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Clinical Study

Clinicopathologic correlates of giant pituitary adenomas

Geeta Chacko [a,*], Ari George Chacko [b], Matilde Lombardero [c], Sunithi Mani [d], M.S. Seshadri [e], Kalman Kovacs [f], Bernd W. Scheithauer [g]

[a] Section of Neuropathology, Department of Neurological Sciences, Christian Medical College, Vellore, 632004, Tamil Nadu, India
[b] Department of Neurosurgery, Christian Medical College, Vellore, India
[c] The Department of Anatomy and Animal Production, University of Santiago de Compostela, Lugo, Spain
[d] Department of Radiology, Christian Medical College, Vellore, India
[e] Department of Endocrinology, Christian Medical College, Vellore, India
[f] Department of Laboratory Medicine, St Michaels Hospital, Toronto, Ontario, Canada
[g] Department of Laboratory Medicine, Mayo Clinic, Rochester, Minnesota, USA

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ABSTRACT

Giant adenomas comprise a clinical/therapeutic subset of pituitary adenomas that pose a surgical challenge. The study population consisted of 28 patients who had giant pituitary adenomas, which are defined as tumors with a diameter greater than 5 cm. Clinically, five tumors (18%) were endocrinologically functional and 23 (82%) were not. During surgery, one tumor was radically excised, four were subtotally excised, 12 were partially excised, and 11 were biopsied. All of the tumors showed typical histological features of pituitary adenoma. Of the 23 clinically non-functional adenomas, 18 were gonadotrophic tumors, four were null cell adenomas and one was a silent corticotroph adenoma. The MIB-1 labeling indices ranged from 0.1% to 2.0%. The mean topoisomerase labeling index was 0.75%. Microvessel density ranged from 0.42% to 5.55%, and there was moderately intense immunostaining for vascular endothelial growth factor. The present study found giant adenomas to be invasive but slow growing, histologically benign and often gonadotrophic in subtype.

1. Introduction

As a rule, pituitary adenomas grow slowly, enlarge by expansion, and become demarcated from normal pituitary tissue by what appears to be a pseudocapsule.[1] Only with continued growth does the dura contribute to "encapsulation". Tumors with their greatest diameter of less than 10 mm are classified as "microadenomas", whereas those with a diameter of 10 mm or more are considered "macroadenomas".[2]

Due to their benign nature and variable clinical presentation, pituitary adenomas may become very large, a factor that complicates treatment. Widespread surgical and radiologic interest in these tumors has resulted in various definitions of large or "giant" pituitary adenomas. Both Fisher et al.[3] and Symon et al.[4] defined giant adenomas as those showing suprasellar extension of more than 40 mm in any direction from the midline of the jugum sphenoidale. Symon et al. also considered giant adenomas to be tumors extending within 6 mm of the foramen of Monro.[4] Others considered adenomas with suprasellar extension of Hardy grades C and D as being large or giant.[5] Mohr et al. felt that having a superior margin more than 20 mm above the jugum sphenoidale was the key to identifying giant adenomas.[6] More recently, Goel et al. defined giant adenomas as those greater than 4 cm in maximum diameter, further subclassifying them into four grades according to invasion and patterns of extension.[7] Despite definitional variation, all of the authors agree that very large tumors are difficult to treat by surgery alone, and that adjuvant therapy is necessary. The lack of studies correlating histopathologic and immunohistochemical data for giant adenoma prompted us to undertake a detailed examination of 28 patients who all had adenomas that measured 5 cm or more in maximum diameter.

2. Material and methods

Between 2001 and 2004, we surgically treated 214 patients with pituitary adenoma in a tertiary care hospital. All had undergone MRI studies, which were stored using a picture archiving and communications system (PACS; General Electric Company, Schnectady, NY, USA). The maximum craniocaudal and transverse diameters of the adenomas were measured in the coronal plane, while the anteroposterior diameters were measured in the sagittal plane by a radiologist. A total of 28 patients who had tumors with a maximum diameter of greater than 5 cm in any direction were included in this study. One author (AGC) assessed the extent of tumor resection on post-operative CT scans and MRI. Authors GC and AGC obtained all of the relevant clinical details and laboratory

* Corresponding author. Tel.: +91 416 228 3032; fax: +91 416 223 2035.
E-mail address: geetachacko@cmcvellore.ac.in (G. Chacko).

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data from the institutional pituitary adenoma database. Biochemical tests included an estimation of the serum levels of growth hormone (GH), prolactin (PRL), adrenocorticotropin (ACTH), thyroxine (T4), triiodothyronine (T3), luteinizing hormone (LH), follicle-stimulating hormone (FSH) (8 a.m.), and 4 p.m. cortisol and testosterone. Three independent observers (GC, KK and BWS) examined all of the 28 tumors histologically and immunohistochemically. The specific histologic features assessed included nuclear atypia, mitotic rate and apoptotic activity. Immunohistochemistry testing for GH, PRL, ACTH, thyroid stimulating hormone (TSH), LH and FSH, as well as alpha subunit, was performed according to a standard protocol.[2] In addition, immunohistochemical staining by the avidin-biotin-peroxidase complex (ABC) technique employed monoclonal antibodies directed against the proliferation markers MIB-1 (Dako-Patts, Copenhagen, Denmark) and topoisomerase II alpha (Dako-Patts); labeling indices (LI) were assessed in the regions of maximum staining using a Leitz Dialux microscope (Leitz Wetzlar, Wetzlar, Germany) at $\times$400 magnification, without any knowledge of the clinical or histologic data. An average of 1000 cells were counted, and the resulting MIB-1 and topoisomerase LI were expressed as a percentage of labeled nuclei. Immunohistochemistry testing for the vascular endothelial growth factor (VEGF) was performed using a goat anti-VEGF antibody (Santa Cruz Laboratories, Santa Cruz, CA, USA) according to a standard, previously published protocol.[8] The immunostaining results for each patient were graded as being 0 (negative), 1+ (weakly positive), 2+ (moderately positive) or 3+ (strongly positive). The mean level of staining intensity was calculated. A mean value of between 1.5 and 2 was considered as 2+ staining, while a mean value of between 2.5 and 3 was considered as 3+. The tumoral microvessel density (MVD) was studied using CD34 labeling (Dako-Patts) and quantified according to a published protocol.[9]

3. Results

3.1. Clinical and biochemical findings

Of the 214 patients in our series, 28 (13%) had giant adenomas. The male to female ratio was 1.8:1. The mean patient age

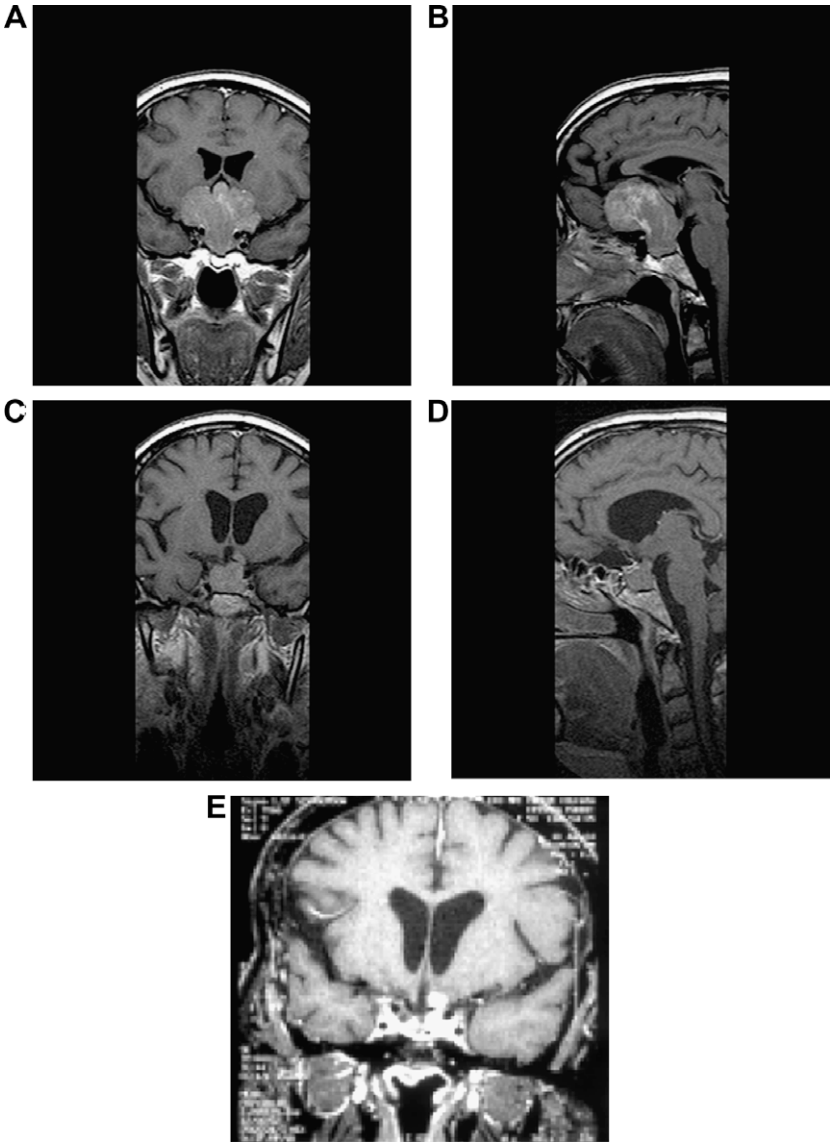

Fig. 1. A giant pituitary adenoma treated with 2 stage resection. (A) Coronal and (B) sagittal T1-weighted MRI scans after gadolinium administration showing a large tumor enlarging the sella, extending into the suprasellar region and involving the cavernous sinuses bilaterally. (C) Coronal and (D) sagittal T1-weighted MRI scans after transcranial surgery showing residual tumor within the sella and along the pituitary stalk on the left side. (E) A coronal T1-weighted MRI scan with gadolinium enhancement taken after the second stage transsphenoidal excision showing a small tumor residue along the pituitary stalk.