Diagnosis and Treatment of Pineal Region Tumors

Edited by

Edward A. Neuwelt

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Edward A. Neuwelt, M.D.

Associate Professor of Neurosurgery
Assistant Professor of Biochemistry
Division of Neurosurgery
Oregon Health Sciences University
Portland, Oregon

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To P.C.—a terrific wife
and mother

Foreword

Doctor Edward Neuwelt and his contributors, with this book, have made an outstanding contribution to the neurosurgical literature. As he points out the management of pineal region tumors is most controversial, especially in the United States. A major reason for that controversy is the lack of a definitive reference for the physician who is confronted with a patient harboring one of these unusual lesions. The book does not dictate a course of action; indeed, it should not. Instead it very successfully accomplishes the goal of the authors which is "to review the diagnosis and treatment of these tumors so that the practitioner can make an intelligent decision as to the proper course of treatment in an individual patient."

It successfully outlines, in depth, current understanding of both the basic science and clinical science of these disorders. I would not do the authors justice by trying to comment on their individual contributions. Suffice it to say the book is extremely well written and illustrated. Unlike most multi-authored texts it is well balanced with no anemic chapters. This is a tribute to the genius of the editor, Dr. Neuwelt, and the qualifications and expertise of his contributors. As a surgeon I was most impressed by the anatomical description of the pineal region and the technical detail of the surgical procedures. I believe all neurosurgeons who peruse this book will second my opinion. The basic scientists and nonsurgeons who wish a comprehensive survey of the subject will likewise be satisfied. It will serve as the standard reference on this topic for years to come, both for the student and the practitioner.

Clark Watts, M.D.
Columbia, Missouri

Preface

Although tumors of the pineal gland are not the most common tumors of the central nervous system, they are certainly one of the most controversial. The controversy in part relates to the fact that current neurodiagnostic techniques are sensitive in picking up even small lesions, but are not specific as to the underlying type of pathology. As a result, the standard mode of therapy for lesions of the pineal in the past, empiric radiation without a tissue diagnosis, is called into question. This is particularly true in the United States where a very significant proportion of tumors in the pineal region are either benign lesions or lesions in which a gross total excision can be achieved. Indeed our current series of malignant pineal region tumors shows 9 of 13 successful gross total excisions. Only 3 of these 13 patients had pure germinomas. Seven of the nine with a gross total removal remain tumor free in a 3 month–6 yr follow-up. An initial surgical approach is probably less applicable in Japan where the highly radiosensitive germinoma remains by far the most common tumor. Thus, a major area of the controversy in the United States relates to whether the 20 or so pathological types of tumor that can be found in the pineal region should first be diagnosed with tissue histology or alternatively, be treated with an initial trial of empiric radiotherapy.

Because of the magnitude of this controversy, as evidenced by the plethora of recent publications on the topic, the purpose of this monograph is to review the diagnosis and treatment of these tumors so that the practitioner can make an intelligent decision as to the proper course of treatment in an individual patient. The monograph begins with a review of the pathology and epidemiology of tumors of the pineal region and then proceeds to the diagnosis of these lesions. Diagnosis, neuro-ophthalmology and neuroradiology are particularly important and are therefore emphasized. The question of therapy is then discussed in the following chapters commencing with an historical overview. Because the anatomy of veins in this region is so key to surgery, a separate chapter on the microsurgical anatomy of this region is given, followed by chapters relating to surgical approaches to the pineal gland. In separate chapters written by both neurosurgeons and radiotherapists, an alternative form of initial therapy, empiric radiation, is presented. Finally, some more recent advances with regard to tumor markers and chemotherapy as well as postoperative radiotherapy in the treatment of lesions in the pineal region are discussed. It is our feeling that making this information available to the practicing physician in a complete and coordinated fashion will have a significant impact on improving the diagnosis and treatment of tumors in the pineal region.

To facilitate the use of this text as a reference, the bibliographies of all the chapters are combined at the end of the book and each paper is listed alphabetically by the last name of the senior author.

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EDWARD A. NEUWELT

Contributors

Eustacio O. Abay III, M.D.
Neurosurgeon
Bel-Air Village
Makati, Metro Manila
Philippines

Robert E. Anderson, M.D.
Professor and Director
Neuroradiology Section
Department of Radiology
University of Utah School of Medicine
Salt Lake City, Utah

Erik-Olof Backlund, M.D., Ph.D.
Professor and Chairman
Department of Neurosurgery
Universitetet I Bergen
Haukeland Hospital
Bergen, Norway

H. Hunt Batjer, M.D.
Assistant Professor
Neurological Surgery Service
University of Texas Southwestern
Medical School
Dallas, Texas

James E. Bruckman, M.D.
Clinical Assistant Professor
Department of Radiation Therapy
Bishop Clarkson Memorial Hospital
Omaha, Nebraska

Barbara Danoff, M.D.
Associate Professor
Department of Radiation Therapy
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

Lawrence H. Einhorn, M.D.
Professor
Department of Medicine
Indiana University School of Medicine
University Hospital
Indianapolis, Indiana

Glenn S. Forbes, M.D.
Associate Professor of Radiology
Department of Diagnostic Radiology
Mayo Clinic
Mayo Medical School
Rochester, Minnesota

Eugene P. Frenkel, M.D.
Professor
Department of Internal Medicine
University of Texas Health Science Center
Dallas, Texas

Rebecca Gelman, Ph.D.
Assistant Professor
Department of Biostatistics
Dana-Farber Cancer Institute
Harvard School of Public Health
Boston, Massachusetts

Gordon L. Grado, M.D.
Clinical Assistant Professor
Department of Radiation Therapy
Bishop Clarkson Memorial Hospital
Omaha, Nebraska

Mary Kay Gumerlock, M.D.
Assistant Professor
Division of Neurosurgery
Oregon Health Sciences University
Portland, Oregon

Maie Kaarsoo Herrick, M.D.
Neuropathologist
Santa Clara Valley Medical Center
San Jose, California
Clinical Assistant Professor
Pathology (Neuropathology) and Neurology
Stanford University Medical Center
Stanford, California

Fred Hochberg, M.D.
Assistant Professor
Neurology Service
Massachusetts General Hospital
Boston, Massachusetts

Harold J. Hoffman, M.D., F.R.C.S.(C)
Professor of Surgery
Division of Neurosurgery
Hospital for Sick Children, Toronto
University of Toronto
Toronto, Ontario
Canada

Mark T. Jennings, M.D.
Memorial Sloan-Kettering Cancer Center
New York, New York

Claude Lapras, M.D.
Professor
Neuro-Chirurgien des Hopitaux de Lyon
Lyon, Cedex
France

Edward R. Laws, Jr, M.D.
Professor
Department of Neurological Surgery
Mayo Clinic
Mayo Medical School
Rochester, Minnesota

Richard P. Moser, M.D.
Assistant Professor of Surgery
Department of Head and Neck Surgery
University of Texas Cancer Center
M. D. Anderson Hospital and Tumor Institute
Houston, Texas

Edward A. Neuwelt, M.D.
Associate Professor of Neurosurgery
Assistant Professor of Biochemistry
Division of Neurosurgery
Oregon Health Sciences University
Portland, Oregon

Gerhard Pendl, M.D.
Associate Professor of Neurosurgery
Allgemeines Krankenhaus der Stadt Wien
Neurochirurgische Univ. Klinik
Vienna, Austria

Russel J. Reiter, Ph.D.
Professor
Department of Anatomy
The University of Texas Health Science Center-San Antonio
San Antonio, Texas

Mark Scott, Ph.D.
Stuart Pharmaceuticals
Wilmington, Delaware

Glenn E. Sheline, M.D.
Professor
Department of Radiation Oncology
University of California Medical School
San Francisco, California

William T. Shults, M.D.
Physician and Surgeon
Chief, Neuro-Ophthalmology
Good Samaritan Hospital and Medical Center
Assistant Professor
Department of Ophthalmology
Clinical Associate Professor
Department of Neurology
Oregon Health Sciences University
Portland, Oregon

Bennett M. Stein, M.D.
Byron Stookey Professor and Chairman
Department of Neurological Surgery
The Neurological Institute
Columbia University College of Physicians and Surgeons
Director of Neurosurgery
Presbyterian Hospital
New York, New York

Kintomo Takakura, M.D.
Professor and Chairman
Department of Neurosurgery
University of Tokyo Hospital
Hongo, Bunkyo-ku, Tokyo
Japan

Clark Watts, M.D.
Professor and Chief
Division of Neurosurgery
University of Missouri
Health Sciences Center
Columbia, Missouri

Benton M. Wheeler, M.D.
Fellow
Department of Hematology/Oncology
Indiana University School of Medicine
University Hospital
Indianapolis, Indiana

Stephen D. Williams, M.D.
Associate Professor
Department of Medicine
Indiana University School of Medicine
University Hospital
Indianapolis, Indiana

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CHAPTER 1

The Challenge of Pineal Region Tumors

EDWARD A. NEUWELT, M.D. and MARY KAY GUMERLOCK, M.D.

INTRODUCTION

Pineal region tumors offer the neurosurgeon a challenge of no small magnitude. The patients may present at any age usually with symptoms and signs of obstructive/noncommunicating hydrocephalus. This initial pattern is complicated by the wide range of tumors arising in this region, each with its own course, prognosis, and optimal treatment. Neuroradiologic evaluation is sensitive but nonspecific regarding etiology. When surgery is a part of the management, further technical challenge is encountered. Because the pineal gland has been relatively unapproachable until recently, little is understood about the malfunctioning human pineal, its clinical presentation, and implications thereof. Much is yet to be learned about its role in circadian rhythms and reproduction. How specific tumor pathology relates to these remains to be studied as well. Thus, besides being a microneurosurgical challenge, pineal region tumors provide new avenues of basic clinical investigation. The following cases emphasize each of these various aspects in treating pineal region tumors.

CASE 1

"Jet Lag" as the Presenting Symptom in a Pineoblastoma

A 51-yr-old neurosurgeon presented with inability to regain his day/night diurnal variation after two transatlantic trips in 6 months. In addition to increased fatiguability, the patient began having episodes of intractable nausea with some vomiting. A CT scan was obtained which showed a 2 cm calcium-containing contrast-enhancing tumor in the pineal region (Fig. 1.1). Angiography showed minimal tumor blush. A ventriculoperitoneal shunt was placed and the patient symptomatically improved. Serum and CSF levels of beta human chorionic gonadotropin (β-HCG) and alpha fetoprotein (AFP) were normal. Ten days later, he was taken to the operating room where gross total excision of a semiencapsulated pineal tumor was carried out. Final pathologic diagnosis returned pineoblastoma. The patient tolerated surgery well but was left with a definite Parinaud's syndrome and a dense hemianopsia both of which resolved over a year. One month following resection, the patient returned to the hospital with evidence of increased intracranial pressure and a CT scan showed an epidural hygroma. This was drained at which time his ventriculoperitoneal shunt was also ligated. The shunt was later removed. Three months postoperatively the patient received radiation therapy (4000-rad whole head, 1500-rad boost to pineal region, and 4000 to 4500-rad spinal). Currently 2 yr after surgery, the patient is quite functional and is swimming every day. His CT scan continues to show a small amount of pineal region calcification, but no evidence of tumor (Fig. 1.2). For obvious reasons he has opted not to return to his profession as a neurosurgeon at this point.

Studies in basic pineal gland function suggest a role in diurnal variation (44). However, it is rare to see a patient with a pineal region tumor complain of insomnia or difficulty with day/night cycles. Perhaps this is in part secondary to the lack of data on human pineal function. While Moore-Ede et al (28) mention melatonin in their review of circadian rhythms in health and disease, there is no mention of pineal region tumors. Nonetheless early work in "diurnal treatment" of such disorders is being reported (20).

It is also unusual for a patient of this age to have such a primitive neuroectodermal tumor. Prognosis is guarded but currently this patient is without evidence of disease clinically or radiographically. Regarding his preoperative "jet lag" symptoms, the patient has not been on any long airplane trips postoperatively to test his diurnal variability. Diurnal melatonin and hormone se-

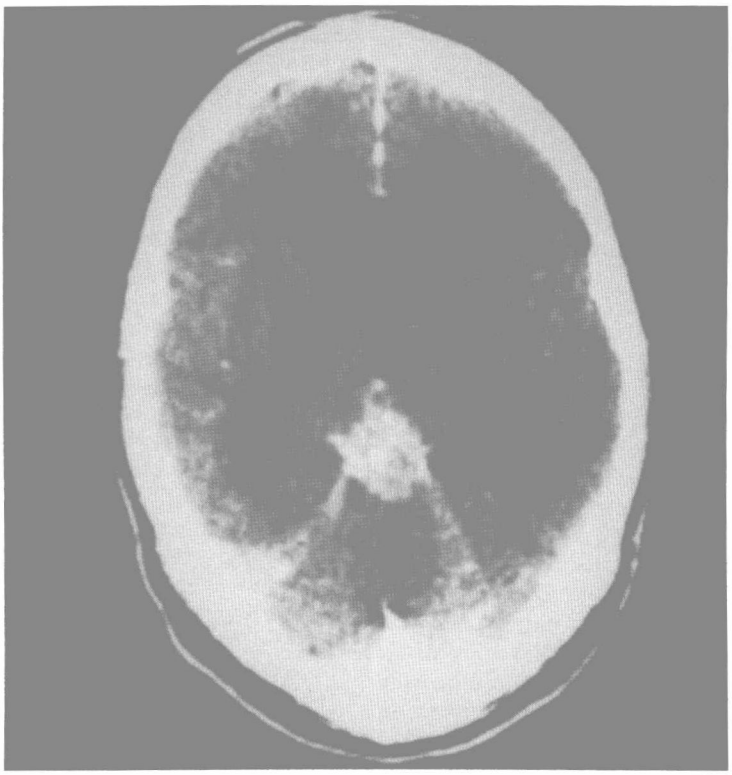

Figure 1.1. Uniformly enhancing pineal region tumor which at the time of surgery was found to be a pineoblastoma.

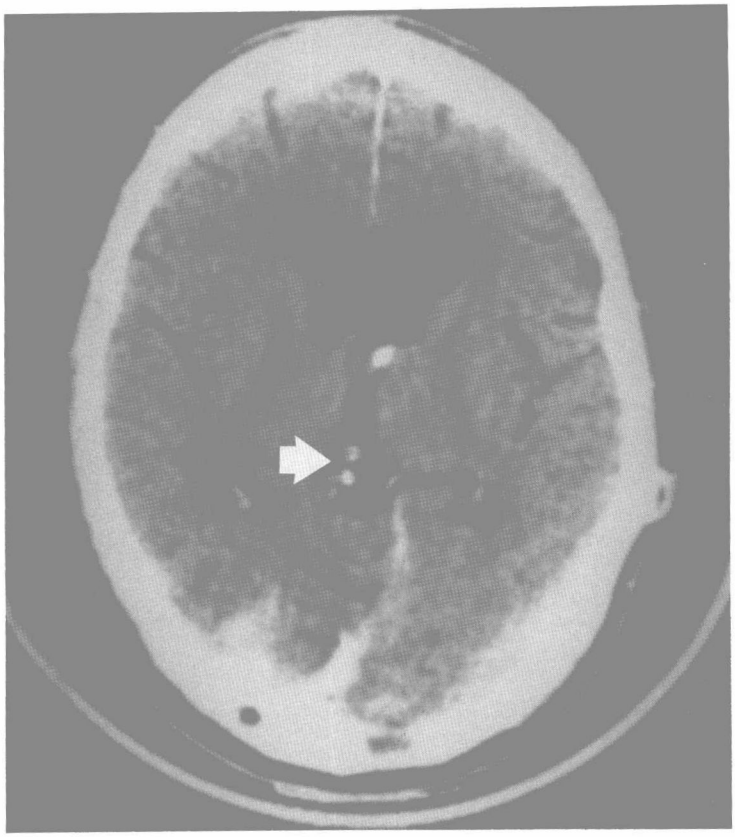

Figure 1.2. Postoperative CT scan 9 months following surgery and radiotherapy, no longer demonstrating an enhancing pineal region tumor. There is a small amount of calcification that remains in the pineal region (*arrow*).

cretion might be interesting to check and follow in a patient such as this.

CASE 2

Disappearance of Plasma Melatonin after Removal of a Neoplastic Pineal Gland

This 17-yr-old white male presented in August of 1981 with progressively severe nocturnal headaches, but no abnormal findings on either general physical or neurologic exam were observed. A CT scan revealed a calcified enhancing partially cystic tumor in the region of the pineal gland. In addition, the CT ventriculogram showed clear evidence of obstructive hydrocephalus (Fig. 1.3). CSF cytology was negative. CSF and serum levels of AFP, and β-HCG were undetectable. Anterior pituitary function was within the normal range. A ventriculoperitoneal shunt was placed and 4 weeks later gross total excision of a well encapsulated pineal tumor was carried out. Microscopic examination revealed a predominantly low grade astrocytoma with Rosenthal fibers (Fig. 1.4*A*). It also contained some less differentiated cells thought to be rests of pineoblastoma (Fig. 1.4*B*). Postoperatively, the patient had a transient left homonymous hemianopsia and Parinaud's syndrome. He subsequently received a localized port of mega-voltage radiation for a total of 5040 rad. Two years postoperatively, aside from some diplopia on far lateral gaze, the patient is doing well and CT scan shows no evidence of tumor.

If complete pinealectomy of a diseased pineal gland is attempted microsurgically, it would be very worthwhile to document complete excision with a marker. In many germ cell tumors of the pineal, for example, the beta subunit of human chorionic gonadotropin and alpha fetoprotein can be useful both diagnostically and in following therapeutic efficacy (31,32,34). In this case, a young man presenting with a typical pineal region tumor was evaluated both pre- and postoperatively for 24-hr variations of plasma me-

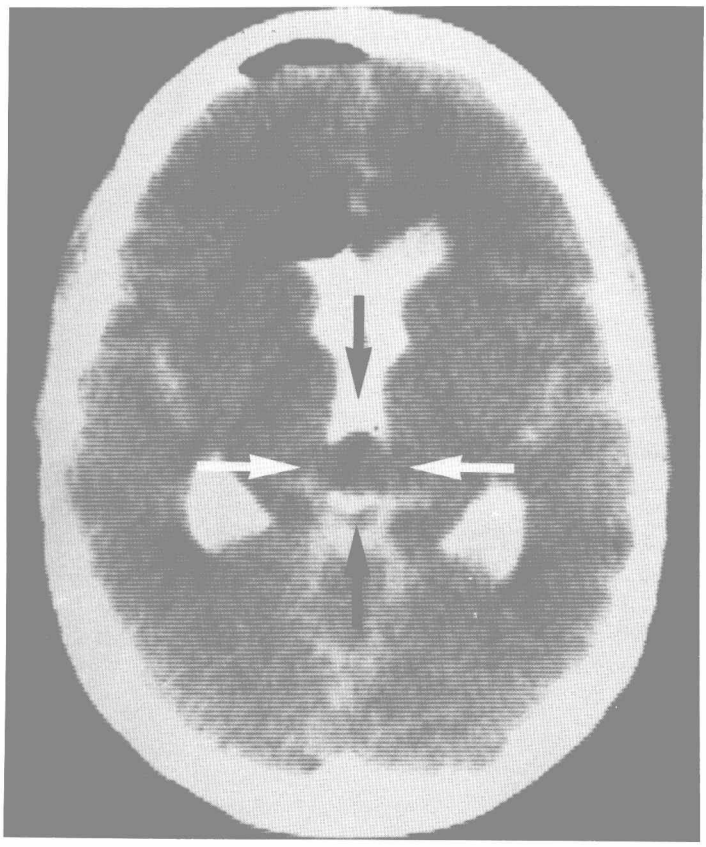

Figure 1.3. Preoperative transaxial CT metrizamide ventriculogram at the level of the lateral ventricles demonstrating a spherical pineal region mass (*arrows*). The low density in the left anterior lateral ventricle is air. (From Neuwelt EA, Levy A: *New England Journal of Medicine*. 308:1132–1135, 1983 (33).)

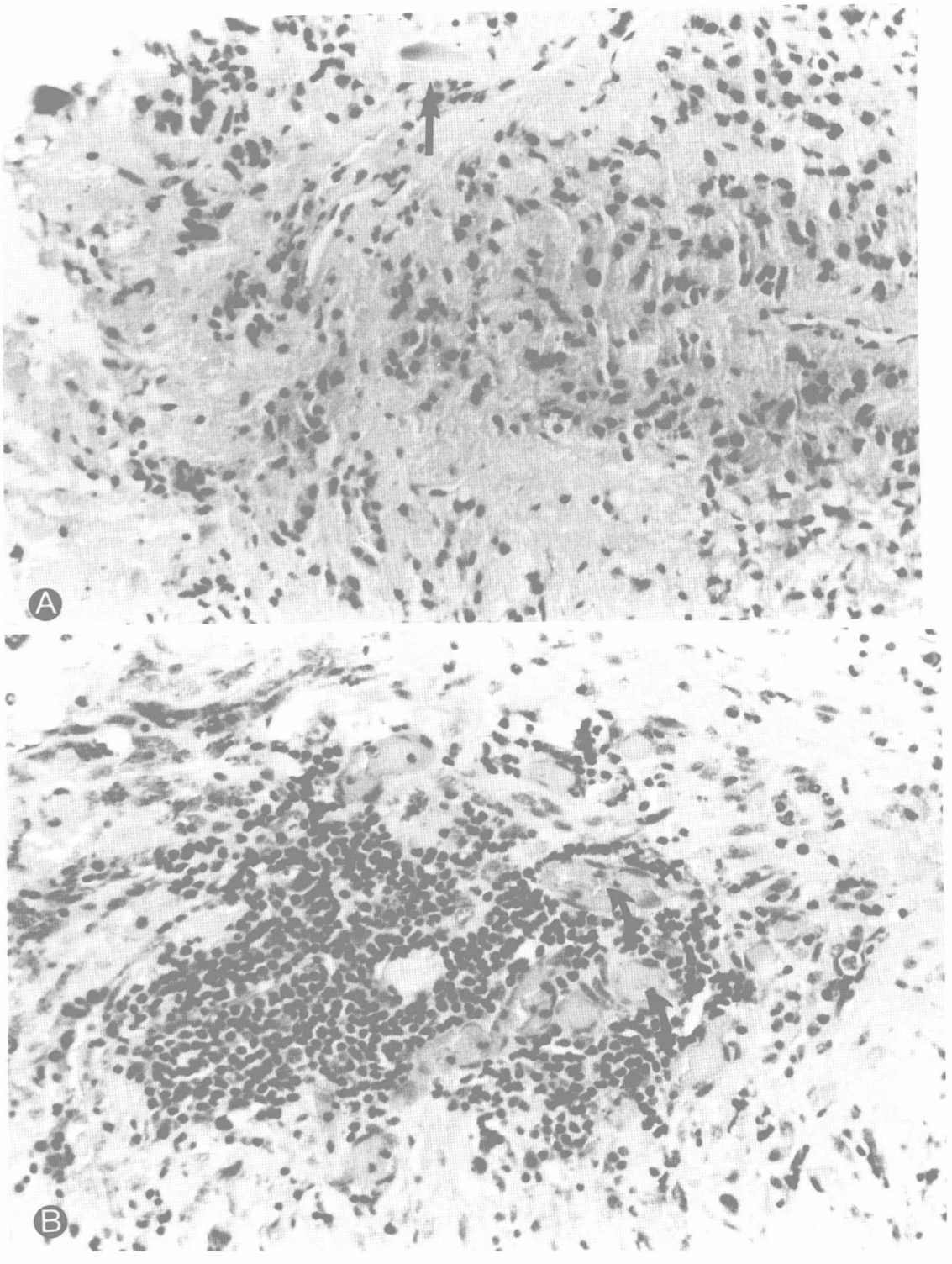

Figure 1.4. *A*, photomicrograph (H & E × 100) of that portion of the well encapsulated pineal tumor thought to be a low grade astrocytoma with Rosenthal fibers (*arrows*). *B*, photomicrograph of that portion of the tumor thought to be pineoblastoma (small dark-staining cells). It also shows capillary proliferation (*arrow*). (From Neuwelt EA, Levy A: *New England Journal of Medicine*. 308: 1132–1135, 1983, (33).)

latonin levels using the gas chromatography-negative chemical ionization mass spectrometric (GC-MS) assay of Lewy and Markey (24). This assay has received increasing recognition for its high degree of accuracy (specificity), sensitivity, and precision (2,17,26,46). Preoperative melatonin plasma levels drawn every 2 hr showed a normal circadian secretory rhythm with levels increasing during the night to 70 pg/ml and decreasing during the day to between 1.5 and 10 pg/ml (Fig. 1.5). Six weeks postoperatively plasma levels were again evaluated every 2 hr over a 24-hr period: at no time could melatonin be detected in the plasma (Fig. 1.5). The patient was on the same drug regimen (phenytoin) during both study periods and was not irradiated until after the second study.

The results of these studies demonstrate that, despite the presence of a pineal tumor, the preoperative circadian variation of plasma melatonin levels was normal. Following gross total tumor resection, plasma melatonin levels disappeared, suggesting that a complete pinealectomy had been performed. More recently another patient (Case 7) was found to have undetectable urinary 6-hydroxymelatonin (a metabolite of melatonin) levels both pre- and postoperatively. The results of his plasma melatonin levels are pending, but it appears that this latter patient's tumor *did* affect pineal function in contrast to the present case.

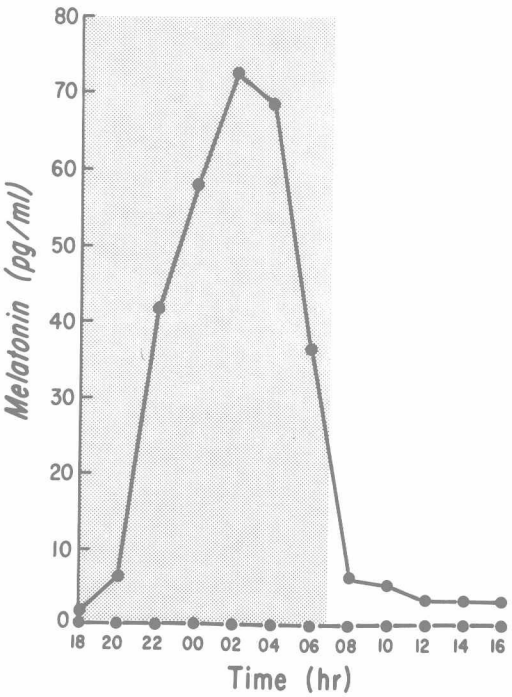

Figure 1.5. Human plasma melatonin levels before and after removal of a tumor-infiltrated pineal gland. Plasma was obtained at 2-hr intervals before (*solid line*) and after (*dashed line*) resection of the pineal tumor. Levels determined by mass spectral assay. The *shaded area* depicts nighttime. The minimal detectable plasma melatonin level by the mass spectral assay is < 1 pg/ml. (From Neuwelt EA, Levy A: *New England Journal of Medicine*. 308: 1132–1135, 1983, (33).)

Plasma melatonin levels may be useful as a marker for neoplasms and other lesions of the pineal gland (3,4,18,56). In previous work using this assay, Lewy and associates (21) and Markey and co-workers (27) were not able to detect any melatonin in the plasma of pinealectomized rats. While such studies have been done in a variety of mammals (1,23,37,38,55,57) they have been difficult to do in man, because pinealectomy is not a common operation. Although the precise utility of melatonin as a tumor marker remains unclear, the fact that the pineal gland appears to be the sole source of plasma melatonin in man indicates that measurement of this hormone may be a reliable means of assessing the completeness of pinealectomy. Moreover, our findings help to validate the measurement of plasma melatonin as a marker for the adrenergic innervation of the pineal gland (54), the phase and period of its endogenous circadian pacemaker (56), and the effects of light in man (22,25).

By age, sex, and neuroradiologic criteria, our patient had a preoperative presumptive diagnosis of germinoma (48,49). At surgery, a well encapsulated pineal tumor with elements of both low grade astrocytoma and pineoblastoma was found and completely removed with little permanent sequelae. Indeed, this patient highlights three crucial issues in the diagnosis and therapy of pineal tumors. First is the danger of presuming that a young male with a pineal tumor has a germinoma or even a radiosensitive tumor. A very similar young patient was recently reported by DeGirolami and Armbrustmacher (5) who was treated with a VP shunt and empiric radiotherapy for a presumed germinoma. The patient expired 7 months after a shunt and radiotherapy, and at autopsy was also found to have a "sharply demarcated, encapsulated" low grade astrocytoma. Clearly, radiotherapy and a shunting procedure alone in our patient would have been a less than adequate therapy. Second, as has been reported previously (32,52), pineal tu-

mors can be of mixed histology. Thus, a stereotactic needle biopsy of a pineal tumor can be not only dangerous due to its proximity to the deep venous system which surrounds the pineal gland (i.e. the vein of Galen, the internal cerebral veins, and the basilar vein of Rosenthal), but also may not provide an adequate tissue sample. Finally, with the advent of microsurgery which can minimize damage to the deep venous drainage system, benign and even malignant pineal tumors can often be completely excised with minimal morbidity and mortality.

On the basis of a 30 month follow-up in one patient, no untoward clinical sequelae have been associated with what appears to be a complete pinealectomy. With regard to the usefulness of melatonin as a tumor marker, further studies are underway.

CASE 3

Presence of Lymphocyte Membrane Surface Markers on "Small Cells" in a Pineal Germinoma

A 16-yr-old boy was first seen with an 18-month history of progressive blurred vision, bifrontal headaches, ataxia, and difficulty with higher cortical functions. About 2 weeks prior to admission he developed projectile vomiting. Physical examination revealed that the left pupil was slightly larger than the right. Both pupils reacted sluggishly to light. There was paralysis of upward gaze; attempts at upward gaze were accompanied by retraction nystagmus. The patient had a decreased ability to converge, although on conjugate lateral gaze to either side he was able to adduct his eyes normally. Motor examination revealed mild right-sided weakness. The remainder of the neurological examination was normal. The patient's CT scan (Fig. 1.6) revealed a massive pineal lesion that enhanced markedly with contrast. Angiography showed the tumor to be essentially avascular. Occipital transtentorial exploration of the lesion and subtotal decompression were carried out. Histological examination showed a germinoma; sections revealed diffuse proliferation of large cells amidst a background of small mononuclear cells (Fig. 1.7). Beta human chorionic gonadotropin and alpha fetoprotein were undetectable by radioimmunoassay in serum and cerebrospinal fluid samples obtained at surgery.

In some series, germinomas account for as many as 50% of tumors in the pineal region (6). Histologically (14) and ultrastructurally (53), the tumor is identical to seminoma of the testes (34). It is characterized by the presence of two types of cells: large cells with abundant clear cytoplasm and sharp cytoplasmic borders; and small mononuclear cells with only scanty cytoplasm. Both histologically (14) and ultrastructurally (53) the "small cells" appear to be lymphoid, although at least at the level of the light microscope they are somewhat similar to pinealoblasts and medulloblasts. To characterize this small cell population further, we assayed for surface markers of lymphocytes in a single-cell suspension prepared from this patient's pineal germinoma.

In this single-cell suspension (32), 81% of the small cells formed rosettes with sheep erythrocytes. The rosetted cells were centrifuged onto slides and stained with Leishman's-Giemsa stains (15). The rosette-forming population (T lymphocytes) was composed exclusively of small mononuclear cells (Fig. 1.8).

The presence of surface immunoglobulins, a B lymphocyte marker (41), was determined using a fluorescence-activated cell sorter. As determined with the cell sorter, 15% of the single-cell suspension bore surface κ-light chains and 18% bore surface λ-light chains. The cells possessing the surface immunoglobulins were of approximately the same diameter as peripheral blood lymphocytes as determined by the laser beam scatter distribution provided by the cell sorter.

Thus, the majority of the small cells have a T cell surface marker. A smaller number of the cells possess surface immunoglobulins characteristic of B cells. Also of interest, a number of plasma cells were seen on the Leishman's-Giemsa stained slides prepared with the cytocentrifuge. Similar studies on a pineocytoma and on a pineoblastoma were negative for B and T cell markers.

The results obtained in this study were confirmed on frozen sections of this patient's germinoma. The hanging drop technique was used to show that the tumor contained many erythrocyte rosette-forming cells and few complement receptor-bearing cells. Thus, these frozen section studies also indicate that the majority of the small cells are T lymphocytes and that a few are B lymphocytes. In addition surface marker studies in a suprasellar germinoma ("ectopic pinealoma") have also confirmed that the small cells are T lymphocytes (34).

Lymphocyte infiltration is characteristic of a number of malignant tumors (40), particularly