8
Tumors of the Endocrine System

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Introduction

The grading of endocrine gland tumors has been difficult, inconsistent, and unrewarding. While the reasons for these problems vary from organ to organ, and from one tumor type to another, in general grading has been hampered by the following issues:

- In many endocrine organs, the transition of hyperplasia to benign neoplasia and then to malignancy includes a spectrum of morphologic changes that are not always easily defined.
- The proposed grading systems are often complex and include a number of variants that are not acceptable to all pathologists. The lack of consensus among pathologists has been one of the main hindrances to grading endocrine tumors.
- The correlation between the microscopic grading and the prognosis of tumors is often poor, and therefore with a few notable exceptions, clinicians do not find the pathologic grading of endocrine tumors to be as useful as that for tumors of other organs systems.

Pituitary Tumors

Most pituitary tumors are classified as adenomas, which are further subtyped as hormonally active or inactive. Hormonally active adenomas are classified on the basis of laboratory and immunohistochemical data as prolactinomas, growth hormone–secreting adenomas, corticotrophic adenomas, gonadotrophic adenomas, thyrotrophic adenomas, and plurihormonal mixed tumors.

Small tumors measuring less than 10 mm in diameter are called microadenomas; those that exceed 10 mm in diameter are macroadenomas. Some macroadenomas have an aggressive growth and tend to recur after surgical resection. Pituitary carcinomas with extracranial metastases are extremely rare (1).

Microscopic grading of pituitary tumors is of no clinical value, because it is not possible to predict which tumors will be aggressive and recur after surgical resection and which will be cured by the initial surgery.

Comments

1. The aggressiveness of pituitary adenomas cannot be predicted from their histologic appearance. Thus,one can disregard the following microscopic findings:
   - Areas of necrosis
   - Bizarre enlarged nuclei
   - Ring or giant nuclei
   - Prominent nucleoli
   - Mitotic figures
2. Prognostic indicators have been reviewed recently by Suhardja et al. (2). The use of modern techniques, such as DNA flow cytometry, has been found to be of no clinical predictive value in assessing the invasiveness or persistence/recurrence pituitary tumors (3).

Thyroid Tumors

Thyroid tumors are classified as benign or malignant. Thyroid adenomas outnumber carcinomas, which account for less than 1% of all thyroid neoplasms.

Thyroid carcinomas are a heterogeneous group of tumors that occur in many histologic forms. Papillary carcinoma accounts for approximately 80% of all such carcinomas, and along with follicular carcinoma, medullary carcinoma, and undifferentiated (anaplastic) carcinoma form the majority of all thyroid tumors seen in general surgical pathology practice. The grading of thyroid tumors is of relative limited clinical significance.

Comments

1. Papillary carcinoma of the thyroid may be graded microscopically (4,5). However, this grading system has not been widely used, and recent reviews of the prognostic factors indicate that the size of the tumor and TNM (tumor-nodes-metastasis) staging are still the best predictors of tumor recurrence or resistance to therapy (6–9).

2. Although follicular carcinoma cannot be graded adequately, the insular component, poorly differentiated carcinoma, the trabecular component, the serum thyroglobulin level before surgery, the patient's age at the time of presentation, the solid component, and vascular invasion have adverse prognostic implications (10,11). The search for insular components seems to be warranted, since this pattern of growth has proven to be an independent risk factor. Hürthle cell pattern also has an adverse prognosis (11).

3. Medullary carcinoma cannot be reliably graded. Nevertheless, it has been observed that certain microscopic findings correlate well with the aggressiveness of these tumors (12). These findings include:
   - High mitotic activity
   - Foci of necrosis
   - Small cell type
   - Squamous differentiation

   The prognosis is adversely affected by the finding of intravascular invasion, perineural invasion, extrathyroidal extension, and lymph node metastases (13). The use of molecular biology and other probes has not contributed significantly to predicting the outcome of treatment (13,14).

4. Undifferentiated carcinoma has an overall poor prognosis. Advanced age of the patient, the presence of necrosis (either focal or extensive), and mitotic count of more than 3 per 10 high-power fields (hpf) are associated with the worst outcome (15).

Parathyroid Tumors

Most parathyroid tumors are benign; parathyroid carcinomas are rare and may occur in both the usual location and ectopically (16,17). Microscopic grading of parathyroid tumors is not warranted, but the pathologist may be asked to contribute to a clinicopathologic effort to distinguishing parathyroid adenoma from parathyroid carcinoma.

Comments

1. Parathyroid adenomas often contain cells with enlarged hyperchromatic nuclei, but these nuclear changes are not a sign of malignancy (18).
2. The clinical and pathologic features favoring the diagnosis of parathyroid carcinoma are:
   - Large size of the tumor
   - Adhesion of a hard tumor to adjacent structures
   - Extremely high serum levels of calcium and parathyroid hormone
   - Persistence of hyperparathyroidism after surgery
   - Microscopic invasion of the capsule and adjacent tissues
   - Vascular invasion
   - Fibrous bands subdividing the tumor into segments
   - Spindle shaped nuclei of tumor cells
   - Mitotic activity
   - High labeling indices with MIB-1 antibodies
3. Many parathyroid tumors thought to be malignant do not recur, and better criteria to distinguish aggressive from nonaggressive parathyroid tumors need to be developed (19).

Adrenal Cortical Tumors

Adrenal cortical tumors can be benign or malignant, hormonally active or inactive (20). Most adrenocortical tumors are benign, and so are classified as adenomas. Adrenocortical carcinomas are rare, with an incidence in the population of 0.5 to 2.0 cases per million.

The malignancy of adrenal cortical carcinomas is not routinely graded. However, microscopic analysis is useful for distinguishing a malignant tumor from a benign adenoma.

Comments

1. The distinction of adrenocortical adenomas from carcinomas is not always simple. The tumor size is important: those weighing more than 50 g and measuring 5 cm or more at the greatest diameter are most likely malignant, whereas those that weigh less and are smaller are usually benign.

2. Several microscopic systems have been proposed to make the distinction more precise. Lau and Weiss (19) recently reviewed 4 of the most widely used systems. Here we present only the system developed by Weiss, because it is the simplest and the easiest to use.

3. The Weiss system for diagnosing adrenal cortical carcinoma and separating it from adrenal cortical adenoma requires finding at least 3 criteria from the following list:
   - High nuclear grade
   - Mitotic rate exceeding 5 mitoses per 50 hpf
   - Atypical mitoses
   - Cells with clear cytoplasm accounting for more than 25% of all cells

- Diffuse growth pattern in more than 30% of the tumor
- Necrosis
- Invasion into the veins
- Invasion into the sinusoids
- Invasion into the capsule

The nuclei are graded according to the system developed by Fuhrman for renal carcinoma, and "high nuclear grade" corresponds to Fuhrman grades 3 and 4. Aubert et al. (20) applied this system to their own material and found a correlation with clinical outcome in 98% of the cases. The same authors reported that immunohistochemical staining with MIB-1 also may help in predicting the malignancy of adrenocortical tumors.

Adrenal Medullary Tumors

Adrenal medullary tumors comprise 2 groups: peripheral neuroblastic tumors (pNT), including neuroblastoma, ganglioneuroblastoma, and ganglioneuroma, and pheochromocytomas, i.e., tumors composed of chromaffin cells that resemble adult medullary adrenal cells. Grading is an important part of the pathologic work-up of peripheral neuroblastic tumors. Pheochromocytomas are not graded microscopically, but microscopic study of these tumors may help in distinguishing the benign from the malignant.

Peripheral Neuroblastic Tumors

Neuroblastoma, ganglioneuroblastoma, and ganglioneuroma are tumors derived from immature sympathetic neuroblasts (21,22). Neuroblastomas most often occur in the adrenals of infants and children, and less commonly in the extra-adrenal locations of the abdomen and thoracic cavity. Ganglioneuroblastomas and ganglioneuromas also can occur in the adrenals, but more often are found in extra-adrenal sites.

For practical purposes, these tumors are grouped under the heading of peripheral neuroblastic tumors and stratified according to the criteria of the International Neuroblastoma Pathology Classification (INPC). The INPC is based on the system developed by Shimada et al. (23) in 1984 and revised subsequently to incorporate molecular/genetic indicators (24–27).

On the basis of clinical, pathologic, and genetic/molecular findings, pNT are classified as tumors with favorable indicators or unfavorable indicators (Table 8-1). By combining these 5 indicators, these patients can be subdivided into 3 groups: low risk, intermediate risk, and high risk (23–25).

The microscopic grading system is based on analysis of the differentiation of tumor cells into Schwann cell-rich stroma and by estimating the proliferative capacity of tumor cells by calculating the mitosis-karyorrhexis index (MKI).

Table 8-1. Classification of peripheral neuroblastic tumors according to the prognostic parameters.

Parameter	Favorable	Unfavorable
Age at diagnosis	Less than 1 year	1 year or more
Clinical stage	Stage 1 or 2 or 4S	Stage 3 or 4
Histopathology	Favorable	Unfavorable
MYCN oncogene	Nonamplified	Amplified
DNA ploidy	Hyperdiploid	Diploid
Urinary catecholamines	Elevated	Low

Source: Modified from Wenig et al. (1997) and Shimada et al (21).

The first step in the classification includes gross examination of tumors for the presence of nodules and a microscopic examination to determine the extent of schwannian differentiation. According to the degree of schwannian differentiation, pNT can be subdivided into 2 major groups (Figure 8-1): tumors that contain less than 50% of schwannian stroma (called "schwannian stroma-poor," or "stroma poor"), corresponding to neuroblastomas, and those with more than 50% of schwannian stroma ("schwannian stroma-rich or dominant," or "stroma rich"), ganglioneuromas, and ganglioneuroblastomas.

Stroma-Rich Peripheral Neuroblastic Tumors

The second step for evaluating schwannian stroma-poor pNT (neuroblastomas) is to analyze them microscopically and classify them into 3 groups undifferentiated, poorly differentiated, and differentiating neuroblastoma (Figure 8-2).

- **Neuroblastoma, undifferentiated**. This tumor is composed of undifferentiated cells whose neuroblastic nature can be definitely proven only by additional immunohistochemical or ultrastructural studies. These neuroblasts have small to medium-size nuclei surrounded with scant cytoplasm that has indistinct borders. The nuclei contain finely granular or stippled ("salt and pepper") chromatin and occasional nucleoli. There is no discernible neuropil between the cells. Foci of necrosis, exudates of fibrin, or collagenous stroma may be seen but should not be mistaken for schwannian differentiation.
- **Neuroblastoma, poorly differentiated**. This tumor contains undifferentiated neuroblasts but also has streaks of neuropil corresponding to focal schwannian differentiation. Up to 5% of all tumor cells differentiate into ganglion cells. These ganglion cells must be distinguished from neuroblasts that have pleomorphic and anaplastic or bizarre nuclei and multiple nucleoli. The extent of neuropil formation varies from tumor to

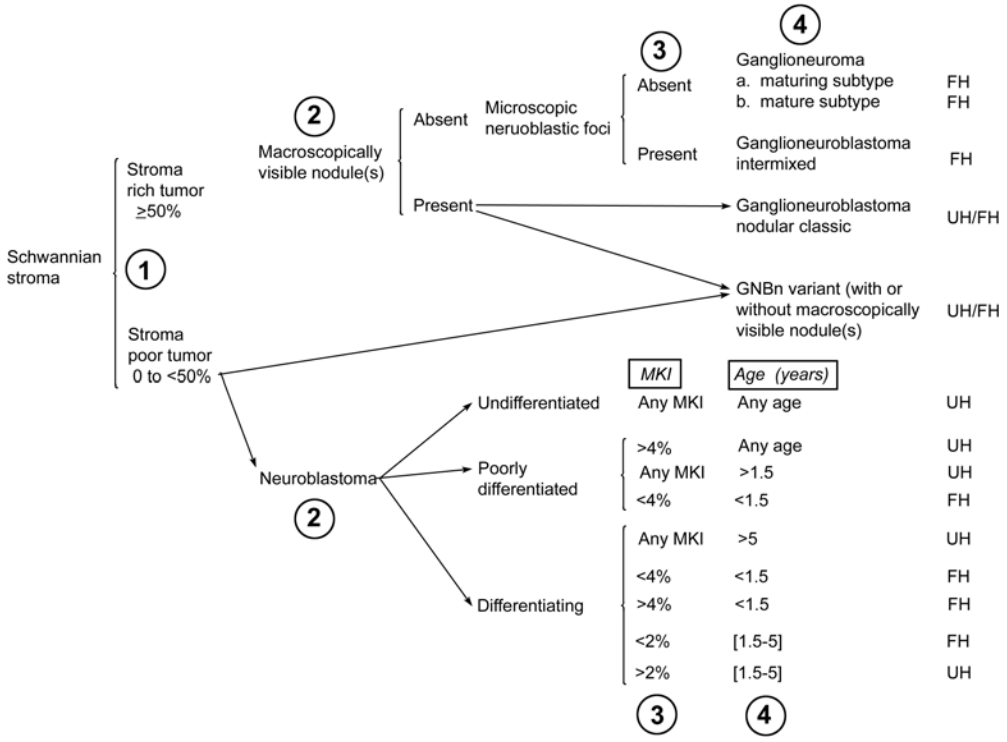


FIGURE 8-1. International Neuroblastoma Pathology Classification. The circled numbers correspond to the recommended steps described in the text, and are based on diagrams in the papers of Shimada et al. (21–23), and Peuchmaur et al. (24).

tumor, as well as from one section of the same tumor to another.

- **Neuroblastoma, differentiating**. This tumor is composed of neuroblastic cells that show focal neuronal differentiation. Differentiating neuroblasts and ganglion cells account for 5% or more of all tumor cells. Differentiating neuroblasts show synchronous enlargement of nuclei and cytoplasm. The vesicular nucleus of these cells is located excentrically in a well-developed cytoplasm, which appears eosinophilic or amphophilic and has clear-cut cell borders. Mature ganglion cells may be observed as well.

The extent of schwannian stroma formation varies, but by definition stroma comprises less than 50% of the entire tumor. The amount of schwannian neuropil is not critical for distinguishing poorly differentiated from differentiating neuroblastoma. It is usually most prominent at the periphery of tumor nests, but does not lead to the formation of nodules or a distinct separation of the undifferentiated from the differentiated part of the tumor. The continuity between the stroma-poor and stroma-enriched parts of differentiating neuroblastoma is an important feature of these tumors, allowing them to be distinguished from ganglioneuroblastoma nodular type.

The third step in evaluating schwannian stroma-poor pNT includes counting of mitoses and karyorrhectic nuclei (MKI). Mitotic figures are recognized by their rod-shaped condensation of chromatin, spiked projections of chromatin, and a lack of nuclear membrane. Karyorrhexis leads to condensation of the chromatin and fragmentation of nuclear material, accompanied by eosinophilic condensation of the cytoplasm. It is necessary to count 5000 cells and then express the MKI as low (2% [<100/5000]), intermediate (2–4% [100–200/5000]), or high (>4% [>200/5000]).

The fourth step involves inclusion of clinical data, primarily the age of the patient. Using the guidelines outlined in Figure 8-1, the histologic findings are then classified as favorable histology (FH) or unfavorable histology (UH).

Stroma-Rich Tumors

The second step for tumors that contain more than 50% of schwannian stroma, or "stroma-rich tumors," involves evaluation for nodularity. Nodules may be visible on gross examination or only microscopically.

The third step for evaluating tumors that show no nodularity includes a microscopic examination to determine whether the tumor contains neuroblastic cells. If no neuroblastic foci are found, the tumor is classified as ganglioneuroma, maturing subtype; if microscopic neuroblastic cells are present, it is classified as ganglioneuroblastoma, intermixed. Both of these tumors

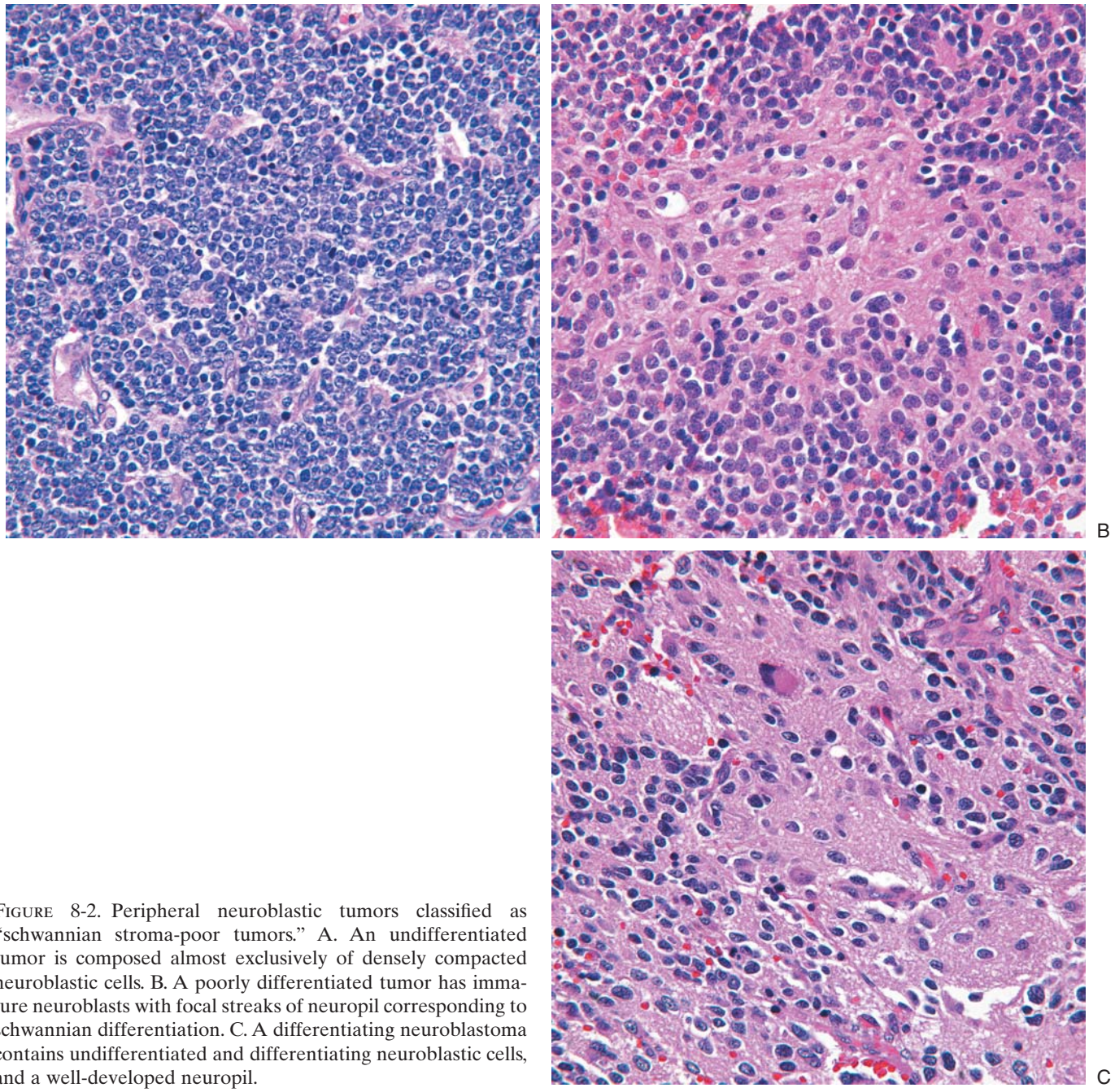
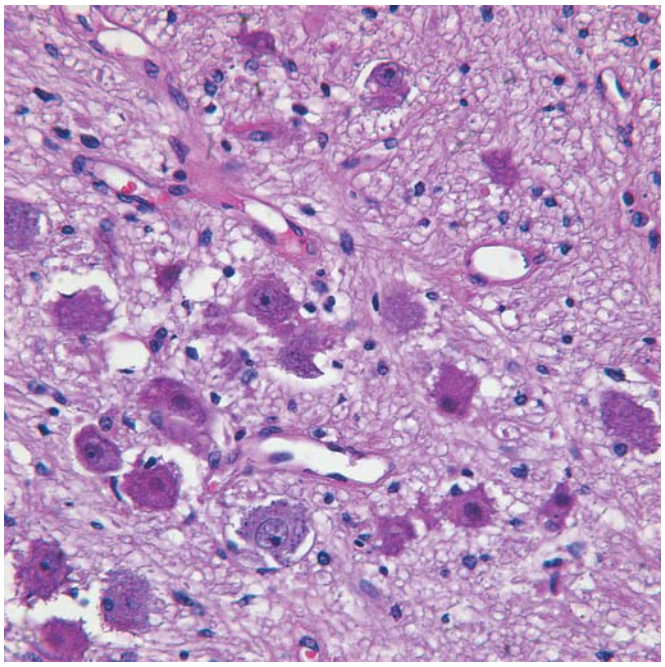


FIGURE 8-2. Peripheral neuroblastic tumors classified as "schwannian stroma-poor tumors." A. An undifferentiated tumor is composed almost exclusively of densely compacted neuroblastic cells. B. A poorly differentiated tumor has immature neuroblasts with focal streaks of neuropil corresponding to schwannian differentiation. C. A differentiating neuroblastoma contains undifferentiated and differentiating neuroblastic cells, and a well-developed neuropil.

have favorable histology. If macroscopically visible nodules are present, the tumor may be classified as ganglioneuroblastoma nodular, classic, or variant (GNBn). Some of the ganglioneuroblastoma variants have no macroscopically visible nodules, but are associated with metastases that show neuroblastomatous features.

The principal features of the stroma-rich tumor are illustrated in Figure 8-3 and briefly summarized as follows:

- **Ganglioneuroma.** This tumor is composed predominantly of ganglioneuromatous stroma. If it is composed of mature Schwann cells and ganglion cells, it is subclassified as ganglioneuroma, mature subtype. If it also contains foci of differentiating neuroblasts, it is subclassified as ganglioneuroma, maturing subtype. Maturing neuroblastomatous cells are intermixed with schwannian cells and do not form distinct nests, as in the intermixed form of ganglioneuroblastoma.
- **Ganglioneuroblastoma, intermixed**. Ganglioneuromatous tissue forms more than 50% of the tumor mass. However, this tumor also contains residual microscopic neuroblastic foci, and it must be differentiated from ganglioneuroblastoma, nodular subtype, a tumor that



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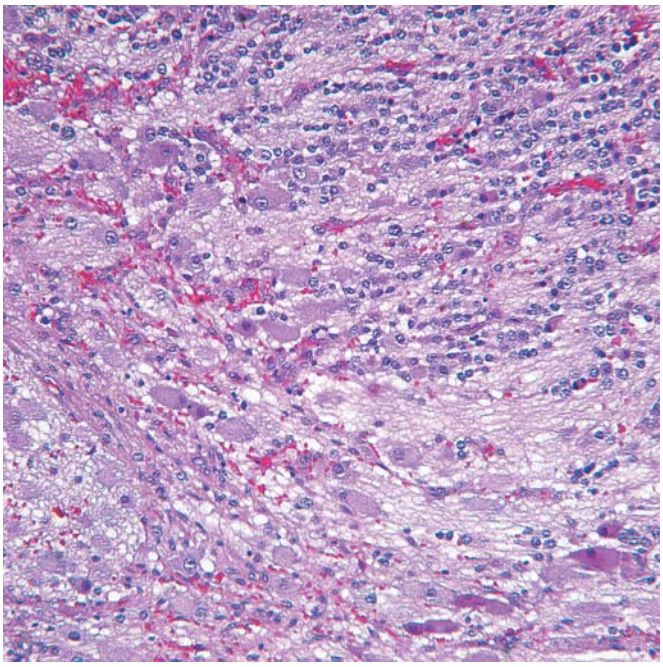

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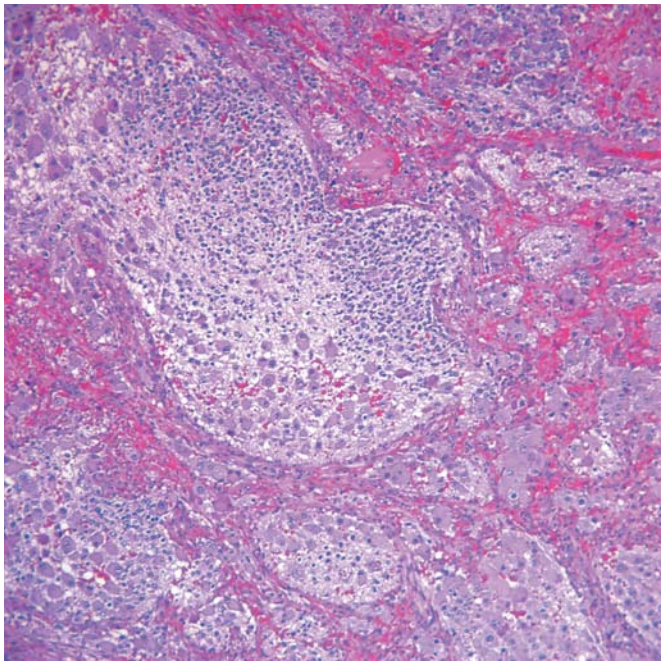

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FIGURE 8-3. Peripheral neuroblastic tumors classified as "schwannian stroma-rich tumors." A. A ganglioneuroma, mature, reveals ganglion cells and schwannian cells. B. A ganglioneuroma, maturing subtype, consists of maturing neuroblasts and ganglion cells in a schwannian stroma. C. Ganglioneuroblastoma, intermixed, is composed predominantly of ganglioneuromatous tissue, which forms more than 50% of the entire tumor. However, it also contains residual microscopic neuroblastic foci, seen as small blue cells.

contains a hemorrhagic nodule or nodules composed of highly aggressive tumor cells.

- **Ganglioneuroblastoma, nodular.** Typically, this tumor may present a single hemorrhagic nodule, or several hemorrhagic nodules surrounded by grayish white tissue. Microscopically, it has a characteristic composite nature, containing both stroma-rich and stroma-poor nodules. Thus, some nodules are composed of undifferentiated neuroblastic cells, whereas others have the features of ganglioneuroblastoma intermixed, and ganglioneuroma.
- **Ganglioneuroblastoma variant**. This tumor can be nodular on gross examination or show no nodularity (26). Those that are not nodular may have metastases. Some tumors in this category have more and some have less than 50% of schwannian stroma, and the nodules can be classified as favorable or unfavorable. The favorable nodules include poorly differentiating or differentiating, and low or intermediate MKI tumors in children under age 1.5 years. The unfavorable nodules in children under age 1.5 years are composed of undifferentiated cells and have a high MKI. In the age group

Table 8-2. Classification of pancreatic islet cell tumors.

Tumor type	Size (cm)	Mitoses (per 10 hpf)	Proliferation index (% cells reactive with Ki-67 or MIB-1)	Hormonal activity
Adenoma	<2	<2	<2	Yes
Tumor of uncertain malignant potential	>2	0–3	1–5	Yes
Low-grade endocrine carcinoma	>3	1–10	1–10	Yes
High-grade endocrine carcinoma	>10	>10	>10	No or weak

Source: Modified from Solcia et al. (1997).

from 1.5 to 5 years, the nodules are composed of undifferentiated or poorly differentiated tumors, with an intermediate or high MKI. In children over age 5 years, all tumors of this type are considered to have unfavorable histology.

Comments

1. The grading and prognostic stratification of peripheral neuroblastic tumors are constantly upgraded with data obtained by studies based on the application of cytogenetics, immunohistochemistry, and molecular biology (26,27). Ultimately, this will lead to new revisions of the INPC criteria.

2. Pheochromocytomas are not routinely graded. Most pheochromocytomas are benign, but approximately 10% are malignant (22). Microscopic data are used for predicting the malignancy of these tumors, although this might be extremely difficult (28). Findings favoring a diagnosis of malignancy include:

- Invasive growth such as capsular invasion, vascular invasion, or invasion of the periadrenal fat tissue
- Architectural features that include "large nests" exceeding 3 to 4 times the size of normal paraganglia, diffuse growth of tumor cells, increased cellularity with nuclear monotony, and central confluent necrosis
- Cellular and nuclear features such as spindle-shaped or small cells, cellular and nuclear pleomorphism, nuclear hyperchromasia, and macronucleoli
- Mitoses, with increased activity (>3 per 10 hpf) and atypical mitoses

Thompson has proposed a scoring system for predicting the malignancy of pheochromocytoma (29).

Islet Cell Tumors of the Pancreas

Tumors of the islets of Langerhans can be classified as hormonally active and hormonally inactive, and benign or malignant (30,31). Microscopic grading is not routinely practiced.

Comment

1. On the basis of microscopic findings, it is not easy to predict which islet cell tumor will be clinically benign and which will have more aggressive growth and metastasize. The only exception is the small cell carcinomas that resemble small cell ("oat-cell") carcinomas of the lungs, which are highly malignant and are readily identifiable microscopically.

2. The criteria for classifying islet of Langerhans cell tumors include:

- Macroscopic data, such as the size of the tumor and the presence of metastases
- Microscopic findings
- Immunohistochemical data
- Mitotic activity and immunohistochemical staining of nuclei with antibodies to proliferation markers (Ki-67 or MIB-1)
- Hormonal activity of tumors and hormonal syndromes

3. Overall, small and functionally active tumors and those that have few mitoses and show low proliferative activity tend to be benign, whereas the opposite is true for large tumors and those that have already metastasized. Thus, most insulin-secreting tumors are small and benign, but even in this group some are malignant (32). Keeping in mind that precision is not possible at present, it is advisable to apply a multimodal analysis to every islet cell tumor and try to classify it into 1 of the 4 possible categories: adenoma, tumor of uncertain malignant potential, low-grade endocrine carcinoma, and high-grade endocrine (small cell) carcinoma (Table 8-2).

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