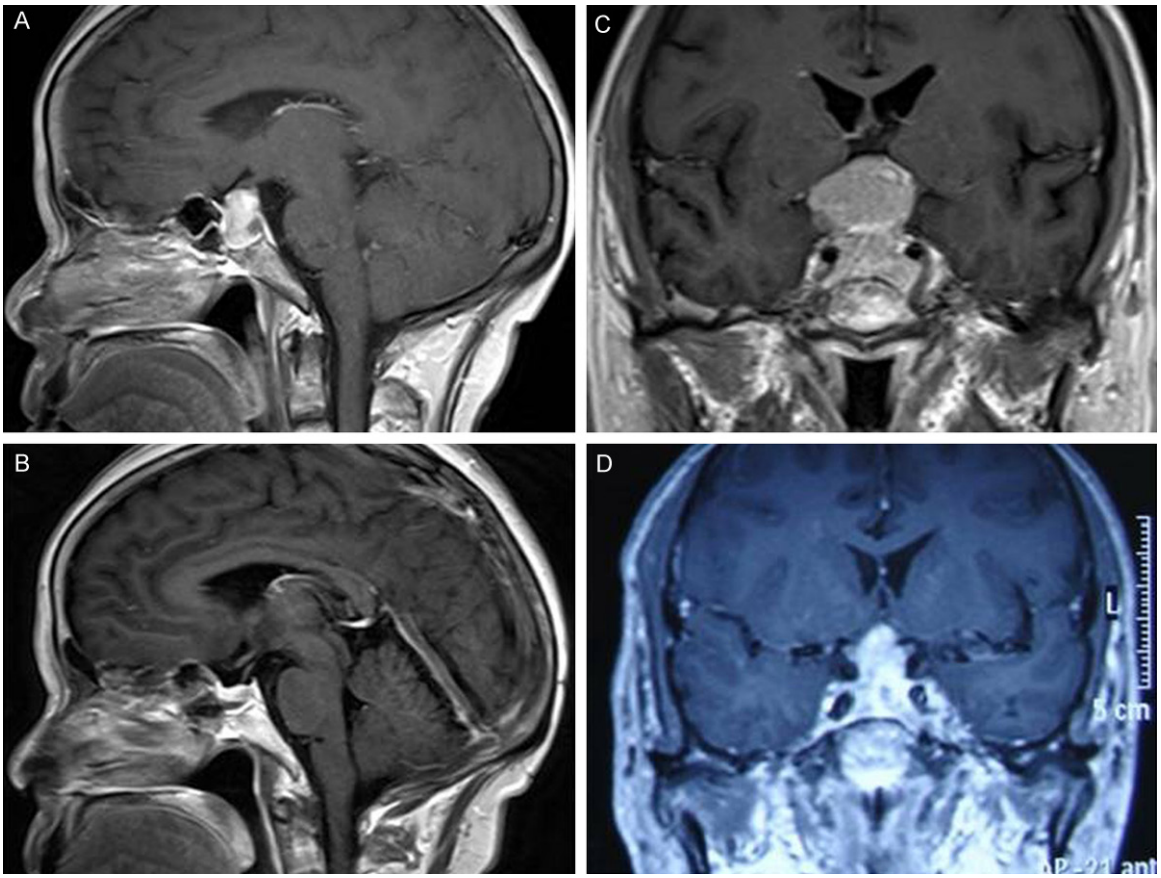

Figure 1. Pre- and post-operative MRI scans. A. The sagittal-T1-weighted enhanced image displays a tumor of the sellar region that invaded into the suprasellar region. B. Enhanced MRI scan was performed after radiotherapy, revealing the regression of the tumor, the pituitary stalk and optic chiasm. C. A coronal-T1-weighted enhanced image presenting a tumor located within the sella and the suprasellar region is shown. D. Enhanced MRI scan after radiotherapy showing substantial tumor regression.

Endocrine examinations revealed no abnormalities. Surgical treatment via the transsphenoidal approach was performed, and a subtotal removal of the tumor was achieved. The texture of the tumor was dense and firm. The tumor had an abundant blood supply and was rich in fibrous matter. Histologically, these tumors were composed of sheets of round-to-oval nuclei with a scantyclear or eosinophilic cytoplasm embedded within a fine neuropil background (**Figure 2A**). Cells were mostly arranged in sheets, ribbons and clusters. Acellular fibrillary areas were observed. Cells were isomorphous and had an around or oval nucleus with a finely speckled chromatin and an occasional nucleolus (**Figure 2B**). Immunohistochemically, these tumor cells revealed diffuse positivity for Synaptophysin (SYN), MAP-2 and neurofilament (NF) in the cytoplasm and fibrillary stroma and diffuse negativity for GFAP, CK8/18, EMA and NeuN (**Figure 2C-E**). In addition, the proliferation index of Ki67 was approximately 2%. No loss of heterozygosity at 1p/19q was demonstrated (**Figure 2F**). The pathological diagnosis was EVN (WHO grade II). MRI revealed tumor regression after post-operative radiotherapy (54Gy total dose/27f/6W; **Figure 1B**). No recurrence was reported after a three-year follow-up.

Case 2

A 62-year-old man with diminished vision quality in both eyes and a narrowed visual field was admitted to our hospital. One year prior to admission, he underwent partial tumor removal via the transsphenoidal approach. Physical examinations revealed that visual acuity of the patient was 0.5 in each eye, and homonymous hemianopia of the temporal visual fields pre-

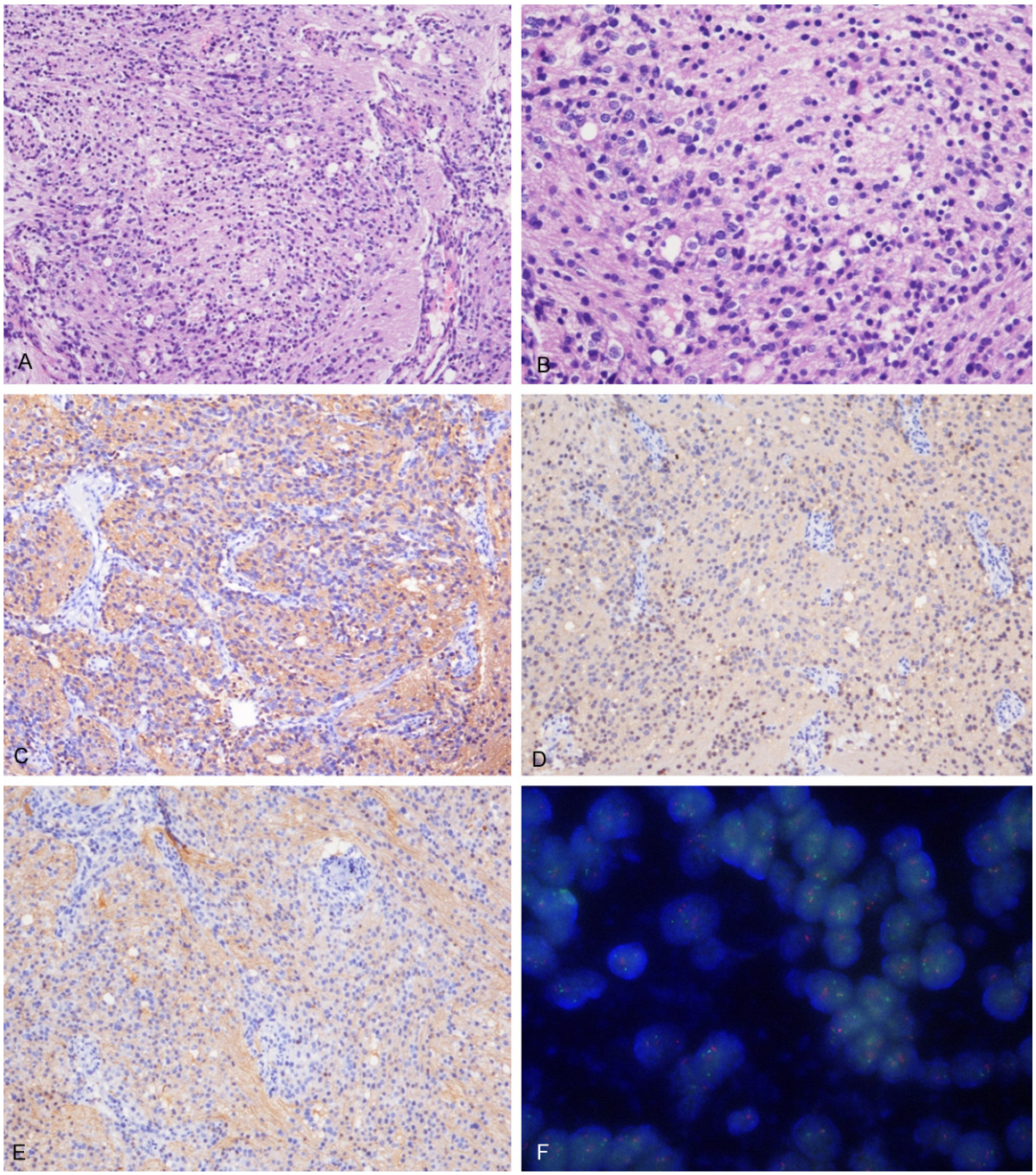

Figure 2. Histological and immunophenotypic findings. A. Tumors were composed of sheets of round-to-oval nuclei with scanty clear or eosinophilic cytoplasm embedded within a fine neuropil background (hematoxylin and eosin, ×100). B. Cells were mostly arranged in sheets, ribbons and clusters. Acellular fibrillary areas were observed. Cells were isomorphous, having a round or oval nucleus with a finely speckled chromatin distribution and an occasional nucleolus (hematoxylin and eosin, ×200). C. Diffuse immunoreactivity to Synaptophysin is shown (IHC, ×100). D. MAP-2 expression is shown (IHC, ×100). E. Neurofilament expression was positive (IHC, ×100). F. The co-deletion of chromosomes 1p/19q was not presented.

sented on both eyes. MRI revealed solid irregular lesions with a well-defined periphery located within the sella and at the suprasellar region (**Figure 1C**). Endocrine examinations revealed decreased levels of progesterone (<0.2 ng/ml) and testosterone (2.19 ng/ml). Surgical treatment via the subfrontal and interhemispheric approach was performed. At the time of surgery, a firm tumor rich in fibrous matter and blood supply was found closely adherent to the

hypothalamus, bilateral optic nerve and optic chiasm. Visual acuity of the patient decreased to 0.1 in the left eye, but no change was found in the right eye. Pathological examination demonstrated a small round cell tumor with a diffuse growth pattern. The nuclei of tumor cells were round or oval, and cytoplasmic vacuoles were found in several cells. Few ganglion-like cells were also observed. A neuropil-like background with vascular endothelial cell proliferation was also found. Immunohistochemical examinations revealed that these tumor cells were positive for SYN, NeuN, Map-2, NF, Chromogranin A and Vimentin. Immunostains for GFAP, CK8/18 and P53 were negative. Ki67 level was less than 2%. No loss of heterozygosity at 1p/19q was demonstrated. The pathological diagnosis was EVN (WHO grade II). After post-operative radiotherapy for the treatment of the residual tumor (50.4Gy total dose/28f/6W), MRI revealed tumor regression (**Figure 1D**). No progression was found after a three-year follow-up.

Discussion

CN was first described by Hassoun et al. [4] in 1982 and accounts for approximately 0.25% to 0.5% of all central nervous system neoplasms. As a tumor with a generally good prognosis, CN was thought to locate only within the intraventricular system (especially at the foramen interventriculae and septum pellucidum). The incidence rate of CN is not significantly different between males and females (with a male to female ratio of 1.02:1). However, the young adult subpopulation is affected by CN the most (with a mean age at onset of 29 years). In a study published in 1989, Ferreol and Nishio [5, 6] first described CN located outside the ventricular system. The 3rd edition of the WHO Classification of Tumors of the Central Nervous System described EVN as an oligodendroglioma-like tumor. However, in the 4th edition issued in 2007, EVN was classified as a neuronal tumor with a distinct entity [2].

EVN can occur at any nervous tissue site outside the ventricles. However, most of the EVN have been described within the cerebral hemispheres, followed by the spinal cord, cerebellum, skull base and brain stem. The incidence rate of EVN of the sellar region is very low, and merely two cases have been reported to date [3]. The histopathogenetic mechanisms of EVN of the sellar region remain largely unknown. Since there is no neuronal or neural progenitor cell in existence in the sellar region, investigators postulate that EVN of the sellar region is caused by an abnormal migration of neurons during embryogenesis [7].

Impaired vision, especially changes in visual fields, was present in both cases previously reported and in both cases reported in this report. Endocrine changes caused by a stalk effect could also occur. However, no significant endocrine changes were found in any of these four patients. Through MRI examination, equisignal intensity in T1-weight images and equisignal or high signal intensity in T2-weight images were commonly found in these four cases.

Nodular and peripheral enhancement was found in these patients, in which two patients were found with partial cystic degeneration and bleeding. Stippled calcification was also found by CT imaging, which should be distinguished from craniopharyngioma. Since the incidence rate of EVN of the sellar region is very low and no diagnostic criterion is available to date, the diagnosis of this tumor mainly relies on pathological examination. The main findings in immunohistochemistry assessments included the positive expression of SYN, NeuN and NSE, and the negative expression of GFAP. Sensitivity and specificity of SYN is highest in diagnosing EVN of the sellar region. However, electron microscopy and molecular pathological examinations should also be performed to further clarify the diagnosis of this tumor when SYN is found to be negative.

Imaging manifestations of EVN of the sellar region must be carefully reviewed to distinguish these from other tumors located at the sellar regions such as the pituitary adenoma, craniopharyngioma and meningioma. Similarly, pathological examination results should be distinguished from oligodendroglioma, oligoastrocytoma, ependymoma, ganglioglioma and dysembryoplastic neuroepithelial tumors. In particular, NeuN and SYN could be found to be positively expressed in oligodendroglioma and oligoastrocytoma when neural cellular differentiation occurs, which actually makes it much more difficult to distinguish from EVN. Loss of heterozygosity at 1p/19q was reported by

Rodriguez et al. [8, 9] in EVN, which contributed complexity to differential diagnoses of EVN distinct from oligodendroglioma. Fortunately, Cooper et al. [10] found that IDH was hardly expressed in neuronal tumors, which could facilitate the differentiation between oligodendroglioma and other tumors with similar morphology to that of oligodendroglioma. In addition, Olig2 is also rarely expressed in neuronal tumors, and this antigen could also be an important biomarker in the differentiation diagnosis of EVN.

With the development of molecular pathology, EVN has been better understood in recent years. Rodriguez et al. [8] performed a study in 21 patients with EVN, and 25% of them were found with loss of heterozygosity at 1p/19q. Furthermore, histological invasiveness was also found in these tumors. Jae KM et al. [11] demonstrated that the molecular pathological features of EVN mainly included the lack of p53 expression, promoter methylation of the MGMT gene, and low frequency amplification of the EGFR gene; which could help differentiate EVN from astrocytoma or oligodendroglioma. Recurrence was found in patients, which was probably associated with the highly amplified gene expression of EGFR. Array-CGH studies on some cases revealed different chromosomal aberrations, suggesting that EVN is genetically heterogeneous and might have several different subtypes [11]. However, no molecular pathological examination was performed for these two previously reported cases.

Previous studies have also demonstrated that EVN could be classified into two subtypes, namely, typical and atypical, according to the results of pathological examinations [11-14]. Such assessments could help determine clinical treatment strategies and prognosis of the disease. The criteria for atypical EVN were as follows: mitotic activity ≥3/10 HPF, vascular proliferation, necrosis, and an MIB-1 labeling index greater than 3%. Although the 1p/19q co-deletion was associated with aggressive histological features, more cases are needed to conform whether it can be used as an independent parameter. In the present report, these two cases were of atypical EVN type, Ki67 levels were found to be less than 2% in each case, and no loss of 1p/19q was found.

Total removal was reported to be the preferred treatment for EVN. However, the texture of EVN is generally firm, and abundant fiber is commonly found in tumors with rich blood supply. In addition, the sellar region is adjacent to neurovascular structures, and the tumor could invade the cavernous sinus. All these features make it very difficult to achieve total removal of the tumor. In the present report, total removal was not achieved in either of the cases (subtotal removal in one case and partial removal in the other case). Similarly, in a previous study performed by Kane AJ et al. [1], total removal was achieved in only 13% of patients with atypical EVN.

Although most researchers believe that postoperative radiotherapy is required, controversy continuous to remain. In a study performed by Kane AJ et al. [1], the authors found that recurrence rate and mortality rate was 36% and 4% for typical EVN, 28% and 5% for typical CN, 68% and 44% for atypical EVN, and 40% and 20% for atypical CN, respectively. These findings have suggested that the prognosis of patients with EVN was significantly worse than CN, especially for atypical EVN, which accounts for approximately 27% of all EVN; and the recurrence rate was almost twice than that for typical EVN.

In our expert opinion, no radiotherapy is needed for patients with typical EVN that achieved total removal of the tumor. However, for patients with atypical EVN or patients with typical EVN who have not achieved total removal, postoperative radiotherapy is required to improve survival rate and prognosis in these patients. In the present study, post-operative radiotherapy was performed in both cases and resulted in satisfactory outcomes, with no recurrence reported to date. These observations suggest that post-operative radiotherapy is very important in treating EVN of the sellar region. However, the effectiveness of chemotherapy remains unclear for EVN, since only three cases with EVN that received post-operative chemotherapy have been reported to date [8, 15]. Further studies with large sample size are clearly warranted.

Similar to CN, EVN is also a low-grade malignant tumor (WHO grade II). However, the recurrence rate and mortality rate of EVN are significantly higher than CN. The prognosis of EVN is closely related to the existence of atypical pathological features. Studies have reported that

an MIB-1 proliferation index (Ki67) higher than 3% and an age of more than 50 years are predictors of poor prognosis. However, multi-centered randomized clinical trials are warranted to validate this hypothesis. These two reported cases did not present any atypical pathological feature, the expression levels of Ki67 were both lower than 2%, and neither of them exhibited loss in 1p/19q. To date, these patients have been followed-up for three years with no progression. However, further clinical and radiographic follow-ups are needed to clarify the prognosis of these cases.

Conclusion

We report two cases with EVN of the sellar region that were treated by surgical removal, and reviewed these cases against evidences from previously published articles. This study demonstrated similar pathological features with CN. Immunohistochemical examination could help in the diagnosis of this tumor. In the present report, no loss of 1p/19q or other atypical pathological features were found in either of the two cases. However, as achieving total removal remains very challenging in treating EVN of the sellar region, post-operative radiotherapy should be performed.

Disclosure of conflict of interest

None.

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