Granular-cell pituicytoma associated with multiple endocrine neoplasia type 2

Case report

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Granular-cell pituicytomas of the neurohypophysis have a controversial histogenesis and oncological behavior. The occurrence of such a tumor in a patient whose father and daughter had endocrine neoplasms suggests a neuroectodermal origin for these tumors. Although all of the conditions considered in this report are unusual clinical entities, their correlation offers considerations in understanding the importance of genetic factors in tumor development.

KEY WORDS - granular-cell pituicytoma - multiple endocrine neoplasia type 2 - neuroectoderm - neurohypophysis

ALTHOUGH collections of oval and faintly granulated eosinophilic cells have been noted in the neurohypophysis as incidental findings in a small percentage of routine autopsy examinations, it is rare for these granular-cell masses to enlarge enough to present as space-occupying lesions. The poorly defined natural history of this entity and the divergent histogenic interpretations applied to granular-cell tumors of the neurohypophysis as well as those histomorphologically similar tumors occurring elsewhere in the body create difficulties in establishing both their prognosis and treatment.

This paper describes a case of a granular-cell "pituicytoma" of the neurohypophysis presenting clinically as a pituitary tumor in a patient with a family history of multiple endocrine neoplasia (MEN) Type 2. Evaluation of this association offers possible clarification of the puzzling histogenesis of these tumors and their possible participation in certain genetic syndromes that manifest neoplasia of the central or peripheral nervous system.

Case Report

This 36-year-old woman was referred for evaluation of a 4-month history of oligomenorrhea and galactorrhea associated with an elevated basal prolactin level of 107 ng/ml. At 19 years of age, she had the onset of a persistent and poorly defined facial dermatitis, and, at 22 years, she received thyroid hormone replacement therapy for an "enlarged thyroid gland." She has given birth to three children at term. Over the last 5 years, she has had three hospitalizations for febrile illnesses of undetermined origin. Family history is pertinent in that her father has been treated for medullary carcinoma of the thyroid and a parathyroid adenoma. In addition, a daughter died at 19 months of age from a neuroblastoma.

Examination. On admission, skull series demonstrated duplication of the sellar floor, and high-resolution contrast-enhanced computerized tomographic (CT) scanning showed a homogeneous intrasellar mass with suprasellar extension (Fig. 1). Visual field examination demonstrated a superior bitemporal quadrantanopsia. The basal prolactin level was 49 ng/ml, but the remainder of the laboratory tests, including pentagastrin stimulation for calcitonin and urinary evaluation for catecholamines and metanephrines, were normal. A tentative diagnosis of an expanding pituitary adenoma was made.

Operation. The patient underwent operative removal of the mass by the transsphenoidal approach. A grayish-white tumor with a firm and relatively avascular character was found, tenaciously adherent laterally, and piecemeal subtotal removal was carried...
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Fig. 1. Contrast-enhanced computerized tomography scan, coronal projection, showing a homogeneously enhanced intrasellar mass with suprasellar extension. Opacification shown unilaterally in the sphenoid sinus represents chronic thickening of the mucosal membranes.

FIG. 2. Photomicrograph of the tumor consisting of cells with abundant granular cytoplasm and small eccentric nuclei. H & E, x 12.5.

out. Its relationship to surrounding structures and the pituitary gland or stalk could not be determined. Histological analysis showed the neoplasm to be composed of predominantly polygonal cells with a large amount of cytoplasm of faintly eosinophilic granular quality (Fig. 2). These cells demonstrated eccentrically located, small, oval-to-round and mildly vesiculated nuclei which occasionally had a small eosinophilic nucleolus. In many areas, the cells were separated by small vascular spaces and exhibited a trabecular pattern. Many of these cells were positive on periodic acid-Schiff (PAS) staining. The histological diagnosis of the surgical specimen was granular-cell myoblastoma (choristoma or granular-cell pituicytoma).

Postoperative Course. The postoperative course was uneventful, and radiation therapy was administered with 5000 rads in 29 fractions. Examination 2 months after surgery showed complete resolution of the visual field defects.

Discussion

The controversy regarding the origins of these foci of large granular cells in the neurohypophysis is illustrated by the variety of synonyms in their nomenclature. The term "choristoma" was initially used by Sternberg to characterize his impression that the entity was a developmental anomaly of displaced neuroectoderm. Subsequent autopsy series demonstrated the presence of such islands of cells in the neurohypophysis in 5.7% to 6.45% of unselected subjects; however, the failure of these studies to identify such lesions in subjects less than 20 years of age did not support the congenital nature implied by Sternberg's terminology. Liss and Kahn noted the close resemblance of these cells to the bipolar variety of pituicytes with granular cytoplasm that are normally found in the neurohypophysis, and they therefore termed these tumors "pituicytomas." Their contention is supported by the fact that pituicytes, which are considered to be modified astrocytes, are the main cellular component of the neurohypophysis, and that no theoretical or practical reasons exist to deny their capability to produce tumors.

Because of their close histomorphological resemblance to granular-cell myoblastomas that occur in the tongue, cutaneous tissues, and viscera, other reports have defined these lesions as "myoblastomas" of the neurohypophysis. This latter term derives from the early concept that these extracranial tumors were of myogenic origin. Although the histogenesis of these extracranial tumors is still debatable, the general consensus is that these tumors are closely related to peripheral nerve tissue and most likely represent altered Schwann, perineural, or endoneural cells. The concept that the granular-cell tumor of the neurohypophysis most likely arises from pituicytes and that similar-appearing extracranial tumors arise from Schwann cells, suggests a common neuroectodermal origin for these lesions. The association in our present case with the MEN Type 2 (Sipple's) syndrome supports this concept. In the MEN Type 2 syndrome, there is a spectrum of diseases ranging from medullary thyroid carcinoma (MTC) or C-cell hyperplasia, parathyroid disease, pheochromocytoma, or a subgroup of patients with MTC, pheochromocytoma, and mucosa neuromas (Type 2b). All these components, except for the hyperparathyroidism, which may be a secondary phenomenon, can be attributed to a neuroectodermal origin and even more specifically to the neural crest. In our present case, the patient's daughter had a neuroblastoma, which not only supports the developmental pedigree of the MEN Type 2 syndrome, but also raises the possible relationship of familial neuroblastoma
and MEN Type 2 syndromes with von Recklinghausen's neurofibromatosis. Certain shared stigmata of these processes (mucosal neuromas, café au lait spots, a pheochromocytoma relationship, and the common neuroectodermal (neural crest) origin of the Schwann cell and the neuroblast) have encouraged this speculation. Furthermore, the proposed schwannian ontogeny for extracranial granular-cell myoblastomas and their histomorphological relationship to granular-cell tumors of the neurohypophysis leads to additional conjecture regarding the embryological and genetic relationships shared by all of these entities.

The initial clinical and radiological findings indicative of an expanding pituitary adenoma in the present case did not support inclusion of this patient as having her kindred's MEN Type 2 syndrome. The association of a pituitary adenoma with the MEN syndromes is almost exclusively with the Type 1 variety (parathyroid adenoma, pancreatic islet-cell tumors, nonfunctioning adrenal-cortical tumors or nonfunctioning thyroid adenomas), and, as would be expected with their different cellular origins, crossover between the MEN Type 1 and Type 2 syndromes is rare. The subsequent identification of a neurohypophyseal tumor of probable neuroectodermal origin indicated that this neoplasm may form part of the spectrum of the MEN Type 2 syndrome. This syndrome, like the other MEN syndromes, has an autosomal-dominant mode of inheritance with high gene penetration as well as a high degree of variability in its spectrum of lesions in a specific patient or among members of the same family. These considerations offer additional support to the concept that the granular-cell tumors of the neurohypophysis are true neoplasms and not a local thesaurosis as suggested by Symon and others. Review of the literature indicates that these tumors are usually of the slow-growing type, but occasionally have been noted to have a more aggressive course with infiltrative characteristics. The suspected presence of this infiltrative quality in our case and our acknowledgment that this entity represented a true neoplasm encouraged us to follow the recommendations of certain other investigators and to proceed with surgical decompression and radiation therapy. Other investigators, however, do not support the value of adjunct irradiation. Becker and Wilson have recently reviewed the role of this treatment modality and, basing their opinion upon an updated summary of the long-term survival of previously reported patients who had subtotal tumor removal with and without postoperative irradiation, they supported the recommendation by Symon, et al., that radiation therapy is not indicated in the treatment of these tumors. The scarcity of experience with these rare tumors, however, does not permit a definitive understanding of their natural history, and in this respect, the present case study offers some clarification by implying a cell origin arising from neuroectoderm.

References


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