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REVIEW ARTICLE

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New developments in the pathology of skull base tumors

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Abstract As an anatomical interface between various tissues, the skull base harbors an exceptionally broad variety of neoplasms, some of which pose a major challenge for surgical pathology. The characterization of distinct immunohistochemical expression profiles and the identification of molecular genetic alterations associated with different tumor entities have significantly advanced this field. The new World Health Organization (WHO) classification of tumors of the nervous system lists 15 histopathological variants of meningioma. Of clinical importance are those entities that carry an increased risk of recurrence and a poor prognosis, i.e., the atypical meningioma (WHO grade II), clear-cell meningioma (WHO grade II), chordoid meningioma (WHO grade II), rhabdoid meningioma (WHO grade III), papillary meningioma (WHO grade III), and anaplastic meningioma (WHO grade III). Diagnostic criteria for atypical and anaplastic meningioma variants have now been stringently defined. The differential diagnosis of meningiomas includes hemangiopericytoma, hemangioblastoma, solitary fibrous tumor, sarcomas, and chordoid neoplasms. Recent data highlight the importance of distinguishing chordoma and chondrosarcoma of the skull base since chondrosarcomas show a significantly better clinical outcome. Among the less common, aggressive tumor entities in this anatomical region, infiltrating pituitary adenoma/pituitary carcinoma, superficial malignant gliomas, rhabdomyosarcoma, olfactory neuroblastoma, various sarcomas, and malignant lymphoma must be considered. Profiles of molecular genetic alterations have been established for several of these neoplasms and may facilitate the differential diagnosis. This review summarizes recent developments in the histopathological characterization, classification, and molecular pathology of neoplasms arising at the skull base.

Keywords Skull base · Molecular genetics · Immunohistochemistry · Meningioma · Chordoma · Chordoidchondroid · Rhabdoid · Pituitary adenoma · Sarcoma · Glioma

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Introduction

The exceptionally broad variety of tumors that may affect the skull base reflects its boundary and bridging function for various tissues of different histogenetic origin. Major tumor entities include meningiomas, non-meningothelial tumors of the meninges, such as hemangiopericytoma and solitary fibrous tumor, schwannomas, chordomas, various types of sarcomas, and metastatic lesions. Here, we present an overview of this group of neoplasms and highlight some recent developments concerning their differential diagnosis and molecular genetic properties.

Meningiomas

The World Health Organization (WHO) classification of brain tumors subdivides the tumors of meningothelial cells into benign meningiomas of WHO grade I (including eight different histopathological subtypes and metaplastic variants), atypical meningiomas of WHO grade II, anaplastic meningiomas of WHO grade III, and rare meningioma subtypes of WHO grade II or III [45]. In contrast to the common types of benign meningiomas (Fig. 1a), such as meningothelial, fibrous, transitional, psammomatous, or angiomatous meningiomas (all WHO grade I), the following meningioma variants are less frequently observed, display distinct histopathologic fea-

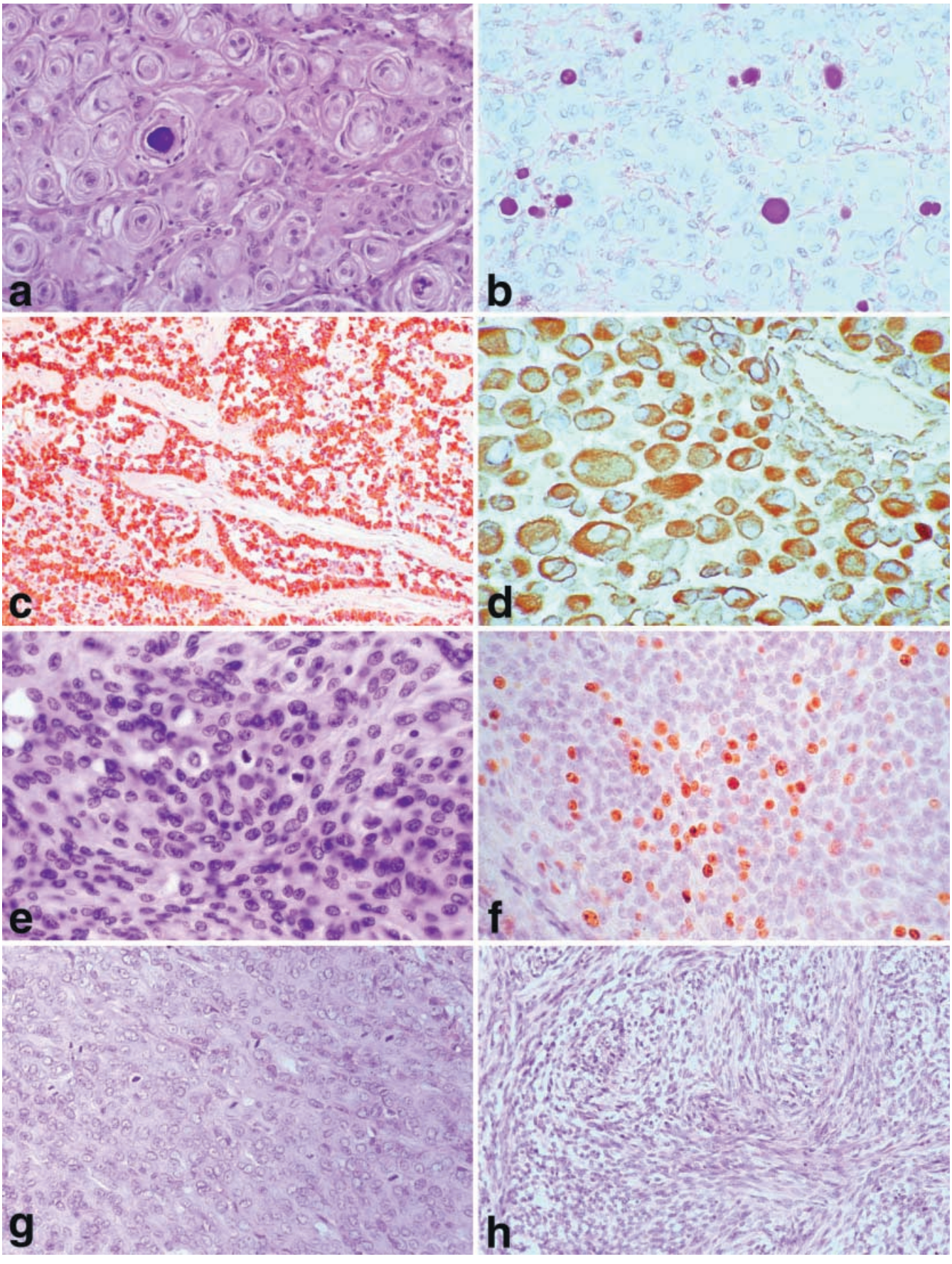
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Table 1 Common subtypes of meningioma World Health Organization (WHO) grade I

	Meningothelial	Fibrous/fibroblastic	Transitional (mixed)	Psammomatous	Angiomatous
WHO grade	I	I	I	I	I
Characteristic features	Lobules of arachnoidal-like cells, often syncytial arrangement	Spindle-shaped fibroblast-like cells, collagen rich	Combination of fibrous/meningothelial, concentric whorls	Abundant psammoma bodies	Numerous blood vessels may obscure meningioma component

Table 2 Rare subtypes of meningioma WHO grade I. *PAS* periodic acid–Schiff; *CEA* carcinoembryonic antigen

	Secretory	Microcystic	Lymphoplasmacyte-rich	Metaplastic
WHO grade	I	I	I	I
Characteristic features	Keratin+ cells, PAS+ CEA+ pseudopsammoma bodies	Tumor cells with elongated processes in a microcystic matrix, "astrocytoma"-like	Chronic inflammatory infiltrates relegate meningothelial component to the background	Osseous, cartilaginous, lipomatous, myxoid, or xanthomatous

Table 3 Subtypes of meningiomas with higher risk for recurrence, aggressive behavior, or malignant transformation

	Atypical	Clear-cell (intracranial)	Chordoid	Anaplastic (malignant)	Papillary	Rhabdoid
WHO grade	II	II	II	III	III	III
Characteristic features	4–19 s mitoses/10 HPF and/or ≥3/5: high cellularity, small-cell population with enlarged nuclei, prominent nucleoli, patternless, necrosis	Cytoplasmic vacuolation, PAS+, more aggressive	Lobules or trabeculae of chordoid cells in a myxoid matrix	≥20 mitoses/10 HPF, features of frank malignancy far in excess of atypical meningioma, cytology similar to sarcoma, carcinoma or malignant melanoma	Perivascular pseudopapillary pattern, cytokeratin may be positive	Rhabdoid tumor-cell component, frequently signs of anaplasia

tures, and may show an aberrant clinical behavior (Table 1, Table 2, Table 3).

Secretory meningiomas (WHO grade I) are characterized by epithelial differentiation as demonstrated by the presence of glandular lumina containing periodic acid–Schiff (PAS)-positive (Fig. 1b) and carcinoembryonic antigen (CEA)-immunoreactive globules. Such pseudo-psammoma bodies are surrounded by meningothelial tumor cells showing cytokeratin expression. Radiologically, secretory meningiomas are often characterized by a marked peritumoral edema in the adjacent brain [1]. A microcystic matrix and a loose mucinous background are major features of the microcystic meningioma (WHO grade I) [45]. In clear-cell meningioma (WHO grade II), classical meningioma architecture may be scarce. The tumor cells are characterized by a PAS-positive, vacuolated or clear cytoplasm. The preferred location of this tumor in the cerebellopontine angle and the cauda equina should be pointed out. Intracranial clear-cell meningiomas may be associated with a more aggressive behavior [97]. This variant corresponds to WHO grade II. Chordoid meningiomas (WHO grade II) show trabeculae of eosinophilic, vacuolated (chordoid) cells in a myxoid matrix (Fig. 2g) and thus may mimic the histological appearance of chordoma (Fig. 2a). Typical physaliphorous tumor cells, however, are absent in

◀ **Fig. 1** Meningiomas of different type and World Health Organization (WHO) grade, including rare subtypes. **a** Classic feature of transitional meningioma (WHO grade I) with concentric (onion bulb-like) tumor cell formations [hematoxylin and eosin (HE)]. **b** Secretory meningioma (WHO grade I) with intensively periodic acid–Schiff (PAS)-positive secretory cytoplasmic inclusions (pseudo-psammoma bodies). **c** The rare papillary meningioma (WHO grade III) is characterized by the formation of perivascular pseudopapillary architectures (vimentin). **d** Immunostaining for vimentin highlights the accumulation of intermediate filaments in rhabdoid tumor cells of rhabdoid meningioma (WHO grade III). Atypical meningiomas (WHO grade II) show an increased proliferative activity with a significant mitotic rate (**e**) and increased MIB-1 labeling as a marker of cell proliferation (**f**). Anaplastic meningiomas (WHO grade III) present with highly increased mitotic activity (**g**) and/or signs of frank malignancy, such as sarcoma-like growth (**h**) (**g** and **h**, HE)

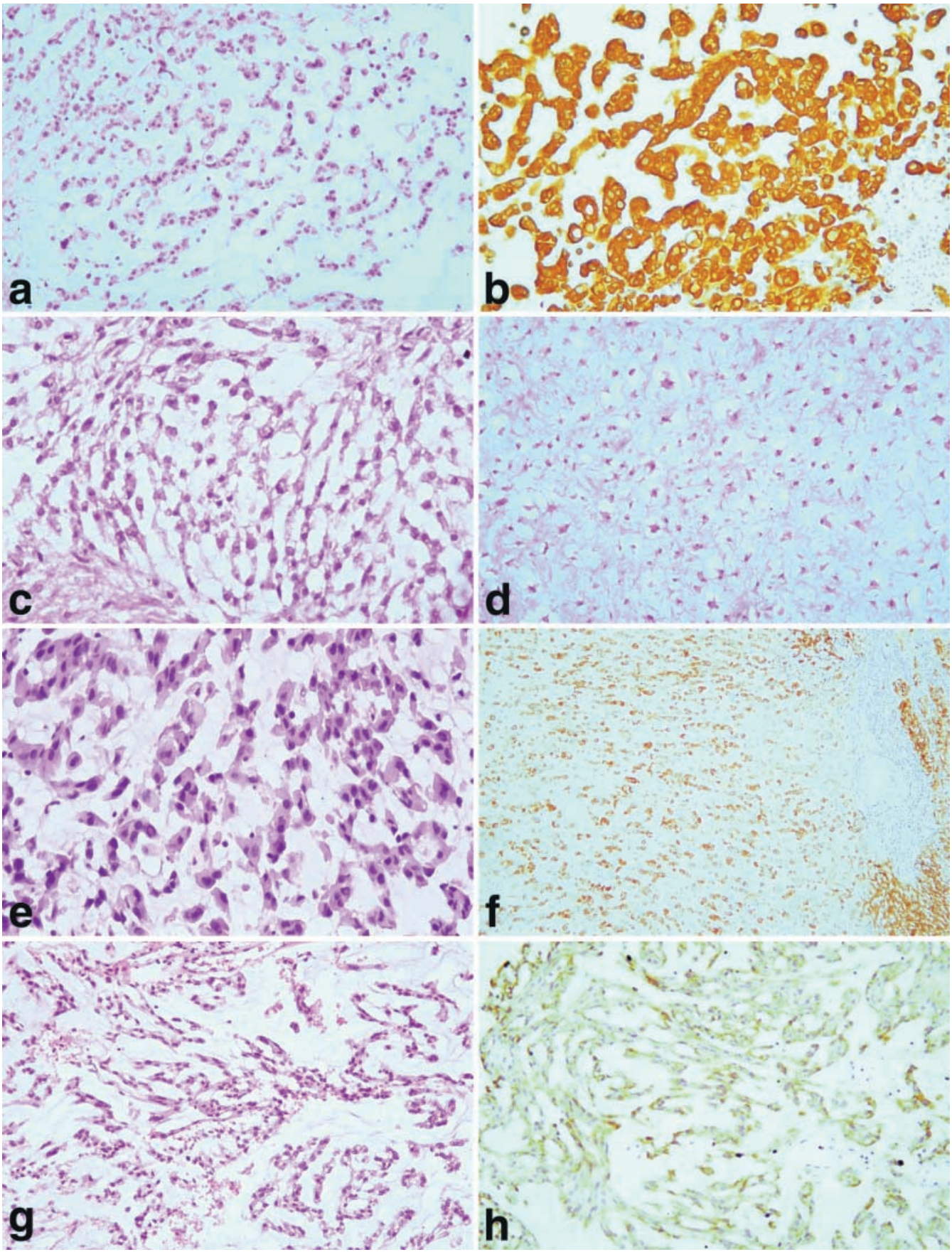
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Table 4 Histologic criteria for the grading of atypical and anaplastic meningiomas. *WHO* World Health Organization

	Atypical meningioma	Anaplastic meningioma
WHO grade	II	III
Histologic criteria	Increased mitotic activity (≥4 mitoses/10 HPF) and/or ≥3 of the five following features: Increased cellularity Small-cell population with high nucleus/cytoplasmic ratio Prominent nucleoli Uninterrupted patternless or sheet-like growth Foci of spontaneous or geographic necrosis	(≥20 mitoses/10 HPF) and/or features of frank malignancy far in excess of the abnormalities in atypical meningioma, i.e., cytology similar to sarcoma, carcinoma, or melanoma
	Brain invasion may be seen in both atypical and anaplastic meningioma	

chordoid meningiomas. In addition, the presence of histologic and immunohistochemical features of a classical meningioma, i.e., whorl formation and immunostaining for vimentin and epithelial membrane antigen (EMA; Fig. 2h) in the absence of prominent cytokeratin expression, facilitates the differential diagnosis. Peri- and intratumoral lymphoplasmacellular infiltrates may be prominent in some cases of chordoid meningiomas, particularly in tumors from young patients and may cause systemic manifestations of Castleman syndrome [39].

Polyclonal gammopathy and/or anemia can be associated with lymphoplasmocyte-rich meningioma (WHO grade I), a rare meningioma subtype in which inflammatory infiltrates often relegate the meningothelial component to the background. Care must be taken to exclude the diagnosis of other hematologic conditions arising in the meninges or the bony skull base [45]. Another rare variant of meningioma is the papillary meningioma, which tends to occur in children [49]. These tumors are histologically characterized by the formation of perivascular pseudopapillary architectures (Fig. 1c). Clinically, papillary meningiomas frequently show an aggressive behavior with a tendency for recurrence, brain invasion, and distant metastases [61]. Consequently, these tumors are graded as WHO grade III [44, 45]. An only recently described novel entity of meningioma with unfavorable prognosis is the rhabdoid meningioma [40, 64]. In addition to a prominent rhabdoid tumor cell population (Fig. 1d), rhabdoid meningiomas frequently show histological signs of anaplasia, including a high mitotic rate and an elevated labeling index for the proliferation-associated antigen Ki-67 (MIB1). Because of their aggressive clinical course, rhabdoid meningiomas commonly correspond to WHO grade III. A minority of meningiomas present only focal rhabdoid features but otherwise do not meet the histological criteria of malignancy; the behavior and the grading of these tumors is yet unclear [45].

Of great clinical importance is the histological distinction of the common benign meningiomas (WHO grade I) from atypical meningiomas (WHO grade II) [43] and the rare anaplastic (malignant) meningiomas (WHO grade III). Atypical meningiomas (Fig. 1e, f) are histologically defined as meningiomas with increased mitotic activity (Fig. 1e) and/or high cellularity, small-cell population with nuclear atypia, prominent nucleoli, patternless growth, and necrosis. Clinically, atypical meningiomas are associated with a significantly higher rate of recurrence than meningiomas WHO grade I [63]. Thus, patients with an atypical meningioma should be followed up at regular intervals after surgery. Anaplastic meningiomas (Fig. 1g, h) are characterized by histologic features of frank malignancy far in excess of the abnormalities in atypical meningioma [45]. These tumors require adjuvant postoperative radiotherapy. Some investigators have proposed more stringent criteria for the grading of meningiomas, which are mainly based on the mitotic index [51]. At a recent expert meeting for the revision of the WHO classification of tumors of the central nervous system [45], the criteria for the grading of meningiomas have been substantially revised (Table 4). The diagnosis of atypical meningioma requires either a mitotic rate of four or more mitotic figures per 10 HPFs (defined as 0.16 mm^2) or at least three of the following features: (1) increased cellularity, (2) small-cell population with high nucleus:cytoplasmic ratio, (3) prominent nucleoli, (4) uninterrupted patternless or sheet-like growth, and (5) foci of spontaneous or geographic necrosis. The major diagnostic criterion for anaplastic meningioma will be a striking mitotic activity (Fig. 1g), exceeding 19 mitoses per 10 HPF [65] and/or a frankly malignant phenotype, i.e., carcinoma-, sarcoma- (Fig. 1h) or melanoma-like features and large areas of necrosis. A major clinical factor associated with the risk of recurrence in

◀ **Fig. 2** Chondroid and chordoid neoplasms of the skull base **a** Chordoma displays either highly vacuolated "physaliphorous" or "hepatocyte-like" epithelial cells arranged in rows and embedded in a mucoid matrix [hematoxylin and eosin (HE)]. **b** An intensive cytokeratin expression (Lu 5) is typical for chordomas. **c** and **d** Myxoid chondrosarcoma may present in some areas with a more chordoid (**c**), in other areas with a more chondroid (**d**) appearance (**c** and **d**, HE). **e** Cords and clusters of epitheloid eosinophilic tumor cells in a mucoid matrix are also hallmarks of the chordoid glioma (HE). **f** Chordoid gliomas, however, are characterized by immunoreactivity for glial fibrillary acidic protein (GFAP). **g** Typical appearance of a chordoid meningioma (HE). **h** These tumors express the epithelial membrane antigen (EMA)

meningiomas is the extent of surgical resection [30, 32], which can be influenced by the site of occurrence, attachment to intracranial structures, and the age of the patient. Other clinical parameters have not been confirmed as predictors for the risk of recurrence [45]. The tumor grade [51] is the most important histological property to determine the likelihood of recurrence (Table 1, Table 2, Table 3). Malignant histological features are associated with shorter survival times [35]. Brain invasion suggests a greater likelihood of recurrence but does not by itself allow the diagnosis of anaplastic meningioma (WHO grade III). Brain-invasive meningiomas which otherwise do not fulfill histological criteria of anaplasia appear to behave similarly to atypical meningiomas [63]. MIB-1 labeling indices above 5–10% (Fig. 1f) suggest a greater likelihood of recurrence [45]. However, due to the variability of this reaction between different laboratories, an increased MIB-1 index does not qualify as a single diagnostic criterion for a WHO grade II. Atypical or anaplastic meningiomas more frequently lack progesterone receptors [17]. Progesterone receptor-negative meningiomas tend to be larger than progesterone receptor-positive meningiomas [6, 27].

Meningiomas were among the first solid human tumors for which characteristic cytogenetic changes could be identified [95]. The most consistent karyotypic alteration is the loss of one chromosome 22 [94]. More recent molecular genetic studies (Fig. 3) have identified mutations in the neurofibromatosis 2 (*NF2*) gene on the long arm of chromosome 22 as an important alteration associated with the development of meningiomas [73], especially those with fibrous or transitional histological appearance [91]. Mutations of the *NF2* gene are detected in 40–60% of sporadic meningiomas [91]. These mutations result in a loss of expression of the *NF2* gene product merlin (schwannomin). Loss of heterozygosity (LOH) at chromosome 22q is found at an ever higher rate, up to 50–70%, indicating that this chromosomal arm may harbor yet another meningioma-related gene [84]. Increased degradation of merlin by the proteolytic enzyme calpain has been suggested as an alternative mechanism of *NF2* inactivation in some meningiomas and schwannomas without *NF2* gene mutations [41]. To determine a correlation between merlin loss and *NF2* gene alterations or calpain activation, Ueki et al. [84] carried out a molecular genetic analysis of 50 sporadic meningiomas and examined the expression status of merlin and micro-calpain. LOH analysis of five microsatellite markers flanking *NF2* revealed LOH in 22 cases; single-strand conformation polymorphism analysis detected six frameshift mutations, two splicing mutations, one nonsense mutation, and one missense mutation, all accompanied by LOH 22q. In addition, a multiplex polymerase chain reaction (PCR) assay showed homozygous deletion of *NF2* in two cases. Interestingly, a marked decrease of merlin expression was seen exclusively in those 22 cases with LOH 22q. Increased micro-calpain expression was observed in 28 cases but showed no correlation with merlin status. These data strongly support the notion that *NF2* is

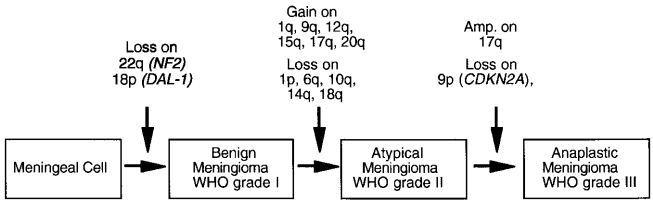

Fig. 3 Model of genomic alterations in meningioma progression [89]. Gains and losses are given before the tumor grade in which they are first detected at a frequency of more than 30%

the major target of LOH 22q in meningiomas and that loss of merlin expression is usually caused by genetic alterations of *NF2*, following the classic "two hit" theory. Merlin is a member of the protein 4.1 family of membrane-associated proteins, which also includes ezrin, radixin, and moesin. Recently, another protein 4.1-related tumor suppressor gene, *DAL-1*, located on chromosome 18p11.3 was identified [22]. Reduced expression of *DAL-1* was reported as an early event in the pathogenesis of meningiomas [22].

Progression to atypical and anaplastic meningioma (Fig. 3) is associated with an accumulation of multiple genetic and chromosomal alterations [89]. Atypical meningiomas frequently show loss of genetic information at putative tumor suppressor gene sites on chromosome arms 1p, 6q, 10q, 14q, and 18q [89]. These chromosome arms are even more frequently affected by deletions in anaplastic meningiomas. In addition, anaplastic meningiomas may show homozygous deletion of the *CDKN2A* tumor suppressor gene on 9p21 and amplification of sequences from 17q23 [89]. Demonstration of some of these genetic alterations, i.e., loss on 1p, may eventually become important as a molecular diagnostic tool for meningioma grading and prognostication (Fig. 3).

Other non-meningothelial neoplasms of the meninges

The fact that hemangiopericytomas may primarily develop in the meninges has previously led to their classification as a subtype of meningioma, i.e., the hemangiopericytic meningioma [98]. However, meningeal hemangiopericytomas are morphologically identical to hemangiopericytomas arising at other sites (Fig. 4e, f). Furthermore, hemangiopericytomas demonstrate distinct immunohistochemical, ultrastructural, and molecular genetic features that clearly separate these tumors from the meningiomas. Thus, the revised WHO classification lists hemangiopericytomas as a separate tumor entity under the category of non-meningothelial tumors of the meninges. Hemangiopericytomas are graded as WHO grade II or grade III tumors depending on histological features of malignancy, such as increased mitotic activity, necrosis, and cellular pleomorphism. Determination of the MIB-1 labeling index may also be of prognostic value [54]. Molecular genetic studies have revealed that hemangioperi-

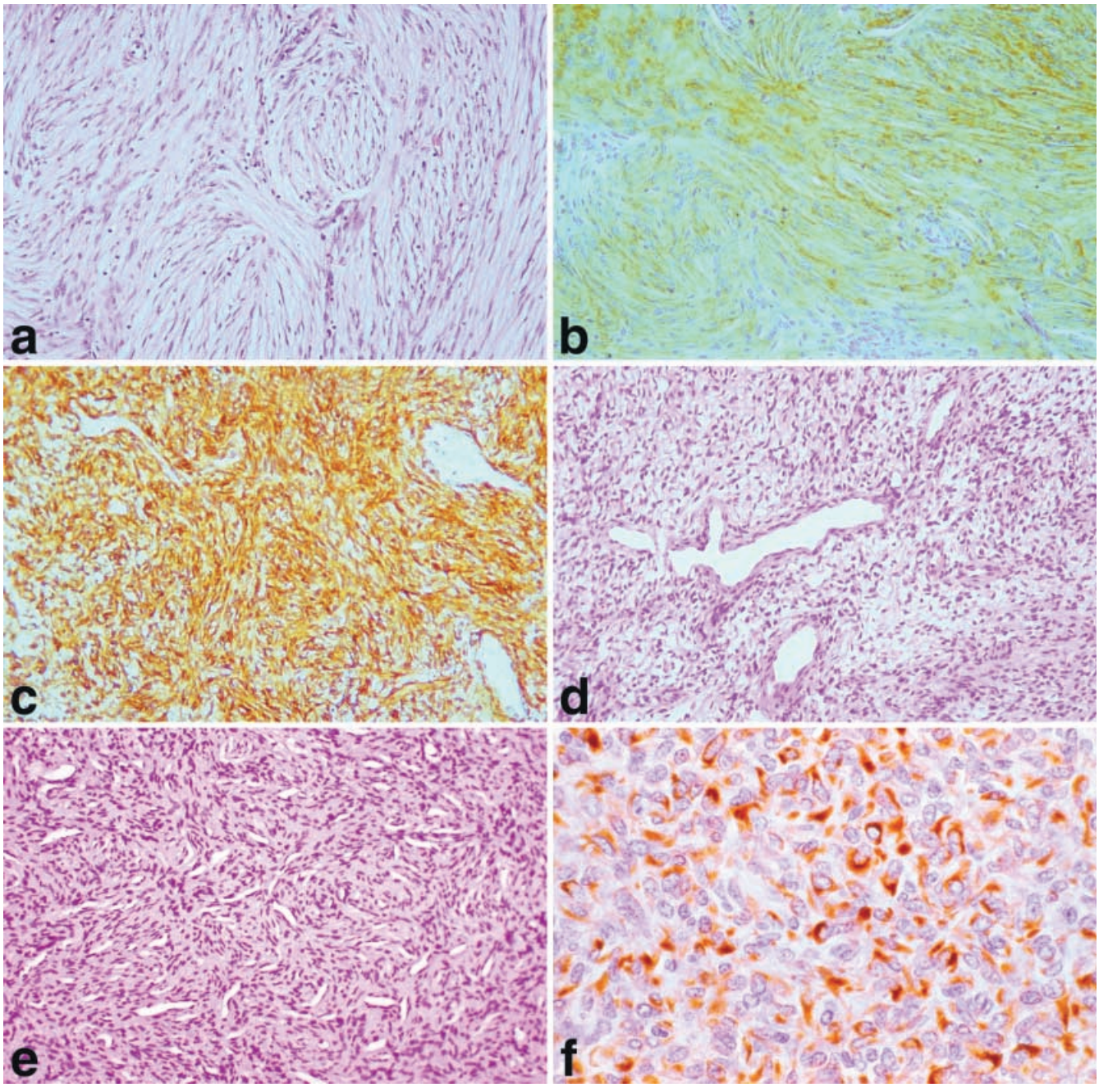

Fig. 4 Histogenetically different tumors of the meninges with histologically similar appearance. Fibrous/fibroblastic meningioma [World Health Organization (WHO) grade I] with elongated tumor cells [**a**, hematoxylin and eosin (HE)] are embedded in a fibrous matrix. Immunohistochemically, the tumor cells stain positive with antibodies to epithelial membrane antigen (**b**, EMA). The solitary fibrous tumor (SFT) is immunohistochemically characterized by an intensive staining reaction for CD34 (**c**). Slit-like or large gaping, stag horn-shaped, diluted blood vessels may be seen in SFT (**d**). However, such vessels are more characteristic for meningeal hemangiopericytoma, the typical histological appearance of which is shown in **e** and **f** (**e**, HE; **f**, vimentin)

cytomas generally lack mutations in the *NF2* and *TP53* genes but do carry homozygous *CDKN2A* deletions in about 25% of the cases [34, 59]. Cytogenetically, hemangiopericytomas usually demonstrate near diploid or hyperdiploid karyotypes and lack deletions of chromosome 22 [96]. Translocations involving the long arm of chromosome 12 have been reported as recurrent alterations [24, 25].

Recently, the solitary fibrous tumor (SFT) has been described as a novel tumor entity. Primary locations of SFT include the visceral pleura or mediastinum and, less commonly, the orbit [92]. Occasionally, SFT may arise in the meninges [12] (Fig. 4c, d). Here, it may pose problems in surgical pathology, because the differential diag-

nosis (Fig. 4a–f) of SFT from meningeal hemangiopericytoma (Fig. 4e) and fibrous meningioma (Fig. 4a) can be a difficult task [12]. However, SFTs are generally strongly positive for CD34 (Fig. 4c), in contrast to a weaker and usually patchy CD34 expression seen in hemangiopericytomas and a fraction of fibrous meningiomas [62]. Fibrous meningiomas can be further distinguished by their expression of EMA (Fig. 4b) and, less consistently, S-100 [62]. Data on molecular genetic alterations in meningeal SFT are not yet available. A study employing comparative genomic hybridization (CGH) for the analysis of SFT from pleura and other soft tissue sites revealed that tumors larger than 10 cm in diameter usually carry multiple chromosomal imbalances, most commonly including gains on chromosomes 5, 7, 8, 12, and 18 [55]. These alterations were neither detected in small SFTs of less than 10 cm in diameter nor in hemangiopericytomas.

In addition to hemangiopericytomas and SFTs, various other non-meningothelial tumors may arise in the meninges, including various benign and malignant mesenchymal tumors that are typically found in peripheral soft tissues.

Various melanotic neoplasms may affect the skull base region. Whether melanotic meningiomas really exist remains to be determined [45]. Primary melanocytic lesions of the central nervous system and its coverings are thought to arise from leptomeningeal melanocytes that are derived from the neural crest. These neoplasms include not only malignant melanoma but also benign melanocytoma and melanocytoma of intermediate dignity. Diffuse melanosis carries a poor prognosis even in the absence of histologic malignancy [70]. Melanocytoma lacks anaplastic features, but it is prone to undergo multiple local recurrences and to invade adjacent structures, such as bone [19, 33]. Malignant melanoma is a highly aggressive and radioresistant tumor with poor prognosis. It may metastasize to remote organs. The prognostic significance of a histologic pattern intermediate between melanocytoma and malignant melanoma is uncertain [45].

Schwann cell neoplasms

Schwannoma is a common tumor of peripheral nerves and accounts for about one-third of spinal and approximately 8% of intracranial tumors [43]. Intracranial schwannomas preferentially arise from the vestibular branch of the eighth cranial nerve and are located in the cerebello-pontine angle. Most of these vestibular schwannomas occur sporadically. Bilateral vestibular schwannomas are pathognomonic for neurofibromatosis type-2. The *NF2* gene is altered by mutations or deletions in both NF2-associated and sporadic schwannomas [31]. Various terms have previously been used for malignant variants of Schwann cell neoplasms, such as malignant schwannoma, anaplastic neurinoma, neurofibrosarcoma, or neurogenic sarcoma. These tumors are now uniformly classified as malignant peripheral nerve sheath tumors (MPNST). MPNST may arise either sporadically or in patients with neurofibromatosis type-1 (von Recklingshausen's disease). In the latter patients, progression from low-grade peripheral nerve sheath tumors, such as the pathognomonic plexiform neurofibroma may occur. A recent molecular cytogenetic investigation of MPNST reported on frequent gains of genomic material on chromosomal bands 17q24-q25, 7p11-p13, 5p15, 8q22-q24, and 12q21-q24 and losses on 9p21-p24, 13q14-q22, and 1p [52]. Furthermore, MPNST demonstrate increased levels of Ki67- and/or p53-positive tumor cells, a finding that is of diagnostic and prognostic importance [42].

Chordoma and other chordoid and chondroid neoplasms

Chordomas are neoplasms derived from remnants of the embryonic notocord. Major sites of manifestation include the clivus (cranial margin of the notochord) and the caudal spinal canal. A puzzling feature of chordomas is their aggressive behavior, which frequently contrasts with a differentiated morphological phenotype (Fig. 2a, b). Cranial and cervical chordomas can spread by para- or retropharyngeal extension to the region of the salivary glands or the jaw and may simulate a primary tumor of these structures. Metastasizing chordomas, however, are extremely rare. Spinal seeding has been reported in only five cases [85]. For the surgical neuropathologist, the distinction of chordoma, pleomorphic adenoma, mucinous carcinoma, and chondrosarcoma (Fig. 2c, d) may pose a diagnostic challenge. Immunohistochemical techniques are required to establish the diagnosis [75]. Coexpression of S-100 and cytokeratin (Fig. 2b) is characteristically encountered in chordomas [10].

In 1973, Heffelfinger et al. [23] described a variant of chordomas that contained cartilaginous areas indistinguishable from certain chondrosarcomas (Fig. 2c). They designated these tumors as chondroid chordomas and observed a better prognosis compared with classic (non-chondroid) chordomas. Since this original observation, there has been an ongoing debate whether chondroid chordoma represents a distinct clinicopathologic entity separable from chondrosarcoma and classic chordoma or whether it constitutes a variant of chondrosarcoma. Clinical and histopathological observations suggest that many of the tumors previously classified as chondroid chordoma may, in fact, be low-grade myxoid chondrosarcomas [68].

In 1987, Brooks et al. hypothesized that chondroid chordoma displays a hybrid or mixed pattern of immunoreactivity. Thus, an epithelial phenotype would be expected in chordomatous areas and a mesenchymal (non-epithelial) phenotype in cartilaginous areas. An analysis of 7 chondroid chordomas was performed and compared with results obtained on fetal notochord and fetal cartilage of 9-week and 12-week gestational age, 18 classic

chordomas, 2 peripheral chondromas, and 8 peripheral chondrosarcomas. All 18 chordomas exhibited the expected epithelial immunophenotype with positive staining reactions for both monoclonal and polyclonal antibodies to cytokeratin and EMA. In contrast, all chondromas and chondrosarcomas failed to express any of the epithelial markers and contained only S-100 immunoreactivity. Chondroid chordoma resembled cartilaginous tumors immunohistochemically; no mixed pattern with focal or widespread epithelial marker reactivity was identified. The authors concluded that chondroid chordoma either does not exist or is extremely rare and that these tumors are usually cartilaginous in nature [8].

Given the observation that classic or nonchondroid chordomas were uniformly immunoreactive for keratins and that the vast majority of chondroid chordomas lack epithelial markers, these tumors indeed appear to represent chondrosarcomas. Mitchell et al. (1993) performed immunohistochemical studies on 25 patients with chondroid chordoma (mean age 40.0 years) and on 16 patients with classic chordoma (mean age 44.2 years). All classic chordomas reacted for keratins as did 8 (32%) of the 25 chondroid chordomas; 44% of classic and 85% of chondroid chordomas were positive for S-100 protein. At 5 years, all patients younger than 40 years of age were alive in both the classic and chondroid groups. In contrast, of those patients older than 40 years of age, only 22% with classic chordomas and 38% with chondroid chordomas were alive. This finding led to the conclusion that regardless of tumor subtype, age is the single most important variable determining survival; patients younger than 40 years of age do better than older patients. There were no significant survival differences between patients with cartilage-containing tumors that are keratin immunopositive ("true" chondroid chordomas) or negative (chondrosarcomas). Immunostaining for keratins was, therefore, of no prognostic value in assessing chondroid lesions of the spheno-occiput [56].

In another attempt to clarify the issue, Rosenberg et al. (1994) studied 12 chondroid chordomas, 38 classic chordomas, and 28 chondrosarcomas that arose at the base of the skull or in the spine. As a reference, they also analyzed the immunohistochemical profile of fetal notochord, ecchordosis physaliphora, and fetal hyaline cartilage. It was found that all chondroid and nonchondroid chordomas were positive for cytokeratin, and the majority was also positive for EMA and CEA. In contrast, none of the chondrosarcomas stained for cytokeratin, EMA, or CEA. Vimentin and S-100 were positive in more than 95% of both classic chordomas and chondroid chordomas, and chondrosarcomas. The immunohistochemical profile of these tumors was similar to their nonneoplastic counterparts. The authors concluded that chondroid chordoma is a variant of chordoma and should not be confused with chondrosarcomas. Because chondroid chordomas have been reported to have a better prognosis, they felt that this nosologic term should be preserved and that chondroid chordoma should continue to be a focus of clinical and pathologic study [71].

A critical review of the literature and their own experience with cartilaginous tumors of the skull base led Ishida and Dorfman [29] to the following conclusions: chondrosarcoma of the skull base is a distinct clinicopathological entity. The immunohistochemical staining pattern (cytokeratin negative, EMA negative; S-100 positive) can be helpful in distinguishing it from chordoma with chondroid differentiation (chondroid chordoma; cytokeratin positive, EMA positive). The chondroid chordomas originally described by Heffelfinger et al. may have included some true chondrosarcomas with focal areas of myxoid chordoma-like appearance. Focal chondroid differentiation in chordoma is not a rare phenomenon. Further studies are needed to define whether chordoma with chondroid foci should be distinguished from conventional chordoma and considered a distinct entity associated with a better prognosis [29].

Recent data suggest that immunohistochemical detection of tau proteins [28] and molecular genetic analysis [9] can facilitate the distinction of chordoma and chondrosarcoma. However, these findings need to be confirmed. Clinical studies indicate that the distinction between chordoma and low-grade chondrosarcoma may be clinically relevant, with a significantly better outcome for the chondrosarcoma group. Gay et al., in 1995 [18], analyzed 60 patients with cranial base chordoma (n=46) or low grade chondrosarcoma (n=14) treated by extensive surgical resection. They found that chondrosarcoma had a better prognosis than chordoma (recurrence-free survival rates at 5 years: 90% and 65%, respectively; P=0.09) [18]. Castro et al. [13] reviewed their experience with charged particles to irradiate primary neoplasms of the skull base and those extending to the skull base from the nasopharynx and paranasal sinuses. From 223 patients, 126 patients had lesions of the cranial base (53 chordomas, 27 chondrosarcomas, 27 paraclival meningiomas, and 19 patients with other tumors, such as osteosarcoma or neurofibrosarcoma). In addition, 31 patients with primary or recurrent squamous carcinoma of the nasopharynx extending to the skull base, 44 patients with salivary gland tumors, mostly adenocarcinoma, and 22 patients with squamous carcinoma of the paranasal sinuses, all with cranial base extension were also included. The results demonstrated Kaplan–Meier 5-year local control rates of 85% for meningioma, 78% for chondrosarcoma, 63% for chordoma, and 58% for other sarcomas [13].

The differential diagnosis of chordoma includes other chordoid neoplasms (Fig. 2a–h), in particular chordoid meningioma (Fig. 2g, h) and chordoid glioma (Fig. 2e, f). The term "chordoid glioma" was recently introduced to denote a circumscribed, apparently low-grade neoplasm arising in the suprasellar/third ventricular region. These tumors were originally described in 1998 by Brat et al. [7], who reported on a series of eight patients (seven females and one male; age ranging from 31 years to 70 years) which, on neuro-imaging, presented with well-circumscribed, contrast-enhancing third ventricular masses. A cystic component was noted in two patients.

Histologically, chordoid gliomas consist of cords and clusters of epithelioid cells with abundant eosinophilic cytoplasm and relatively uniform nuclei in a mucoid matrix (Fig. 2e). Significant mitotic activity is not found, and the MIB-1 labeling index is usually low. Lymphoplasmacellular infiltrates may be prominent throughout the tumor and at its well-defined borders. Adjacent brain tissue displays reactive changes with gliosis and numerous Rosenthal fibers. Immunohistochemically, the majority of neoplastic cells are positive for glial fibrillary acidic protein (GFAP) (Fig. 2f), vimentin, and CD34 [69]. Minor fractions of tumor cells may be immunoreactive for S100 protein, EMA, and cytokeratins. There is no evidence for neuroendocrine differentiation or for expression of estrogen and progesterone receptors. Ultrastructural examination of chordoid gliomas revealed focal microvilli, scattered "intermediate" junctions, and focal basal lamina formation. Molecular genetic investigations showed neither chromosomal imbalances nor detectable alterations in the TP53, CDKN2A, EGFR, MDM2, and CDK4 genes [69]. At present, this tumor is considered a novel glial tumor entity of uncertain histogenesis but with distinct clinicopathologic features.

Metastatic tumors and neoplasms infiltrating per continuitatem

The base of the skull can be the site of hematogenic metastases of various malignancies. More often, it is infiltrated per continuitatem by malignant and benign tumors originating from surrounding tissues [13]. The pituitary gland, as an endocrine organ, can be a target for metastasizing carcinomas of other endocrine glands or hormonally regulated organs. Diffusely infiltrating pituitary adenomas may extend through the dura mater and spread via adjacent bones into the mucosa of nasal and paranasal cavities; 15% of such invasive adenomas have also been found to express p53 immunoreactivity, a feature generally lacking in noninvasive adenomas and present in nearly all pituitary carcinomas, also according to the new WHO classification of endocrine tumors [79]. The new WHO classification of endocrine tumors [79] introduces the term "atypical adenoma" of the pituitary gland, the criteria for which include conspicuous mitotic activity and a MIB-1 labeling index greater than 3%. The diagnosis of "typical" and "atypical" adenoma is not based upon an expansive or invasive growth pattern, respectively. The term "pituitary carcinoma" should be restricted to such tumors of adenohypophyseal cells showing craniospinal or systemic metastases, and/or aggressive brain invasion [79]. Consequently, atypical adenoma and carcinoma of the pituitary gland correspond to WHO grade II and WHO grade III/IV, respectively.

Histologically, benign meningiomas may infiltrate the skull base and destroy the orbit and/or nasal cavities [11]. Olfactory neuroblastoma is a malignant neuroectodermal tumor which may extend through the bony structures of the nasal and paranasal cavities into the anterior intracranial fossa [44]. The melanotic neuroectodermal tumor of infancy (MNTI) or melanotic progonoma constitutes a rare neoplasm that generally arises in the maxilla. Involvement of bones of the cranial vault or other extracranial bones is rare [11]. MNTIs consist of both variably pigmented epithelium and islands of neuroblastic cells that may create a fibrillary background. The pigmented cells form clusters, glands, or tubules that, in some cases, surround islands of neuroblasts. Because of similar cellular components, melanotic medulloblastoma may be difficult to distinguish. MNTI is, however, almost always benign and located extracranially [44]. Sinunasal carcinomas and other carcinomas of the upper respiratory tract and adenocarcinomas and adenoid-cystic carcinomas of the salivary and lacrimal glands may show diffuse infiltration and destruction of the cranial base. Pilocytic astrocytomas sometimes grow diffusely into the subarachnoidal space and may extend into structures of the base of the brain, such as cranial nerves and the optic chiasm, hypothalamus, and other suprasellar structures [11]. In rare cases, glioblastoma and, more often, gliosarcoma, may infiltrate dura and bone. Mesenchymal elements in the skull base region may give rise to a variety of soft tissue tumors.

Major examples include the following entities:

Rhabdomyosarcoma

Rhabdomyosarcomas are malignant neoplasms that show evidence of primary skeletal muscle differentiation. In the skull base region, the embryonal subtype of rhabdomyosarcomas is predominantly observed [53, 67]. The diagnosis of rhabdomyosarcoma relies on features of skeletal muscle differentiation at the light microscopic (Fig. 5a), immunohistochemical (Fig. 5b), molecular, or electron microscopic level. The most specific markers for skeletal muscle differentiation include antibodies to MyoD1 and myogenin (myf 4) [81, 88, 93], both of which are members of the regulatory MyoD family [60]. Their expression can also be studied using a reverse transcriptase PCR protocol [16].

The prognosis of embryonal rhabdomyosarcoma is intermediate, while alveolar and pleomorphic subtypes are associated with poor outcome [58]. *TP53* mutations and nuclear accumulation of p53 protein appear to be associated with an adverse outcome [3, 37]. Cytogenetic studies may aid in separating these subtypes. Most cases of alveolar rhabdomyosarcomas carry either a t(2;13)(q35;q14) translocation or, less frequently, a t(1;13)(p36;q14) translocation, as demonstrated by interphase fluorescent in situ hybridization (FISH) [4, 77]. The translocation results either in a fusion between *PAX3* on chromosome 2 and the transcription factor gene *FKHR* on chromosome 13 [5] or in a fusion of *FKHR* with *PAX7* [15]. These fusion products can be detected using reverse transcription PCR [2]. They are not present in embryonal rhabdomyosarcomas, which exhibit a deletion on the short arm of chromo-

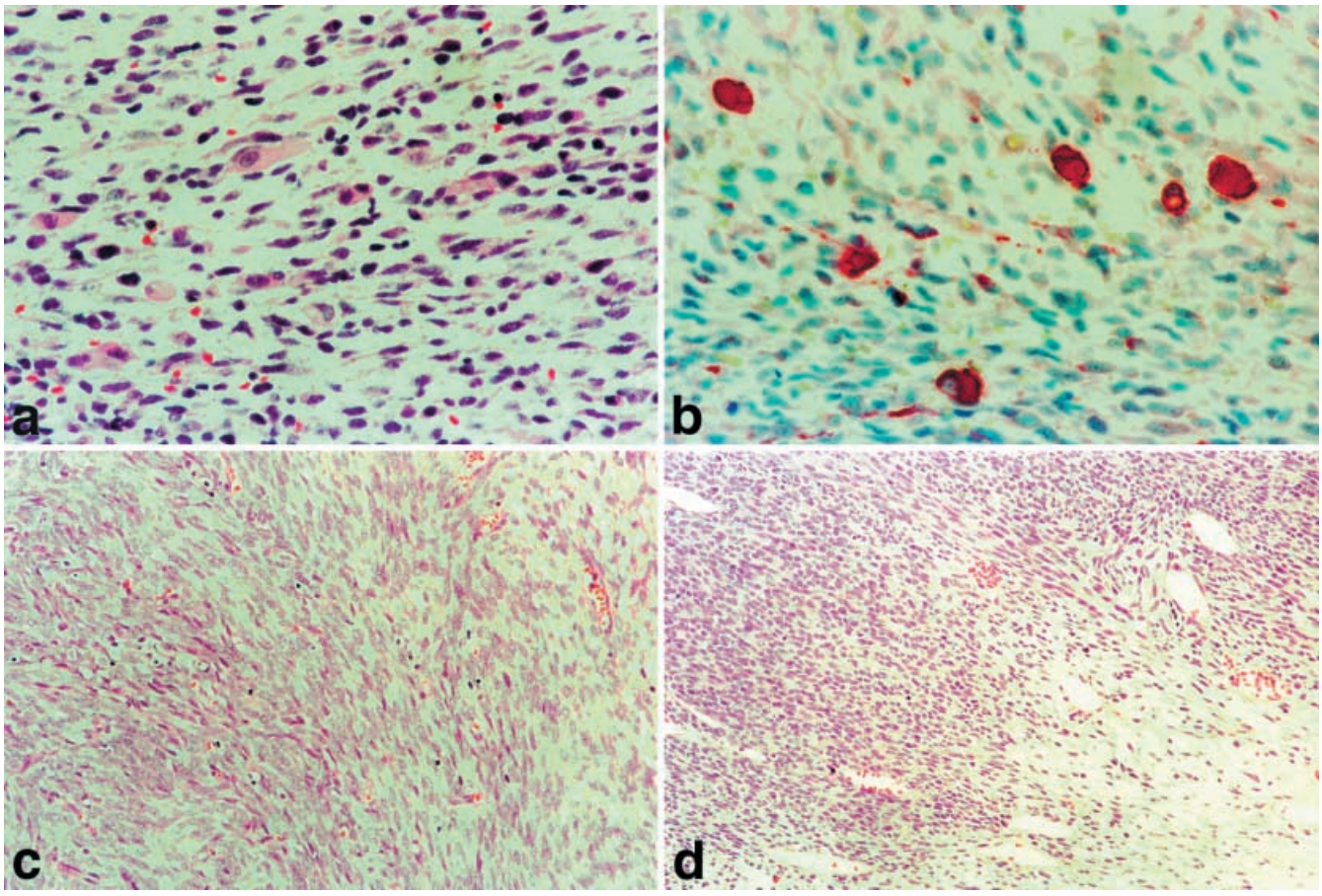

Fig. 5 **a**, **b** Mesenchymal tumors of the skull base and their histologic characteristics. Embryonal rhabdomyosarcoma with rhabdomyoblasts [**a**, hematoxylin and eosin (HE)], which immunohistochemically stain positive for desmin (**b**). **c**, **d** Monophasic fibrous synovial sarcoma may present with variable histologic features (HE)

some 11 [74]. These findings may aid in the differential diagnosis, but it has to be emphasized that they cannot replace a conventional histologic examination. Some alveolar rhabdomyosarcomas carry no chromosomal translocation.

Synovial sarcoma

Synovial sarcoma represents a malignant mesenchymal neoplasm with biphasic morphologic appearance. It occurs at any age and at various anatomic locations. A small but significant proportion of cases develop intracranially and may involve the skull base [46, 78].

Morpholol gically, biphasic (Fig. 6b) and monophasic-fibrous tumors (Fig. 5c, d) can be distinguished. Immunohistochemical evidence for epithelial differentiation (cytokeratin and/or EMA positivity) is helpful in differentiating the monophasic-fibrous variant from other spindle-cell sarcomas (i.e., malignant peripheral nerve sheath tumors or fibrosarcomas). Many synovial sarcomas are bcl-2 and CD99 positive [26, 82]. CD99 positivity may pose differential diagnostic problems in distinguishing poorly differentiated synovial sarcomas from peripheral primitive neuroectodermal tumors (pPNET). Approximately one-third of pPNETs react with antibodies to broad spectrum cytokeratins. Machen and coworkers have recently shown the utility of immunohistochemistry to cytokeratin 7 in identifying synovial sarcomas and excluding pPNET [50]. Approximately 30% of synovial sarcomas are S-100 protein positive [21], which raises the differential diagnosis towards malignant peripheral nerve sheath tumors. The combination of S-100 protein, cytokeratin, and EMA positivity supports the diagnosis of synovial sarcoma. In addition, CD99 immunoreactivity appears more common in synovial sarcoma compared with MPNST [47].

Most synovial sarcomas (90–95%) carry a chromosomal translocation involving chromosomes X and 18 (t(X;18)(p11.2;q11.2) [14, 83]. This particular translocation (Fig. 6c) has not been found in other soft tissue sarcomas [86]. It generates a fusion transcript between *SYT* on 18q11.2 and either *SSX1* or *SSX2* (two highly homologous genes at Xp11) [48]. These hybrid genes can be useful diagnostic markers for distinguishing synovial sarcomas from malignant peripheral nerve sheath tumors [4]. Moreover, a better prognosis has been reported for those synovial sarcomas carrying a *SYT/SSX2* fusion gene [38].

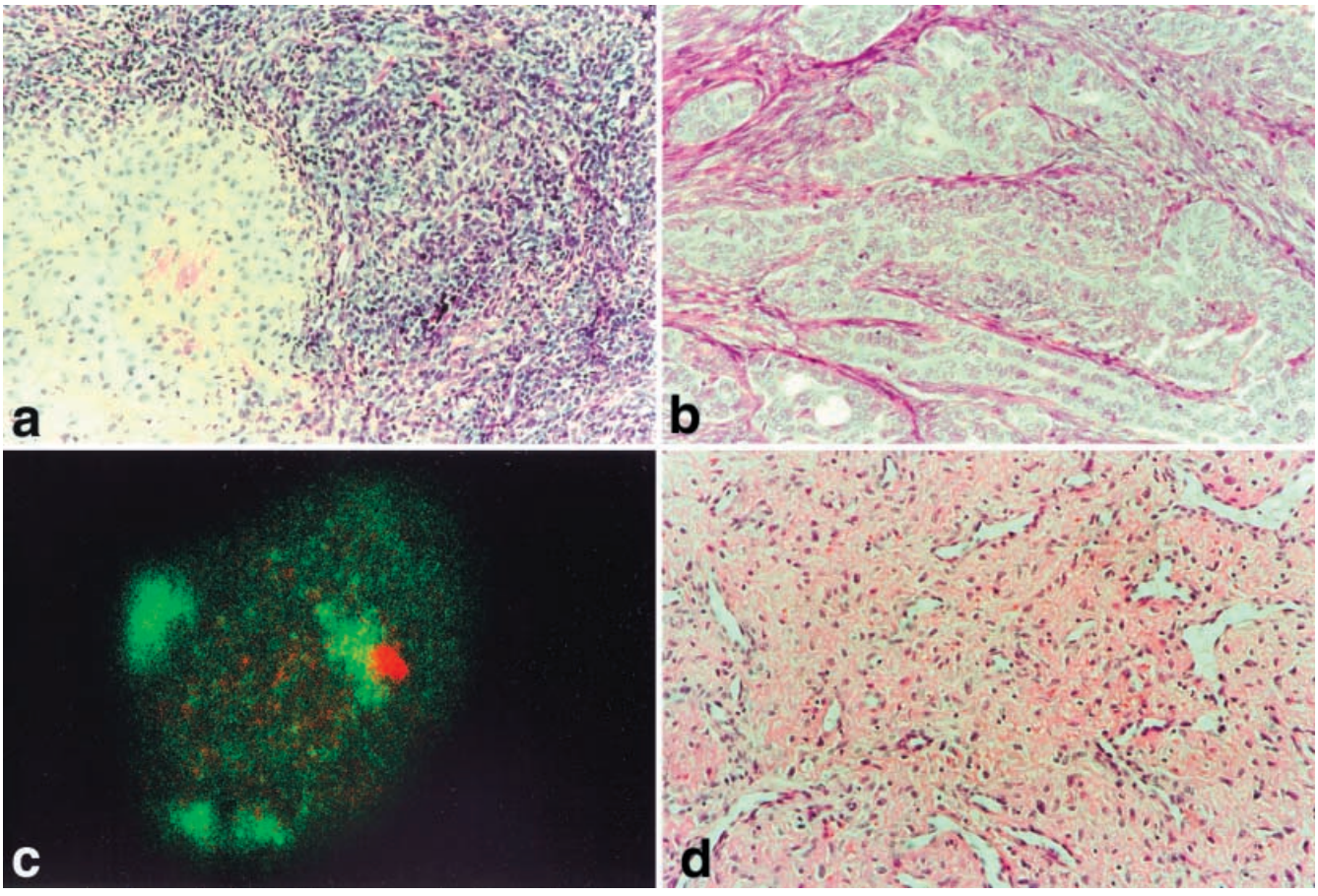

Fig. 6 Mesenchymal tumors of the skull base and their histologic characteristics. **a** The microscopic appearance of mesenchymal chondrosarcomas is divergent. Well-differentiated tumor areas with formation of cartilage contrast with undifferentiated small-cell areas [hematoxylin and eosin (HE)]. **b** Typical appearance of a biphasic synovial sarcoma (HE). **c** Nucleus from paraffin-embedded synovial sarcoma. Double-color fluorescent in situ hybridization (FISH) with chromosome 18-specific paint, direct labeled with fluorescein isothiocyanate (FITC; VYSIS) and chromosome X centromere-specific probe labeled with digoxigenin and detected with rhodamine (ONCOR). Appearance of chromosome 18 painting probe showing three *green fluorescent signals* of unequal size. One of the smaller signals and the red X centromere signal are adjacent in one region, indicating the derivative X chromosome. The derivative 18 chromosome is indicated by the other small *green fluorescence signal*. **d** Nasopharyngeal angiofibromas are histologically characterized by vascular spaces of varying caliber and a fibrous stroma with stellate or spindle-shaped cells. Most stromal cells are fibroblasts (HE)

The enigmatic malignant fibrous histiocytoma

According to the WHO classification of soft tissue tumors [90], malignant fibrous histiocytoma (MFH) represents a pleomorphic spindle-cell sarcoma without a distinct line of cellular differentiation. With these properties, the term "pleomorphic sarcoma, not otherwise specified" would appear more appropriate for these tumors. It is well known that a wide range of other sarcomas may mimic MFHs; even carcinomas, melanomas, and lymphomas may show a similar morphologic pattern. MFHs have been described in nearly every anatomic location [36, 66], including the skull base [57]. Cytogenetic studies have supported the concept that MFH encompasses a heterogeneous group of neoplasms [87].

Extraskeletal mesenchymal chondrosarcoma

Approximately, 30–50% of mesenchymal chondrosarcomas develop in soft tissues [76]. Remarkably, nearly one-third of extraskeletal cases arise in the brain and meninges and may show invasive growth into the skull base [76, 80]. The microscopic appearance of mesenchymal chondrosarcomas is characterized by a combination of well-differentiated tumor areas with formation of cartilage and undifferentiated small-cell elements (Fig. 6a). The former areas may appear benign or display features of a well-differentiated chondrosarcoma. In the malignant, small-cell component, staghorn-shaped vascular spaces reminiscent of the vascularization in hemangiopericytoma can be encountered. Thus, the differential diagnosis includes hemangiopericytoma but also other small-cell malignancies, such as Ewing's sarcoma/pPNET, small-cell osteosarcoma, and malignant lymphoma. Recently, Granter et al. [20] demonstrated a consistent, strong CD99 positivity in mesenchymal chondrosarcomas, which renders their distinction from Ewing's sarcoma/pPNET difficult in some cases [72]. Although small-cell osteosarcoma may show chondroid differentiation

and a hemangiopericytomatous pattern, the occurrence of islands of well-developed cartilage is extremely unusual for these tumors.

In conclusion, a broad spectrum of tumors may involve the base of the skull. Neuroectodermal, meningothelial, epithelial, and mesenchymal tumors and hematological malignancies have to be considered in the differential diagnosis. Recent progress in the immunohistochemistry and molecular genetics of major tumor types have greatly facilitated the nosologic classification and differential diagnosis of the various skull base neoplasms. It is hoped that the identification of novel molecular alterations will further refine the diagnosis of these tumors and provide more reliable molecular markers for predicting the prognosis and the response to adjuvant therapy of individual patients.

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