Abstract. Intrasellar meningiomas are rare tumors that have the ability to mimic non-functioning pituitary adenomas. The majority of meningiomas are slow-growing and benign, therefore an intrasellar meningioma with malignant histological features is extremely rare. The present study describes the case of a malignant diaphragm meningioma that was controlled through combined chemotherapy, following subtotal surgical resection. The patient's symptoms ceased and no tumor recurrence was detected at the 3-year follow-up. Hormone levels were also observed as normal. Further investigation of similar cases may aid in achieving an accurate pre-operative diagnosis. This would prove particularly beneficial in regards to intrasellar meningiomas due to their specific location and surgical treatment. The present study analyzes the requirement of chemotherapy for the treatment of these unique tumors.

Introduction

Meningiomas account for 34.7% of all primary intracranial tumors observed in adults, the majority of which are benign (1). However, these tumors rarely develop at the intrasellar region; only 12 pathologically diagnosed cases have been reported previously (2-12), and the presence of a malignant intrasellar meningioma is even rarer (2-4). The current study describes the case of a female patient presenting with a malignant intrasellar meningioma appearing to mimic a non-functioning invasive macroadenoma. This particular type of meningioma demonstrates unique features when compared with meningiomas in other locations (2,3,5-8,13,14). An accurate pre-operative diagnosis is necessary in order for the required treatment to be administered or surgery to be completed. Due to the high risk of recurrence and cavernous sinus invasion following an initial surgery, re-operation is often required and may lead to an increased risk of complications when compared with similar tumors at other locations. In the present study, the patient benefited from active treatment, including chemotherapy and radiotherapy. The findings also presented evidence that malignant meningiomas closely associated with important adjacent structures should be treated extensively initially, since reoperation may cause serious neurological impairment. Written informed consent was obtained from the patient.

Case report

A 35-year-old woman described a 2-month history of a persistent, bilateral, parieto-occipital headache combined with 1 week of vomiting. The patient was therefore referred to the Department of Neurosurgery, West China Hospital (Chengdu, China) in July 2011, with an initial diagnosis of a non-functioning pituitary adenoma. The patient noted the onset of right ptosis and diplopia 2-days after hospital admission. Physical examination found mild right III and VI cranial nerve disturbance. No other abnormal signs were observed.

Hormone tests prior to surgical intervention revealed decreased levels of triiodothyronine (T3) (1.01 nmol/l; normal range, 1.30-3.10 nmol/l) and free T3 (2.92 pmol/l; normal range, 3.60-7.50 pmol/l), with a slightly elevated prolactin level (38.47 ng/ml; normal range, 6.0-29.9 ng/ml). Other hormone levels were all normal. Specific cancer-associated serum markers, including α-fetoprotein (AFP), carcinoembryonic antigen (CEA), cancer antigen (CA)15-3, CA19-9, CA-125, CA72-4 and cytokeratin 19 fragment 21-1 were also normal.

A magnetic resonance imaging (MRI) scan revealed a 1.7x1.9x2.1-cm, enhanced, heterogeneous, intrasellar mass with invasion into the right cavernous sinus, and the optic chiasm was slightly displaced (Fig. 1A-C). No lesion was observed on the enhanced computed tomography (CT) scan of the chest and abdomen.

The slightly hypervascularized mass was removed subtotally through a transsphenoidal approach. The tumor was soft enough to remove with gentle curettage, unlike previously reported fibrous lesions (5,13). The cavernous sinus wall was invaded under intraoperative visual inspection and no post-operative complications were detected. Tissue samples were formalin-fixed, paraffin-embedded and cut into 3-µm sections, prior to staining with hematoxylin and eosin. When observed under the microscope, the tumor tissue exhibited increased cellularity, a sheet-like growth pattern and necrosis.
Neoplastic cells with anaplastic prominent nucleoli and high mitotic activity were also noted [>20/10 high-power fields (HPFs)] (Fig. 2A-C), with a Ki-67 labeling index of up to 40%. Immunohistochemical (IHC) examination revealed positive staining for vimentin (Fig. 2D), focally positive staining for epithelial membrane antigen (EMA) and S100,
and negative staining for chromogranin, synaptophysin, glial fibrillary acidic protein, AFP, placental alkaline phosphatase, octamer-binding transcription factor 3/4, B-cell lymphoma 2, cluster of differentiation (CD)34, leukocyte common antigen, CD117, melan A, human melanoma black 45, CEA, myeloperoxidase, desmin, cytokeratin 8 and CD30. No pituitary hormone was expressed. A diagnosis of malignant meningioma [World Health Organization (WHO) grade III (1)] was formed based on the pathological findings and clinical features.

Following surgery, the patient's headache was partially alleviated, whilst the oculomotor paralysis persisted. Adjuvant three-dimensional conformal radiation therapy (3D-CRT) with a 32-Gy dose was implemented 1 week after surgery, aiming to target the residual tumor in the cavernous sinus. Subsequently, three 4-week cycles of combined chemotherapy treatment with cyclophosphamide (3 g, days 1-3) and nimustine (125 mg, day 1) were administered. The patient's symptoms ceased ~2 months after chemotherapy, with no tumor regrowth detected during the 8-month (Fig. 1D-F) and 3-year follow-ups (Fig. 3).

Discussion

Meningiomas are common primary intracranial tumors observed in adults that arise from the meningotheial cells of the arachnoid mater, subsequently attaching to the adjacent dura mater (15). Currently, meningiomas are classified based on histological features, accepted as benign (grade I), atypical (grade II) or anaplastic/malignant (grade III) (1). Anaplastic or malignant meningiomas account for only 1.0-2.8% of all meningiomas (6,16). The surface area of the dura mater, located at the sella turcica, is relatively small (<6 cm²), and meningiomas originating from the sellar turcica have not been frequently reported (17). Hardy and Robert (18) first described an intrasellar meningioma originating from the inferior leaf of the diaphragma. Kinjo et al (14) classified diaphragmatic meningiomas into three types, including type C, which originates from the inferior leaf of the diaphragma sellar. Type C diaphragm meningiomas resemble non-functioning pituitary adenomas, and are commonly complicated by bitemporal hemianopsia and hypopituitarism. Previously, Nozaki et al (2) reported the case of a hypervascularized anaplastic intrasella meningioma and to the best of our knowledge, the present study describes the second known case diagnosed as malignant intrasellar meningioma originating from the dura mater of the sellar turcica.

Intrasellar meningioma and pituitary adenoma share comparable features on CT and MRI scans. Enlargement of the sellar turcica is frequently observed, but an hourglass appearance is rare among intrasellar meningiomas. CT and MRI scans may reveal a well-enhanced intrasellar or intrasuprasellar mass that is difficult to distinguish from pituitary adenoma, or even pituitary apoplexy (7). Dural enhancement, including the tail sign, is not specific, as it is one of the most common manifestations of meningioma. However, a differential diagnosis may still be conducted efficiently the majority of the time. External carotid angiograms may demonstrate marked tumor blush, and dynamic scanning techniques may be useful, as the meningiomas exhibit complete enhancement with maximum signal intensity during the early phase and a significantly different time-intensity curve from that of pituitary adenomas (8).

We hypothesize that the transtemporal approach should be considered to provide a moderately safe route to an intrasellar mass (even with small suprasellar extension), regardless of the pathological nature of the lesion. However, in certain cases, it may not be the leading choice for intrasellar meningiomas, as the tumor may be too firm to be extirpated and it would therefore be difficult to control the hemorrhage, which requires reoperation via transcranial approach. The combined transtemporal and transcranial approach could be applied for large intra-suprasellar masses. For cases with anaplastic or malignant meningiomas, adjuvant radiotherapy should be administered, as these tumors have a high rate of recurrence and distant metastases. Despite chemotherapies and hormonal therapies largely being proved as ineffective against the majority of meningiomas, chemotherapies may, however, have potential in cases demonstrating distant metastasis and an excessive mitotic index. In the present study, 3D-CRT and concurrent chemotherapy were selected due to the presence of tumor invasion into the cavernous sinus, which leads to a high recurrence risk and subsequent adjacent nerve adhesion. The alleviation of the patient's symptoms
and an extended tumor-free phase confirmed the effectiveness of the treatment.

Anaplastic/malignant meningiomas represent a higher degree of cell cycle dysregulation and loss of differentiation, with focal or diffuse findings of an excessive mitotic index (>20/10 HPFs) and/or evident anaplasia (6,16). Tumor necrosis and hemorrhage may also be present. The tumor cells may be carcinoma-, sarcoma- or melanoma-like in appearance. Therefore, IHC examinations, including EMA, vimentin, CK, S-100 and CEA, are required to demonstrate meningothelial features that differ from other malignant tumors. Geographic necrosis and brain invasion may also be observed. In the current study, the tumor acquired several anaplastic features with invasion to the cavernous sinus. A variety of genetic changes have been identified in anaplastic meningiomas, including N-myc downstream-regulated gene 2 (NDRG2) hypermethylation, 17q23 amplification, loss of tumor suppressor in lung cancer-1 and progesterone receptor expression, and alterations in chromosomes, such as the loss in 1p, 6q, 9p21, 10, 14q and 18q (19). Recent research has supported the theory that molecular genetics serves a role in the pathogenesis of atypical and anaplastic meningiomas, which may promote anti-angiogenic and targeted molecular therapies to improve the prognosis of high-grade meningiomas (20).

In conclusion, intrasellar meningioma mimicking pituitary adenoma is rare and even rarer when malignant. WHO grade III meningiomas have a recurrence rate of 50-80% and life expectancy following diagnosis is ~2 years. With regard to malignant intrasellar meningioma, substantial damage may incur due to its location. However, in the present case, no recurrence was observed in the 3 years following combined therapy. Further research may aid in achieving an accurate pre-operative diagnosis, confirming whether surgery and subsequent treatment is required. Compared with possible recurrence affecting adjacent nerves when patients are treated conservatively, those individuals with malignant meningiomas in unique locations may benefit from aggressive treatment combining chemotherapy and radiotherapy. Research to elucidate the molecular hallmarks of anaplastic tumors would be likely to aid the production of multi-modal and molecular-targeted therapy in the future.

References


