Paragangliomas of the Sellar Region: Report of Two Cases

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TWO CASES OF paraganglioma arising from the parasellar region are presented. Both occurred in middle-aged women who sought treatment of headaches but who had no endocrinological dysfunction; one case was associated with ophthalmoplegia from cavernous sinus involvement. Diagnosis in both cases was confirmed by typical histological appearance and cytochemical demonstration of immunoreactive chromogranin in tumor cells. The pathological features and possible pathogenesis of parasellar paragangliomas are discussed. (Neurosurgery 32:844–847, 1993)

Key words: Cavernous sinus, Chemodectoma, Paraganglioma, Pituitary tumor

Paragangliomas are tumors of cells derived from neural crest origin and include neoplasms of the adrenal medulla and paraganglia (12, 17). They occur at multiple locations within the body; tumors of the carotid body and glomus jugular account for more than 80% of extra-adrenal cases (9). Other reported sites in the head and neck have included the orbit, larynx, thyroid, vagus nerve, paranasal sinus, and nasal cavity (2, 3, 5, 9, 11, 12, 17, 18). Some paragangliomas have been reported in regions of the body where paraganglionic tissue is not normally located, e.g., cauda equina (14), duodenum, and pineal region (15).

Paraganglionic cells have not been demonstrated in the pituitary gland or adjacent structures (1). Paragangliomas arising from the pituitary region are very rare lesions, with only two previous cases described in the literature (1, 4); one arose within the pituitary fossa, and one arose from the lateral wall of the cavernous sinus. We report two further cases of paragangliomas arising from the parasellar region.

PATIENT 1

A 44-year-old white woman sought treatment at the University of Washington Medical Center in February 1991 of an increase in the frequency of long-standing migraine-like headaches. The headaches were intermittent for 3 years and typically involved the left hemicranium. She had normal menses with no symptoms of endocrine or visual dysfunction. Physical and neurological examinations revealed nothing abnormal, including a normal visual field examination. Magnetic resonance imaging (MRI) demonstrated a lobulated lesion arising from the pituitary fossa that was isointense to brain on T1 sequence and uniformly contrast enhancing with gadolinium–GPTA. The mass filled the pituitary fossa, projecting laterally into the left cavernous sinus with encasement of the left carotid artery, inferiorly into the sphenoid bone, and superiorly into the left mesial temporal lobe. It did not appear to involve the clivus (Fig. 1). Cerebral angiography including the external carotid arteries demonstrated no tumor blush. Preoperative endocrine studies including prolactin, growth hormone, follicle-stimulating hormone (FSH), luteinizing hormone, adrenocorticotropic hormone (ACTH), and thyroid function tests were all within normal limits.

A transseptal, transsphenoidal approach to the lesion was performed. Upon entering the sphenoid sinus, a soft white to slightly pink encapsulated tumor was encountered that had eroded through the floor of the pituitary fossa on the left and appeared to arise from the region of the cavernous sinus laterally. A normal-appearing pituitary gland was visualized in the superior portion of the sella after subtotal resection of the mass. The patient made an uncomplicated recovery with normal postoperative endocrine function.

A histological examination demonstrated a tumor composed of round to oval cells with a tendency to form nests or lobules, commonly designated *Zellballen* (Fig. 2). The cells had centrally located nuclei of moderate to marked pleomorphism in abundant granular eosinophilic cytoplasm. No mitotic figures were observed. In areas, the nests were separated by vascular connective tissue septa. Immunocytochemistry revealed strong positivity for immunoreactive chromogranin (Fig. 3). Staining for cytokeratins, pituitary hormones (prolactin, ACTH, FSH, and growth hormone) and S-100 protein were negative.

On electron microscopy, large numbers of dense core granules ranging in diameter from 100 to 200 nm were visible in cytoplasm, which contained minimal smooth endoplasmic reticulum and scattered mitochondria. The morphological features of the cell combined with the immunocytochemical characteristics confirmed the histological diagnosis of paraganglioma (7, 9).

The patient was treated with radiation therapy consisting of 4500 cGy in 25 fractions. She remains stable 12 months after the procedure with some diminution in the frequency of her headaches. Follow-up MRI scans demonstrate no progression of tumor size.

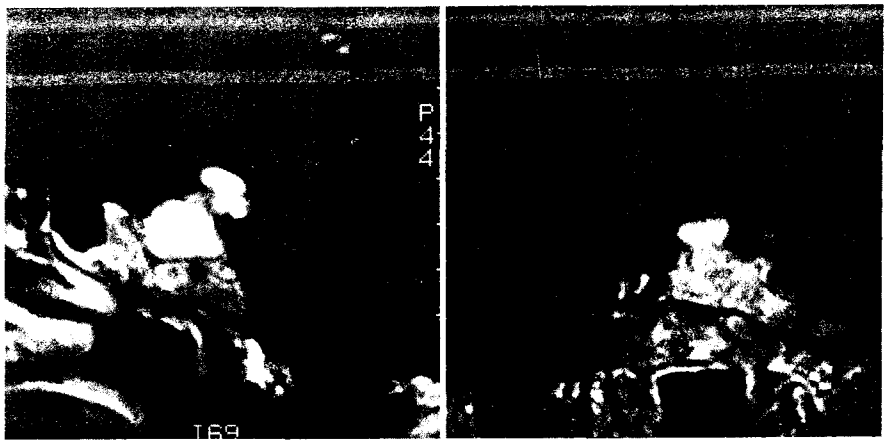

FIGURE 1. Patient 1. Left, sagittal MRI scan with Gd-GTPA enhancement demonstrating the lesion filling the pituitary fossa, with significant suprasellar extension. Right, coronal MRI scan with Gd-GTPA showing the pituitary fossa filled with tumor with extension laterally to encase the carotid artery and inferiorly eroding into the sphenoid bone.

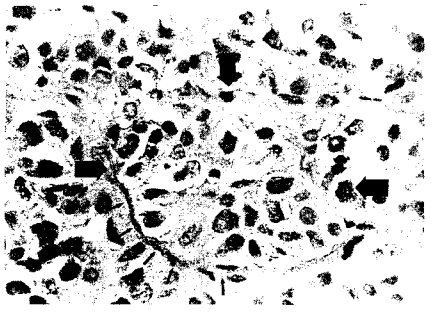

FIGURE 2. Photomicrograph of a tumor specimen from Patient 1 demonstrating round to oval cells with centrally located nuclei and scant cytoplasm in a lobulated or nest (zellballen) arrangement (large arrows), with surrounding vascular connective tissue septae (small arrows) (hematoxylin and eosin, ×310).

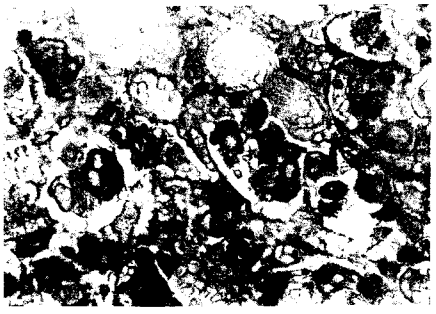

FIGURE 3. Photomicrograph of the immunohistochemistry of the tumor specimen from Patient 1, displaying strong immunoreactivity for cytoplasmic chromagranin (magnification, ×310).

PATIENT 2

A 41-year-old white woman sought treatment after two episodes of left pupillary dilation and ptosis associated with global headaches, nausea, and vomiting. She had no diplopia or decreased visual acuity and had no symptoms of endocrinological dysfunction. At the time of admission, the physical examination was normal, including formal visual field testing. An endocrinological profile revealed nothing abnormal, including normal prolactin, growth hormone, FSH, luteinizing hormone, ACTH, and thyroid-stimulating hormone tests.

MRI with Gd-GTPA demonstrated a large, uniformly contrast-enhancing lesion arising from the region of the sella. The lesion encased both carotid arteries, extending laterally to compress the left mesial temporal lobe, posteriorly to compress the left cerebral peduncle, and inferiorly to the left foramen ovale (Fig. 4). Cerebral angiography demonstrated no abnormal vascularity.

A left frontotemporal craniotomy was performed to expose the tumor. A soft pinkish-white tumor arising from within the cavernous sinus was encountered that bled readily upon incision. After the tumor was removed from around the 3rd, 4th, and 6th cranial nerves, subtotal resection of the tumor was performed with residual tumor left within the sinus and attached to the tentorium.

A histological examination revealed a neoplasm composed of round to polyhedral cells with extensive granular cytoplasm, arranged in sheets with occasional tendency to nest. The cell nuclei showed mild to moderate pleomorphism and hyperchromasia. No areas of necrosis and no mitotic figures were seen. There was a prominent vascular capillary network throughout the tumor. Electron microscopy demonstrated polyhedral cells, with cytoplasm containing neurosecretory granules about 100 to 200 nm in diameter (Fig. 5). Moderate numbers of mitochondria and variable amounts of smooth endoplasmic reticulum were seen.

Immunocytochemical staining revealed immunoreactive chromogranin with scattered associated cells staining positive for S-100 protein. The neoplasm stained negative for cytokeratins, glial fibrillary acidic protein, and epithelial specific antigen. Immunohistochemistry for pituitary hormones (FSH, luteinizing hormone, ACTH, prolactin, and growth hormone) showed no reactivity.

Postoperatively, the patient experienced transient 3rd and 6th nerve paresis that resolved 6 weeks after the surgery. She underwent adjunctive radiotherapy of 5000 cGy over 30 days. Follow-up MRI scanning at 12 months demonstrated stable tumor size.

DISCUSSION

Extra-adrenal paragangliomas arise from elements of the dispersed neuroendocrine system (i.e., paraganglia), which are derived from neural crest progenitor cells (8). They occur most often in the head and neck region, with the vast majority occurring at the sites of the carotid body, the temporal bone, and the vagal body (5, 18). Other reported locations in the head and neck regions have included the larynx, trachea, orbit, nasal cavity, maxillary sinus, and thyroid and along the course of the vagus nerve (2, 5, 12, 17, 18). Two previous cases of parasellar paraganglioma have been reported. Bilbao et al. (1) described a 37-year-old man with long-standing hypopituitarism who was found to have a paraganglioma aris-

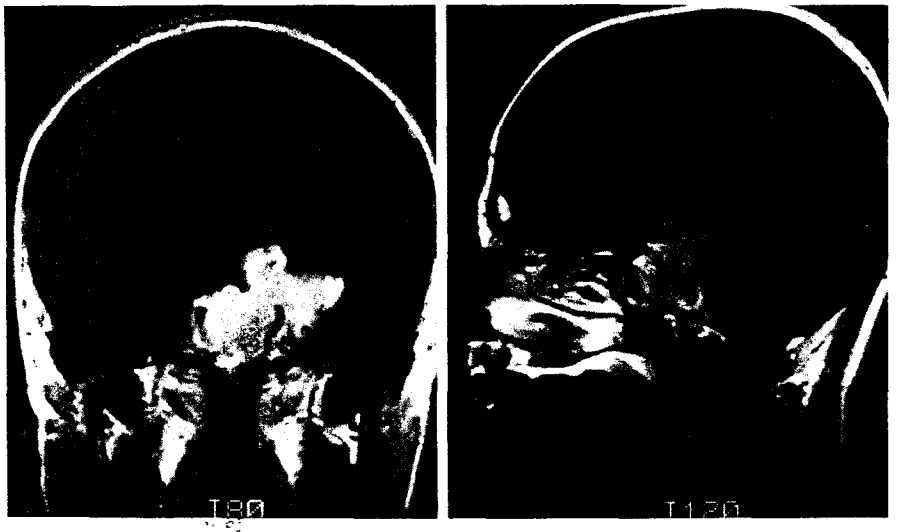

FIGURE 4. Patient 2. Left, coronal MRI scan with Gd-GTPA showing the lesion filling the pituitary fossa, with encasement of both carotid arteries and extension into the left mesial temporal lobe. Right, sagittal MRI scan with Gd-GTPA demonstrating suprasellar extension of the tumor compressing the left cerebral peduncle.

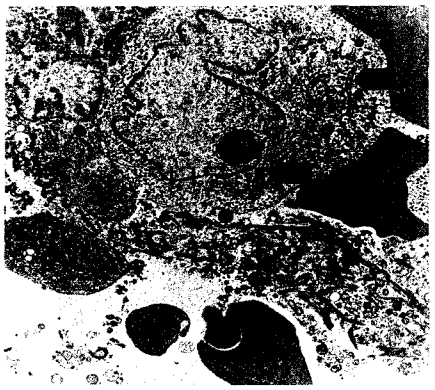

FIGURE 5. Electron micrograph of the tumor from Patient 2, revealing a polyhedral cell containing minimal smooth endoplasmic reticulum (large arrows) and scattered mitochondria with large numbers of dense core cytoplasmic granules (small arrows), 100 to 200 nm in diameter (magnification, ×4400).

ing from the pituitary fossa. The patient was treated by transsphenoidal resection and hormone replacement. The second case involved a 65-year-old man with facial pain and diplopia with a paraganglioma arising from the right cavernous sinus (4). This lesion was treated by subtotal resection via craniotomy and subsequent radiotherapy. One case of a paraganglioma originating from within the middle cranial fossa has been reported: a 63-year-old man with a tumor arising from the petrous ridge (10).

The origin of extra-adrenal paragangliomas remains obscure. Their occurrence in multiple sites in the head and neck suggests a widespread distribution of the specialized chemoreceptor cells. However, the distribution and role of cells derived from the neural crest outside of the carotid and aortic bodies are poorly understood (18). The paraganglion system is considerably more extensive in the fetus and neonate (4), and this may explain why paragangliomas have been found in areas that do not normally contain paraganglionic cells in the adult, such as the duodenum, small bowel, kidney, cauda equina, and pineal region (1, 14, 15).

Paraganglionic cells have not been demonstrated in the pituitary gland or in adjacent structures (1). Bilbao et al. (1) postulated that neural crest tissue may be involved with the development of the normal pituitary and that a nest of paraganglionic tissue may have been included in or around the developing adenohypophysis. This would be appropriate for a tumor arising from within the pituitary fossa itself.

The second proposed mechanism for the origin of such tumors involves abnormal migration in the fetus or neonate. Small aggregates of paraganglion cells have been found along the course of the tympanic branch of the glossopharyngeal nerve within the petrous bone (4, 16, 17). It is possible that aberrant migration of these cells along branches of the tympanic or ciliary nerves to within or close to the cavernous sinus may occur. Ho et al. (4) suggested this mechanism to explain their reported case, and this would seem a likely pathogenesis for our cases where the tumor appears to arise from the cavernous sinus structures rather than from within the pituitary gland itself. The rare reported occurrences of lesions in the orbit, nasopharynx, maxillary sinus, and larynx suggest a widespread distribution of specialized neural crest cells within proximity of the pituitary fossa and may represent similar examples of tumor pathogenesis.

Paragangliomas are characterized by the presence of two cell types, classically arranged into lobules or "Zellballen." The predominant cell type is the chief cell, which is round to oval in shape with abundant eosinophilic granular cytoplasm. Typically, the cells stain positively for chromogranin and neurosecretory granules are found in the cytoplasm on electron microscopy. The second cell type is the sustenacular or supporting cell. These resemble vascular pericytes and stain positively for S-100 protein. The loss of the normal paraganglionic architecture in paragangliomas of the head and neck has been associated with more aggressive or malignant behavior (11). In neither of our cases was the typical Zellballen conspicuous, with both tumors showing only a mild tendency to form nests.

In our first patient, no sustenacular cells were visible either by light microscopy or by immunocytochemical staining with S-100 protein. In our second patient, scattered sustenacular cells were seen but are not prominent within the neoplasm. The paucity or absence of sustenacular cells in paraganglionic neoplasms has also been demonstrated to be an indicator of aggressive or malignant behavior (8, 9, 13). In both of our patients, pleomorphism of the cell nuclei was evident, more noticeably in our first patient, in whom sustenacular cells were absent. Although necrosis and mitotic

figures were not observed in either case, standard light microscopy indicators of malignancy are in general not applicable to paragangliomas (8). No mention is made of the presence or absence of sustenacular cells in either of the two previously reported cases, nor is long-term follow-up provided. It is possible that these lesions may represent a more aggressive type of paraganglionic neoplasm, similar to paragangliomas of the orbit and larynx, which tend to be more locally invasive and have a higher rate of regional or distant metastases (2, 17). Paragangliomas are typically slow-growing tumors (12, 15), and longer follow-up of our cases will be necessary to demonstrate whether this is the case.

With most paragangliomas of the head and neck, surgical excision is advocated as the treatment of choice, with adjunctive radiotherapy for cases of subtotal resection (6, 12, 17). Because of the incomplete resection in both cases reported here and the favorable response to radiation for other paragangliomas of the head and neck, we treated both cases with adjunctive radiotherapy after the surgery.

Received, June 4, 1992.
Accepted, December 3, 1992.
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COMMENT

The authors have made an important contribution to the sizable literature concerning tumors of the sellar and parasellar regions. Neoplasms in these regions provide a large differential diagnosis, and these two documented cases solidify the recognition of a paraganglioma as part of this differential diagnosis. Given the considerable similarity pathologically between this tumor and the standard pituitary adenoma, one must be very careful in identifying a true paraganglioma.

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