An Algorithmic Approach to Sellar Region Masses

B. K. Kleinschmidt-DeMasters, MD; M. B. S. Lopes, MD, PhD; Richard A. Prayson, MD

• ***Context.***—**Most sellar region masses (85%–90%) are pituitary adenomas; however, other neoplasms or even inflammatory or cystic nonneoplastic lesions may occasionally be encountered in this location. A practical, non–electron-microscopically based approach is essential for the daily practice of diagnosing and subclassifying adenomatous and nonadenomatous sellar region lesions.**

Objective.—**To provide an algorithmic approach to sellar region masses for the pathologist and to formulate a cost-effective, limited panel of stains and immunostains that can be used in daily practice at most small to medium-sized centers.**

Design.—**Pool collective experience of 3 neuropathologists practicing at academic medical centers with expertise in diagnosis and treatment of sellar region masses to craft a single-page algorithmic diagram and to liberally illustrate the range of lesions present in the sellar region.**

Results.—**After formulating a differential diagnosis, the general pathologist can generate a confident final diagnosis of adenoma using 1 histochemical (reticulin) and 1 immunohistochemical (synaptophysin) stain, supplemented by 5 immunohistochemical stains (CAM5.2, follicle-stimulating hormone, growth hormone, prolactin, and adrenocorticotropic hormone), which provide subtyping of the adenoma in the overwhelming majority of examples. CAM5.2 and clinical information further help identify clinically aggressive variants such as sparsely granulated growth hormone adenomas and silent adrenocorticotropic hormone adenomas, respectively. MIB-1, thyroid transcription factor 1, and S-100 protein can be of further assistance in select cases where increased mitotic activity or possible nonadenomatous spindle cell lesions are suspected.**

Conclusions.—**Adenomas, normal anterior or posterior gland, and nonadenomatous masses can be easily diagnosed in a nontertiary pathology laboratory setting.**

(*Arch Pathol Lab Med.* 2015;139:356–372; doi: 10.5858/arpa.2014-0020-OA)

The overwhelming majority of sellar region masses are pituitary adenomas (85%), followed by craniopharyngiomas (3%), Rathke cleft cysts (2%), meningiomas (1%), and metastases (0.5%); all other lesions, such as hypophysitis, pituicytoma, spindle cell oncocytoma, and granular cell tumor of neurohypophysis, are rare lesions.[1] Therefore, an algorithmic approach to diagnosing these lesions, some of which are quite uncommon, is warranted for the general surgical pathologist.

The algorithmic approach to pituitary region masses starts at the time of intraoperative consultation. Pathologists are varied in their use of touch preparations (TPs), squash/crush preparations, and/or frozen sections.[2] Touch preparations may be the least familiar to pathologists but have the advantage of excellent cytologic detail and usually readily allow distinction between pituitary adenoma and normal anterior or posterior pituitary gland, based on the abundant number of cells that exfoliate from pituitary adenomas with a disrupted acinar pattern and the usual absence of large numbers of shed cells from either normal anterior or posterior gland.

Distinguishing normal nonadenomatous anterior pituitary gland from pituitary adenoma is best achieved through a combination of information gleaned from the TP and the frozen/permanent sections, because the latter may show crush artifact and the ability to distinguish preservation of acinar pattern either at frozen or permanent section can be seriously compromised by this. Pituitary adenomas will usually have sufficient disruption of the acinar pattern that the cells readily shed onto the slide when gentle pressure is applied to the specimen; numbers of cells are relatively parallel to the size of the tissue fragment. Identifying monotony of the shed cells is critical in diagnosing adenoma, as opposed to the mixed cell population (chromophobes, acidophils, basophils) of normal anterior pituitary. Hematoxylin-eosin (H&E), rather than Diff-Quik or other monochromatic stains, should be used on both touch imprints and frozen sections to distinguish the cytoplasmic differences in the 3 anterior pituitary general cell types.

Accepted for publication April 9, 2014.

From the Departments of Pathology, Neurology, and Neurosurgery, Anschutz Medical Campus, University of Colorado School of Medicine, Aurora (Dr Kleinschmidt-DeMasters); the Departments of Pathology and Neurosurgery, University of Virginia School of Medicine, Charlottesville (Dr Lopes); and the Department of Anatomic Pathology, Cleveland Clinic Foundation, Cleveland, Ohio (Dr Prayson).

The authors have no relevant financial interest in the products or companies described in this article.

This manuscript represents information presented by the authors at the 2013 United States and Canadian Academy of Pathology American Association of Neuropathologists companion meeting; March 2, 2013; Baltimore, Maryland; and a short course presented at the 2013 College of American Pathologists annual meeting; October 13, 2013; Orlando, Florida.

Reprints: B. K. Kleinschmidt-DeMasters, MD, Department of Pathology, University of Colorado School of Medicine, 12605 E 16th Ave, MS F768, Aurora, CO 80045 (e-mail: bk.demasters@ucdenver.edu).

Because TPs are not routinely used by all pathologists, examples from various types of pituitary adenomas are illustrated in Figure 1. Numerous (Figure 1, a) and monotonous (Figure 1, b) adenoma cells allow distinction from normal anterior pituitary gland. Extensive necrosis or fibrosis in an adenoma may reduce the numbers of adenoma cells that exfoliate, but this is uncommon. In general, it can be difficult to diagnose with confidence the specific subtype of adenoma from the TP. In general, gonadotroph or null cell adenomas tend to have scant cytoplasm and bland nuclear cytologic features (Figure 1, b). Occasional examples with rosettelike clusters should not be mistaken for ependymomas or metastatic papillary adenocarcinomas (Figure 1, c). Densely granulated growth hormone (GH) adenomas (Figure 1, d) often show more cytoplasm than gonadotroph/null cell adenomas (Figure 1, b), and sparsely granulated GH adenomas (Figure 1, e) may additionally show considerable nuclear pleomorphism. Salt-and-pepper "neuroendocrine" nuclei are most typical in TPs from prolactinomas (Figure 1, f). Among the several variations that can occur in adenomas are multinucleation (Figure 1, g), individually enlarged nuclei (Figure 1, h), rare mitotic figures (Figure 1, i), and focal hemosiderin pigment (Figure 1, j), the latter seen in cases with remote clinical or subclinical bleeding into the adenoma. None of these features should alter diagnosis of pituitary adenoma at time of intraoperative consultation.

Frozen sections, in addition to TPs, are optimal in samples with sufficient amounts of submitted tissue, and thus multiple different types of preparations can be made on the same specimen for comparison and diagnosis. Frozen sections have the distinct advantage of illustrating architectural details of both pituitary adenomas and their less frequent sellar region counterparts.

At the time of examination of either frozen or permanent section, an algorithmic approach to sellar region masses can be useful. In keeping with our previous work on developing relatively simple 1-page algorithms that can be useful in practice,[3,4] we have now developed an algorithmic approach to sellar region masses, illustrated in Figure 2.

IS THIS NORMAL PITUITARY GLAND?

The first decision point is whether the submitted tissue is normal pituitary gland or the most common sellar region mass, a pituitary adenoma. At time of permanent section, the single most valuable stain is the reticulin stain to distinguish the preserved pattern in normal anterior pituitary gland from the disrupted pattern in pituitary adenoma; unfortunately, reticulin stains at the time of intraoperative consultation are usually unavailable and/or impractical.

Normal gland may be encountered in cases where there is a cyst or actual tumor (adenoma, craniopharyngioma) nearby, but the adjacent tissue is additionally sampled. Normal anterior pituitary gland shows an acinar pattern best outlined by reticulin stain and assortment of cell types with varying tinctures of basophilic, acidophilic, or chromophobic cytoplasm on H&E or special stains, such as periodic acid-Schiff–orange G. Reticulin stain should be performed on all specimens where it is unclear whether one is dealing with either normal anterior gland or adenoma, based on the H&E. A reticulin stain can often reveal small quantities of anterior gland that were not otherwise suspected to be present; these usually occur at the edges of adenoma tissue fragments, and recognizing that these are present can avoid miscalling entrapped normal pituicytes with their varied immunoreactivity patterns as part of the adenoma.

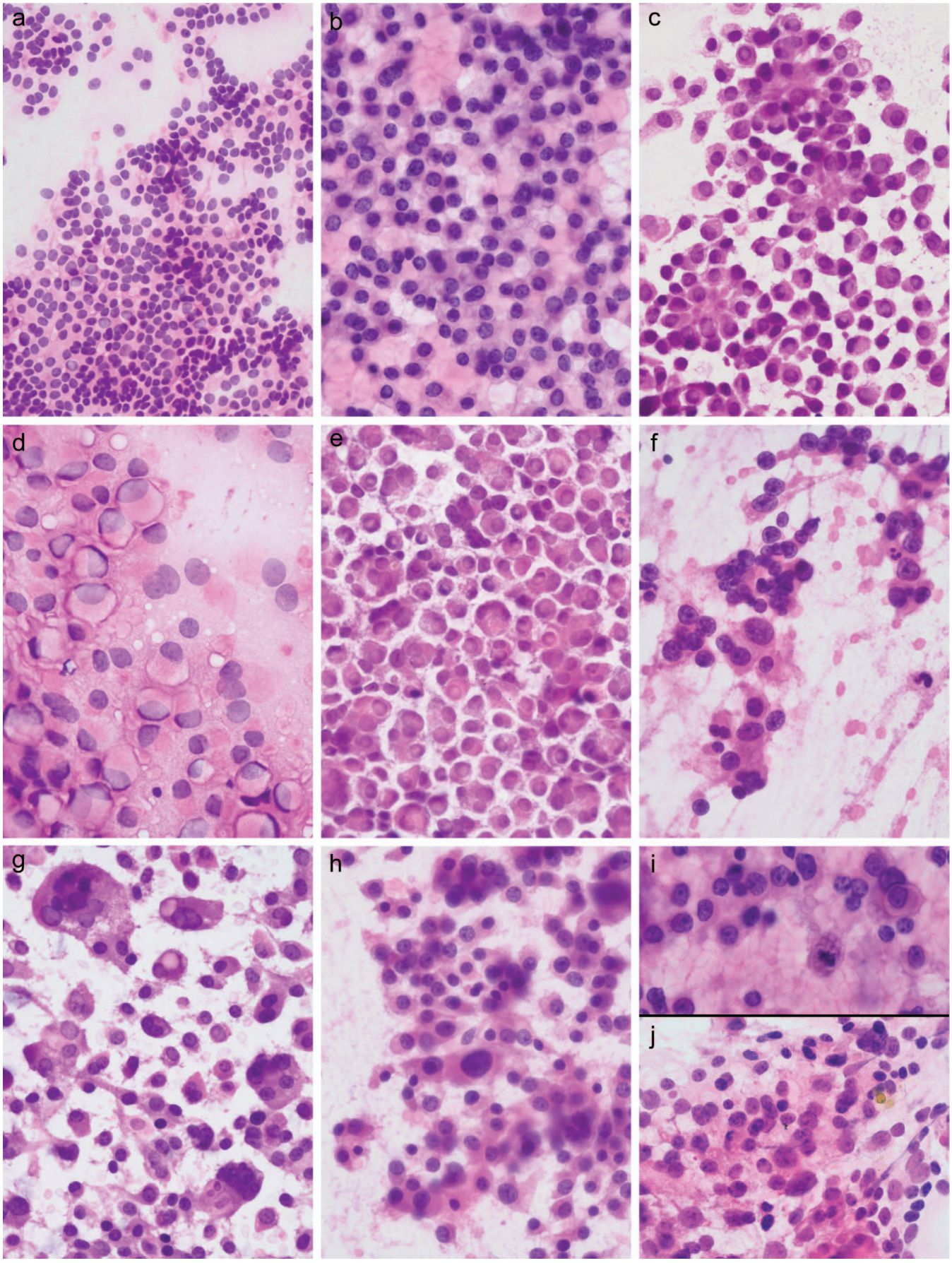
Figure 3 illustrates crushed/compressed normal anterior gland at upper left in an adenoma specimen on H&E (Figure 3, a), but better appreciated on reticulin stain (Figure 3, b). Both normal anterior pituitary gland and pituitary adenoma are immunoreactive for synaptophysin (Figure 3, c); immunostaining for CAM5.2 (anti-cytokeratin peptide with migration ratio of approximately 52 kDa, corresponding with Moll peptide 8) is more variable, both within different normal anterior pituitary cell types and within adenomas, some of which have negligible immunostaining (Figure 3, d). Immunohistochemistry (IHC) for specific anterior pituitary hormones (GH, adrenocorticotropic hormone [ACTH], prolactin [PRL], α subunit [ASU], follicle-stimulating hormone [FSH], thyroid-stimulating hormone, and luteinizing hormone [LH]) highlights the assortment of cell types in any compressed normal anterior pituitary gland in a specimen. This is illustrated in Figure 3, e, where abundant PRL IHC is present in the normal gland at upper left, but not in the gonadotroph adenoma. All other hormones were also present in the normal gland in this case (not illustrated), a feature best appreciated when a full panel of anterior pituitary hormone antibodies is used.

In contrast, in most pituitary adenomas, either a single hormonal type (as in most pure prolactinomas and corticotroph adenomas) is present, or common combinations of hormones (FSH-LH-ASU or GH-PRL with occasional ASU) are found. True plurihormonal adenomas with unusual combinations of hormonal types are uncommon (see algorithm, Figure 2) and the pathologist should always reexamine the specimen in such cases to exclude the possibility of entrapped normal anterior pituicytes, some of which can occasionally be found at the edges of adenoma fragments, admixed with and surrounded by adenoma cells.

Normal posterior gland may be included as a small fragment in what is otherwise obviously a pituitary adenoma or some other sellar region mass (Figure 3, f), or may be the majority of a small biopsy sample, especially if the neurosurgeon is resecting a cystic lesion that occurs at the junction between anterior and posterior pituitary gland, that is, a Rathke cleft cyst. Normal posterior gland is unlikely to be mistaken for a pituitary adenoma, but can readily be misinterpreted as a fibrous meningioma or even an uncommon pituitary region tumor to be discussed below, the pituicytoma. The key feature of the posterior gland at the time of permanent section is that axons can be readily identified with antibodies directed against synaptophysin (posterior gland lower right; Figure 3, g), neurofilament (Figure 3, h) and nuclear thyroid transcription factor 1 (TTF-1; Figure 3, i). Normal posterior gland is relatively hypocellular and devoid of Rosenthal fibers, eosinophilic granular bodies, or a biphasic pattern, but confusion with pilocytic astrocytoma is also possible. One caution is that Herring bodies normally occur in posterior gland and can be confused with the eosinophilic granular bodies seen in pilocytic astrocytomas. Pilocytic astrocytoma is never diffusely immunoreactive for any of these immunostains, however.

IS THIS THE MOST COMMON SELLAR REGION MASS, A PITUITARY ADENOMA?

Once normal anterior or posterior gland is identified or excluded at the time of intraoperative or permanent section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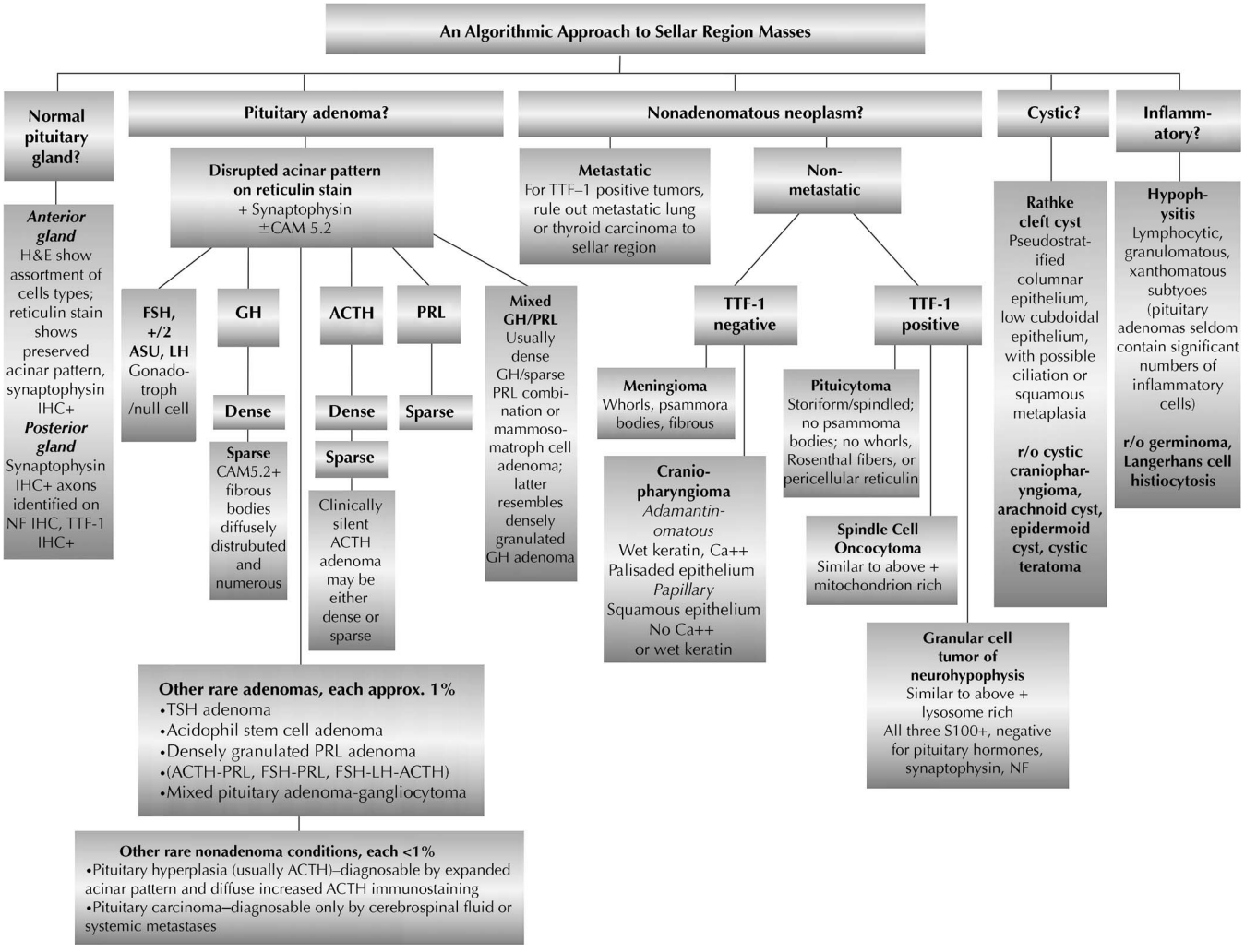

Figure 2. *An algorithmic approach to sellar region masses allows the pathologist to confidently work through the questions of whether this is normal pituitary gland, pituitary adenoma, a neoplasm but not an adenoma, or a nonneoplastic process that is either cystic or inflammatory. Abbreviations: ACTH, adrenocorticotropic hormone; ASU, α subunit; Ca++, calcified psammoma body calcifications; FSH, follicle-stimulating hormone; GH, growth hormone; H&E, hematoxylin-eosin; IHC, immunohistochemistry; LH, luteinizing hormone; NF, neurofilament; PRL, prolactin; r/o, rule out; TSH, thyroid-stimulating hormone; TTF-1, thyroid transcription factor 1.*

review, the second decision is whether the lesion is the most common mass in the sella, a pituitary adenoma. Most adenomas display rather patternless sheets of cells, either on frozen or permanent section, and this is readily appreciated by most pathologists. However, occasional variations in architectural pattern can occur in adenomas and be diagnostically confusing, but unrelated to prognosis. This includes a sinusoidal pattern (Figure 4, a), macronodular

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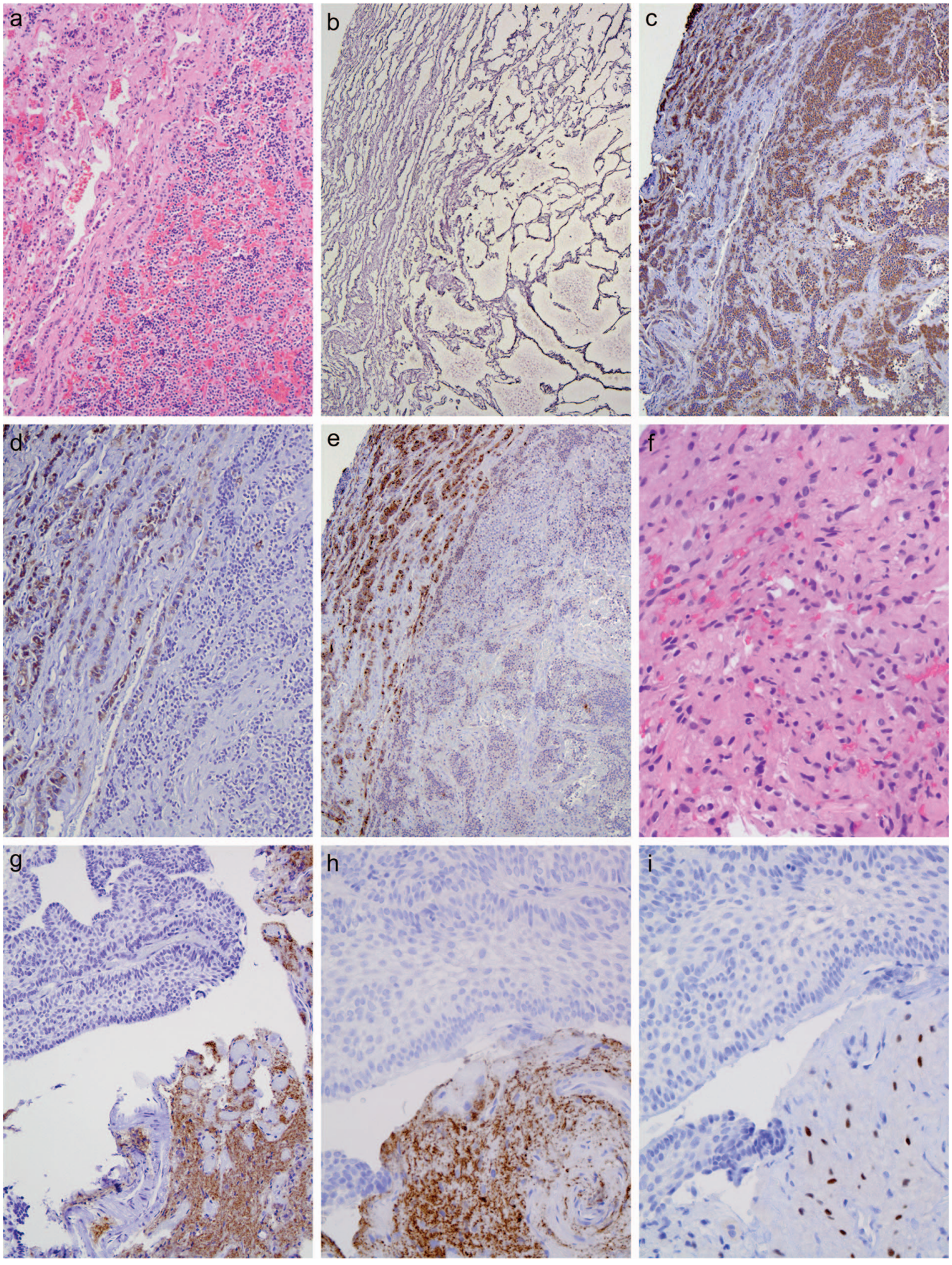
Figure 1. *a, Abundant exfoliation of a monotonous population of cells is typical of a pituitary adenoma on touch preparation; this is the most common type of adenoma to come to surgical excision, a gonadotroph/null cell adenoma. b, High-power photomicrographic view of the same touch preparation further demonstrates the monotony not only of nuclei, but of the cytoplasm; note the scant volume of cytoplasm typical of a gonadotroph/null cell adenoma. Hematoxylin-eosin (H&E) staining is necessary to appreciate this cytoplasmic detail. c, Occasional gonadotroph/null cell adenomas will demonstrate clustering of cells, paralleling the perivascular pseudorosette-like formation that can occur on permanent sections. d, Touch preparation of a densely granulated growth hormone (GH) adenoma demonstrates a larger cytoplasmic volume than is seen in the gonadotroph/null cell adenomas in a through c. However, definitive diagnosis of this as a densely granulated GH adenoma awaits permanent sections and immunohistochemistry. e, Touch preparation from a sparsely granulated GH adenoma can show significant nuclear variation in size and morphology; this pleomorphism should not negate consideration of pituitary adenoma on touch preparation. f, Touch preparation of a prolactinoma demonstrates the typical dotlike nucleolus and chromatin pattern seen in this pituitary adenoma type. g, Rare pituitary adenomas may demonstrate multinucleation, as does this gonadotroph adenoma. h, Occasional nuclear enlargement can be seen in pituitary adenomas and is a helpful feature in distinguishing adenoma from normal anterior pituitary gland when present, although the monotony and volume of the exfoliation is more diagnostic of adenoma. i, The finding of rare mitotic figures further ensures that this is an adenoma and not normal gland; the finding of mitotic figures should prompt performance of MIB-1 cell cycle labeling index on the permanent section. j, Occasional pituitary adenomas will show golden-brown hemosiderin pigment as a product of remote clinical or subclinical bleeding into these vascular pituitary adenomas (H&E, original magnifications ×200 [a] and ×600 [b through j]).*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appearance on reticulin stain (Figure 4, b), or interesting festoonlike features (Figure 4, c). Clear cell–like appearance is usually seen in gonadotroph/null cell adenomas (Figure 4, d). Within some adenomas there may be varying-sized cysts, with or without epithelial lining or mucinous content (Figure 4, e); cholesterol clefts due to previous bleeding into the tumor (Figure 4, f); macrophages (Figure 4, g); and even very rare metaplastic changes such as osseous metaplasia (Figure 4, h; with confirmation of adenoma by synaptophysin immunostaining, Figure 4, i). Rare osseous metaplasia should be distinguished from bony invasion of the sellar floor by adenoma (Figure 4, j), in which the invaded bone has thinner trabeculae. Osteoblastic changes do not occur with pituitary adenomas as they invade bone.

A minimal panel of stains and immunostains necessary to work up a pituitary adenoma includes reticulin (which should be performed on all pituitary tissues submitted for surgical pathologic examination), synaptophysin, and CAM5.2. Pituitary adenomas are uniformly immunoreactive for synaptophysin and variably for chromogranin and CAM5.2. Finally, synaptophysin IHC positivity in a finely fibrillar pattern highlights small fragments of posterior gland that can also be included, especially in specimens being assessed for Rathke cleft cyst.

Reticulin uniformly shows disruption of acinar pattern from normal (see Figure 3, b), but, as noted, variations such as a macronodular pattern (see Figure 4, b) do occur. Gonadotroph/null cell adenomas usually manifest the weakest CAM5.2 immunostaining. In terms of specific anterior pituitary hormones necessary for subtyping pituitary adenomas, we recommend FSH, ACTH, GH, and PRL as a minimal panel of specific anterior pituitary hormone stains. Although gonadotroph adenomas often are immunoreactive for ASU and LH in addition to FSH, it is rare for the latter to be completely absent in a gonadotroph adenoma; thus, having at least FSH in the IHC armamentarium usually suffices to correctly subtype this adenoma. It must be acknowledged, however, that the specific source of commercial antibody may influence the relative distributions of ASU, FSH, and LH in pituitary adenomas. Nevertheless, 2 of the authors (B.K.K.-D. and M.B.S.L.) do not diagnose gonadotroph adenoma in the face of ASU IHC alone without FSH or LH, nor have either of us encountered significant numbers of pituitary adenomas with LH but completely absent FSH by IHC.

WHICH ADENOMAS ARE ESPECIALLY IMPORTANT TO SUBTYPE FOR CLINICAL PURPOSES?

The panel recommended above allows ready subtyping of the most common adenoma to come to surgical excision, namely gonadotroph/null cell adenoma. These tumors are almost invariably clinically hypofunctioning and present with visual changes and/or headache, with or without hypogonadism. Gonadotroph and null cell adenomas derive from the same steroidogenic factor 1 lineage and form a spectrum, the distinction of which is unimportant clinically. However, placing adenomas into this subtype is important because these tumors are biologically indolent and do not require postoperative radiation therapy for control of growth (or a hypersecretory state),[5] even when they present as massive giant adenomas.[6] As noted above, these gonadotroph/null cell adenomas, like all adenomas, are invariably synaptophysin immunoreactive (see Figure 3, c) even when IHC for CAM5.2 is weak or negative (see Figure 3, d).

Growth hormone adenomas not only should be subtyped, but should be further subdivided into dense and sparse variants. Most endocrinologists agree that sparsely granulated GH adenomas behave in an aggressive fashion, presenting as larger tumors, often more invasive of the bony sellar floor,[7,8] and tend to respond less effectively to adjuvant medical therapy.[9] On H&E, the adenoma may either show bland cytologic features (Figure 5, a) or scattered pleomorphic cells (Figure 1, e; illustrated on TP). Growth hormone immunostaining is often less intense (Figure 5, b) than in densely granulated GH adenomas, but diagnosis requires use of CAM5.2 IHC to identify fibrous bodies, their distinguishing feature (Figure 5, c). The presence of numerous small, ball-like collections of keratin immunopositive filaments quickly distinguishes them from densely granulated GH adenomas or, indeed, virtually any other subtype of adenoma (Figure 5, c). A further verification of sparsely from densely granulated GH adenoma type is the loss of E-cadherin immunostaining in sparsely, but not densely, granulated GH adenomas.[10] Fortunately, most pathology laboratories have E-cadherin in their armamentarium for other tumor types.

The second type of adenoma that is known to be aggressive is the clinically silent corticotroph cell adenoma, which may be either densely or sparsely (Figure 5, d) granulated.[11] The corollary is that the amount of ACTH immunoreactivity does not predict whether the adenoma is clinically silent. Some clinically silent ACTH adenomas

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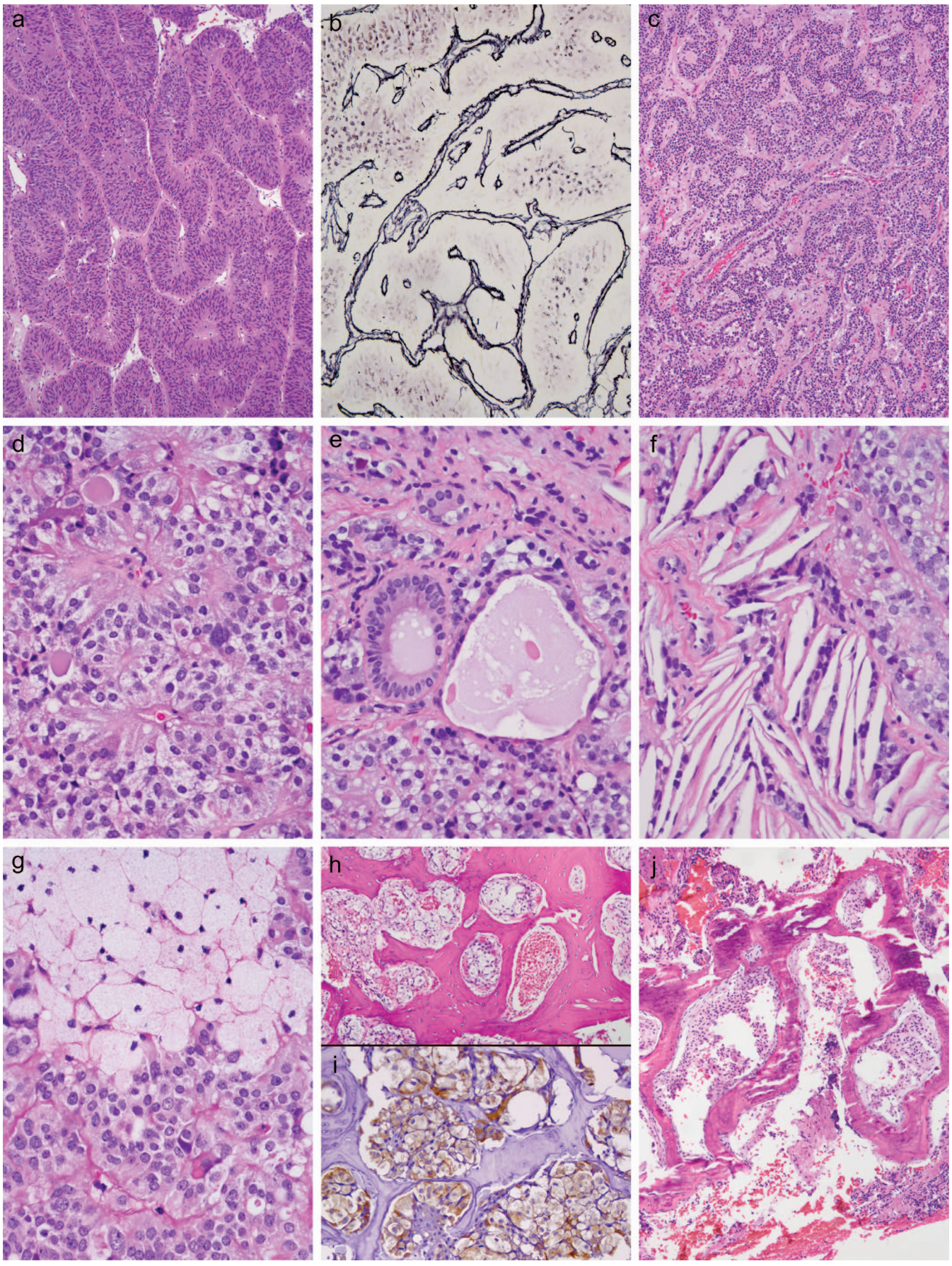
Figure 3. *a, Normal anterior gland is often present at the edge of adenoma resection specimens but can be difficult to distinguish from the adenoma on hematoxylin-eosin (H&E) alone, as illustrated by this H&E section where the adenoma is at lower right and the normal gland at upper left. This degree of sharp circumscription between normal compressed gland and adenoma is most often seen in macroadenomas; on microadenomas, normal pituicytes may be admixed with adenoma cells at the edges of the adenoma. b, Reticulin stain best demonstrates the loss of acinar pattern in the adenoma (right) and the compressed adenoma pattern on reticulin in the normal gland at left. The boundary between the 2 is also best appreciated on reticulin stain. c, Synaptophysin is immunoreactive in all pituitary adenomas (right) as well as in the normal compressed gland (left). d, CAM5.2 (anti-keratin peptide of migration ratio of approximately 52 kDa) is more variable in pituitary adenomas and is often negligible in gonadotroph/null cell adenomas as seen here, at right. In contrast, the normal compressed gland (at left) shows CAM5.2 immunoreactivity, as well as highlighting the normal acinar pattern of the compressed gland. e, Immunostaining for prolactin may be increased in pituitary macroadenomas that compress the infundibular stalk. The pituitary adenoma at right is a gonadotroph adenoma and is completely negative for prolactin; the normal compressed gland at left shows slightly increased prolactin immunostaining because of this stalk compression. Not recognizing this as normal gland can lead to erroneous attribution of hormonal activity to the adenoma. f, Photomicrograph of the normal posterior gland shows the fibrillary glial nature of this part of the pituitary. Normal gland is most often included in specimens of cystic masses such as Rathke cleft cysts. g, Here, normal posterior gland is included in a specimen of an adamantinomatous craniopharyngioma (upper left). The normal gland (lower right) is immunoreactive for synaptophysin. h, Higher-power view of the adamantinomatous craniopharyngioma (top) versus the normal included posterior pituitary gland (bottom) shows the latter strongly immunoreactive for neurofilament. i, Normal posterior gland (lower right) but not the craniopharyngioma (upper left) shows nuclear thyroid transcription factor 1 immunoreactivity (original magnifications ×200 [a, d, and g], ×100 [b, c, and e] and ×400 [h and i]; H&E, original magnification ×400 [f]).*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show only patchy IHC immunostaining for ACTH (Figure 5, e), but others are diffusely and strongly immunoreactive, suggesting that the hormone product may be either biologically inactive or irregularly secreted. This subtype of adenoma can be diagnosed only by correlation between IHC pattern and clinical features. Thus, in any case in which ACTH immunostaining is identified, our practice is to notify a member of the clinical team with the diagnosis so they can make this correlation. Normally, any patient who has undergone pituitary adenoma removal usually receives a short course of postoperative steroids; those patients with clinically silent ACTH-secreting adenomas may have had pulsatile or a low level of hormone secreted preoperatively and may therefore have suppressed their own endogenous cortisol production. Thus, there is the potential that these patients would manifest hypoadrenalism if tapered from their postoperative steroids too quickly, resulting in hypoadrenalism symptoms such as nausea, vomiting, headache, and possible circulatory collapse. Notifying the clinical team allows the patient to be monitored closely and allows the team to determine if this patient will require a prolonged steroid taper to avoid symptoms of acute withdrawal (Kevin O. Lillehei, MD, oral communication, January 2014). As with sparsely granulated GH adenomas, obtaining a MIB-1 level (molecular immunology Borstel unit 1, an improved Kiel antibody number 67 monoclonal antibody that recognizes a nuclear protein present in G1, S, G2, and M phases of the cell cycle and stains epitopes in paraffin sections) cannot serve as a substitute for specific anterior pituitary hormone immunostaining, because both sparsely granulated GH and clinically silent ACTH adenomas often have MIB-1 rates below the suggested level of 3% for a typical pituitary adenoma (Figure 5, f).[12]

In addition to sparsely granulated GH adenomas and clinically silent ACTH adenomas, some groups have noted more adverse long-term outcomes with mixed GH-PRL adenomas.[13] In the literature, a distinction had been made between mixed GH-PRL and mammosomatotroph adenomas, especially at large specialty referral institutions, such as that of one of the authors (M.B.S.L.),[13] but this requires availability of, and expertise in interpreting, electron microscopy. Without electron microscopy, it is difficult, if not impossible, to distinguish mixed GH-PRL adenomas (usually of mixed dense and sparse subtypes, respectively) from mammosomatotroph adenomas. The latter closely resemble densely granulated GH adenomas on light microscopy, but these bihormonal adenomas show immunostaining for both GH and PRL that by special electron microscopic techniques using gold preparations can be identified as coming from the same cell, rather than from 2 distinct cell populations as in a mixed GH-PRL adenoma. On electron microscopy, the mammosomatotroph adenoma in addition often has more pleomorphic secretory granules than a densely granulated GH adenoma.[14(p89)] On IHC alone, mammosomatotroph adenomas can be suspected when there is additional immunostaining for ASU or when the adenoma displays occasional fibrous bodies in a subpopulation of adenoma cells.[14(p89)]

Other rare variants thought to have more adverse prognosis include acidophil stem cell adenoma (usually PRL immunostaining exceeds immunostaining for GH; also, this adenoma subtype contains scattered fibrous bodies on CAM5.2)[14(p101)] and Crooke cell ACTH adenomas, another type of adenoma in which use of CAM5.2 is helpful in subtyping.[15]

Sometimes the use of immunostaining provides additional useful clinical information beyond simply prognosis. Prolactinomas are generally suspected preoperatively in premenopausal women; however, they can come to surgical resection without this subtype being suspected in postmenopausal women, in men, or in situations of pituitary apoplexy where clinical symptoms prompt rapid resection of the mass before endocrinologic test results can be obtained or final results are available (Figure 5, g and h). Giant adenomas in males, sometimes presenting with apoplexy, are not infrequently prolactinomas.[6] Identification of PRL immunostaining in the adenoma by the pathologist allows the possibility of postoperative dopamine agonist therapies if residual tumor and a hypersecretory state persist. As an opposite problem, 80% of ACTH adenomas are microadenomas less than 10 mm in greatest dimension, and often only several millimeters in size; their size may be below the level of identification even with modern neuroimaging. In this instance, the diagnosis of microadenoma on the resected material, and specifically an ACTH-immunoreactive microadenoma, can be made only by the pathologist. Neither giant prolactinomas in males nor ACTH microadenomas have especially adverse prognoses, but the use of immunostaining by the pathologist provides essential clinical information to the treating physicians. An additional rare subtype of adenoma with metaplastic gangliocytoma component also does not specifically have an adverse prognosis, but should be recognized to occur in this region (Figure 5, i). The neurosurgeon intraoperatively may have suspected a tumor other than adenoma because of the different tissue consistency, and identifying this component either at frozen or permanent section provides correlation (Kevin O. Lillehei, MD, oral communication, January 2014). Prognosis for mixed pituitary adenoma-

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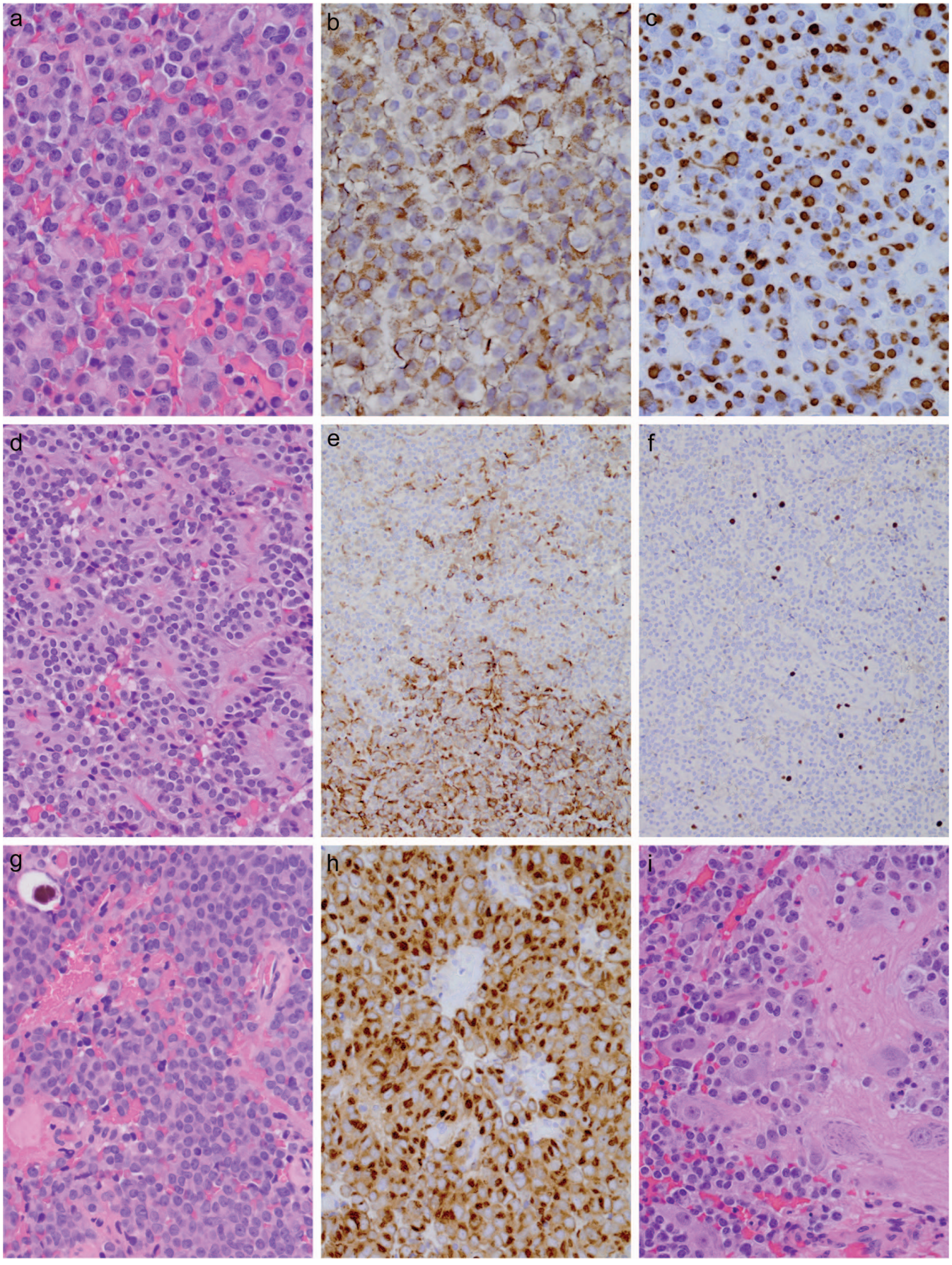
Figure 4. *a, Pituitary adenoma morphology is familiar to most pathologists, but unusual morphologic patterns can cause diagnostic concern for other lesions. This prominent sinusoidal pattern is one of the most interesting. b, Although there is disruption of the acinar pattern on reticulin stain in this tumor, note that in some areas there are macronodules, that is, areas of tumor completely surrounded by reticulin; this is still far from normal and still diagnostic of adenoma. c, This pituitary adenoma displays an even more interesting, elaborate festoon pattern; this is of no specific diagnostic importance. d, Some pituitary adenomas, such as this gonadotroph null cell adenoma, show nearly clear cell features and orientation of cells perpendicular to blood vessels. Small mucin-filled eosinophilic cysts may also be present. e, The same tumor also contained larger cysts, some with and some without prominent epithelium. f, Cholesterol cleft formation in a pituitary adenoma is further indication of a remote bleeding episode that may be either clinical or subclinical in these highly vascular tumors. g, Occasional pituitary adenomas will demonstrate macrophages, likely also secondary to previous bleeding episodes. h, Very rarely, pituitary adenomas will show other types of metaplastic change such as massive ossification. This was deeply embedded within a gonadotroph adenoma and clearly unrelated to bone invasion. i, Synaptophysin immunoreactivity further clarifies that this is a pituitary adenoma and not a metastatic carcinoma. j, Pituitary adenomas often invade the sellar bony floor but do not cause an osteoblastic reaction. Contrast the thin bony trabeculae in this specimen with bony invasion versus the metaplastic ossification in h (hematoxylin-eosin, original magnifications ×100 [a, h, and j], ×200 [c], and ×400 [d and e]; hematoxylin-eosin, original magnification ×400 [f and g]; original magnification ×200 [b and i]).*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gangliocytoma parallels the subtype of adenoma with which the gangliocytoma is associated.

Occasional pituitary adenomas are massive, are laterally displaced, and/or occur in unusual clinical settings that also yield lower preoperative suspicion of an adenoma diagnosis. Figure 6, a and b, illustrates preoperative neuroimaging from a 15-year-old girl who presented with the acute onset of left hemiparesis and hemisensory symptoms as well as right cranial nerve III palsy. In retrospect, she had secondary amenorrhea and weight gain. Magnetic resonance imaging demonstrated a large cystic sellar/suprasellar lesion with extension into the right cavernous sinus and a possible hemorrhagic cystic component. There was significant mass effect on the brainstem and midline shift. A solid component measured 2.5 × 3.2 × 36 cm, with the cystic component 5.3 × 5.7 × 5.4 cm. Imaging suggested a giant adenoma, but this was by no means proven until histopathologic confirmation. This proved to be a giant prolactinoma (Figure 6, c) with diffuse immunostaining for PRL (Figure 6, d) and significantly elevated MIB-1 rate of 8% to 11% (Figure 6, e), well above the suggested 3% cutoff for atypical adenoma.

Whether MIB-1 is part of the routine pituitary panel varies among specialty centers. Some places perform MIB-1 only if mitotic activity is detected on the TP or permanent section. The current recommendation for the criterion of atypical adenoma is a MIB-1 rate of 3% or greater.[12] Even when MIB-1 is elevated, however, we do not use the term *atypical* in our final diagnosis line on such cases with elevated MIB-1 labeling indices, in order to avoid the possibility that a clinician will feel that adjuvant radiation therapy is automatically warranted. We have encountered situations where the treating physician sees the term *atypical* in a pituitary adenoma report and considers it parallel with *atypical meningioma*, World Health Organization grade II, and assumes radiation therapy is indicated. Rather, we note that closer follow-up is advised. Today, radiation therapy is being used even more cautiously than in the past and almost always is a last resort when medical therapies or even reresection fails to control hypersecretory states caused by residual hyperfunctioning pituitary adenoma cells.

IS THE SELLAR REGION MASS A NONADENOMATOUS NEOPLASM SUCH AS METASTASIS?

Usually, the histologic features on H&E, coupled with this IHC panel, are sufficient to exclude metastatic tumors from consideration. In addition, the neuroimaging often allows fairly confident distinction preoperatively. However, there are exceptions, as illustrated in the case shown in Figure 6, f through i, of a metastatic thyroid carcinoma on magnetic resonance imaging (Figure 6, f), TP (Figure 6, g), H&E on permanent section (Figure 5, h), and immunostaining for thyroglobulin (Figure 6, i) and nuclear TTF-1 (Figure 6, j).

What tumor types are most likely to metastasize to the pituitary gland? No one institution, including our own respective institutions, has sufficient numbers of cases for large series, and almost all reports in the literature are single case studies. A very recent literature review of this topic found the incidence of pituitary metastasis even at autopsy to be rare.[16] Indeed, pituitary metastasis occurred at an incidence of 1.9% among autopsied patients with cancer, and constituted 0.87% of all intracranial metastasis.[16] Diabetes insipidus was the single most common symptom among reported cases, with an incidence of 33%. In their review, breast and lung cancers were the most common primary types of cancer responsible for pituitary metastases, followed distantly by prostate and kidney.[16] The range of percentage of breast carcinomas metastatic to pituitary gland taken from 5 autopsy literature reports was very broad, from 4.5% to 28.2% (pooled result 12.8%). It is worth noting that their case of pituitary metastasis came from a patient with hepatocellular carcinoma. Thus, similar to the case illustrated in Figure 6, f through i, of a metastatic thyroid carcinoma, other types of tumors certainly can rarely show this pattern of spread.

Once normal anterior or posterior gland, pituitary adenoma, and metastases have been excluded, the fourth consideration is that of nonadenomatous, nonmetastatic tumors. Meningiomas, craniopharyngiomas, and tumors arising from cells in the posterior hypophysis all are diagnostic possibilities for sellar region masses, and all can mimic pituitary macroadenoma on preoperative neuroimaging studies.

Meningiomas of the sellar region may mimic pituitary adenomas preoperatively on neuroimaging studies (Figure 7, a), but are readily distinguished at the time of intraoperative consultation by the pathologist, based on TP features of spindled tumor cells with low nuclear to cytoplasmic ratios, often occurring in clumps or whorls (Figure 7, b),[17] rather than as nonclumped, patternless individual cells as seen in a monolayer on TPs of pituitary adenomas (see Figure 1, b and c). Indeed, TPs of meningiomas are usually sufficiently recognizable that they can provide instant verification of diagnosis (Figure 7, b). On

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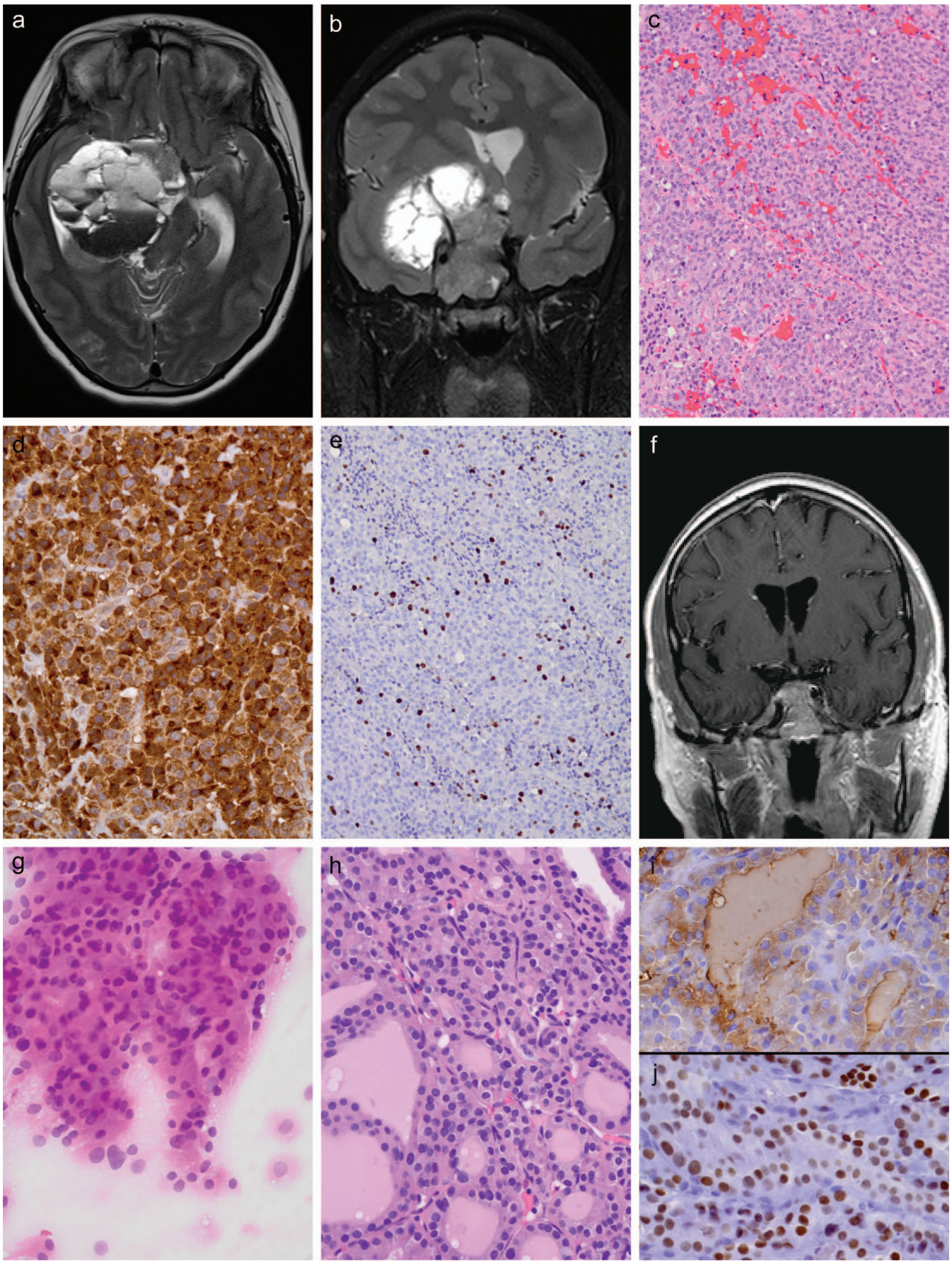
Figure 5. *a, Sparsely granulated growth hormone (GH) adenoma presents as a patternless tumor, with or without nuclear atypia and pleomorphism. b, Immunostaining for GH is usually less strong and diffuse in sparsely granulated than in densely granulated GH adenomas. c, Confident diagnosis of sparsely granulated GH adenomas requires use of keratin stains that reveal numerous, diffusely distributed immunoreactive cytoplasmic ball-like aggregates of keratin filaments known as fibrous bodies. d, Clinically silent adrenocorticotropic hormone (ACTH) adenomas may be either densely or sparsely granulated variants, with the latter seen in this case; diagnosis can only be made by clinical correlation. e. This clinically silent ACTH adenoma with patchy immunostaining for ACTH had already recurred twice before the patient presented to our institution with a third recurrence; the subtype was not known. Immunostaining for ACTH shows patchy, irregularly distributed ACTH immunoreactivity, but only by discussions with the clinical team was it discovered that the patient had a clinically silent lesion. When tapered rapidly from the steroids routinely given postoperatively to pituitary adenoma patients, she experienced nausea and had flulike symptoms; reinstitution of steroids and a slower taper avoided further hypoadrenalism symptoms. f, MIB-1 in this case of a twice-recurrent pituitary adenoma failed to show levels in excess of 3%. g, This man presented with 48 hours of bitemporal visual changes and was found to have a large mass compressing the optic chiasm, prompting rapid surgical removal; some macroprolactinomas in males may present with apoplexy, as did this patient's, and in some cases, endocrinologic test results are not known prior to surgery. h, The pituitary macroadenoma shown in g was found on immunostaining panel to be a prolactinoma with typical immunoreactivity for prolactin in a juxtanuclear pattern; this man had residual tumor in the cavernous sinus, and subtyping allows for use of dopamine agonist therapies. i, Rare pituitary adenomas contain metaplastic ganglion cells; these mixed pituitary adenoma-gangliocytoma cases have prognosis similar to that of the pituitary adenoma subtype (hematoxylin-eosin, original magnifications ×600 [a] and ×400 [d, g, and i]; original magnification ×600 [b]; CAM 5.2 immunohistochemistry, original magnifications ×600 [c] and ×200 [e, f, and h]).*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permanent section, meningiomas manifest spindled, fibroblastic, meningothelial, or transitional/whorled architecture, with or without psammoma body calcifications or other features.[17]

Sellar region masses that can mimic nonhypersecretory pituitary adenomas on neuroimaging studies (Figure 7, c)—and somewhat mimic meningioma on TP (Figure 7, d) and permanent section (Figure 7, e) because of their spindled cell population—are pituicytoma, spindle cell oncocytoma, and granular cell tumor of neurohypophysis. These tumors derive from specialized glial cells in the posterior pituitary gland, but by the time of detection an anterior versus posterior origin is usually not discernible or a distinguishing feature. These 3 tumors were codified in the 2007 edition of the World Health Organization[18–20] and at the time of description[21] were thought to be more different from each other than they are today.

The recent work by Lee et al[22] and Mete et al[23] shows that there is far more in common among pituicytoma, spindle cell oncocytoma, and granular cell tumor of neurohypophysis than was originally suspected. Indeed, early papers on pituicytoma[21] suggested a possible origin from folliculostellate cells of the adenohypophysis, but the more recent work[22,23] suggests that all share nuclear TTF-1 immunoreactivity, a feature also shown by the specialized pituitary cells in the normal posterior pituitary gland. Hence, TTF-1 positivity in the sellar region does not automatically ensure tumor, but once the decision has been made that a tissue biopsy specimen is more cellular than normal posterior gland—that it is a neoplasm—then the use of TTF-1 can be a decision-tree point for distinguishing pituitary adenomas or meningiomas (which are uniformly TTF-1 nuclear negative) from TTF-1 nuclear-positive pituicytoma, spindle cell oncocytoma, and granular cell tumor of the neurohypophysis.

Pituicytoma and spindle cell oncocytoma show spindle cells with low nuclear to cytoplasmic ratios and varying amounts of eosinophilic cytoplasm, with granular cell tumor of neurohypophysis further demonstrating granular cytoplasmic change similar to that seen in granular cell tumors elsewhere in the body due to an accumulation of lysosomes.[20] Pituicytoma and spindle cell oncocytoma appear to exist on a spectrum and distinction is not always possible.

Although the use of vimentin, glial fibrillary acidic protein, or S-100 protein IHC is not of value in diagnosing or subtyping pituitary adenomas, and thus is not recommended as part of the initial basic IHC panel, all can be of significant use when the light microscopic features suggest a spindle cell lesion of the sellar region. Pituicytoma is diffusely vimentin and S-100 protein immunoreactive, but usually shows only focal glial fibrillary acidic protein immunoreactivity.[18,24] The absence of diffuse glial fibrillary acidic protein immunostaining separates pituicytoma from pilocytic astrocytoma. Spindle cell oncocytoma is similar to pituicytoma, but has more abundant plump cytoplasm (Figure 7, e). Strong diffuse immunoreactivity for S-100 protein is seen in most lesions (Figure 7, f), as is diffuse nuclear immunostaining for TTF-1 (Figure 7, g); there may be additional patchy immunostaining for epithelial membrane antigen. Spindle cell oncocytoma is usually glial fibrillary acidic protein immunonegative and contains abundant mitochondria, which must be demonstrated by either specific mitochondrial immunostaining or electron microscopy. Whether the distinction between pituicytoma and spindle cell oncocytoma is important or not has yet to be settled, but a possible clue to their presence at the time of surgery (and thus possibly conveyed to the pathologist at the time of an intraoperative consultation) is that these both have a propensity to bleed much more extensively than a pituitary adenoma.[25] Schwannoma rarely enters into the differential for sellar region masses, but it also shows strong nuclear and cytoplasmic immunoreactivity for S-100 protein; absence of TTF-1 immunoreactivity distinguishes schwannoma, pilocytic astrocytoma, and meningioma from pituicytoma or spindle cell oncocytoma.

Craniopharyngiomas occur in 2 different types: adamantinomatous and papillary. The cystic, calcified, and heterogeneous signal characteristics of adamantinomatous craniopharyngiomas make them usually quite readily diagnosed on preoperative magnetic resonance imaging. In contrast, papillary craniopharyngiomas are much less common and can present as a solid sellar region mass, thus mimicking pituitary adenoma (Figure 7, h). The adamantinomatous type manifests a palisaded basal layer, wet keratin, and calcification (Figures 7i and 8a), and is familiar to most pathologists. This type is readily distinguished not only from pituitary adenoma based on its morphologic features, but also from sellar region meningiomas or pituicytomas, spindle cell oncocytomas, or granular cell tumors of neurohypophysis. However, examples with a paucity of wet keratin (Figure 7, i) or those with such abundant wet keratin that the epithelium is overshadowed (Figure 8, a) can be more challenging. Figure 3, g through i, further contrasts normal posterior gland adjacent to an adamantinomatous craniopharyngioma. The TP of a papillary craniopharyngioma may allow ready distinction from adenoma at the time of intraoperative consultation, based

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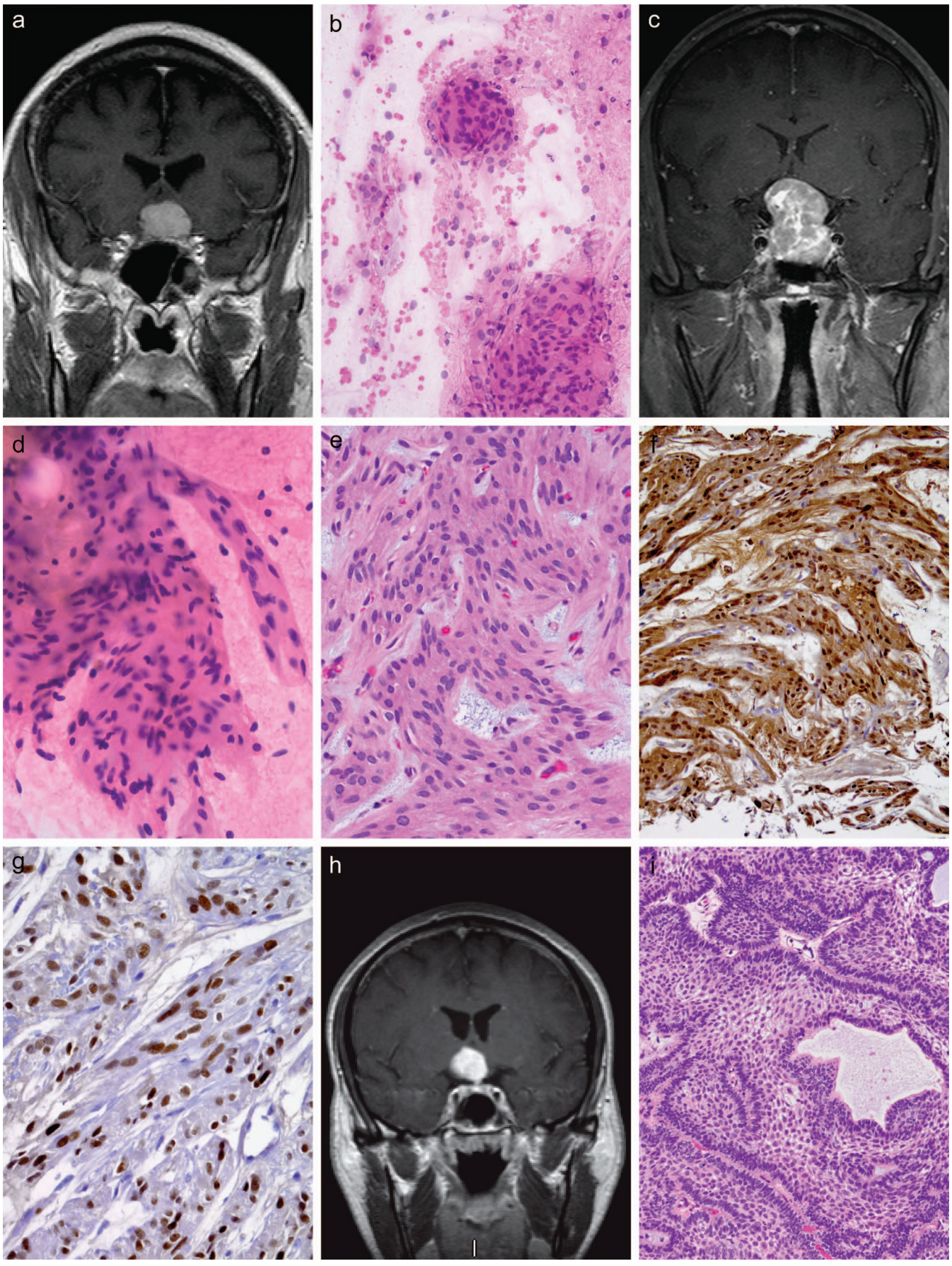
Figure 6. *a, Axial, T2-weighted magnetic resonance imaging (MRI). Most pituitary adenomas are strongly suspected preoperatively based on classic neuroimaging features. This case, however, in a 15-year-old adolescent girl who presented with the acute onset of left hemiparesis and hemisensory symptoms as well as a right cranial nerve III palsy, was not so obvious. In retrospect, she had secondary amenorrhea and weight gain as well. b, Coronal, T2-weighted MRI shows the more lateral displacement of the tumor and the mass effect in this pituitary adenoma. c, The monomorphic features of this pituitary adenoma are readily apparent even on low-power magnification. d, Strong diffuse immunostaining for prolactin in the classic juxtanuclear Golgi pattern demonstrates that this is a sparsely granulated prolactinoma; substantially less than 1% of prolactinomas are densely granulated. e, Elevated MIB-1 rate of greater than 8% suggests that this has features that some might consider atypical. Closer follow-up is recommended for such tumors. f. Coronal, T1-weighted MRI, with contrast. This 54-year-old man had hypopituitarism and a complicated medical history including widely metastatic renal cell carcinoma and a more remote history of thyroid follicular carcinoma. The experienced neuroendocrine team felt that the imaging was more consistent with a pituitary adenoma, although the neurosurgeon noted intraoperatively that the massive bleeding was more consistent with metastasis. g, Touch preparation from this specimen confirms the clumping and the hypercellularity typical of a metastatic thyroid cancer. h, Permanent sections reveal the metastatic follicular carcinoma. i, The metastatic follicular carcinoma is strongly immunoreactive for thyroglobulin. j, Metastatic thyroid carcinoma also showed strong diffuse immunoreactivity for nuclear thyroid transcription factor 1; metastatic tumors to the pituitary gland are rare but must always be a consideration (hematoxylin-eosin, original magnifications ×200 [c] and ×400 [g through i]; original magnifications ×400 [d and j] and ×200 [e]).*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on the "paving-stone" appearance of the cells (Figure 8, b). On permanent section, the absence of dry flaky keratin and a keratohyaline layer exclude epidermoid cyst, and the absence of calcification and wet keratin negate adamantinomatous craniopharyngioma (Figure 8, c and d). Nodules of collagen can occasionally be present in papillary craniopharyngioma (Figure 8, d) and should not be mistaken for wet keratin of an adamantinomatous craniopharyngioma (see Figure 8, a). Wet keratin is characterized by the preserved outline of formerly viable cells albeit with nuclei showing loss of hematoxylin staining, leading to a "ghost cell" appearance.

IS THE SELLAR REGION MASS A CYST?

If the resected tissue is not normal anterior or posterior gland, pituitary adenoma or nonadenomatous neoplasm, metastatic or nonmetastatic, it might be a cyst. Unfortunately, as in many cystic conditions, the cystic nature may be more apparent to the neuroradiologist and neurosurgeon than to the pathologist, who usually gets only a portion of the now-collapsed cyst wall. Nevertheless, the most frequent cyst in the sellar region is Rathke cleft cyst (RCC). Often, the specimen sent to the pathologist will be exclusively or almost exclusively amorphous eosinophilic mucin of varying densities (Figure 8, e). Nevertheless, abundant amorphous eosinophilic mucin received as a surgical specimen from a sellar region mass is virtually pathognomonic for the diagnosis of RCC, and nearly as unique as the wet keratin of adamantinomatous craniopharyngioma.

If the cyst wall is biopsied, an RCC is lined by pseudostratified columnar or low cuboidal epithelium, with or without obvious ciliation (Figure 8, f). Focal squamous metaplasia (Figure 8, g) can be seen as well, and can lead to difficulties in confident distinction from craniopharyngioma. The finding of wet keratin (ghost cells) negates any consideration of squamous metaplasia in an RCC, as does the finding of either dry flaky keratin or a keratohyaline granular layer in the squamous epithelium; these features indicate cystic craniopharyngioma and epidermoid cyst, respectively. Arachnoid cysts do occur in the sellar region and are histologically identical to those located elsewhere in the central nervous system, with a fibrotic strip associated with variable numbers of arachnoidal cells. Cystic teratomas by definition must have tissue from more than germ cell layer and are quite uncommon in the sella. It is unlikely that only pure mucin would be sent as a surgical specimen from a large multicystic teratoma and confused with RCC.

The epithelium from RCC may or may not shed onto a glass slide when performing a TP, and indeed may be very difficult to identify even at the time of permanent section. Either pancytokeratin or CAM5.2 serves to highlight the epithelial strips that may be compressed at the edge of a tissue fragment, and using these stains almost invariably shows more epithelium at the edges of tissue fragments than can be confidently diagnosed on H&E alone. Rathke cleft cyst epithelium was originally thought to have a distinctive cytokeratin profile with strong cytokeratin 7 immunopositivity and cytokeratin 20 immunonegativity that allowed easy distinction from cystic craniopharyngioma,[26] but this has now been recognized to have a far more variable keratin profile.[27] Occasional RCCs will be associated with significant epithelium, raising the issue of inflammatory disease in the sellar region.

IS THE SELLAR REGION MASS INFLAMMATORY?

Inflammatory cells may be readily identified as such on TPs or at frozen section, but crushed anterior pituitary cells must be excluded. At the time of permanent section, application of common immunohistochemical stains quickly clarifies the origin of small dark cells as crushed pituitary cells, neoplastic or normal, versus hematopoietic cells. Both anterior and posterior pituitary are synaptophysin immunopositive, as are all pituitary adenomas, although the intensity of staining varies. Lymphocytes can be proven by CD3 (T cells), CD20 (B cells), CD45, and other similar markers, and presence of histiocytes by CD68 (cluster of differentiation stains). Neither normal anterior or posterior gland nor the overwhelming majority of pituitary adenomas normally contain significant numbers of lymphocytes or histiocytes.[28] Thus, finding significant lymphocytes, histiocytes, or both suggests that hypophysitis is present.

A detailed discussion of subtyping of hypophysitis is beyond this paper and the reader is referred to larger articles on the topic.[24,29–33] Basically, however, whatever the underlying cause, hypophysitis usually presents as a mass lesion in the pituitary gland that can mimic pituitary adenoma on neuroimaging. Hence, if the mass effect is significant enough to require surgical intervention, these patients may come to surgery without a prebiopsy diagnosis of hypophysitis.[29] There are no premortem serum markers that definitively confirm the diagnosis, and histologic confirmation may be required. The condition is not a singular disease, but rather represents a collection of different entities showing a range of histologic features. There are both secondary and primary types of hypophysitis, and there are several subcategories within each.

Secondary hypophysitis is due to systemic disorders that happen to involve the pituitary gland. These include sarcoidosis, Wegener granulomatosis, Sjögren syndrome,

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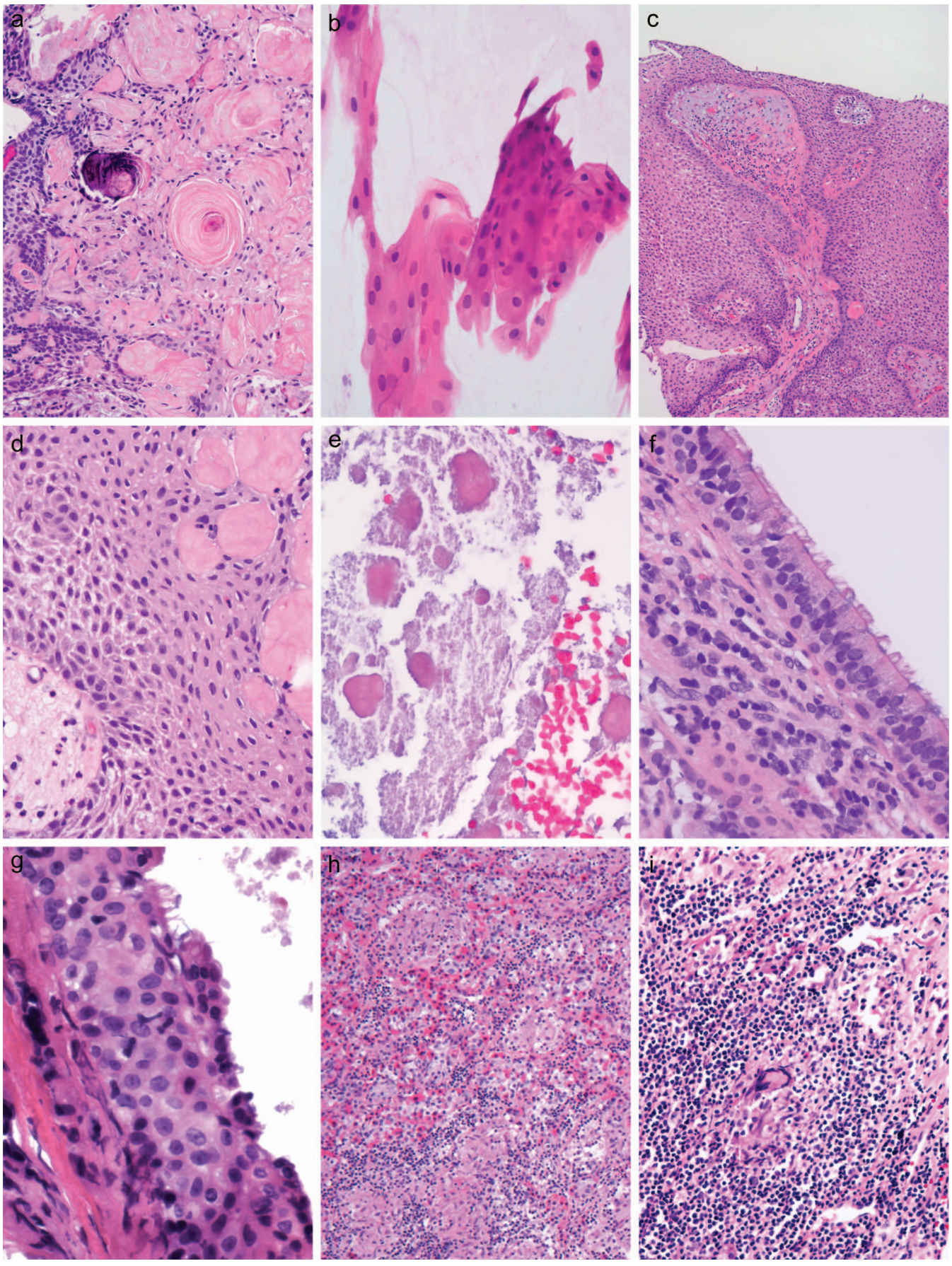
Figure 7. *a, Coronal, T1-weighted magnetic resonance imaging (MRI), with contrast. Meningiomas are frequently seen in the sellar region and may not have an obvious dural tail; preoperatively, they may be mistaken for pituitary macroadenomas. b, Touch preparation readily distinguishes this as a meningioma with the tight whorls and clusters of cells. c, Coronal, T1-weighted MRI, with contrast, of a complex sellar region mass that is indistinguishable from pituitary adenoma. d, Touch preparation shows a spindled neoplasm, which negates consideration of a pituitary adenoma but might still raise concerns about meningioma. e, On permanent section, the tumor cells have plumper, more ovoid nuclei than most meningiomas and lack whorls, psammoma body calcifications, or other features of meningioma. f, Strong diffuse immunoreactivity for S-100 protein in both nuclei and cytoplasm would not be typical for even a fibroblastic meningioma, which tends to show patchy S-100 protein immunostaining. g, Strong diffuse nuclear thyroid transcription factor 1 immunoreactivity completely clarifies this as a non-meningioma tumor. On electron microscopy, this proved to be a spindle cell oncocytoma rather than a pituicytoma based on the abundant mitochondria. The distinction between pituicytoma and spindle cell oncocytoma may be academic; both are currently World Health Organization grade I. h, Coronal, T1-weighted MRI, with contrast. Sellar region mass with a solid appearance again can be easily mistaken for a pituitary macroadenoma. i, Adamantinomatous craniopharyngiomas with a paucity of wet keratin and abundant cysts can be more challenging to diagnose (hematoxylin-eosin, original magnifications ×200 [b and i] and ×400 [d and e]; original magnifications ×200 [f] and ×400 [g]).*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and especially Langerhans and non-Langerhans cell histiocytosis. Particularly in pediatric populations, germ cell tumors of the central nervous system often involve suprasellar/sellar sites and may be accompanied by a profuse lymphocytic or histiocytic/granulomatous reaction that overshadows the neoplastic cells. Uncommon today are cases of tuberculosis or other direct infectious diseases. Lymphoma can affect the pituitary region, but is also uncommon.

Primary hypophysitis by definition is not associated with any underlying condition and is subdivided based on the predominant cell type: lymphocytic (Figure 8, h), granulomatous (Figure 8, i), or xanthomatous/xanthogranulomatous. Some pathologists also recognize a necrotizing form, but in this form, infectious disorders must be especially excluded. Although they were originally thought to be a disorder of predominantly young women in the peripartum and postpartum time period, it is now recognized that lymphocytic and granulomatous hypophysitis can be seen in both men and women and need not be associated with previous pregnancy.[24,29] The treatment is the same regardless of whether the pathologist classifies the condition as lymphocytic or granulomatous, and the prognosis is similar.[30] A slightly different prognosis occurs when there are significant collections of cholesterol and xanthomatous histiocytic debris. At least a subset of these may be related to ruptured RCC and a foreign body–type reaction to it.[24,30,33] The main issue is excluding underlying neoplastic germ cells (usually germinoma) or $CD1a^+$ or $CD1a^-$ histiocytes as part of a Langerhans or non-Langerhans (Erdheim-Chester) histiocytosis involving the sellar region.[24]

In summary, fortunately for pathologists, most sellar region masses are pituitary adenomas and most are readily diagnosable at the time of TP and permanent section. Most, but not all, sellar region masses are suspected to be adenomas preoperatively based on neuroimaging. Normal gland and unusual variations in pituitary adenoma morphology should be considered and excluded by the pathologist before consideration of rarer sellar region masses. Occasionally, diagnosis of pituitary adenoma is made only by the pathologist, such as in the case of ACTH microadenomas, which may not be confidently identified preoperatively even on modern neuroimaging modalities. In addition, preoperative neuroimaging studies cannot confidently distinguish nonsecretory pituitary macroadenomas from meningioma, metastasis, papillary craniopharyngioma, pituicytoma, spindle cell oncocytoma, granular cell tumor of neurohypophysis, RCC, or hypophysitis. An algorithmic approach to differential diagnosis, aided by a limited histochemical and immunohistochemical panel, can allow the practicing pathologist to make these distinctions with confidence.

The authors thank Ms Lisa Litzenberger for photographic expertise and Mrs Diane Hutchinson for manuscript preparation.

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Figure 8. *a, Adamantinomatous craniopharyngiomas may have such abundant wet keratin (at right) and calcification that it overshadows the epithelium (at left), as in this example. Contrast this example with Figure 7, i, where the opposite is true. Wet keratin is also known as "ghost cells" based on the preservation of cell outline, albeit with loss of nuclear hematoxylin staining. b, Touch preparation of a papillary craniopharyngioma shows the abundant cytoplasm and the paving-stone features typical of this tumor. c, Medium-power photomicrograph of a papillary craniopharyngioma shows the absence of ghost cells, calcification, and wet keratin seen in an adamantinomatous craniopharyngioma and further lacks the palisaded basal layer. On the other hand, a keratohyalin layer and dry flaky keratin, as would be seen in an epidermoid cyst, are also absent. d, Nodules of collagen (upper right) can occasionally be present in papillary craniopharyngioma and should not be mistaken for the wet keratin of an adamantinomatous craniopharyngioma (compare with a). e, The finding of dense amorphous mucin from a pituitary region mass is virtually pathognomonic of Rathke cleft cyst, although technically some consideration might be given to a cystic teratoma; the latter is exceedingly rare in this site. f, Rathke cleft cysts are usually lined by columnar to pseudostratified epithelium with or without ciliation. g, Squamous metaplasia in Rathke cleft cysts should not be mistaken for craniopharyngioma, although unfortunately, the distinction may be difficult from papillary craniopharyngioma in particular. Note the focal ciliation overlying the metaplastic squamous epithelium. h, Lymphocytic hypophysitis is a hypercellular process in which small benign lymphocytes can nearly obliterate the background architectural pattern of the normal anterior pituitary gland. i, Granulomatous hypophysitis contains epithelioid histiocytes clustering to form granulomas and may or may not contain multinucleated giant cells as in this case. Systemic disorders, especially sarcoidosis, should be considered and eliminated before diagnosing primary granulomatous hypophysitis (hematoxylin-eosin, original magnifications ×200 [a], ×400 [b, d, and i], ×100 [c], ×600 [e through g], and ×10 [h]).*

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