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LETTER TO THE EDITOR

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Recurrent glomus tumor of the sellar region with malignant progression

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Glomus tumors are small, benign mesenchymal neoplasms, the majority of which occur in the dermis or subcutis of the extremities. The single most common site is the subungual region of the fingers, followed by palm, wrist, forearm and foot. The tumor cells resemble modified smooth muscle cells of normal glomus bodies. Glomus tumors, however, have been reported in locations in which the glomus bodies are sparse or even absent, among them patella, nerve, eyelid, liver, gastrointestinal tract, trachea, nose, bone and sella turcica [3, 9]. Glomus tumors usually show a benign clinical course. However, rare malignant cases have been reported [5, 6, 7]. In a recent review on atypical and malignant glomus tumors, Folpe et al. [3] have proposed a classification scheme, encompassing malignant glomus tumors, symplastic glomus tumors, glomus tumors of uncertain malignant potential and glomangiomatosis.

Glomus tumors in the sellar region are exceedingly rare and to the best of our knowledge only one case has been reported so far in this location [2]. Here we report the case of an intra- and parasellar neoplasm first diagnosed as a benign glomus tumor. Recurrent tumor growth was observed 8 and 10 years after the first surgical intervention and subsequent histology suggested malignant progression of the glomus tumor.

In 1991, 9 months after a moderate cervical spine trauma, the 47-year-old female patient noted intermittent diplopia. Ophthalmological examination revealed a right-sided cavernous sinus syndrome with palsy of the occulomotor, trochlear and abducent nerves. Cranial computer tomography and magnetic resonance imaging (MRI) showed an intrasellar mass lesion that extended into the right-sided supra- and parasellar regions including the cavernous sinus. Microsurgical tumor resection was performed with a right pterional craniotomy approach. The residual tumor was treated by fractioned radiation therapy (27 fractions with a total dose of 54 Gy). Apart from a persisting right-sided trochlear nerve palsy the clinical history was uneventful till May 1999, when the patient developed a right-sided lid ptosis and an intermittent diplopia. On MRI scans, the tumor was found to have recurred and expanded to the right supra- and parasellar regions, now measuring 3 cm in diameter (Fig. 1A). Incomplete tumor resection was performed via a transsphenoidal approach followed by gamma knife radiosurgery with a total dose of 25 Gy. In July 2001 the patient noted further visual impairment and ophthalmological testing revealed loss of visual acuity and visual field defects in the right eye. Endocrinological examination demonstrated panhypopituitarism. Repeated MRI scans again showed tumor growth in the right supra- and parasellar region measuring up to 3.5 cm in diameter. The patient underwent right-sided pterional recraniotomy with incomplete tumor resection. Due to progressive visual impairment a further transsphenoidal tumor resection was undertaken in November 2001. Further radiation therapy was initially refused; however, due to progressive tumor growth (Fig. 1B) a targeted radiotherapy using ^{90}Yttrium-DOTATOC, an Yttrium-labeled somatostatin analogue, was conducted early in 2003. The patient died in October 2003, 12 years after initial manifestation of the tumor. No autopsy was performed.

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Surgical specimens were all fixed in 10% formalin, routinely processed and embedded in paraffin. Five-micrometer thin sections were cut and stained with hematoxylin and eosin, periodic acid-Schiff (PAS) and silver reticulin stain. Immunohistochemistry was performed, following standard protocols using a broad panel of antibodies (see below). Small tumor fragments were cut from paraffin-embedded tissue blocks and processed for electron microscopy.

Histology of the initial tumor revealed a predominantly solid neoplasm composed of sheets of uniform round and polygonal cells interrupted by small thin-walled vessels (Fig. 1C). Vessels were not invaded by the tumor. Tumor cells were of regular shape with a punched-out rounded nucleus, surrounded by clear, slightly eosinophilic cytoplasm. The nuclei contained finely dispersed chromatin with an indistinct nucleolus. Silver reticulin stain revealed a delicate fiber network surrounding individual tumor cells or small cell groups. Mitoses and necrosis were absent.

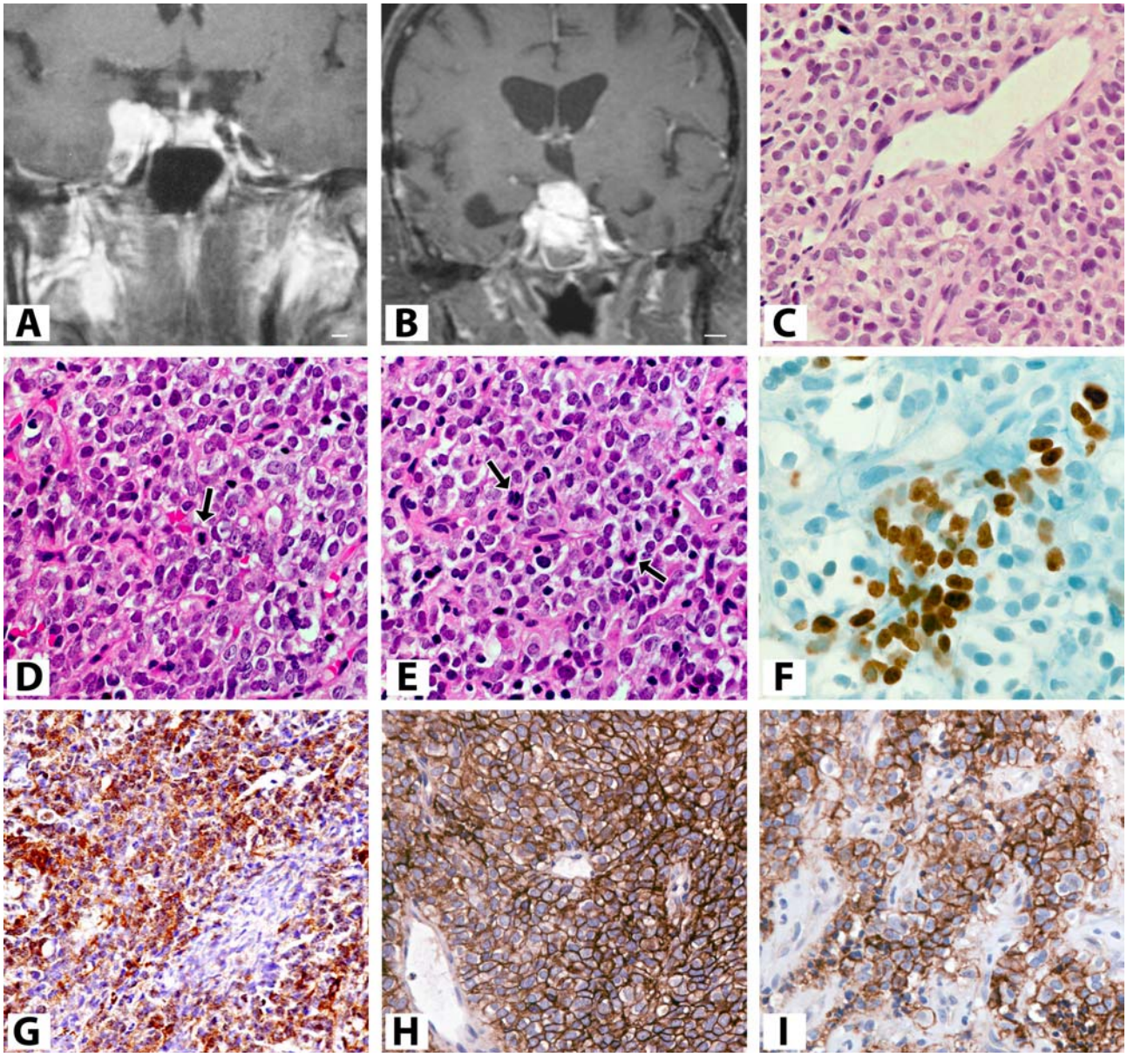

Fig. 1 **A** T1-weighted MRI scan of the first recurrent tumor in 1999, showing predominantly right-sided parasellar contrast enhancing mass with infiltration of the cavernous sinus and compression of the temporal lobe. **B** T1-weighted MRI scan, performed in early 2003, demonstrating the uniformly enhancing intra-suprasellar mass with direct contact to the optic chiasm. **C** Hematoxylin and eosin staining of the initial tumor. Uniform round cells are arranged in sheets and interrupted by small vessels. **D**, **E** The tumor after the second (**D**) and third (**E**) recurrence is hypercellular, tumor cells and nuclei are more polymorphous, and several mitoses can be seen (*arrows*). **F** MIB-1 labeling of the tumor after third recurrence. G–I Immunostaining of the tumor after the first recurrence; **G** smooth muscle actin, **H** CD99, and **I** laminin immunoreactivity. *Bars* **A**, **B** 1 cm; original magnification **C** ×200; **D**, **E**, **G**–**I** ×400; **F** ×500

The histological appearance of the tumor specimens obtained at the time of the second resection was quite similar to that of the first biopsy. However, there were foci of higher cellularity, and tumor cells and the nuclei appeared more polymorphous. One mitosis per 50 high-power fields (HPF) was noted, but there were no atypical mitotic figures (Fig. 1D). Tumor necrosis was absent. Histology from the third and forth biopsies was found to be very similar to the second biopsy. In contrast to the previous tumor specimens, however, there were more cellular and nuclear atypia. Up to 3 mitoses/50 HPF were noted (Fig. 1E). Again, there was no tumor necrosis.

Immunohistochemically, tumor cells stained strongly for vimentin, smooth muscle actin, laminin and CD99 (Fig. 1G–I), and a few cells stained faintly for neuron-specific enolase and epithelial membrane antigen. CD34 only stained the tumor vasculature. The MIB-1 proliferation labeling index was below 1% in the initial tumor, about 2% in the second tumor specimens and up to 10% in the biopsies taken in 2001 (Fig. 1F). Tumor cells were negative for chromogranin A, S-100 protein, cytokeratin, placental alkaline phosphatase, synaptophysin, glial fibrillary acidic protein, desmin, CD117 and pituitary hormones.

Electron microscopy revealed medium-sized cells with interdigitating microvilli on their surface. The tumor cells possessed equally sized, sometimes slightly grooved, nuclei with a nucleolus. The most prominent cytoplasmic features consisted of sparse pinocytotic vesicles, large mitochondria and focal aggregates of microfilaments. Few individual cells were surrounded by a layer of basal lamina. Cells were arranged 'back to back' and were separated by bundles of long spacing collagen.

Glomus tumor of the sellar region is rare. To our knowledge, the case reported by Asa and coworkers more than 20 years ago [2] is the only known case so far. We now report histological, immunohistochemical and electron microscopic findings of a second case of a sellar glomus tumor. Similar to the case reported by Asa et al. [2], recurrent tumor growth was also observed in our patient.

Irrespective of their anatomical location glomus tumors are usually benign, but rare malignant cases have also been described [5, 6, 7]. In our case, benign glomus tumor was diagnosed in a first biopsy. However, in later biopsies, hypercellularity, cellular and nuclear atypia, increased mitotic activity and MIB-1 labeling indices were noted, suggesting malignant transformation of the glomus tumor.

Recently, Folpe et al. [3] proposed a classification of atypical and malignant glomus tumors. Malignant glomus tumors are defined as tumors with: (i) large size (>2 cm) and deep location, (ii) atypical mitotic figures, or (iii) marked atypia with mitotic activity (e.g., >5 mitoses/50 HPF). Symplastic glomus tumors lack criteria for malignant glomus tumor and exhibit only marked nuclear atypia. Glomus tumors of uncertain malignant potential are defined as tumors with: (i) superficial location with high mitotic activity, (ii) large size only, or (iii) deep location only. Finally, glomangiomatosis lacks criteria for malignant glomus tumor or glomus tumor of uncertain potential, and shows features of diffuse angiomatosis and excess glomus cells [3]. In this series, 38% of malignant glomus tumors metastasized, but metastatic disease was not seen in any of the symplastic glomus tumors, glomus tumor of uncertain malignant potential, or glomangiomatosis.

Our case does not fulfill the criteria proposed for symplastic glomus tumors and glomangiomatosis, and is, therefore, very unlikely to correspond to one of these entities. There is still the question of whether our case does represent a malignant glomus tumor or a glomus tumor with uncertain malignant potential. Atypical mitotic figures as well as marked atypia with mitotic activity of more than 5 mitoses/50 HPF were not features in our case. Since the tumor was definitely larger than 2 cm and located deep in the sellar region, it would nevertheless qualify for a malignant glomus tumor. With regard to the sella turcica, however, the criteria of "deep location" and "large size" need further consideration. In their series of unusual glomus tumors, Folpe et al. [3] defined the tumor location as either superficial to the muscular fascia or deep to it. In their study, five out of nine deeply located peripheral soft tissue glomus tumors (all of which were larger than 2 cm) metastasized. In a series of 32 gastrointestinal (GI) glomus tumors, there was only 1 case that metastasized, although all of these tumors by definition were deeply located, and 19 of them were larger than 2 cm [8]. In another series of gastric glomus tumors, none of the 12 tumors metastasized, including those which were larger than 2 cm [1]. Thus, there seems to be a marked difference in the frequency of malignant behavior between deep-seated glomus tumors of the peripheral soft tissue and those located in other "deep" regions. Taking this into account, a deep location as well as a tumor size larger than 2 cm may not per se be features of malignancy of a glomus tumor in the sellar region. Clinical observations over 12 years for our patient did not reveal metastases, and the same is true for the glomus tumor reported by Asa et al. [2], although the follow-up in that case was only 6 years. However, both recurrent glomus tumors showed a locally infiltrative growth pattern into the supra- and parasellar region. Thus, according to an earlier classification proposed by Gould et al. [4], both cases would represent examples of locally aggressive and/or potentially malignant glomus tumors, or as glomus tumors of uncertain malignant potential according to the classification by Folpe et al. [3]. Such tumors may recur locally but usually do not metastasize [4].

In conclusion, our case demonstrates that a glomus tumor can occur within the sella turcica, and that it may recur locally and invade the supra- and parasellar region with an aggressive and infiltrative growth.

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