Neurogenic Tumors

11

Introduction

Primary mediastinal neurogenic tumors in general are rare and can be present in children and adults as well. Even though for the most part the most common tumors are generally of the benign type in the adult population (ganglioneuroma, schwannoma, neurofibroma), that may not be the case in the pediatric age group (ganglioneuroblastoma, neuroblastoma). However, the gamut of these tumors in the mediastinal location is wide and can pose problems in interpretation when limited material is available for evaluation. Even though the posterior mediastinal compartment is the most common location for these tumors, it is not unusual to see any one of these tumors occurring in the anterior mediastinal compartment. Regardless of the anatomic location, for practical purposes, one can separate mediastinal neurogenic tumors into benign and malignant, which in turn may help not only in terms of diagnosis but also in terms of the follow-up that patients with these tumors may obtain.

A simple practical schema based on the occurrence of these tumors would include the following neoplasms:

- Benign neurogenic tumors
  - Neurofibroma
  - Ganglioneuroma
  - Schwannoma
  - Granular cell tumor
- Malignant neurogenic tumors
  - Neuroblastoma/ganglioneuroblastoma
  - Malignant peripheral nerve sheath tumor (MPNST)
  - Peripheral neuroectodermal tumor (PNET/Ewing Sarcoma)
  - Pigmented neuroectodermal tumor of infancy (melanotic progonoma, retinal anlage tumor): considered benign but with the potential to metastatize in a small percentage of cases
  - Ependymoma
  - Meningioma
  - Malignant granular cell tumor

Following this schema, it is likely that the vast majority of tumors may be approachable following morphological, immunohistochemical, ultrastructural, and molecular biological features.

However, it is important to highlight that neurogenic tumors may also be divided into those originating from nerve sheaths and those originating from nerve cells (paraganglia, parasympathetic ganglia). Those originating from nerve sheath are supposed to arise from differentiated adult Schwann cell, thus its name Schwannoma, and these represent one of the most common benign tumors in the posterior mediastinum. The nerve cell tumors are represented by another common neoplasm: ganglioneuroma. It is important to highlight that either nerve sheath or nerve cell tumors may range from benign to their malignant counterparts. Thus, for the nerve sheath tumors, the benign tumor is represented by schwannoma, while the malignant counterpart will be represented by "malignant schwannoma" or "malignant peripheral nerve sheath tumor" (MPNST). Tumors from nerve cells also range from the mature and differentiated ganglioneuroma to the more immature and undifferentiated neuroblastoma. One tumor that may share features of both mature and immature elements is ganglioneuroblastoma. In addition, it is important to recognize that all nerve elements – axons, sheath cells, and connective tissue – form tumors like neurofibromas. Those neurofibromas that show plexiform features are commonly associated with neurofibromatosis. It is of interest to mention that it has been suggested that all these tumors have a neural crest origin, and the term "thoracic neurolophomas" has been advanced [1].

In this chapter, there will not be an attempt to specifically separate by clinical means the different types of neurogenic tumors, except when indicated and appropriate. The clinical features of these tumors, including their radiological features, will be conjointly discussed, and appropriate observations will be made when specifically indicated to separate a benign neoplasm from a malignant one or a specific tumor from others.

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In 1949, Blades [2], in reference to the practice of routine roentgenologic examination of the chest, stated that such practice would uncover that mediastinal tumors are not as rare as it is commonly believed. Blades [2] also stated that successful treatment of mediastinal tumors depends on their detection before clinical signs are apparent, and a discovery of any mediastinal mass demands positive diagnosis. Furthermore, he stated that the mediastinum could harbor any type of tumor, and it would be convenient to classify mediastinal tumors into two groups (anterior and posterior mediastinal tumors); he also stated that posterior mediastinal tumors are chiefly of one common variety: neurogenic. More than 70 years later, one can only agree with what has been proven by many who have studied the mediastinum. Needless to say, sporadic exceptions are not unusual as nothing can be completely fool-proof regarding the location of these tumors.

In 1958, Richards and Reeves [3], in a study of mediastinal tumors and cysts in children, stated that their occurrence in children is rare. The authors made reference to a single case of a 2-year-old child who was diagnosed with neuroblastoma of the posterior mediastinum. The authors stated that there are three other tumors that may occur in this anatomic location: (1) neurinoma, (2) sympathogonioma, and (3) ganglioneuroma. They added that these tumors are often associated with vertebral body or neural arch erosion, which translates into "back pain." In 1960, Carey and colleagues [4] presented a study of 140 cases of what the author called extrapleural mediastinal neurogenic tumors. The patients' ages spanned between 0 and 69 years, and there does not appear to be a gender predilection. The vast majority of tumors belonged to schwannomas and ganglioneuromas, with only six malignant tumors, one "malignant schwannoma" in a patient with neurofibromatosis, and five neuroblastomas. The malignant tumors were seen in patients less than 20 years of age, while the majority of benign tumors were seen in patients older than 20 years. More than half of the patients were asymptomatic, and the frequent complaint was that of "thoracic pain." Horner's syndrome was associated in three cases. What is interesting in this report is that the authors arbitrarily separated all these tumors anatomically into five different compartments: superior, superior and middle, middle, middle and inferior, and inferior. In a study of 50 cases, Pachter and Lattes [5] divided these tumors into two types: (1) tumors of nerve sheath origin, neurilemmoma, neurofibroma, and malignant schwannoma; and (2) tumors of the sympathetic nervous system, ganglioneuroma, ganglioneuroblastoma, and neuroblastoma. Of the 50 cases described, 12 were malignant, while 47 were located in the posterior mediastinum. Three of these neurogenic tumors were located in the anterior mediastinum. The majority of the tumors appear in adult individuals, while the malignant tumors (neuroblastoma, ganglioneuroblastoma) appear to be more common in children. Interestingly, in the two cases of malignant schwannoma, there was no history of von Recklinghausen's disease. Meyer and Ochsner [6] also reported their experience with intrathoracic neurogenic tumors in 32 cases from 1942 to 1965. Four of the reported cases were not located in the posterior mediastinum. The reported patients ranged in age from 3 to 72 years, and the gender distribution was similar between men and women (18 women and 14 men). One third of the cases reported were malignant: five with neurogenic sarcomas (two patients with history of von Recklinghausen's disease) and five patients with neuroblastomas (one adult patient over 50 years of age). Whittaker and Lynn [7] reported 105 mediastinal tumors in children under 16 years of age during the period from 1935 to 1968 and found 37 cases of neurogenic tumors; the majority was basically represented by 16 ganglioneuromas and 11 neuroblastomas. The authors concluded that, in general, mediastinal masses in children may not cause symptoms and that the lack of symptoms should not be interpreted as the lesion being benign. Pokorny and colleagues [8] reported their experience with mediastinal tumors in infants and children: 109 cases between 1954 and 1972. The ages ranged from 2 h to 16 years; 35 of the 109 cases were neurogenic tumors, and the majority of the cases were neuroblastomas (18 cases) followed by ganglioneuroblastoma (8 cases). King and colleagues [9], in a review of benign and malignant mediastinal tumors in children, identified 27 out of 52 tumors in children as benign neurogenic tumors (ganglioneuroma, neurilemmoma, and neurofibroma), while 20 tumors out of 136 were identified as malignant (neuroblastoma, ganglioneuroblastoma). Vidne and Levy [10] reported on 45 patients between 1964 and 1970 (24 males and 21 females between the ages of 7 months and 74 years) and encountered only nine cases corresponding to neurogenic tumors with only one of the nine cases being malignant (neuroblastoma). Davison and colleagues [11] also reported 55 cases of intrathoracic neural tumors over a 25-year period of time. The patients' ages ranged from 7 months to 63 years; 41 patients were asymptomatic, 52 tumors were in the posterior mediastinum, and only 3 tumors were malignant (neuroblastoma). In a more focused study, Akwari and colleagues [12] reported on 69 patients with mediastinal neurogenic tumors, with extension through an intervertebral foramen "dumbbell-shaped" mass. The cases represented 9.8% of all mediastinal neurogenic tumors (706 cases in total). The authors stated that the majority of these patients present with neurologic symptoms of spinal cord compression and that about 10% of these tumors are malignant. In a larger series of mediastinal tumors in the period from 1954 to 1973, Luosto and coworkers [13] reported 208 cases in patients between the ages of 2 and 74 years, of which only 39 belonged to neurogenic tumors. The majority of the tumors were benign (neurilemmoma, neurofibroma, ganglioneuroma), with only two malignant tumors (neurofibrosarcoma and ganglioneuroblas-

toma). In a study of 160 thoracic neural tumors from the radiological point of view, Reed and coworkers [14] argued that radiologists may suggest a specific preoperative diagnosis by combining radiographic appearance and age of the patient, and stated that a posterior mediastinal mass in a young child is most likely a neuroblastoma or ganglioneuroblastoma, while the same presentation in an adult patient would be most likely a ganglioneuroma, schwannoma, or neurofibroma. Harjula and coworkers [15], in a study on mediastinal neurogenic tumors with emphasis on early and late results of surgical treatment, identified 66 cases with a mean follow-up of 12 years. The patients' ages ranged from 13 to 72 years of age (only one 2-year-old child). The vast majority of cases were benign tumors with only a couple of malignant neoplasms. Three patients were identified to have recurrence of a benign tumor (neurilemmoma and neurinoma). Malignant transformation was identified in two of eight neurofibromas 5 and 13 years postoperatively. Blegvad and coworkers [16] reported on 129 mediastinal tumors in 72 men and 57 women over a period from 1971 to 1987; the patients' ages ranged from 3 months to 81 years, and the mean age was 44 years. Twenty-seven tumors were identified as neurogenic, and, of those, 12 were in children. Of the 27 cases identified as neurogenic, 5 were malignant and all were in children. Saenz and coworkers [17], in a study of 63 patients with focus on posterior mediastinal tumors, described 63 patients between the ages of 1 day and 26 years; the median age was 6 years. While 89% of the tumors were categorized as neurogenic, the symptomatology presented included respiratory symptoms or chest pain 45% and neurologic symptoms 13% (half related to spinal cord compression). Palpable masses were discovered in 5% of the patients. In 32% of the patients, the discovery of the posterior mediastinal mass was an incidental finding. Neuroblastoma was the most common malignant neoplasm, and malignancy was identified in 60% of all patients. Follow-up in patients with neuroblastoma showed that 4 out of 32 patients had died after a period of 7–289 months; the median was 73 months. The authors stated that patients in whom the diagnosis of neuroblastoma was made during the first year of life had better prognosis than older patients. In addition, the authors stated that MRI is superior to CT in the evaluation of posterior mediastinal tumors. In that regard, Sakai and coworkers [18], in a study of nine patients with intrathoracic neurogenic tumor using MRI, stated that some of these tumors have a characteristic appearance that may be helpful in the differential diagnosis. Also, Strollo and coworkers [19], in a review of middle and posterior mediastinal tumors, stated that on MRI schwannoma and neurofibroma typically have low to intermediate signal intensity on T1-weighted images and may have areas of intermediate to high signal intensity on T2-weighted sequences. The authors also added that MRI should be performed preoperatively in all patients with suspected neurogenic tumors to definitely exclude intraspinal tumor extension. Tanaka and coworkers [20] made similar observations in a study of neurogenic mediastinal tumors using MRI. Carachi and coworkers [21], in a study of 145 children with neuroblastoma over a 20-year period of time (1961–1980), identified 30 children with thoracic neuroblastoma with a mortality rate of 16%. In a similar study of 196 infants and children, Grosfeld and coworkers [22] found that 72% of the mediastinal tumors in this group were malignant. Despite this, lymphoma was the most common malignancy, and neuroblastoma was the second most common malignancy in this group. Ganglioneuroma, schwannoma, and neurofibroma together represented 21 of the 196 tumoral cases. From the anatomic point of view, Sugio and colleagues [23] reported 39 cases of neurogenic tumors of the mediastinum, specifically identifying two neurilemmomas originating from the vagus nerve. Takeda and colleagues [24] reviewed 50 years of experience from a single institution in Japan and accounted for 146 patients (74 male and 72 female, 60 children and 86 adults). The posterior mediastinum was the most common location, with 136 tumors located in that anatomic area with 118 tumors belonging to ganglioneuromas, schwannomas, and neurofibromas. Only 23 cases were identified as neuroblastomas and ganglioneuroblastomas. Most patients were asymptomatic: 84% of adults and 60% of children. Overall, about 20% of the tumors were malignant, and most of them occurred in the first 5 years of life. In a more general study of mediastinal tumors from patients ranging from 6 months to 62 years, Shrivastava and colleagues [25] documented 106 patients with mediastinal tumors, with only 16% of these tumors located in the posterior mediastinum. Other authors have also found a similar trend when all mediastinal tumors are put together [26], determining that the presence of neurogenic tumors in the posterior mediastinum still is not a common occurrence. Other authors have focused mainly on the most adequate surgical procedure for the treatment of benign neurogenic tumors, stating that video-assisted thoracoscopic surgery (VATS) is the procedure of choice [27]. In a more recent review of intrathoracic neurogenic tumors, Bicakcioglu [28] reported on 149 patients (including 4 patients with paragangliomas): 90 females and 59 males between the ages of 7 months and 77 years (average, 24.5 years), comprised of 29 infants and children and 120 adults. Of the 149 patients reported, 113 had benign neurogenic tumors (schwannoma, neurofibroma, ganglioneuroma), while 13 had ganglioneuroblastoma/neuroblastoma, and 10 patients had malignant schwannoma. The majority of these tumors was located in the posterior mediastinum (131 cases), while 3 were in the anterior mediastinum. The rest of the tumors were distributed in other parts of the thoracic cavity. Seven patients had a history of von Recklinghausen's disease. The authors concluded that complete surgical resection is the treatment of

choice for malignant and benign thoracic neurogenic tumors, and that after histopathologic analysis other treatment options should be considered.

Based on the published literature on intrathoracic tumors, it is likely that benign neurogenic tumors are more common than their malignant counterparts. However, it is also likely that malignant neurogenic tumors are more common in the pediatric age group. Also important to highlight is the fact that benign neurogenic tumors – ganglioneuroma, neurofibroma, and schwannoma – are likely to be treated with complete surgical resection alone, while malignant neoplasms may also be treated with complete surgical resection plus additional medical therapy.

Benign Tumors

Ganglioneuroma

In 1947, Stout [29] presented 10 cases of his own and reviewed previous literature, which included 233 additional cases of what the author called ganglioneuroma of the sympathetic nervous system. In this review, Stout [29] gave credit to Loretz who, in 1870, described a similar tumor in the mediastinum. In Stout's review of 243 cases, 62 occurred in the mediastinum. In addition, Stout suggested that it is possible to divide ganglioneuromas into three groups: (1) fully differentiated, (2) ganglioneuromas with diffusely scattered cells of a lesser degree of differentiation, and (3) composite tumors made up of two or more parts, one being ganglioneuroma and the other neuroblastoma. Based on that categorization, 146 tumors reported would belong to the fully differentiated tumors, 23 to those showing diffusely scattered cells of a lesser degree of differentiation and 20 to the composite group. He also added that the fully differentiated tumor should be considered benign contrary to the other two groups. It is important to highlight that the occurrence of ganglioneuromas has been hypothesized as possibly occurring by spontaneous maturation of neuroblasts [30].

Clinically, ganglioneuromas are often asymptomatic, and their presence is discovered as an incidental finding [31–33]. In general, ganglioneuromas in the mediastinum are more common in the posterior compartment. Spinelli and colleagues [31] reported 14 surgical cases of ganglioneuromas in which their original diagnosis was an incidental finding; these were treated by complete surgical resection. In this report, only two cases were located in the costovertebral space, while the rest of the tumors were in extrathoracic location. However, in a review of reported cases of ganglioneuromas by specific site, the authors [31] stated that the mediastinum might be involved in about 22% of the cases. In addition, it is also stated that cough, back pain, and dyspnea may be seen in those tumors occurring in the mediastinum. Interestingly, Shea and Abshire [34] reported a case of thoracic ganglioneuroma in a previously healthy 11-year-old child with an associated Philadelphia chromosome-positive chronic myeloid leukemia, an occurrence that is unusual. Another association that has been described is the presence of a mediastinal ganglioneuroma and retroperitoneal non-functioning pheochromocytoma in a 52-year-old woman [35].

From the radiological point of view, Guan and colleagues [36], in a study of 23 cases of thoracic ganglioneuromas, concluded that ganglioneuromas show hypodensity in plain CT, while on CT and MRI, non-enhancement or slight enhancement in artery phase and progressive mild enhancement in delay phase are features of this tumor. Ozawa and colleagues [37] study the morphological differences between schwannomas and ganglioneuromas in the mediastinum in 22 cases using craniocaudal length (CC) to major axis ratio (CC/M R) using CT/MRI. The authors found that ganglioneuromas show higher mean CC/M R than schwannomas, which the authors concluded as being important in separating those tumors by such means.

Because ganglioneuromas are considered benign neoplasms, complete surgical resection is the treatment of choice and offers the best alternative. Although recurrences have been reported, it is likely that this rare occurrence may take place in tumors that are incompletely removed.

Pathological Features

Ganglioneuromas appear to be well defined but not encapsulated tumors that may range in size from a couple of centimeters to more than 10 cm in greatest diameter. Usually, the tumors are tan in color with a smooth surface (Fig. 11.1). Areas of necrosis and hemorrhage are not common.

Histologically, the tumor is composed of a mixture of ganglion cells characterized by larger cells with eosinophilic cytoplasm, round eccentrically placed nuclei and prominent nucleoli. In some of these ganglion cells, it is possible to identify basophilic granules, which represent Nissl substance (granules). In addition to the ganglion cells, the tumor also shows a spindle cell proliferation characterized by elongated cells with scant cytoplasm, fusiform nuclei, and inconspicuous nucleoli. These components are commonly arranged in a tightly or loose growth pattern. Mitotic activity is not common, and areas of necrosis and hemorrhage are rare. In some cases, the tumor may show areas of calcifications and myxoid change (Figs. 11.2, 11.3, 11.4, 11.5, 11.6, and 11.7).

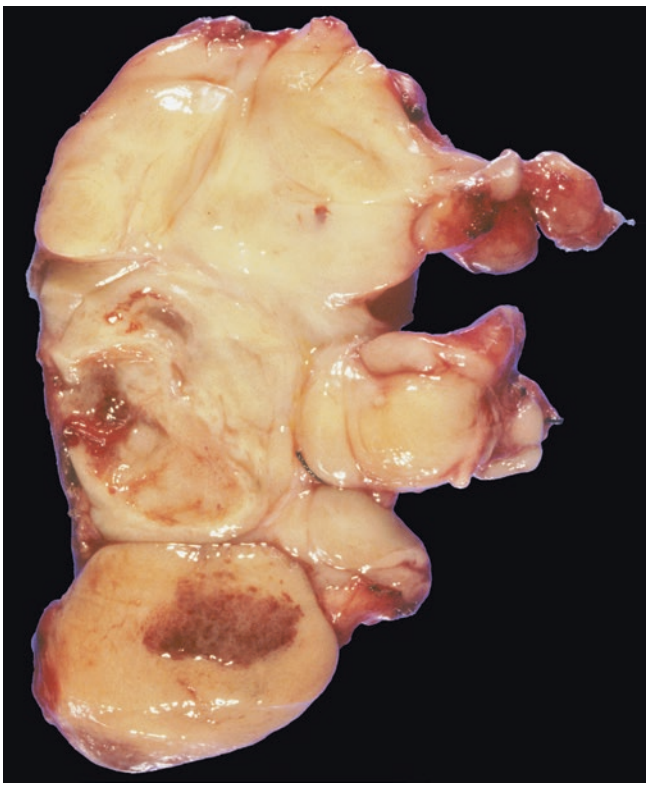

Fig. 11.1 Gross image of a ganglioneuroma showing a light tan, solid tumor without areas of necrosis or hemorrhage

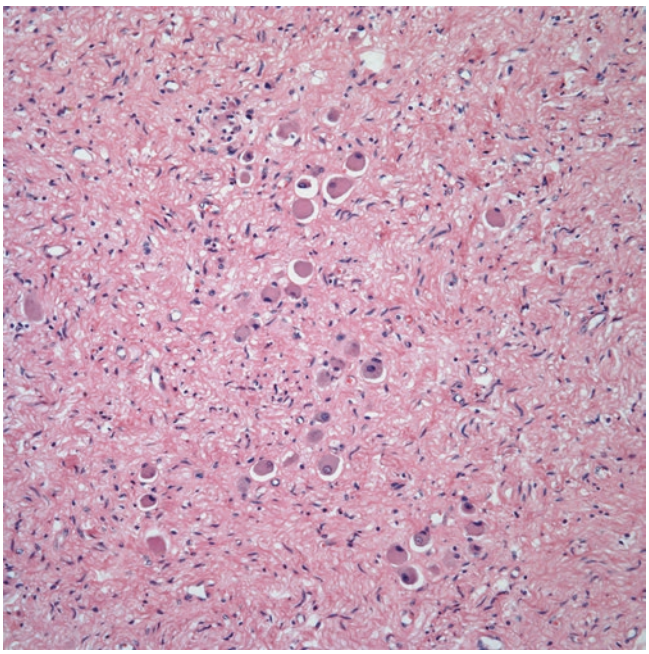

Fig. 11.3 Ganglioneuroma showing areas of a more solid component in which the ganglion cells are haphazardly displayed

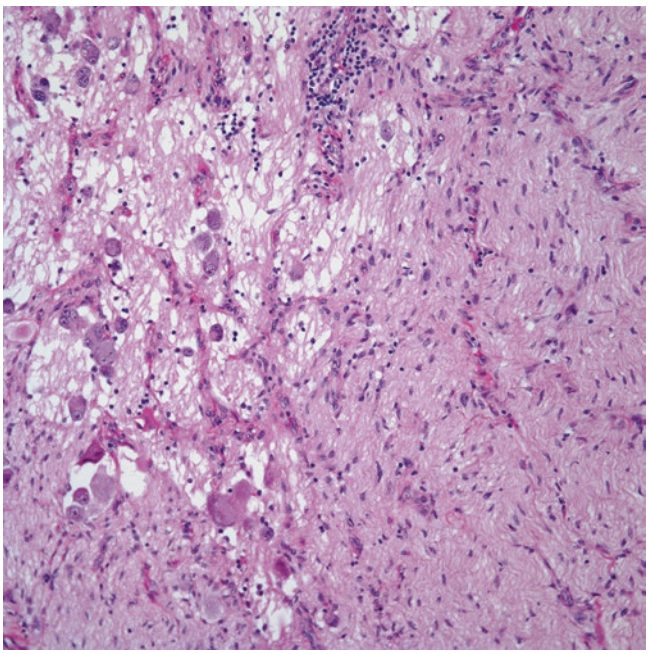

Fig. 11.2 Ganglioneuroma showing a loose fibroconnective tissue with numerous mature ganglion cells

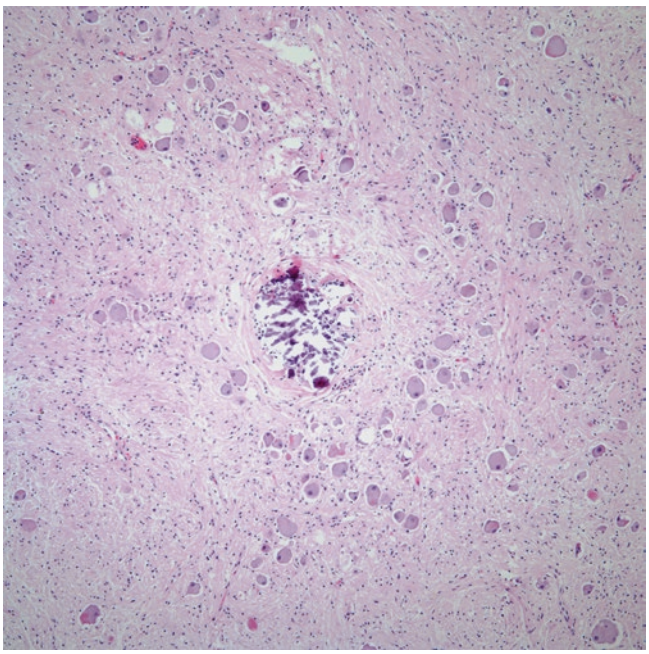

Fig. 11.4 Ganglioneuroma with focal calcification and numerous mature ganglion cells

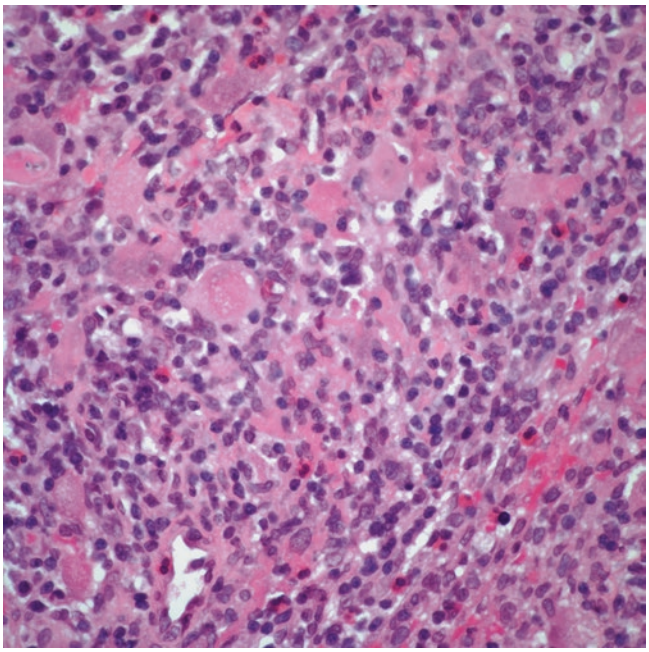

Fig. 11.5 Ganglioneuroma with prominent inflammatory reaction in which the ganglion cells are more difficult to identified

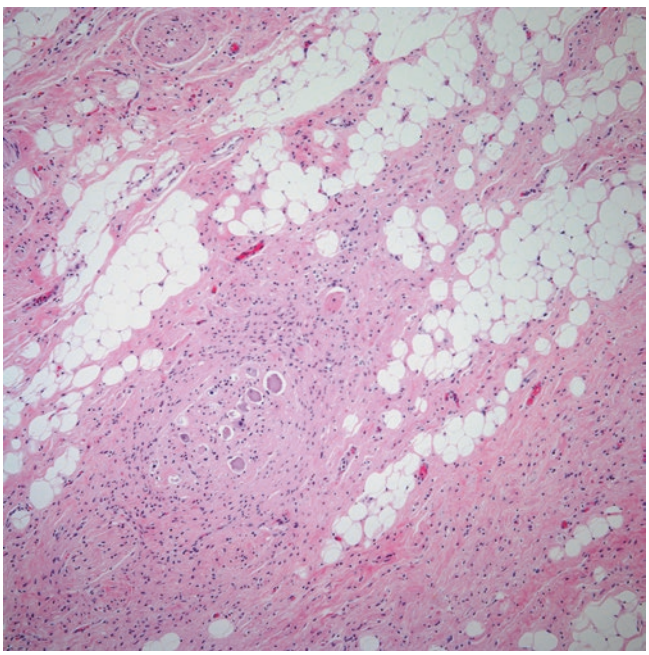

Fig. 11.6 Ganglioneuroma showing areas of adipose tissue and mature ganglion cells

Ancillary Diagnostic Tools

Even though the diagnosis of ganglioneuromas is rather straightforward by morphological means, the use of electron microscopic studies in these tumors has shown the presence of neurofilaments, microtubules, and dense-core vesicles. On the other hand, immunohistochemical studies may show immunoreactivity for S-100 protein and

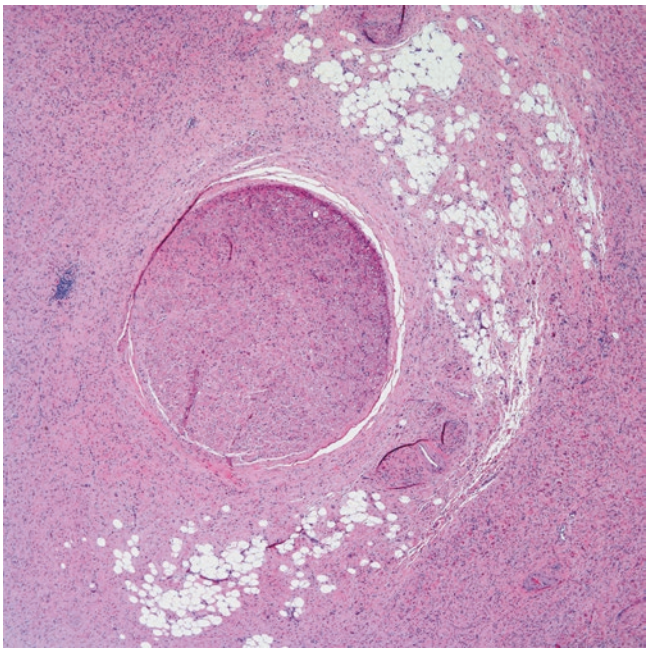

Fig. 11.7 Ganglioneuroma with more solid proliferation involving adipose tissue and encircling a nerve trunk

neurofilament protein in the spindle cell component, while the ganglion cell component may show some reactivity for synaptophysin and NeuN.

Differential Diagnosis

Because ganglioneuromas occur in the posterior mediastinum more often, it is often logical to include other neurogenic tumors in the differential diagnosis. In small biopsy samples in which the presence of ganglion cells may not be apparent, other spindle cell lesions such as neurofibromas or schwannomas are usually considered in the differential diagnosis. Important to consider is the fact that both of those lesions may also show positive staining for S-100 protein and possibly with neurofilament protein, thus making an unequivocal interpretation more challenging. One other consideration would be with a smooth muscle neoplasm; however, in this setting, the use of immunohistochemistry, namely, S-100 protein, would aid in arriving at a correct interpretation.

Neurofibromas

As stated earlier in this chapter, neurofibromas are tumors that have a mixture of all nerve elements (axons, sheath cells, and connective tissue). In general, similar to ganglioneuromas, these tumors in the mediastinum are more common in the posterior compartment. A common association for neurofibromas is the presence of von Recklinghausen's disease or neurofibromatosis type 1 (NF1). NF1 disease is an autosomal dominant disorder with an approximate incidence of 1 in 3000 patients with no specific gender

predilection [38]. However, it is also important to highlight that neurofibromatosis may be associated with other conditions including mental retardation, Bourneville's syndrome, Morquio's syndrome, and Batten's type of lipofuscinosis, among others [39].

Clinically, patients may present with upper respiratory symptoms, tracheal compression, or scoliosis [38]. Ueda and colleagues [40], in a computed tomography (CT) study of 88 patients with NF1, identified 13 patients with mediastinal masses of which 3 were neurofibromas and 7 other lesions were considered to be neurofibromas. However, it is also important to highlight that, even though the occurrence of neurofibromas is more common in the posterior mediastinum, sporadic cases can also be present in the anterior mediastinum. Yano and colleagues [41], in a study of 43 patients with "small-size" anterior mediastinal tumors, detected one case of neurofibroma in the anterior mediastinum. One other unusual association that has been described in the literature includes an intrathoracic meningocele in a 43-year-old man with multiple neurofibromatosis [42]. In addition, in some unusual cases, the coexistence of ganglioneuroma and neurofibroma in the background of NF1 has been reported [43]. Reports of unusual occurrences such as intrathoracic neurofibromas of the phrenic nerve, bilateral mediastinal neurofibromas of the vagus nerve, and giant intrathoracic neurofibroma with mediastinal shift have been reported [44–46].

Just as with other benign neurogenic tumors of the mediastinum, complete surgical resection is the treatment of choice for these neoplasms and is considered curative.

Pathological Features

These tumors are usually well circumscribed with no capsule. They are whitish in color and of soft consistency (Fig. 11.8). Neurofibromas usually track along the nerve giving the appearance of an elongated tumor rather than a spherical lesion. In patients with neurofibromatosis, the plexiform neurofibroma appearance is that of an elongated and nodular tumor that may extend along a nerve.

Histologically, neurofibromas are not encapsulated tumors; characteristically, the tumors show a spindle cellular proliferation composed of cells with scant cytoplasm, fusiform nuclei with a wavy appearance, and inconspicuous nuclei. This cellular proliferation is often embedded in a loose fibroconnective tissue, which may show myxoid or edematous changes. In some areas, the tumor may show inflammatory changes that may vary from area to area (Figs. 11.9, 11.10, 11.11, 11.12, 11.13, 11.14, 11.15, 11.16, 11.17, 11.18, and 11.19). In general, neurofibromas do not

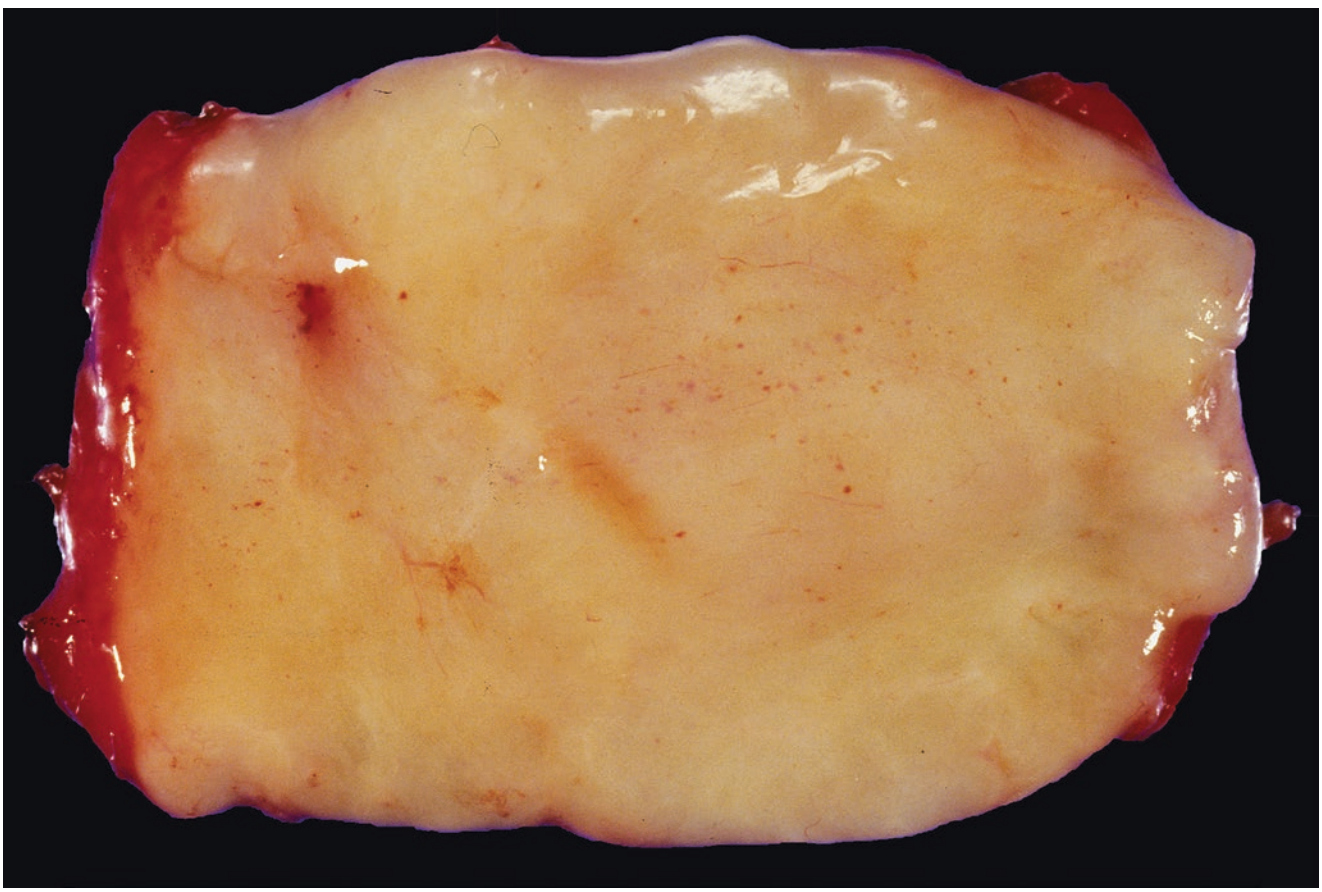

Fig. 11.8 Neurofibroma showing a tumor yellowish in color, well circumscribed and with no areas of necrosis and hemorrhage

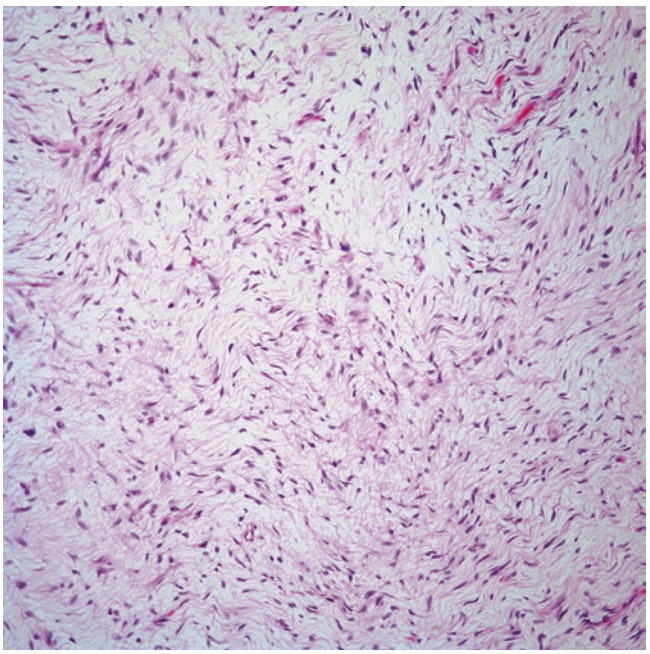

Fig. 11.9 Neurofibroma showing spindle cell proliferation in a loose fibroconnective tissue stroma

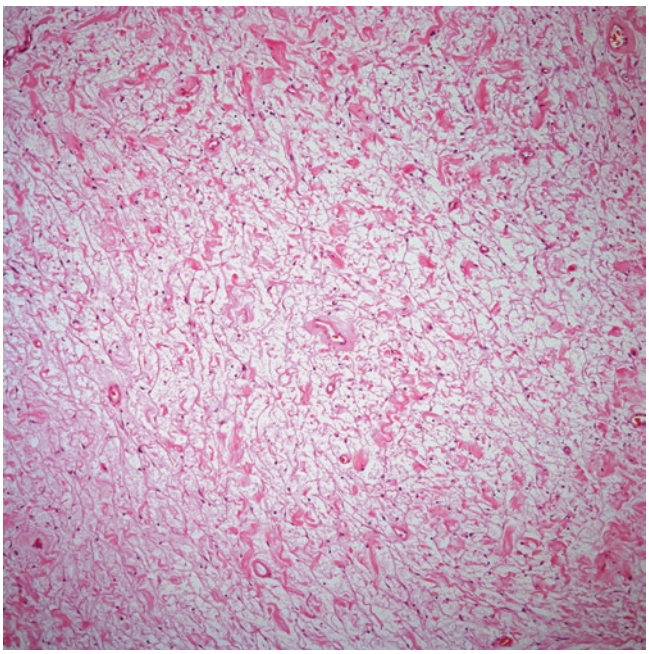

Fig. 11.11 Neurofibroma composed almost exclusively of loose fibroconnective tissue in which the spindle cell proliferation is more subtle

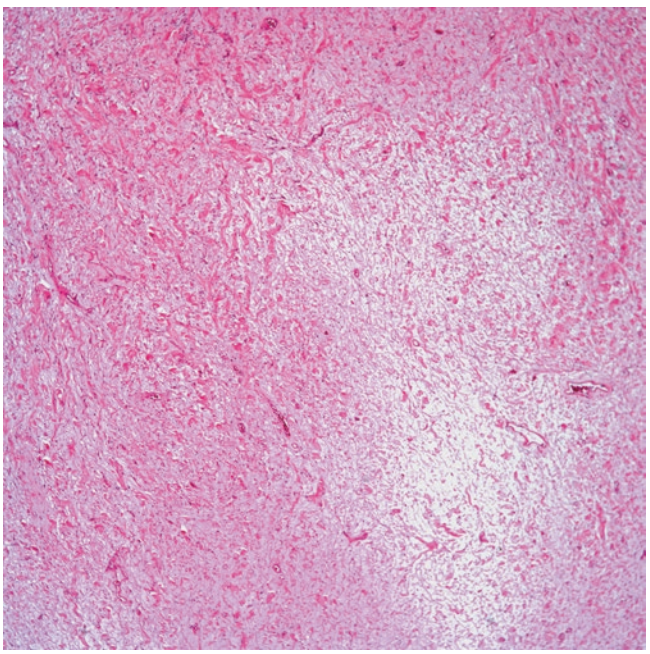

Fig. 11.10 Neurofibroma showing more loose fibroconnective tissue areas and focal myxoid changes

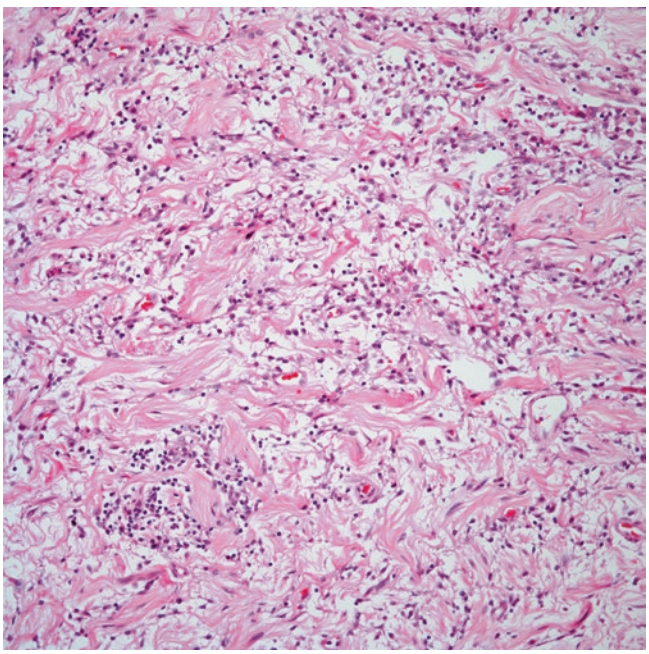

Fig. 11.12 Neurofibroma with inflammatory component

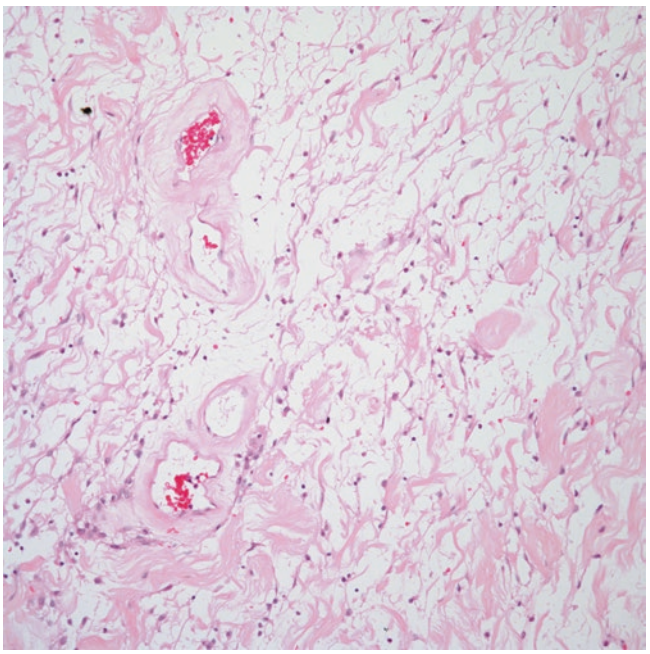

Fig. 11.13 Higher magnification of a neurofibroma with degenerative changes

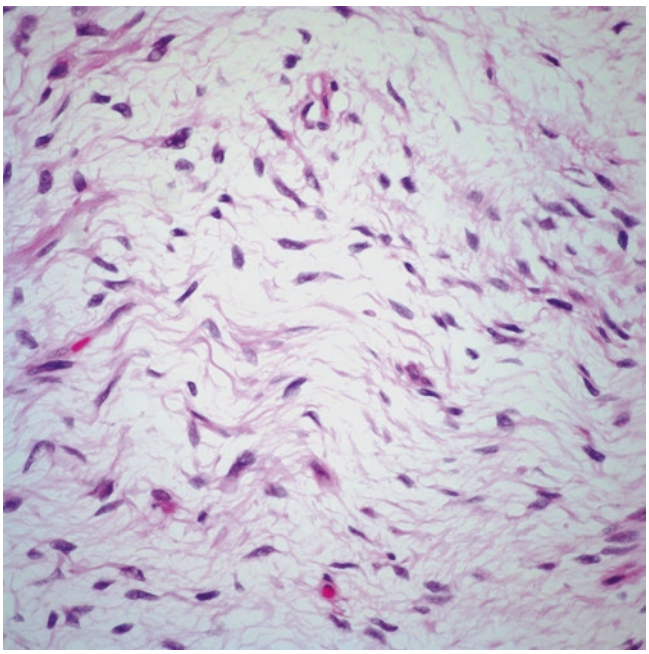

Fig. 11.15 Higher magnification of a neurofibroma showing spindle cells with elongated nuclei and inconspicuous nucleoli. No mitotic activity or nuclear atypia are present

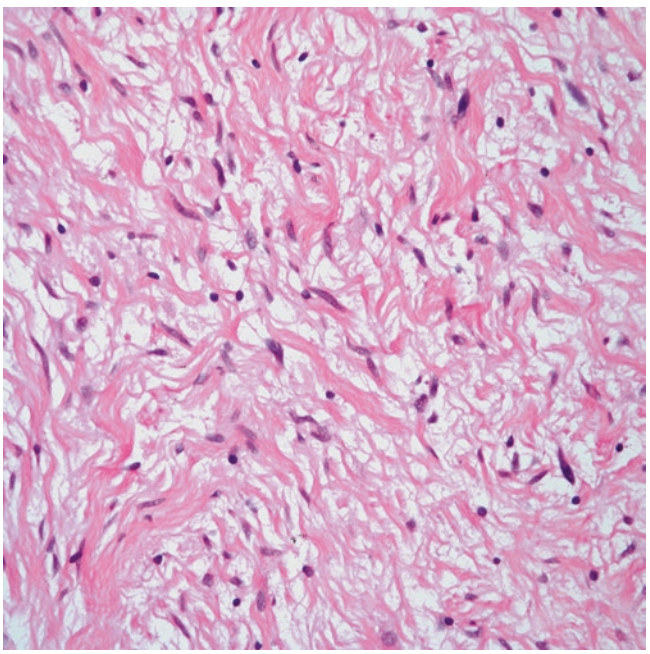

Fig. 11.14 Higher magnification of a neurofibroma showing a tumor with no cellular atypia

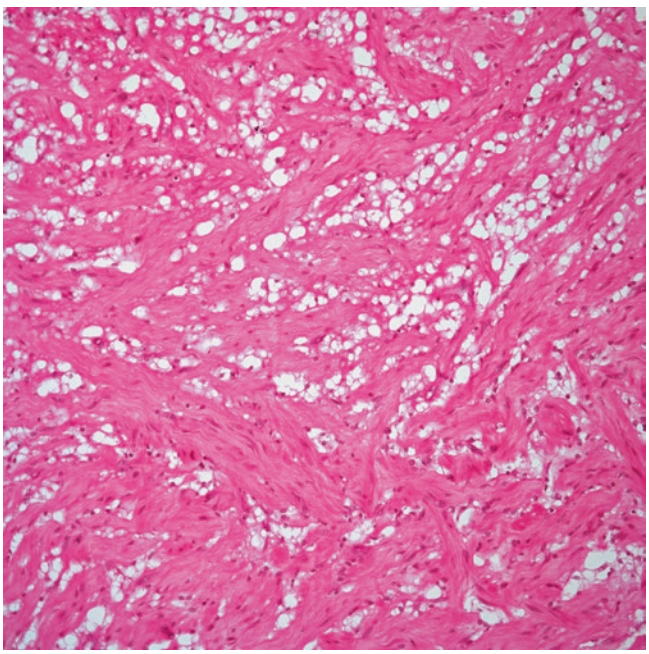

Fig. 11.16 Neurofibroma with extensive vacuolization of the cells giving an appearance of clear cell component

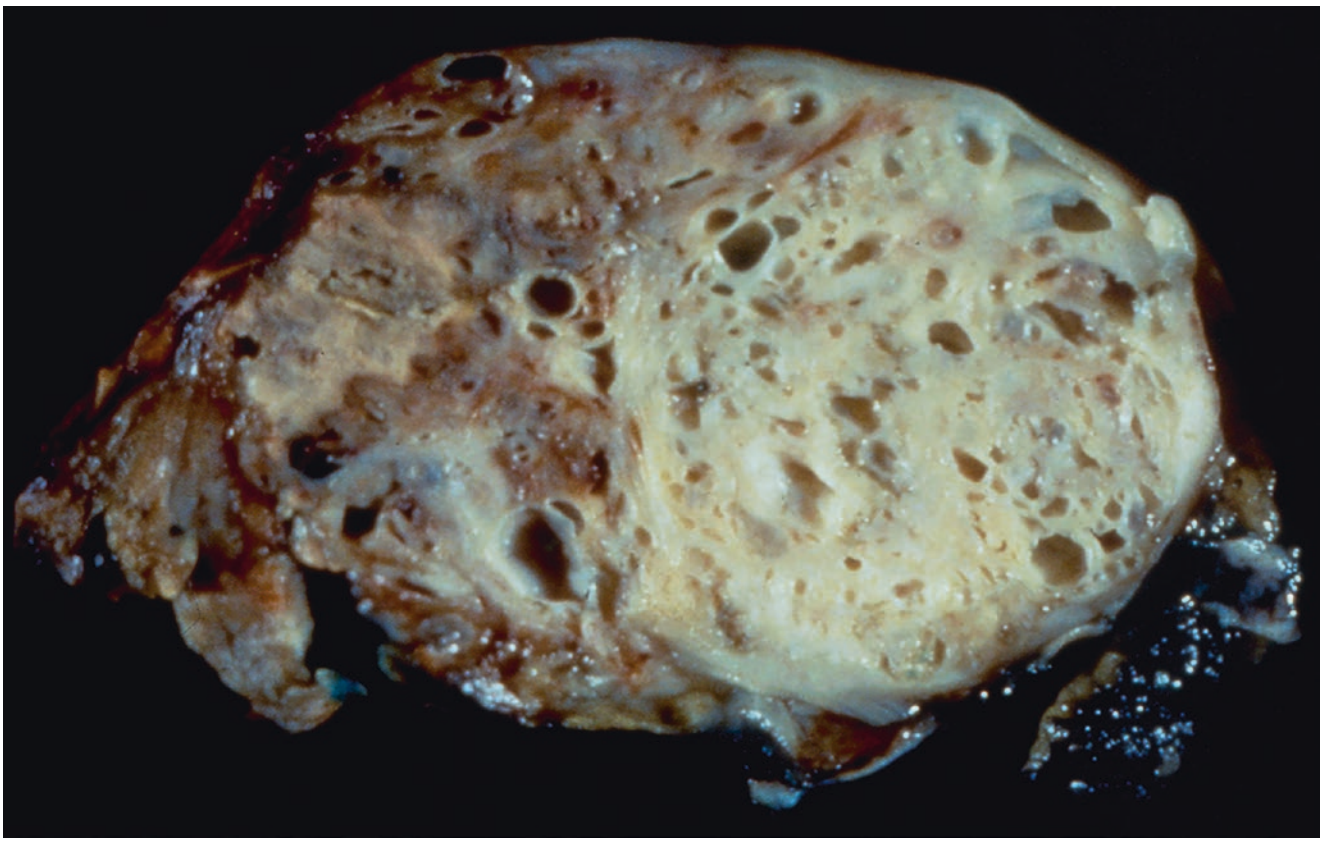

Fig. 11.17 Gross image of a mediastinal schwannoma with cystic changes

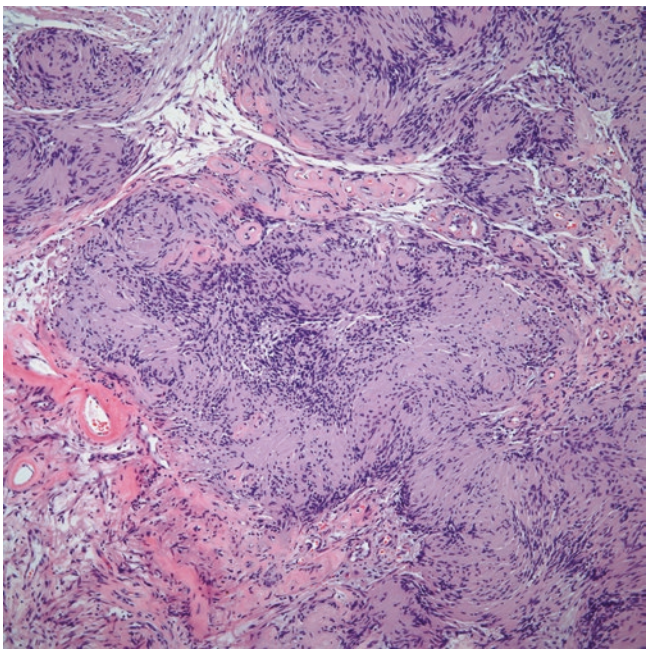

Fig. 11.18 Low power view of a conventional schwannoma showing the classical features of hypo and hyper cellular areas

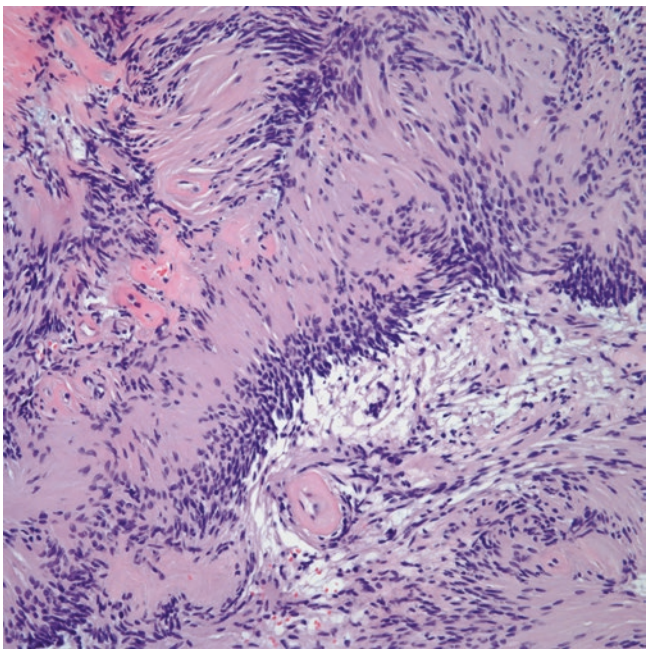

Fig. 11.19 Schwannoma showing palisading of the nuclei

show marked cellular atypia, necrosis, or increase mitotic activity. However, in some tumors in which there is the background of neurofibromatosis, the tumors may show more cellularity and nuclear atypia, which should in some cases raise a suspicion for sarcomatous transformation. It has been stated that malignant transformation may occur in approximately 2–10% of the cases. In such cases, reasonable sampling with careful evaluation of the histology plays an important role. Other unusual features that have been associated with neurofibromas include the presence of Pacini's corpuscles, Wagner-Meissner bodies, pigment, and gland formation [47, 48].

Ancillary Diagnostic Tools

Just like with ganglioneuroma, the diagnosis of neurofibroma is straightforward on morphological grounds. However, the use of immunohistochemical stains for its diagnosis may be reserved for small biopsies in which the morphological features may not be so apparent. Immunohistochemical studies that may aid in the diagnosis of neurofibromas are rather limited. S-100 protein may be helpful, but it is usually weakly positive or negative in many cases. Neurofilament protein also may show positive staining, but again it is usually a weak positivity, and many cases are negative. Ultrastructural studies have shown cytoplasmic processes interspersed with occasional myelinated and unmyelinated axons in an extensive collagenous stroma with a well-defined basement membrane coating the plasmalemma [49].

Differential Diagnosis

The differential diagnosis of neurofibromas logically will include other neurogenic posterior mediastinal neoplasms such as schwannoma, ganglioneuroma, perineurioma, and neurothekeoma. However, other neoplasms of non-neurogenic origin such as liposarcomas and myxomas may also enter in the differential diagnosis. In small biopsies, the challenge of separating any of these entities may prove difficult as there may not only be an overlap in some histological features but there may also be an overlap in the immunohistochemical profile. From the morphological point of view, ganglioneuromas would show the presence of ganglion cells, which can facilitate the separation from neurofibromas. Schwannomas may also show classical features such as the presence of Verocay bodies and strong positive staining for S-100 protein. Perineuriomas may show positive staining for EMA, which will also lead to the correct interpretation. Neurothekeomas may show more myxoid component, which may help in arriving at a more correct interpretation. Myxomas and liposarcomas will not originate from a nerve, which may help in arriving at a more correct interpretation. Needless to say, those considerations may be more common in a small biopsy; surgical resection of the tumor with enough tissue to evaluate should rarely pose a serious difficulty in the diagnosis.

Schwannoma

This tumor has also been known as neurilemmoma and neuroma. The tumors originate from the nerve sheath and are supposed to arise from differentiated adult Schwann cells. These tumors are more common in the third and fourth decade of life, and there does not appear to be gender predilection for their occurrence. They may also occur in the background of neurofibromatosis (NF1/von Recklinghausen's disease). It is likely that the size of the tumor plays an important role in the symptomatology that these patients may have. Small tumors are often diagnosed during routine radiographic films, while large tumors may compress adjacent structure, and the patients may develop symptoms related to the structures involved. Despite the fact that it is well known that these tumors occur in the posterior mediastinal compartment, there are no large series of these tumors in this locations, and most of what is known about schwannomas is derived from the experience of these tumors in other locations where they may occur more often. For instance, in a review of 75 cases of intrathoracic peripheral nerve sheath tumors, Boland and colleagues [50] documented only 13 cases of schwannomas, even though the authors stated that the most common peripheral nerve sheath tumors are of the benign type. Based on this finding, we can estimate the occurrence of schwannomas in the thoracic cavity at approximately 15–20% of all of this family of tumors.

Clinically, these tumors do not appear to have any predilection for gender or age, although most cases are seen in adult individuals. Just like with other nerve sheath tumors, schwannomas may be associated with neurofibromatosis (von Recklinghausen disease). However, intrathoracic schwannomas have also been associated with other conditions such as Horner's syndrome [51, 52]. Horner's syndrome is characterized by miosis, blepharoptosis, enophthalmos, and anhidrosis due to blocking of the sympathetic pathway at any point. Miura and colleagues [51] documented a 48-year-old woman with a dumbbell-shaped tumor discovered during routine chest radiography. Apparently, the patient had noticed some of the symptoms of right-sided Horner's syndrome, which improved after the tumor was resected. Mathew and colleagues [52] also documented another unusual case of a mediastinal schwannoma with Horner's syndrome. In Mathew's case, a 21-year-old man was found to have a superior mediastinal sympathetic chain benign schwannoma 7 years after the onset of

Horner's syndrome and unilateral headaches. In general, outside of the specific association of schwannomas with specific conditions and syndromes, a large number of patients will present with non-specific symptomatology, which in many patients will be caused by the size of the tumors and by the anatomic structures that may be compromised due to the size of the neoplasm. Therefore, non-specific symptoms such as cough, chest pain, dyspnea, and neuralgia are commonly seen in association with these tumors. Nevertheless, it is important to highlight that, even though the majority of schwannomas occur in the posterior mediastinum, there is a small number of cases that may present in the anterior mediastinum; thus, such an occurrence needs to be kept in mind. One such case is the one described by Tajima and colleagues [53], who documented a case of a 23-year-old man with no symptoms of von Recklinghausen's disease, asymptomatic, and in whom diagnostic imaging – CT and MRI – demonstrated an anterior mediastinal tumor.

Regardless of the clinical association that schwannomas may have, the treatment of choice for these tumors is complete surgical resection, which apparently can be accomplished via minimally invasive approach [54].

Pathological Features

Schwannomas are usually well-circumscribed neoplasms with round or oval shape. The tumors may have extensive calcifications and cystic changes (Fig. 11.17). They are usually light tan, and areas of necrosis and hemorrhage are not common. They may vary in size from a few centimeters to more than 10 cm in greatest diameter. In some cases, it is possible to identify their attachment to a nerve.

Histologically, the majority of schwannomas have a very characteristic growth pattern, which allows for an easy morphological diagnosis. The tumors may show a well-defined fibrous capsule, and the tumor is composed of a proliferation of spindle cells with a fusiform nuclei, eosinophilic cytoplasm, and indistinct cell borders. The spindle cell proliferation is arranged to form hypercellular and hypocellular areas, also known as Antoni A and B, respectively (Figs. 11.18, 11.19, 11.20, 11.21, and 11.22). In addition, the tumor usually shows the presence of Verocay bodies, which are represented by the palisading of nuclei in the Antoni A areas. This latter feature is commonly associated with the benign schwannomas. The spindle cells do not show nuclear atypia, and mitotic activity is generally absent or minimal. Other commonly observed features in schwannomas are the presence of edematous areas, calcifications, cystic changes, and thick blood vessels (Figs. 11.23, 11.24, 11.25, 11.26, 11.27, and 11.28). However, areas of necrosis and hemorrhage are generally absent.

Even though the majority of schwannomas will not pose a difficulty for arriving at a correct interpretation, some cases of schwannomas may show unusual histological features that may pose a challenge in the diagnosis. Among those cases are cases of pigmented schwannomas and the so-called cellular schwannomas; these require special attention.

Pigmented Schwannoma

Essentially, the presence of melanin pigment in these tumors may be seen in either benign or malignant schwannomas. The presence of melanin pigment may be only a minor component of the tumor, while in other tumors, it may be prominent enough to pose a challenge in arriving at a definitive separation between schwannoma and melanoma. One important issue to highlight is that even though this particular histopathological feature of schwannomas may be seen with some frequency in tumors of the soft tissue, the occurrence of pigmented or melanotic "melanocytic" schwannomas in the mediastinal compartment is not common [55–59]. Paris and colleagues [55], in 1979, described a single case in a 49-year-old woman who presented with right arm pain in the distribution of the eighth cervical nerve root. Radiographic evaluation disclosed a right upper mediastinal mass, while spinal films showed widening of the intervertebral foramen between the seventh cervical and first thoracic vertebrae. Histologically, the tumor was described as a cellular schwannoma with no mitotic activity, and the cells were filled with variable amounts of small black pigment granules. Histochemical stain for Fontana showed the melanin nature of the pigment. Abbott and colleagues [56] reported two cases of this occurrence in two patients, one a 20-year-old man with a posterior mediastinal tumor and the other a 30-year-old woman with a right paravertebral tumor. The posterior mediastinal tumor was described as a tumor with rare mitoses and variable amount of melanin pigment in the cells. Prieto-Rodriguez and associates [57] also described a similar case of a posterior mediastinal tumor that the authors were able to diagnose by fine needle aspiration cytology. The tumor was not only pigmented but in addition it was also described as psammomatous. More recently, Zhang and associates [58] described 13 melanotic schwannomas in diverse anatomic locations; only one of these 13 cases was in a patient with a mediastinal tumor, which raises the possibility that these tumors in the mediastinum account for approximately 5–10% of all these particular neoplasms. Even though these tumors may involve the spinal canal, the majority of tumors appear to have a relatively small size of under 10 cm.

Pathological Features

The pathological features of these tumors are similar to tumors without pigment. Grossly, the tumor is well circumscribed. Histologically, the tumors are composed of a spindle cellular proliferation of elongated cells, with small oval nuclei, and inconspicuous nucleoli. Areas of Antoni A and B are present. The cells have a moderate amount of eosinophilic cytoplasm. Mitotic activity is rare or nonexistent.

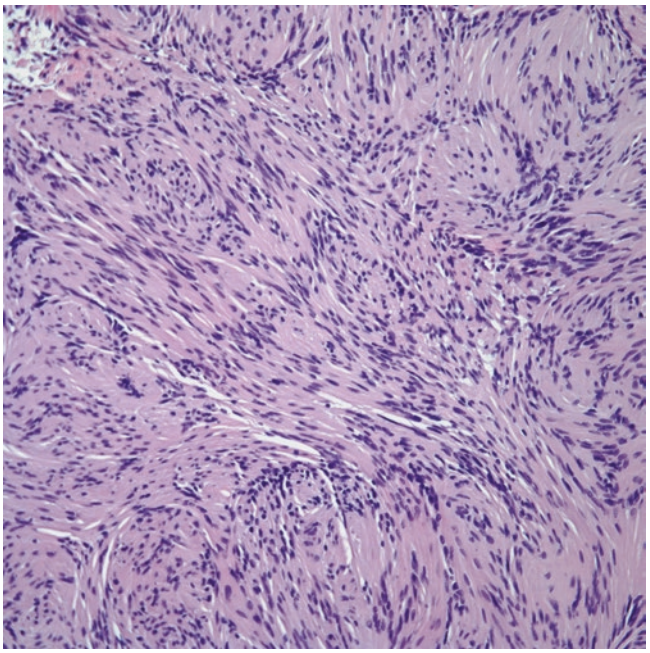

Fig. 11.20 Schwannoma showing spindle cell proliferation without areas of necrosis or hemorrhage

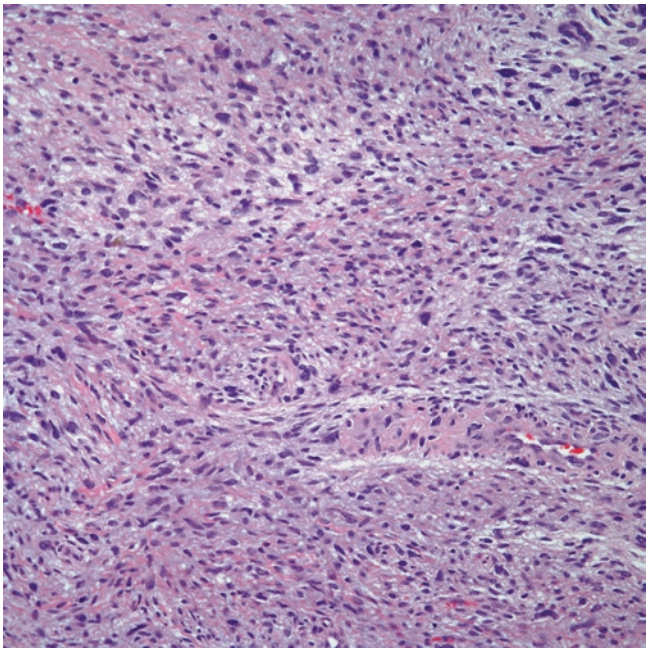

Fig. 11.22 Schwannoma with focal epithelioid features

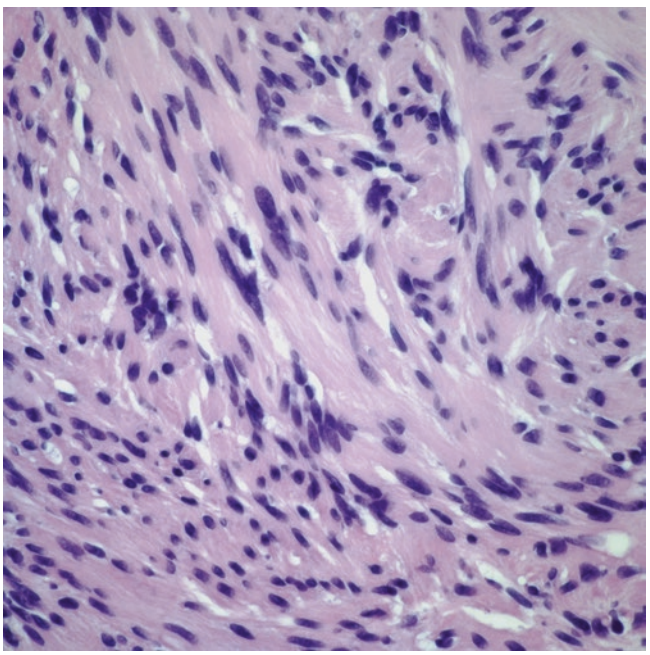

Fig. 11.21 In focal areas, conventional schwannomas may show nuclear atypia

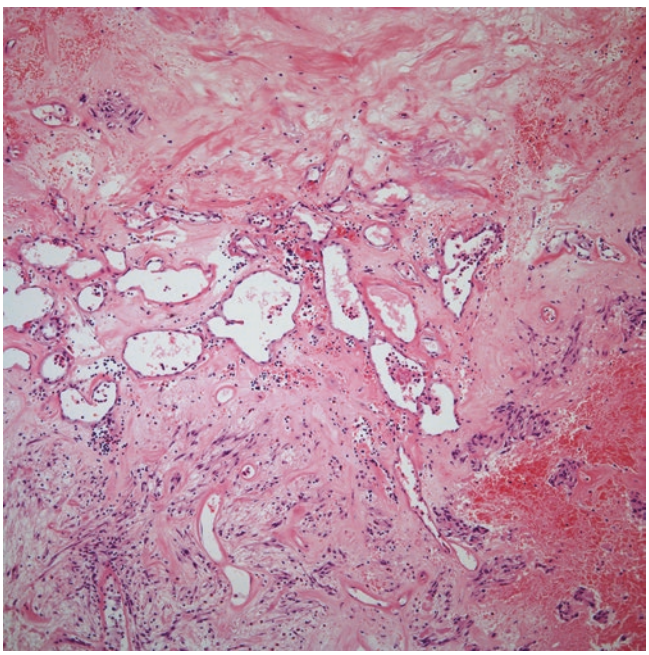

Fig. 11.23 Schwannoma with extensive hyalinization and vascular proliferation

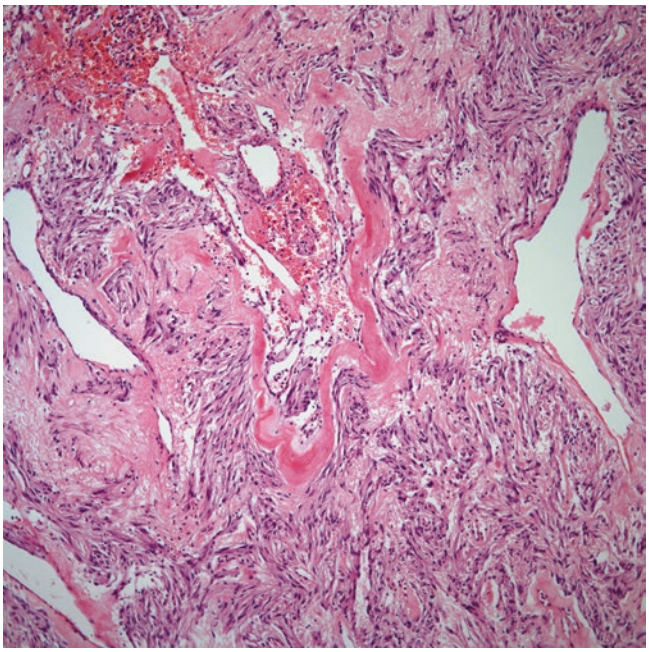

Fig. 11.24 Schwannoma with numerous ectatic blood vessels

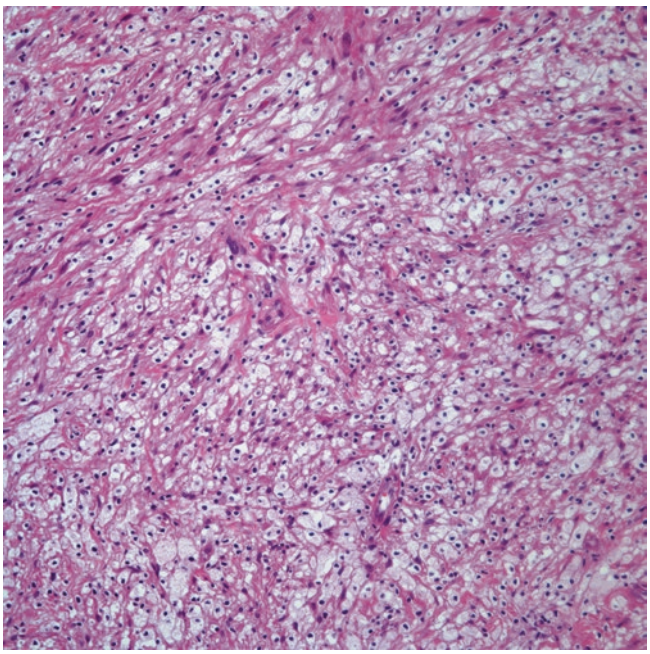

Fig. 11.26 Schwannoma with collections of macrophages

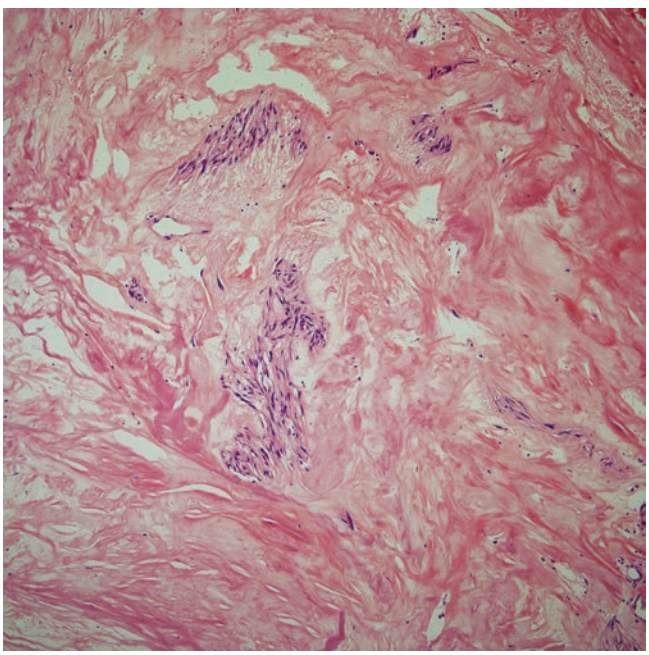

Fig. 11.25 Schwannoma with extensive hyalinization and only focal areas of spindle cells

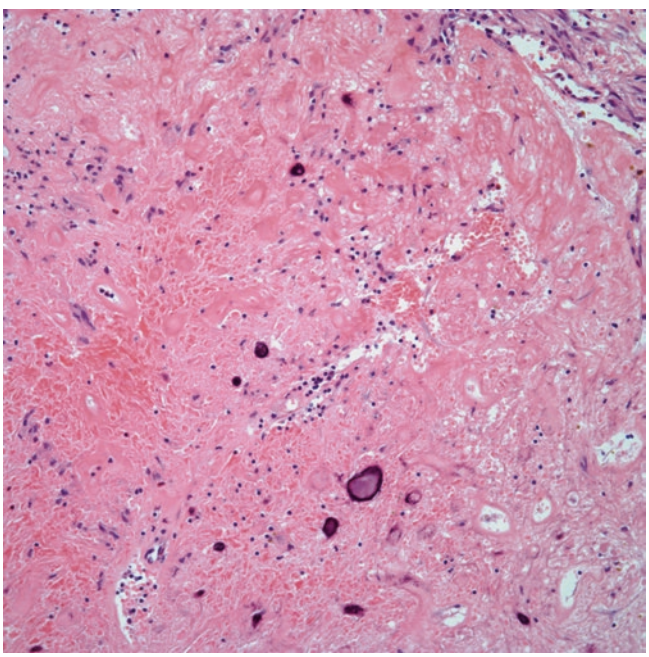

Fig. 11.27 Schwannoma with focal calcifications

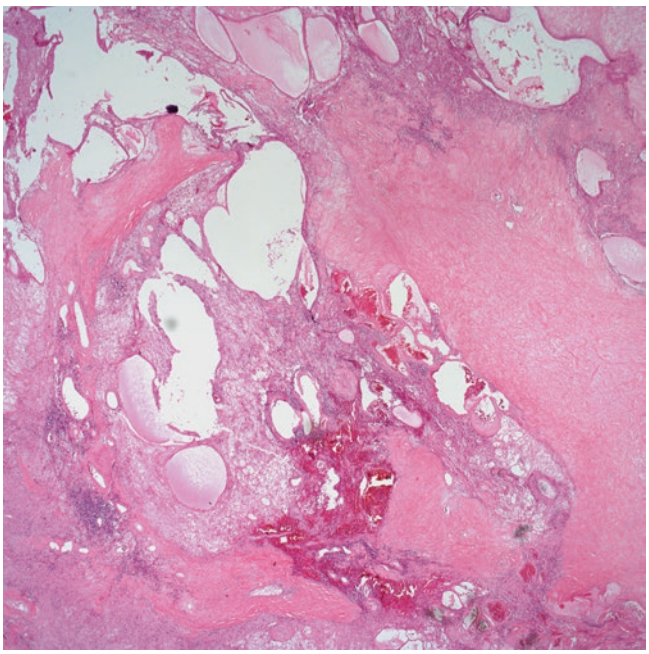

Fig. 11.28 Schwannoma with extensive cystic changes

Areas of necrosis and hemorrhage are generally not present. The tumors may show variable amounts of melanin pigment in some cases; the presence of pigment may be marked while in others it is subtler.

Cellular Schwannoma

The original description of this type of schwannoma is credited to Woodruff and associates [59], who, in 1981, described 14 cases of such a tumor, which histologically could be confused with malignant neoplasms. The authors stated that this type of tumor has no gender predilection; the patients' ages ranged from 25 to 81 years of age, and the tumors appeared to be more common in the neck, posterior mediastinum, and pelvis. In 1990, White and associates [60] described 57 patients with this tumor to reemphasize the benign nature of these neoplasms. In the cases described, there was a slight female predominance, with 63% of the tumors described in female patients. Anatomically, the tumors were more common in the paravertebral area of the retroperitoneum, pelvis, and mediastinum. Interestingly, the author stated that, in 28% of these tumors, a malignant diagnosis had been made. However, follow-up in those patients, which ranged from 1 to 24 years, revealed that three patients had recurrence, while none of the patients had developed metastatic disease. Also, Lodding and associates [61] described their experience by reporting on 29 cases of a similar tumor. In this particular series of cases, there was a female predominance of 82% with an age range of between 15 and 79 years. Twenty tumors were located in the mediastinum, which accounts for over half of the tumors described. One of the patients described had von Recklinghausen's neurofibromatosis. Follow-up information with a median duration of 7 years showed that no deaths, local recurrences, or metastatic disease were documented in any of the patients presented.

Pathological Features

Grossly, these tumors, similarly to the conventional schwannomas, have been described as well demarcated or encapsulated neoplasms, which at cut surface may show a homogenous light tan color, firm consistency, and some may have cystic changes. Areas of necrosis and hemorrhage are commonly absent. Histologically, since the initial description by Woodruff [59], the tumors have been characterized by the absence of Verocay bodies and the presence of fascicles of spindle cells (which can be arranged in a storiform or herringbone pattern), mitotic activity (usually fewer than 5 × 10 hpf), nuclear atypia, and in some cases microscopic focus of necrosis. Areas of collections of foamy histiocytes and inflammatory reaction composed of lymphocytes may be present. In other areas, the presence of thick wall vessels can be prominent. The tumors may erode bony structures.

Ancillary Diagnostic Tools

In general, the immunohistochemical features of conventional schwannomas are those of a tumor that shows strong positivity for S-100 protein and vimentin. However, the tumor may also show focal positive staining for glial fibrillary acid protein, while showing usually negative staining for neuroendocrine markers, neurofilament protein, and epithelial markers such as keratin and epithelial membrane antigen. In addition, the tumor also shows negative staining for CD-34, STAT6, and muscle markers (smooth muscle actin, desmin, caldesmon, myoglobin, Myo-D). Cellular schwannomas may show similar immunohistochemical profile to conventional schwannomas; however, in these particular variants, an immunohistochemical stain for Ki-67 may show an increased labeling of tumor cells, which may also represent a diagnostic pitfall in the interpretation. In this setting, careful evaluation of the histopathological features of the tumor may lead to a correct interpretation. By far the most challenging interpretation of immunohistochemical stains is with the pigmented schwannomas, as these tumors have been reported to be positive for S-100 protein, HMB-45, Leu 7, Melan-A, and vimentin. Thus, it is highly important to separate these tumors from malignant melanoma, which could elicit similar immunophenotype. Perhaps the real problem is not with the conventional schwannoma but rather with the malignant schwannoma (MPNT), which may show nuclear atypia, mitotic activity, and other morphological features similar to those of melanoma. One additional feature that may be considered in difficult cases is the use of electron microscopy, which could show the presence of basement membrane, a feature that is common in schwannomas [49], and the absence of pre-melanosomes, which would be more consistent with melanoma.

Differential Diagnosis

In conventional schwannomas, the most common differential diagnosis is that with smooth muscle tumors, namely, leiomyomas. In this setting, the use of S-100 protein and muscle markers should lead to the correct interpretation. One other possibility includes solitary fibrous tumor, which may show different histopathological patterns and may present as a mediastinal tumor. Once again, in this setting the use of CD-34 and STAT6 should clarify the true nature of the neoplasm. In small biopsies, neurofibroma may enter in the differential diagnosis; however, in this setting, the strong positive reaction for S-100 protein may be more in keeping with schwannoma.

In cellular schwannoma, the tumor may pose a challenge in the separation with a malignant schwannoma based on the cellular atypia and mitotic activity. In this setting, the use of immunohistochemical stains is of limited value as both tumors may share similar immunophenotype. In this setting, the morphological characteristics of the tumor – namely, the absence of an increase mitotic activity, marked nuclear atypia, necrosis, and hemorrhage – will lead to a more correct interpretation. By far the most challenging differential diagnosis may be with pigmented schwannoma; however, conventional schwannomas with pigment will lack increased mitotic activity and nuclear atypia. Even though S-100 protein may sow positive staining in both tumors, the use of other stains such as Mel A and MITF may be of help.

Granular Cell Tumor

Granular cell tumors are neoplasms of ubiquitous distribution; however, they are more common in the head and neck area and in the soft tissues. In the past, it was believed that these tumors had a relation to muscle, thus the previous name of myoblastoma or granular cell myoma. However, more recently, it is believed that granular cell tumors have a probable Schwann cell origin, and this is the reason why they are presented in this section.

The occurrence of these tumors in the mediastinal region is rare, with only few reports in the literature, and all of them in case reports [62–66]. These reported cases have been in patients between 16 and 43 year of age without any gender predilection. Clinically, patients with granular cell tumor may be asymptomatic, and the discovery of their tumors is either during a follow-up evaluation of a different condition or during a routine physical evaluation. However, the case described by Shikatani and associates [63] was that of a 19-year-old woman who presented with left ptosis and miosis (Horner's syndrome), and in whom a CT and MRI revealed the presence of a posterior mediastinal mass.

Pathological Features

Grossly, these tumors have been described as small tumors measuring approximately 1–5 cm in greatest diameter. The tumors are round to oval, and at cut surface, they are yellow-white, soft, with a whorled or smooth surface. Areas of hemorrhage may be present, but necrosis is usually absent.

Histologically, the tumors are fairly well circumscribed but not encapsulated, with sheets of round, oval to spindle cells with ample granular cytoplasm, small eccentric nuclei, and inconspicuous nucleoli (Figs. 11.29, 11.30, and 11.31). In some areas, the tumor may have discrete presence of fibrocollagenous bands separating tumor cells, with presence of ectatic blood vessels. Mitotic activity and necrosis are generally absent.

Ancillary Diagnostic Tools

The morphological appearance of granular cell tumors is characteristic enough to make a morphological diagnosis not a difficult task. However, in some cases, the use of immunohistochemical stains may aid in the diagnosis. Granular cell tumors are commonly positive for S-100 protein and neuron-specific enolase. However, the tumor is generally negative for epithelial markers (keratin, epithelial membrane antigen), for neuroendocrine markers (chromogranin and synaptophysin), and for muscle markers (desmin, muscle-specific actin, and smooth muscle actin). Ultrastructural features of granular cell tumors include the presence of abundant lysosomes.

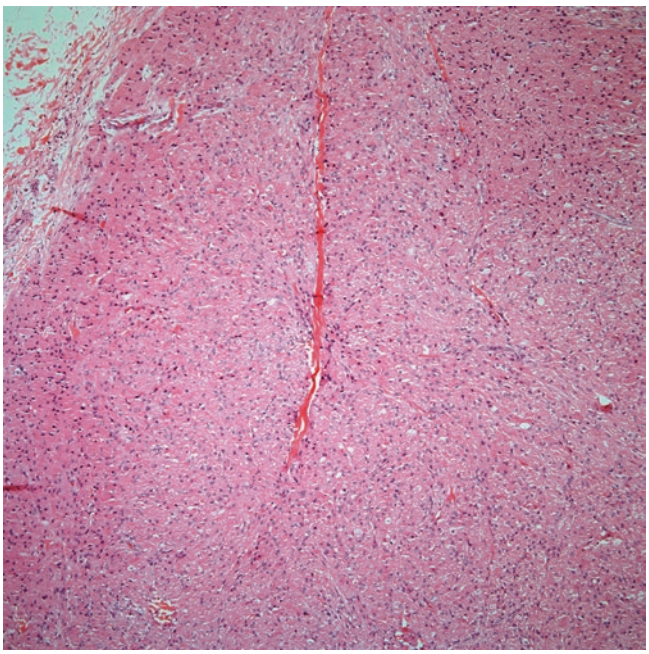

Fig. 11.29 Low power magnification of a granular cell tumor showing a well-defined neoplasm but not encapsulated

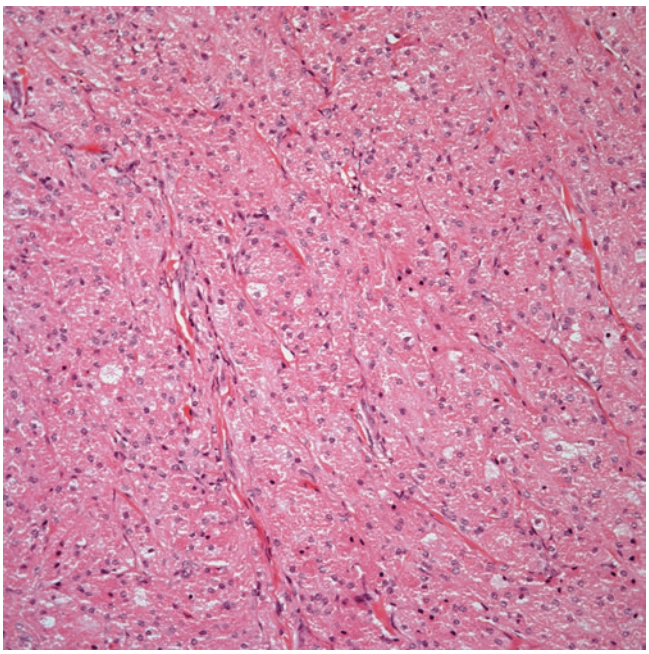

Fig. 11.30 Granular cell tumor showing a subtle nested pattern composed of cells with prominent oncocytic changes

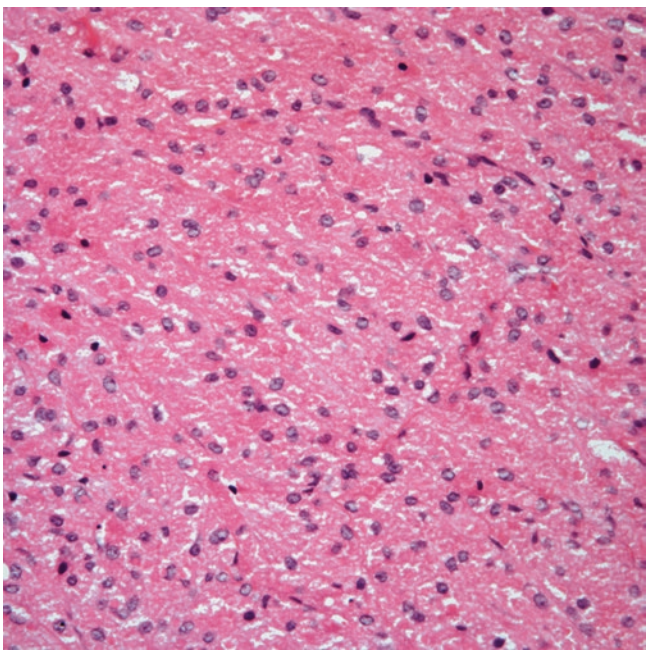

Fig. 11.31 High power view of a granular cell tumor showing cells with ample granular eosinophilic cytoplasm. Note the absence of nuclear atypia or mitotic activity

Differential Diagnosis

Even though the diagnosis of granular cell tumor is rather straightforward, other tumors that may be confused with this tumor, mainly in the mediastinum, include paraganglioma and neuroendocrine neoplasms. In either of these particular settings, the use of neuroendocrine markers including chromogranin and synaptophysin will aid in the diagnosis. Also, the use of keratin will be valuable as neuroendocrine carcinomas are positive for keratin. In addition, in cases of paragangliomas, even though S-100 may show positive staining, such staining is in sustentacular cells, while the positivity in granular cell tumor is in the cytoplasm of the tumor cells.

Malignant Tumors

As stated earlier in this chapter, the occurrence of malignant neurogenic tumors is much more common in the pediatric age group than in the adult population. In addition, even though these tumors are more commonly seen in the posterior mediastinum, occasionally they can also occur in the anterior mediastinum. Almost every benign neurogenic tumor has its malignant counterpart; thus, it is important to adhere to specific histopathological features in order to make such determinations in tumors that may share similar features or in tumors that may show mature and immature elements.

Neuroblastoma/Ganglioneuroblastoma

These two malignant neoplasms will be discussed in this section in a parallel form as the two tumors share some histopathological features: one has complete lack of maturation, while the other has an incomplete maturation. Both tumors originate from the neural crest, and a depiction of their maturation process is presented in Fig. 11.32a–c.

In 1910, Wright [67] analyzed five cases with the idea of highlighting the occurrence of a tumor that at that particular juncture had escaped recognition. Wright considered the tumor cells more or less undifferentiated nerve cells, or neurocytes, or neuroblasts, thus the names neurocytoma or neuroblastoma. Prior to this description, it is likely that most of these tumors now known as neuroblastomas had been called gliomas, sarcomas, or lymphoma. In 1927, Cushing and Wolbach [68] described a 2-year-old child with a paravertebral sympathicoblastoma (neuroblastoma), histologically proven, and 10 years later the recurrence of the tumor was that of a histologically proven ganglioneuroma. The authors interpreted such change as mature differentiation. Such description gave rise to the identification of cases that fall under the designation of ganglioneuroblastoma.

In 1957, Stowens [69], in a review of 236 cases of neuroblastoma and related tumors (ganglioneuroma and ganglioneuroblastoma) from the files of the Armed Forces Institute of Pathology, identified 110 cases coded as neuroblastoma, while only 17 cases belong to ganglioneuroblastoma. The balance of the other tumors corresponded to the mature ganglioneuroma. The vast majority of the neuroblastomas occurred in the

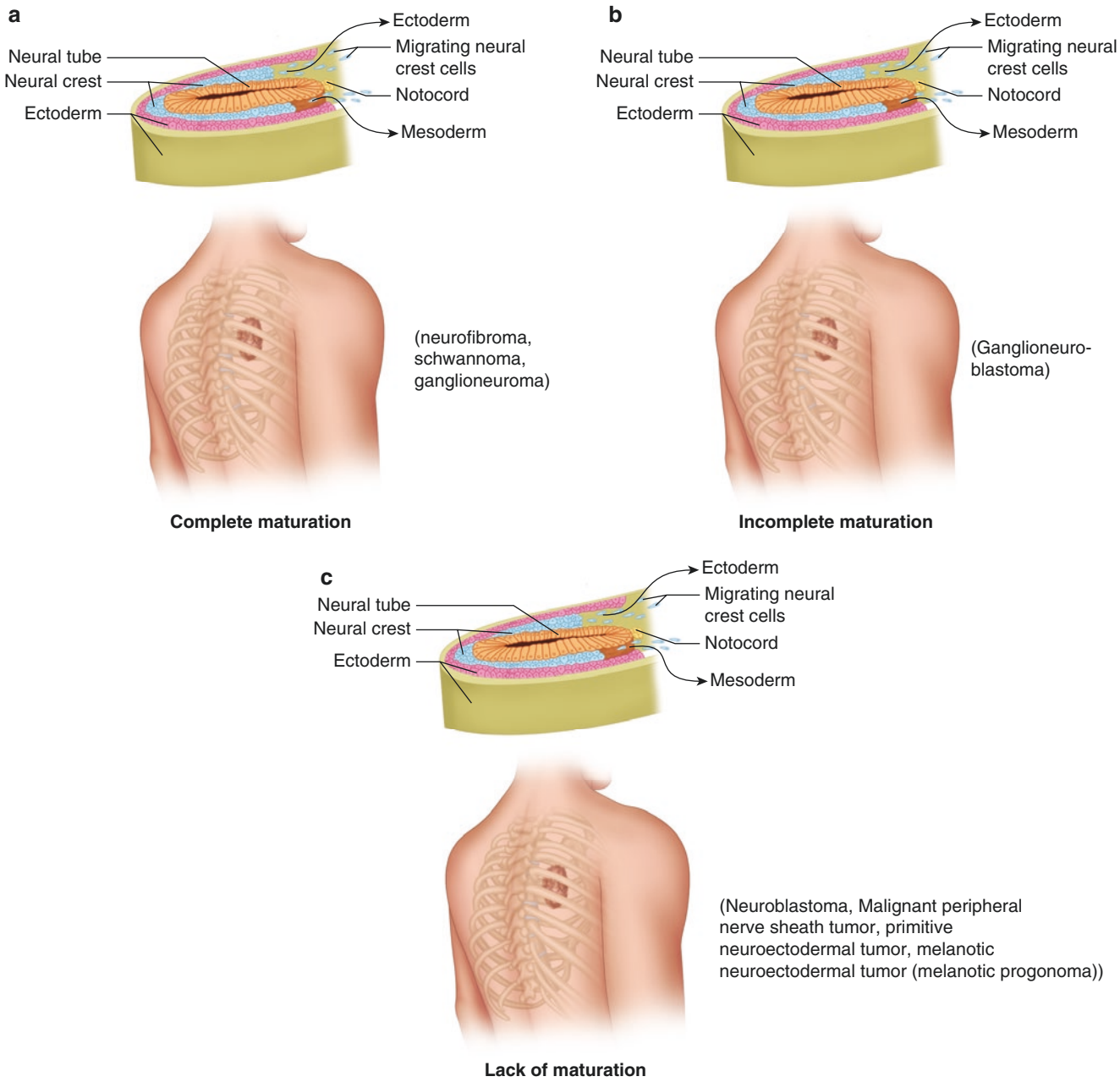

Fig. 11.32 (**a**–**c**) Diagramatic possibility of the development of different neurogenic tumors in the mediastinum

pediatric age group in children under 4 years of age, predominantly before 1 year of age, with only rare cases in older patients. Similar occurrence was also identified in cases designated as ganglioneuroblastomas. In addition, the majority of neuroblastomas and ganglioneuroblastomas predominantly occurred in the abdominal cavity (adrenal and retroperitoneum), while only 16 cases were identified in the mediastinal compartment. The author stated that neuroblastoma is primarily a disease of early childhood, with approximately 70% of the cases occurring in the first 4 years of life, and also adding that some of these tumors may be congenital in origin, whereas ganglioneuroma is predominantly a disease of adult life. Interestingly, Stowens [69], in order to explain the occurrence of ganglioneuroblastoma, advanced the idea of "partial differentiation," which the authors called "pseudodifferential embryogenesis." It is important to highlight that, in publications prior to the 1970s, the terminology of these tumors was somewhat more cumbersome. Oberman [70], for instance, even though acknowledging that these tumors are collectively designated as neuroblastomas, preferred to separate these tumors into "sympathicogoniomas" (the least differentiated of these tumors and composed of small cells the size of a lymphocyte with dark nuclei and indistinct cytoplasm) and "sympathicoblastoma"(greater differentiation, larger cells, thin rim of cytoplasm, and fibrillar stroma). In addition, the preferred nomenclature for ganglioneuromas was that of mature and partially differentiated (ganglioneuroblastoma). Even though it is well known that the occurrence of neurogenic tumors is by far more common in the posterior mediastinum, Buthker and associates [71] described a "sympathicoblastoma" in the anterior mediastinum in a 67-year-old woman. The authors reviewed previous literature on the subject and encountered 15 neurogenic tumors that apparently were in the anterior mediastinal location, but only three of those were "sympathicoblastomas," two of them in patients older than 60 years. In a separate description of a "sympathicoblastoma" of the anterior mediastinum, Oberman [72] alluded to the possibility of ganglionic tissue overlying the heart as a possible origin for this tumor in such location. Hutchinson [73] also described a neuroblastoma of the anterior mediastinum in a 51-year-old man who clinically was thought to have an aneurysm. Due to the unusual occurrence of neuroblastomas in the adult, a few small series of cases have been presented in the literature. Mackay and associates [74] described nine patients between the ages of 18 and 72; however, none of the cases presented had a thoracic origin. Other authors have focused more on the occurrence of ganglioneuroblastoma by reporting such occurrence in adult patients with either primary thoracic or abdominal primaries [75].

In 1981, Adam and Hochholzer presented the largest series of ganglioneuroblastomas of the posterior mediastinum [76]. The authors described 80 such cases in 38 male and 42 female patients; in one third of the patients, the tumor was diagnosed during the first 2 years of life, one half during the first 3 years of life and fourth-fifths during the first 10 years of life. Ten of the 80 patients were between 12 and 20 years and 3 over 20 years of age. Clinically, none of the patients had a history of neurofibromatosis. In half of the patients, the discovery of the tumor was during routine chest films, while 15 patients had some respiratory symptoms. Interestingly, other clinical presentations included Horner's syndrome and chronic diarrhea. Clinical follow-up was obtained in 72 patients; 55 were followed for 2–23 years. The 5-year survival rate was of 88%, and their prognosis was related to the stage of the tumor at the time of diagnosis. Fatal outcome was observed in patients with stage IV disease, while for those patients in stage I surgical resection appeared to be curable. The authors stated that the prognosis for this group of patients is far better than for neuroblastomas or intra-abdominal ganglioneuroblastomas. Even though the vast majority of these tumors occur in the posterior mediastinal location, it is also important to highlight that neuroblastomas and ganglioneuroblastomas in the anterior mediastinum have also been reported. Talerman and Gratma [77] described a 61-year-old woman with an anterior mediastinal ganglioneuroblastoma whose tumor was found incidentally at autopsy. Nagashima and associates [78] also described a ganglioneuroblastoma of the anterior mediastinum in a 79-year-old man who complained of chest pain. Complete surgical resection was performed followed by chemotherapy, and at 5 years the patients had no evidence of recurrence or metastasis. Asada and associates [79] described a case of adult ganglioneuroblastoma in a 61-year-old woman with syndrome of inappropriate secretion of antidiuretic hormone. The symptomatology of the patient was related to the endocrine abnormality, and MRI showed the presence of an anterior mediastinal tumor, which was surgically removed. Similar case of an adult neuroblastoma in the anterior mediastinum was also recorded by Kaye and associates [80] who described among three adult patients with neuroblastoma a 26-year-old woman who also had the syndrome of inappropriate antidiuretic hormone and hypercortisolism due to ectopic production of ACTH. More recently, Jrebi and associates [81] evaluated their collective experience by reviewing all adult cases of neuroblastoma and ganglioneuroblastoma in patients 18 years or older, corresponding to the years 1980–2009. The authors found 15 patients ages 19–66 years, corresponding to six men and nine women, and in five patients the tumor was found incidentally. Anatomically, four tumors were in the pelvis, three in the mediastinum, two in the abdomen, two in the adrenal gland, two in the retroperitoneum, and two were labeled as "mixed locations." The authors concluded that complete surgical resection might lead to long-term disease free survival in patients in stage I.

Regarding the occurrence of ganglioneuroblastoma in children, Bove and McAdams [82] reported their experience

with 19 cases, which the authors designated as "composite ganglioneuroblastoma." The authors review 30-year period (1948–1978) at the Children's Hospital Medical Center in Cincinnati, identifying 19 such cases in children ranging in ages from 56 to 108 months. Eleven of these cases were in stage I, eight cases were in the mediastinum, and six patients followed a fatal outcome. Two patients with tumor in the mediastinum followed a fatal course. In a larger cohort of patients, Adams and associates [83] from the pediatric oncology group evaluated 96 patients with thoracic neuroblastoma. The median age at presentation of the tumor was 9 months. In 49% of the cases in which the tumor was in the posterior mediastinum, the tumor was found incidentally by radiographic films; 16% presented with neurological symptoms, and 16% presented with respiratory distress. Urinary catecholamines were elevated in 76% of the cases. Only 47% of the patients were treated with complete surgical resection. The overall survival was 88% at 4 years. The authors stated that the basic biology of thoracic neuroblastomas appears to be different from other locations in that the majority of patients present at a younger age with localized disease or regional lymph node metastases. In a different study by Demir and associates [84] between the years 1973 and 2007, 87 children with thoracic neuroblastic tumors were identified. Eighty-six of these tumors were located in the posterior mediastinum; the median age was 2.1 years of age. Histologically, 46 were neuroblastomas, 26 ganglioneuroblastomas, and 15 ganglioneuromas. The highest percentage of cases was in stage IV (38.2%), followed by stage III (22.1%). Clinically, the tumor was found incidentally in 20 patients, while the rest showed some symptomatology including Horner's syndrome. Clinical follow-up showed that 10-year overall and event-free survival rates were 71.2% and 67.4%, respectively. The survival of these patients appears to correlate with the stage of the tumor as the 10-year overall survival for stages I and II was 88.8%. An interesting association of ganglioneuroma and ganglioneuroblastoma has been reported by Geraci and associates [85] in three patients between the ages of 4 and 23 years with histories of neurofibromatosis type I. Two patients developed ganglioneuromas (adrenal and parapharyngeal), while one patient developed a ganglioneuroblastoma (posterior mediastinum).

Regarding diagnostic imaging in neuroblastomas and ganglioneuroblastomas, Lonergan and associates [86], in a review of these tumors, stated that the results depend on the modality employed. Plain radiographs may show the presence of a mediastinal, retroperitoneal, or neck mass, which may reveal the presence of calcifications in about 30% of the cases. Upon ultrasonography, these tumors are heterogeneously echogenic. Computerized tomography (CT) may be the most commonly used modality as it can reveal the extent of tumor, organ of origin, invasion, adenopathy, and calcification. Magnetic resonance imaging (MRI) commonly shows a heterogeneous, variably enhancing, and relatively low signal intensity on T1 and high signal intensity in T2-weighted images.

Different studies on the prognosis of neuroblastoma and ganglioneuroblastoma have been presented in the literature. Brook and associates [87] studied 41 neuroblastomas using several immunohistochemical stains including neuron-specific enolase (NSE), protein gene product (PGP) 9.5, and S-100 protein and concluded that there was no significant correlation between immunohistochemical staining and prognosis. Hachitanda and Hata [88], in a more focused analysis of 45 stage IVS neuroblastomas, concluded that most stage IVS neuroblastomas have favorable histology and may have a good prognosis. However, the authors also stated that a poor prognosis group does exist and could be identified on histopathology. Gutierrez and colleagues [89], in a 30-year analysis of 1646 patients with neuroblastoma, estimated an annual incidence of 0.9 per 100,000, with a median age of 1 year. The majority of tumors occurred in the retroperitoneum, accounting for 75.6%, while mediastinal tumors account for 15.3%. Disease-specific survival at 1, 2, 5, and 20 years for the entire cohort was 81, 70, 61, and 59%, respectively. The authors also stated that tumors in the mediastinum and pelvis have a better prognosis, while high-grade tumors with 10 cm or more in greatest dimension have worse prognosis. Kubota and colleagues [90], in a study on prognostic factors related to better clinical outcome in ganglioneuroblastoma, concluded that the better prognosis is related to the absence of N-*myc* amplification.

Clinical Staging

In 1971, Evans and colleagues [91], in an analysis of 100 children with neuroblastoma, proposed a clinical staging system for patients with this tumor. This staging system is also known as Children's Cancer Study Group (CCSG):

Stage I:	Tumor confined to the organ or structure of origin.
Stage II:	Tumors extending in continuity beyond the organ or structure of origin but not crossing the midline. Regional lymph nodes on the homolateral side may be involved.
Stage III:	Tumors extending in continuity beyond the midline. Regional lymph nodes may be involved bilaterally.
Stage IV:	Remote disease involving skeleton, organs, soft tissues, or distant lymph nodes groups.
Stage IV-S:	Patients who would otherwise be stage I or II but who have remote disease confined only to one or more of the following sites: the skin, liver, or bone marrow (without radiographic evidence of bone metastases on complete skeletal survey).

In 1980, Evans [92], in a review of the staging and treatment of neuroblastoma, stated that patients with local resectable tumors probably do not require irradiation or

chemotherapy, while patients with residual disease (stage III) benefit from radiation therapy. For patients with stage IV, surgical resection may not be required as chemotherapy assumes a major role. Also, Evans and colleagues [93], in an analysis of 124 children with neuroblastoma, estimated an overall survival rate of 60% at 2 years. In addition, the authors suggested that a combination of age, stage, serum ferritin, and histologic type might play a role as prognostic factors in neuroblastoma. However, Hata and colleagues [94], in a study of neuroblastoma comparing the Evans system and the International Union Against Cancer (UICC) system (which is essentially a TNM system that includes separate clinical stages (CS) and postsurgical histopathological stages (PS), suggested that, for predicting the prognosis for advanced cases, the UICC staging system and especially the PS staging system may be more rational than the Evans staging system. This TNM system can be summarized as follows:

T 0 = tumor not detected	**N 0** = normal LN	**M 0** = no metastasis
T 1 = tumor <5 cm	**N 1** = abnormal regional LN	**M 1** = metastasis
T 2 = tumor 5–10 cm	**N x** = not available	
T 3 = tumor >10 cm		
T 4 = multicentric tumor		

It is important to highlight that there are two additional staging systems for neuroblastomas in addition to the one proposed by Evans (CCSG) and the TNM system by the UICC. These are the St Jude Children's Research Hospital [95] and the one used by the Pediatric Oncology Group (POG) [96]. These systems can be summarized as follows:

St Jude Staging System

Stage I: Localized disease completely removed; regional nodes and liver negative.

Stage IIA: Microscopic residual primary disease; incorporated lymph nodes may be positive. Regional lymph nodes and liver negative.

Stage IIB: Gross residual primary disease; regional lymph nodes and liver negative.

Stage IIIA (N): Regional spread with positive regional lymph nodes; liver negative.

Pediatric Oncology Group (POG) System

Stage A: Complete gross resection of primary tumor with or without microscopic residual disease. Attached lymph nodes may be positive. Distant liver and nodes negative.

Stage B: Grossly unresected tumor. Nodes and liver same as stage A.

Stage C: Complete or incomplete resection. Unattached nodes positive.

In that regard, Evans and colleagues [97] evaluated the accuracy of the four staging systems in a retrospective study of 251 neuroblastoma patients. The authors concluded that all four systems had value for prognostication, and all identified with accuracy the low-stage patient who fares well. However, the authors also concluded that the CCSG staging system most accurately identifies patients with regional tumor who have a poor prognosis. In view of the different staging systems suggested, however, the international neuroblastoma staging system (INSS) proposed an internationally accepted staging system [98]. This system is as follows:

International Neuroblastoma Staging System (INSS)

Stage 1: Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically; nodes attached to and removed with the primary tumor may be positive.

Stage 2A: Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically.

Stage 2B: Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor. Enlarged contralateral lymph nodes must be negative microscopically.

Stage 3: Unresectable unilateral tumor infiltrating across the midline with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement.

Stage 4: Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs (except as defined for stage 4S).

Stage 4S: Localized tumor (as defined for stage 1, 2A, or 2B) with dissemination limited to the skin, liver, and/or bone marrow (limited to infants <1 year of age).

Shortly after this staging system was proposed, essentially the same group revised some of the definitions to the stages proposed [99]. Essentially, for stage 1, the clarification was made that "adherent nodes in direct continuity and removed with the primary tumor may be positive for tumor." For stage 3, a redefinition of the midline was introduced to basically consider the vertebral column as the midline.

Pathologic Classification

In 1999, the International Neuroblastoma Pathology Committee (INPC) convened to produce a classification system with terminology and morphologic criteria [100, 101]. The proposed terminology and morphologic criteria was

adopted after reviewing 227 cases, using a morphologic approach. Essentially, the INPC adopted the Shimada system, which is based on the differentiation of the tumor, their cellular turnover index, and the presence or absence of Schwannian stromal development. Based on such criteria, neuroblastomas were divided into four categories:

1. Neuroblastoma (Schwannian stroma-poor), undifferentiated, poorly differentiated, and differentiating (Figs. 11.33, 11.34, 11.35, 11.36, 11.37, 11.38, 11.39, 11.40, 11.41, 11.42, 11.43, 11.44, 11.45, 11.46, 11.47, and 11.48)
2. Ganglioneuroblastoma, intermixed (Schwannian stroma-rich)
3. Ganglioneuroma (Schwannian stroma-dominant), maturing and mature
4. Ganglioneuroblastoma, nodular (composite, Schwannian stroma-rich/stroma-dominant, and stroma-poor)

Specific Histological Features

- Mitosis-karyorrhexis index (MKI) is defined as the number of tumor cells in mitosis and in the process of karyorrhexis.
- Mitotic rate (MR) is counted at ten contiguous high-power fields (hpf) at x400 magnification.
  - Tumors with fewer than ten mitoses in 10 hpf belong to the low MR class.
  - Tumors with greater than ten mitoses in 10 hpf belong to the high MR class.
- Calcification – No quantification is required; however, its presence is associated with favorable prognosis.

In 2001, the INPC further defined four categories of tumor, this time by association with the MYCN status and the histology of the tumor [102]. The committee evaluated 535 neuroblastomas, 21 ganglioneuroblastomas (intermixed), 9 ganglioneuromas, and 63 ganglioneuroblastoma (nodular). The tumors were separated into tumor with favorable histology and tumors with unfavorable histology, with their corresponding MYCN amplification or non-amplification. Based on this study, the authors found that favorable histology with non-amplified tumors had a 5-year event-free survival of 92.1%, while 8 tumors with favorable histology and amplified tumor had a 5-year event-free survival of 37.5%. Regarding the tumor with unfavorable histology and non-amplified tumors, the 5-year event-free survival was 40.9%, while similar tumors with amplified tumors had 15.0%. The authors concluded that histopathologic evaluation and MYC status appear to correlate with prognosis. In addition, the authors, in a separate publication, stressed the importance of the histopathology of these tumors and the importance of separating these tumors into favorable and unfavorable histology [103].

A few years after these proposals had been presented, the INPC revised their classification by confirming categories of favorable and unfavorable prognostic subsets for ganglioneuroblastoma, nodular type [104, 105]. Essentially, the evaluation of ganglioneuroblastomas will also involve the macroscopic appearance of the tumor. Thus, the following features:

- Ganglioneuroma – maturing (Schwannian stroma-dominant): essentially a ganglioneuromatous tumor with scattered neuroblasts and/or maturing ganglion cells. Favorable histology.
- Ganglioneuroblastoma-intermixed (Schwannian stroma-rich) (Figs. 11.49, 11.50, 11.51, and 11.52): transitional tumor between neuroblastoma and ganglioneuroma. Microscopic residual foci of neuroblastoma containing neurophil and neuroblasts. The proportion of ganglioneuromatous component to neuroblastomatous component should exceed 50%. Favorable histology.
- Ganglioneuroblastoma-nodular (composite, Schwannian stroma-rich/stroma-dominant, and stroma-poor) (Figs. 11.53, 11.54, 11.55, 11.56, and 11.57): Macroscopic neuroblastomatous nodule(s). The proportion of neuroblastomatous and ganglioneuromatous component varies from case to case. This particular subtype can be further subclassified into favorable and unfavorable histology based on age-linked evaluation, grade of neuroblastic differentiation, and mitosis-karyorrhexis index of the neuroblastomatous nodule.

Histochemical, Ultrastructural, Immunohistochemical, and Molecular Features

Even though the majority of neuroblastomas are purported to be negative for the presence of glycogen, which in turn helps distinguish these tumors from other small round cell tumors such as primitive neuroectodermal tumor (Ewing sarcoma) or rhabdomyosarcoma, there is a group of neuroblastomas that may show the presence of glycogen by staining the tumor with periodic acid-Schiff (PAS) histochemical stain or by ultrastructural studies. Yunis and colleagues [106], in 1979 in a study of 40 cases, encountered the presence of glycogen in four cases of neuroblastomas; at least two of those cases were confirmed neuroblastomas by morphology and electron microscopy. In a separate study of nine patients of adult neuroblastoma, Mackay and colleagues [74] stated that one constant feature of neuroblastomas that reflects the neural crest derivation is the presence of cytoplasmic processes, while the presence of electron-dense granules with limiting membranes is a significant feature. By immunohistochemistry, there is not a specific immunohistochemical profile that is pathognomonic for neuroblastoma. The tumor may show positive staining for NSE (neuron-specific enolase), CD99, PGP 9.5, and S-100 protein, while negative for keratins, EMA, GFAP, chromogranin, and synaptophysin (except in the neutrophil

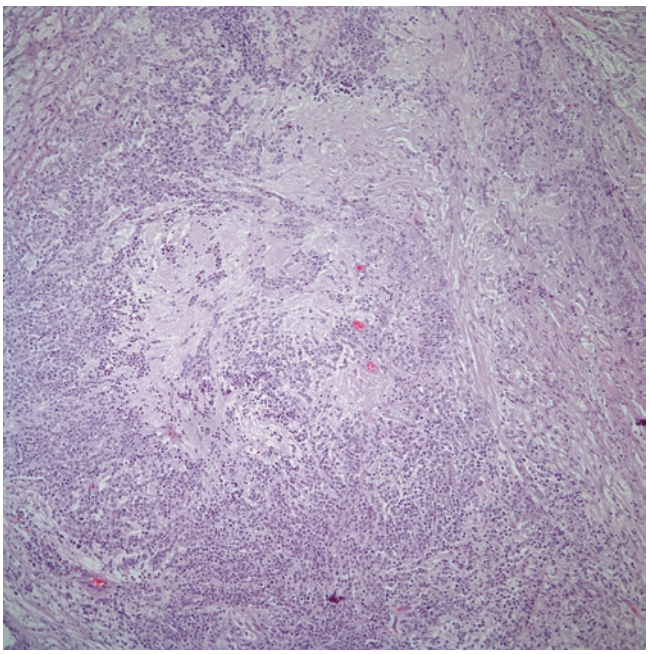

Fig. 11.33 Low power view of a neuroblastoma showing extensive areas of neurophil and sheets of small cells

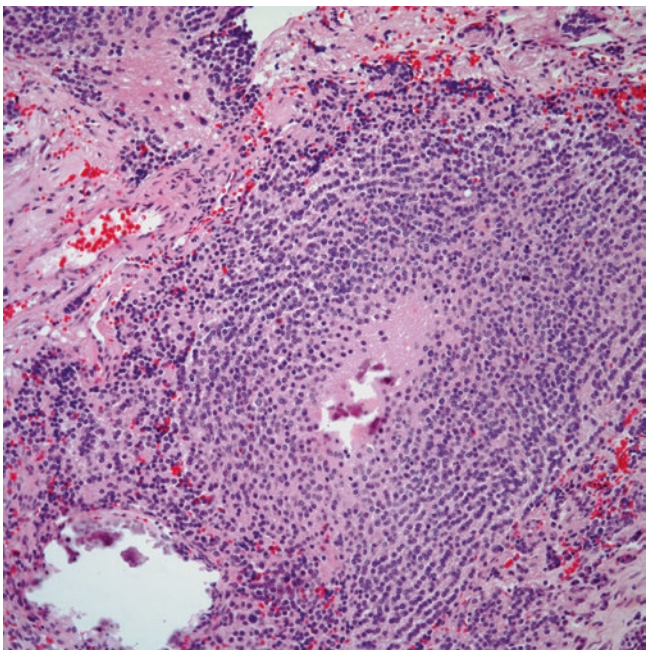

Fig. 11.35 Closer view of a neuroblastoma showing central calcification and areas of neurophil. Note the fairly homogeneous cellular proliferation composed of small cells

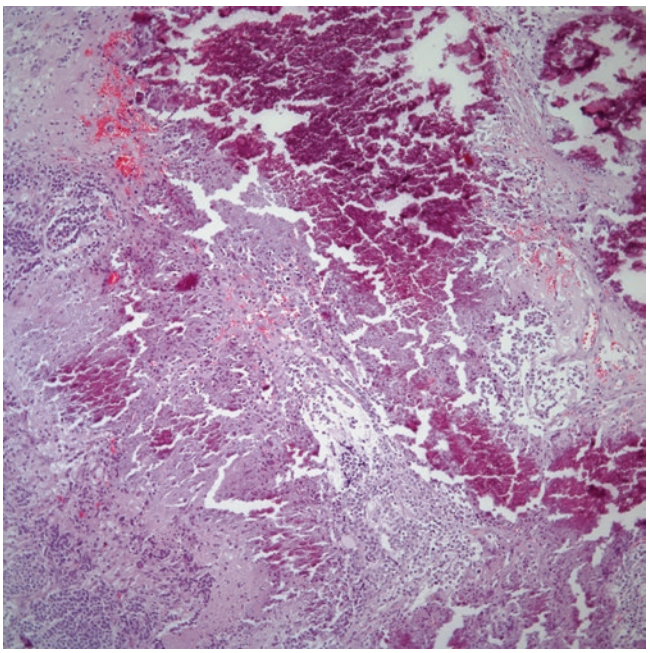

Fig. 11.34 Neuroblastoma with extensive calcification and only focal areas of viable tumor

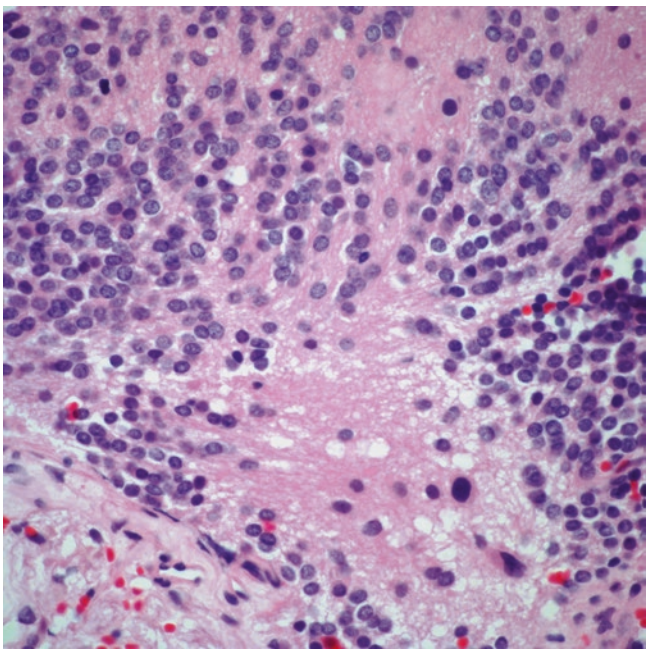

Fig. 11.36 Higher magnification of a neuroblastoma showing the cellular proliferation composed of small cells with scant cytoplasm, round nuclei, and inconspicuous nucleoli embedded in neurophil. No mitotic activity is present

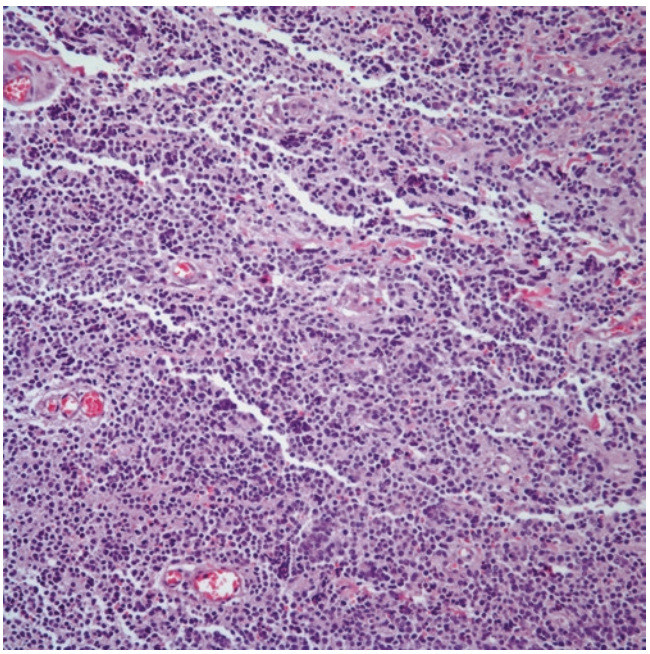

Fig. 11.37 A different view of a less differentiated neuroblastoma showing sheets of small neoplastic cells

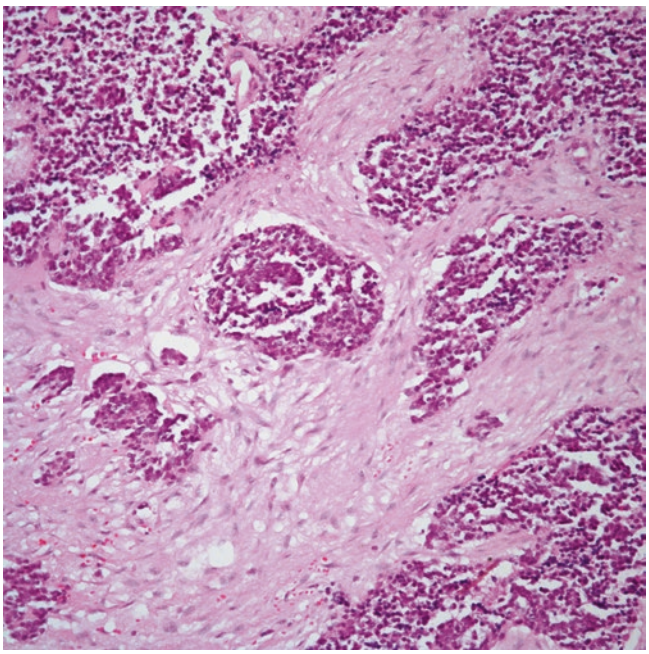

Fig. 11.39 Closer view of the neoplastic cells in this less differentiated neuroblastoma showing small cells arranged in nests and separated by fibrocollagenous tissue

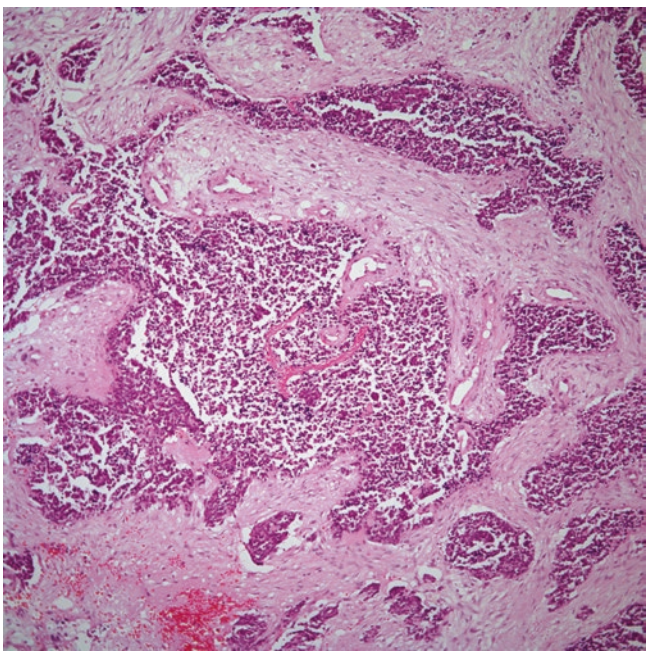

Fig. 11.38 Neuroblastoma with extensive areas of fibrocollagenous tissue and nested areas of tumors cells

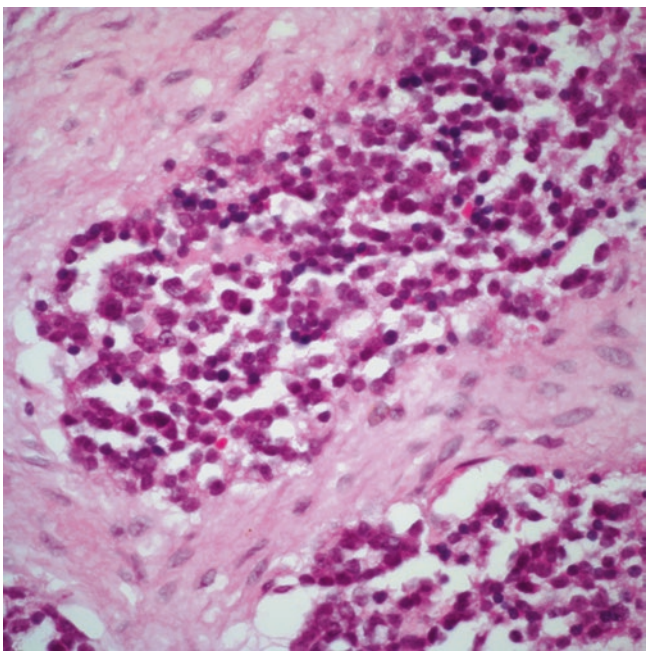

Fig. 11.40 High power view of a less differentiated neuroblastoma showing small cells with round vesicular nuclei and in some cells nucleoli is identified. The tumor does not show areas with neurophil

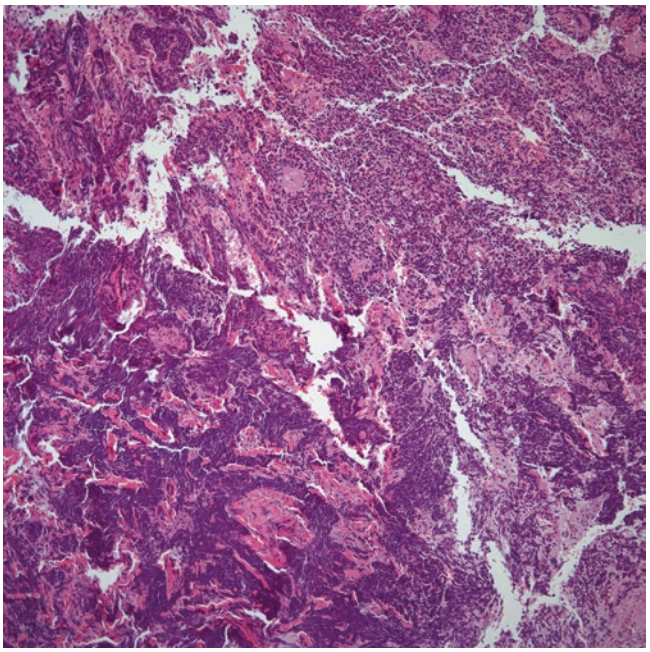

Fig. 11.41 Poorly differentiated neuroblastoma showing extensive crush artifact

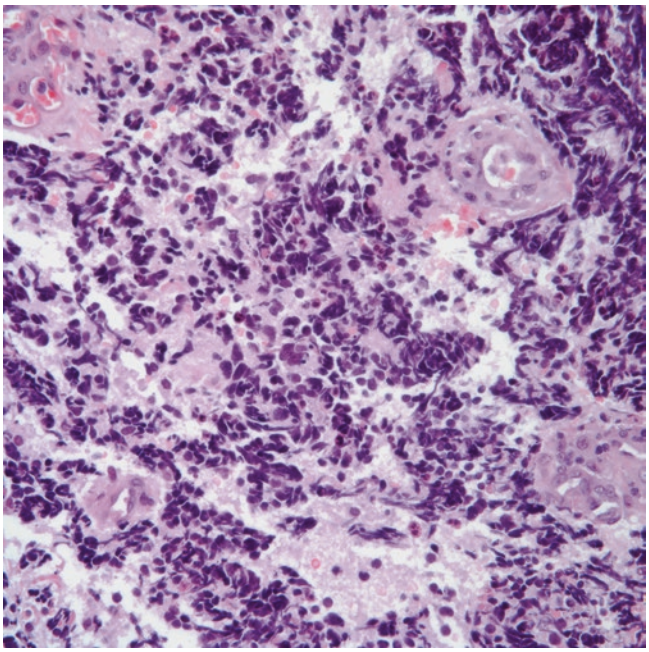

Fig. 11.43 Neuroblastoma with features mimicking small cell carcinoma

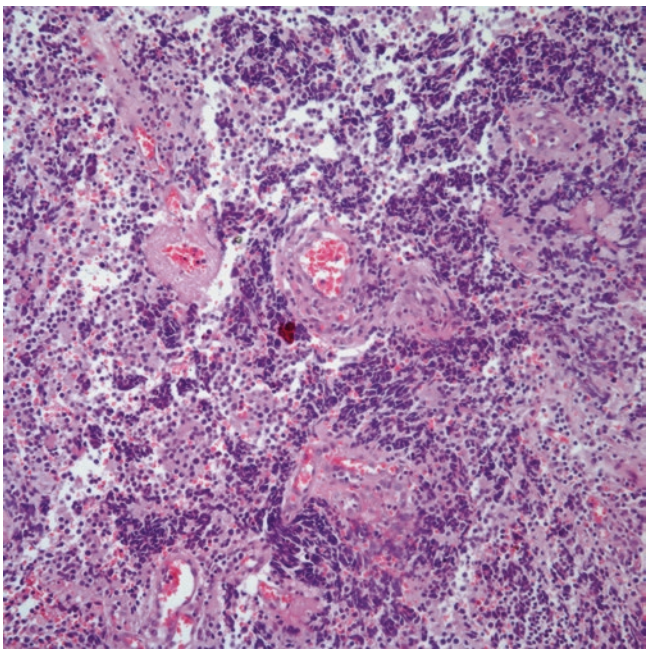

Fig. 11.42 Poorly differentiated neuroblastoma showing small cell proliferation around vessels

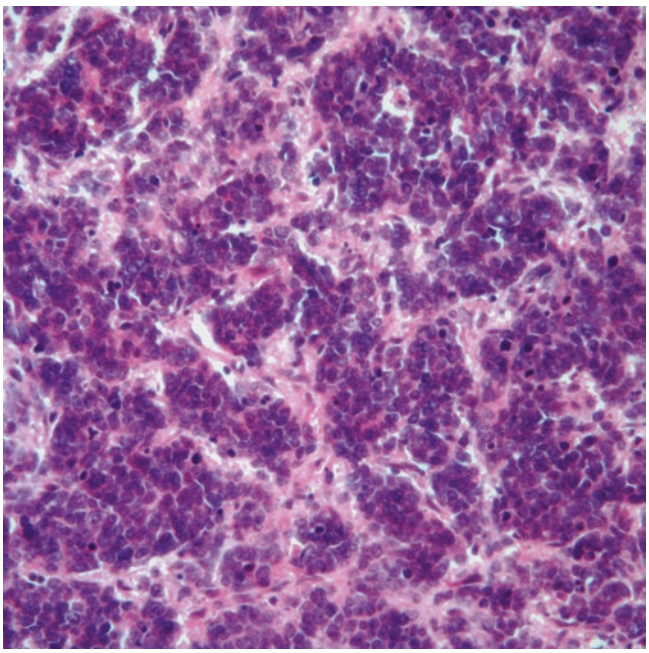

Fig. 11.44 Neuroblastoma showing increased mitotic activity

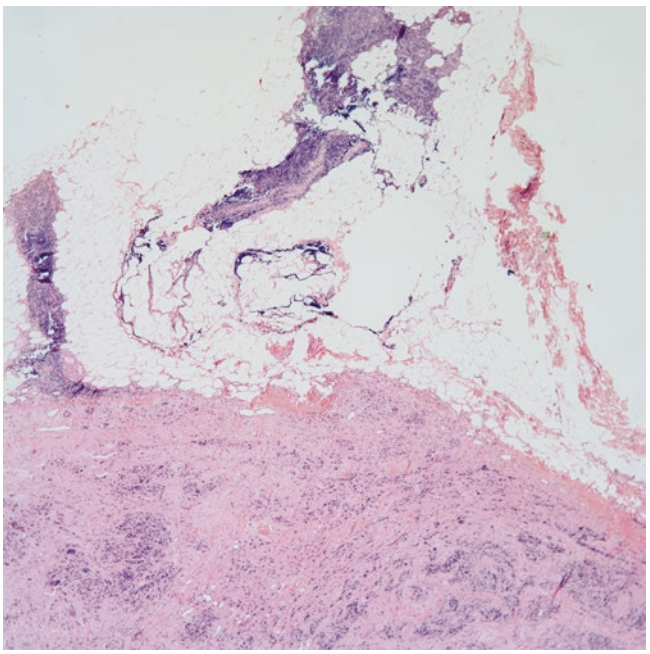

Fig. 11.45 Anterior mediastinal neuroblastoma. Note the presence of remnants of thymic tissue in the periphery

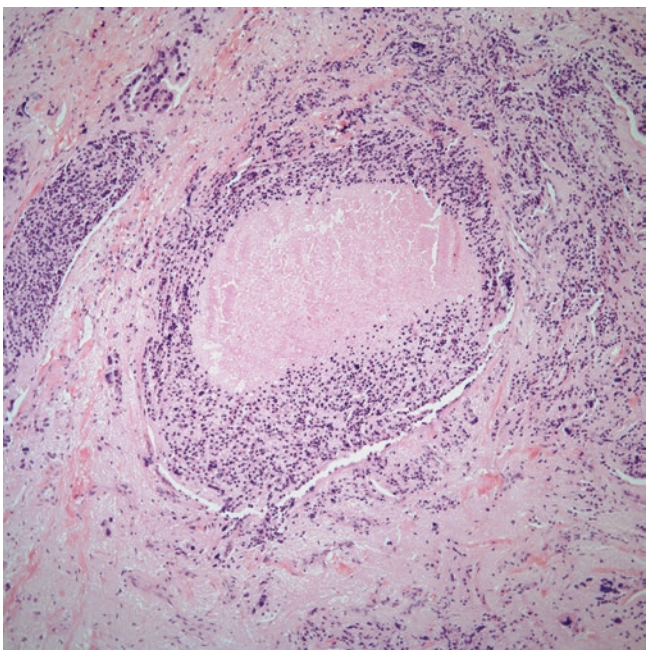

Fig. 11.46 Thymic neuroblastoma showing areas of comedo-like necrosis

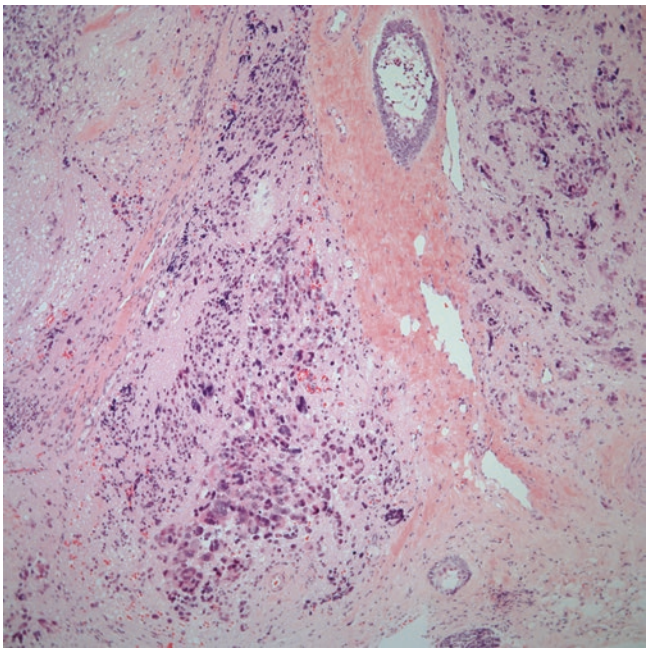

Fig. 11.47 Thymic neuroblastoma showing cellular atypia. Note the remnants of thymic epithelium

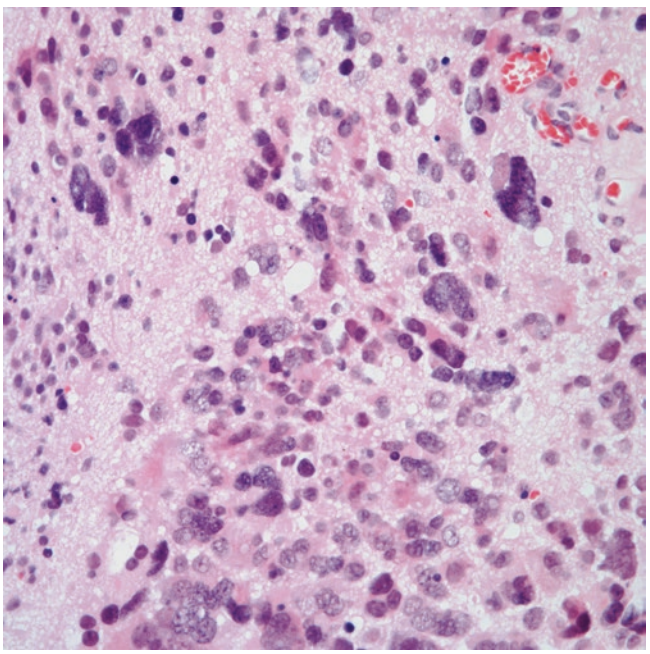

Fig. 11.48 Higher magnification of a thymic neuroblastoma with marked cellular and nuclear atypia

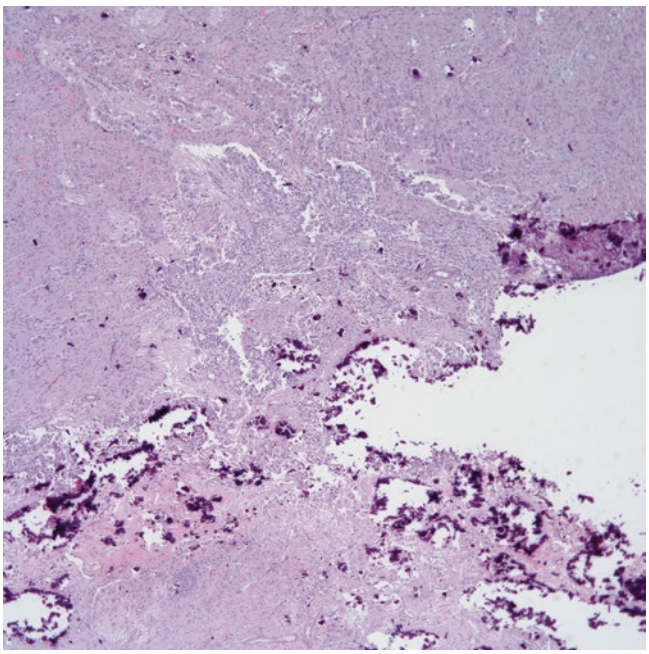

Fig. 11.49 Predominantly ganglioneuromatous component with focus of neuroblastoma and calcifications

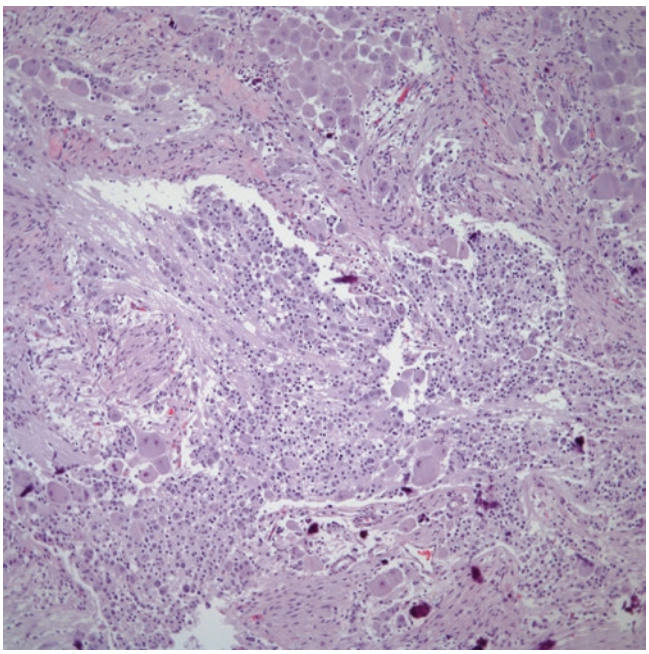

Fig. 11.51 Closer view of a ganglioneuroblastoma showing a microscopic nodule of neuroblastoma. Note the presence of numerous ganglion cells

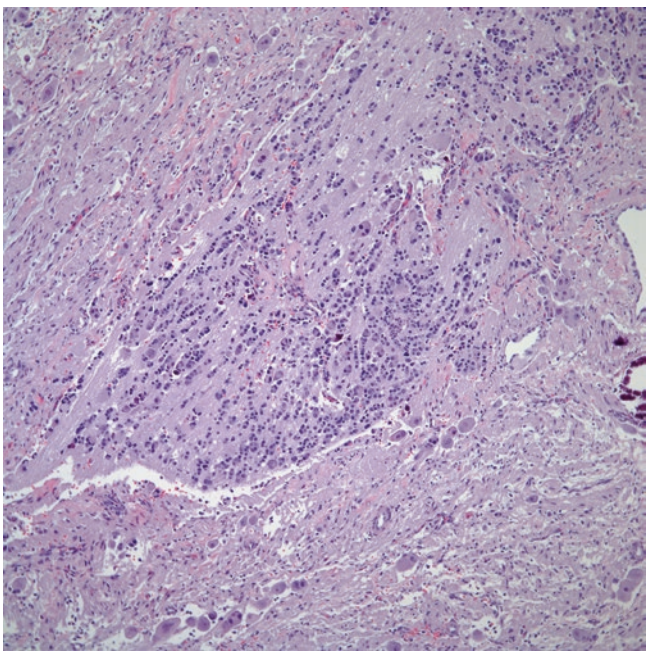

Fig. 11.50 Small nodule of neuroblastoma embedded in a ganglioneuromatous component

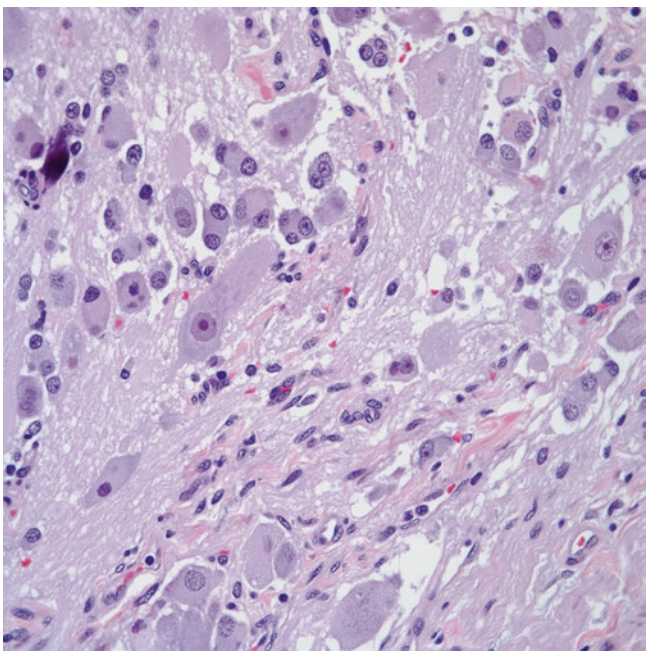

Fig. 11.52 Higher magnification of a ganglioneuroblastoma showing predominantly ganglion cells with scattered neuroblastoma cells

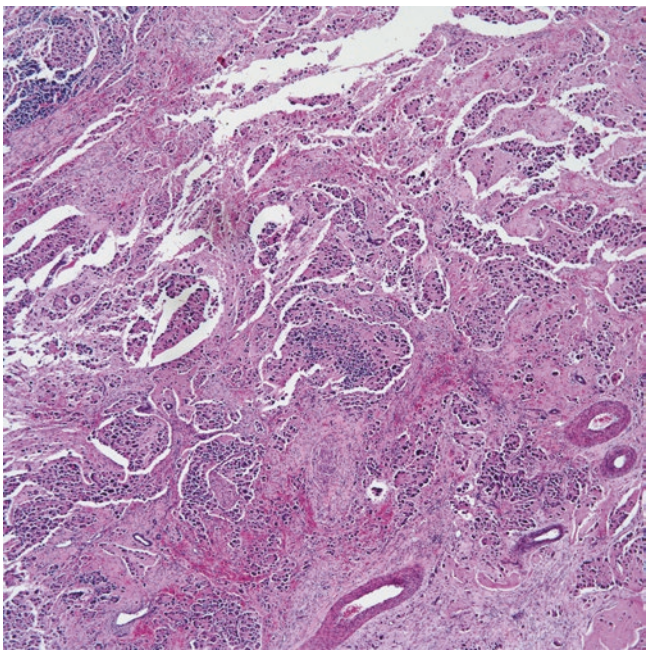

Fig. 11.53 Low power view of a ganglioneuroblastoma showing extensive areas of tumor

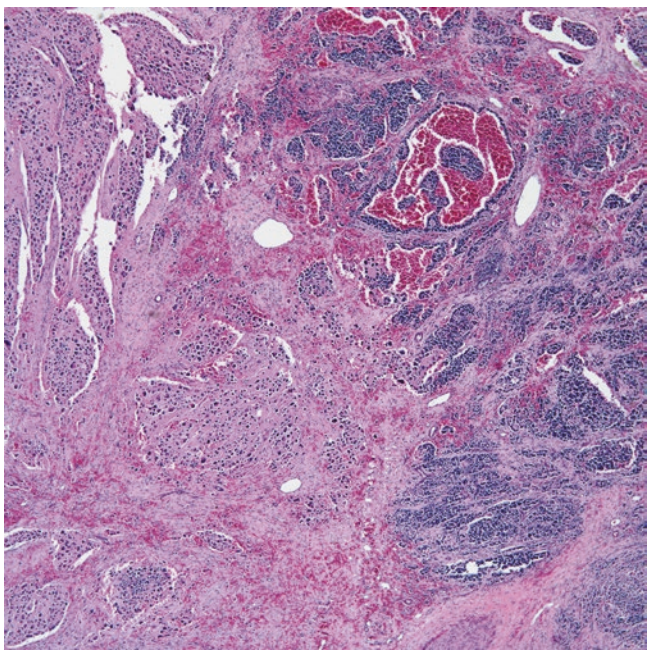

Fig. 11.54 Low power view of a ganglioneuroblastoma showing two populations of cells (larger and smaller cells)

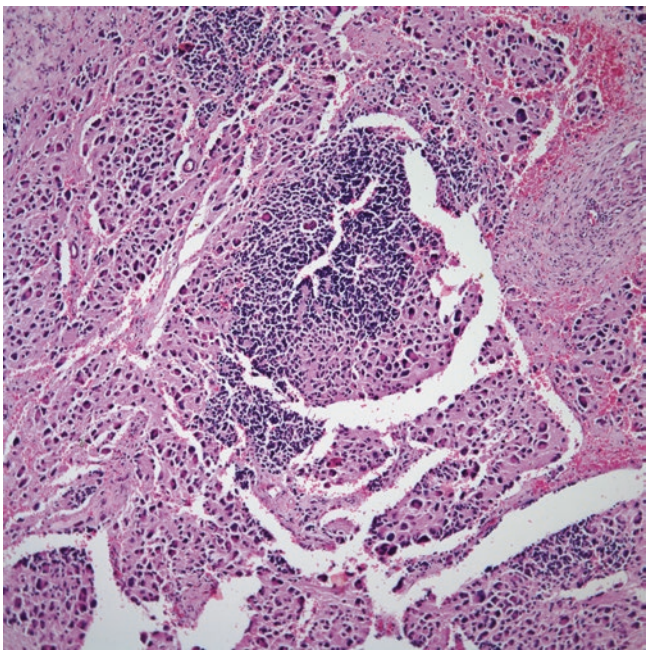

Fig. 11.55 Higher magnification of a ganglioneuroblastoma showing a population of larger cells and a small focus of small dark cells

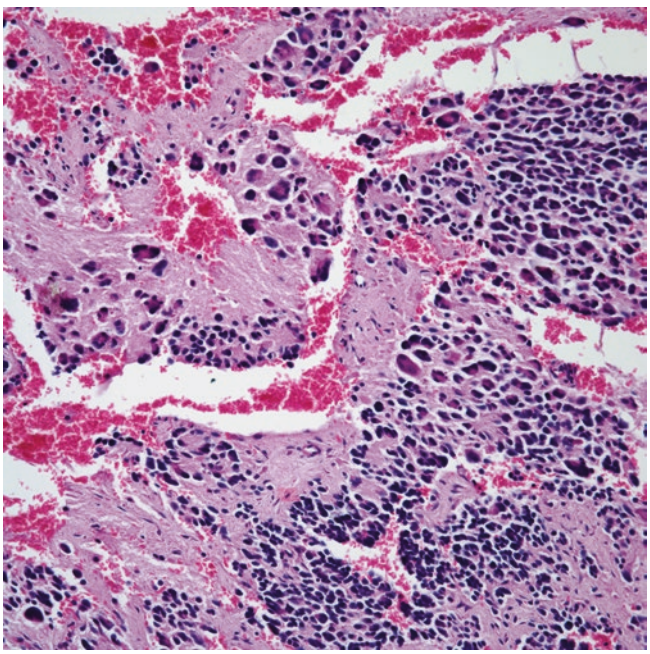

Fig. 11.56 Higher magnification of a ganglioneuroblastoma showing two populations of cells

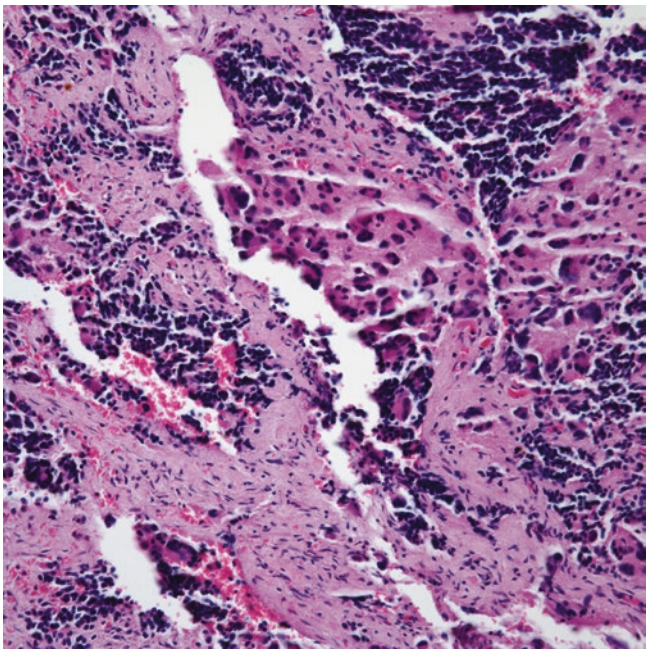

Fig. 11.57 Higher magnification of a ganglioneuroblastoma showing less differentiated neuroblastomatous component (dark cells)

areas), desmin, myoD, or other muscle markers. Favrot and colleagues [107], in a study of 45 neuroblastomas with focus in the expression of integrin receptors, encountered that none of the tumors expressed α-5 chain of the integrins; the majority of tumors expressed α-1 and α-3 chain of the integrins. All the tumors expressed β-1 chain. The authors concluded that the role of integrins in the malignant behavior of the cells is more complex than is usually predicted by experimental models. In a more sophisticated study to determine genomic damage in neuroblastic tumors, Munoz and colleagues [108] did not find an association between genomic damage fraction and tumor location, proliferation index, diagnosis, or age of the patient. However, the authors stated that tumors with MYCN amplification have a higher genomic damage fraction, which may contribute to the genomic instability of neuroblastomas. More recently, Angelini and colleagues [109], in a study of nodular ganglioneuroblastoma in eight children to determine the clonality of the neuroblasts, ganglion cells, and Schwann cells, concluded that the ganglion cells and neuroblasts are genetically related and may arise from the same clone, while the Schwann cells have a different origin and may be derived from a nonneoplastic neural crest precursor.

Differential Diagnosis

Neuroblastomas belong to the generic category of small round cell tumors; thus, the differential diagnosis of these tumors will include similar other tumors that belong to this category, namely, rhabdomyosarcoma and PNET. Since these tumors occur in childhood, it is essential to arrive to a particular diagnosis in order to properly establish treatment and prognosis for these children. Even though, as has been stated earlier, neuroblastomas occur more often in very early childhood, it is still important to keep other small round cell tumors in the differential diagnosis. Similarly, since all these tumors are uncommon in older patients, the same differential is maintained. However, the use of immunohistochemistry in this setting may prove beneficial as rhabdomyosarcomas may show reactivity against some or all muscle markers including Myo-D, desmin, myoglobin, and Caldesmon, which would not be the case in neuroblastomas. Regarding PNET, the use of immunohistochemistry may have some overlapping features with neuroblastoma in terms of positive staining for CD99; however, molecular analysis of PNET would show the proper molecular alteration in cases that are not clear by morphological or immunohistochemical analysis. One more consideration in unusual cases when these tumors occur in the adult population would be small cell carcinoma; however, small cell carcinomas commonly show positive staining for keratin, chromogranin, and synaptophysin. In addition, the clinical presentation and anatomic site of the tumor should lead to the correct interpretation.

In cases of ganglioneuroblastoma, the most important differential consideration would be with a conventional ganglioneuroma, mainly in cases in which the neuroblastomatous component is that of small microscopic nodules. In this setting, careful analysis of the morphological features should prompt the consideration of ganglioneuroblastoma. In addition, the use of *myc* amplification may be of help not only in the diagnosis but also in the prognosis of the tumor.

Malignant Peripheral Nerve Sheath Tumor (MPNST)

The term MPNST as it is used in this section refers to tumors that over the years have been called neurofibrosarcomas or malignant schwannomas [110–112]. It is also important to note that, contrary to the occurrence of other neural tumors, MPNST are more common in the adult population in contrast to neuroblastomas or ganglioneuroblastomas, which are more commonly observed in the pediatric age group [17]. At the same time, it is difficult to determine their exact occurrence as, in the majority of cases, all these tumors have been grouped with other neural tumors, and, in that sense, their occurrence would vary from 10 to more than 25% [113]. However, the exact occurrence of MPNST in the mediastinum is not only rare but also difficult to estimate. It is important to highlight that, in early literature, tumors that were classified as "neurofibrosarcoma" may in current standards be classified differently. For instance, the case described by Rossman [110] as neurofibrosarcoma causing hypoglycemia in a 51-year-old woman with a posterior

mediastinal mass likely may correspond to what we know now as solitary fibrous tumor, which commonly has as a clinical symptomatology hypoglycemia, and tumors that histologically show a variety of growth patterns [114]. Interestingly, even in early literature, cases of anterior mediastinal tumors have already been described [112]. In 1951, Ackerman and Taylor [115] reported 48 neurogenous tumors within the thorax and included four cases of what the author called "malignant schwannoma." The four cases were in adult patients, and all were located in the posterior mediastinum.

Sordillo and colleagues [116], in a study of 165 patients with malignant schwannoma, divided patients into those with solitary malignant schwannoma and those with von Recklinghausen's disease (VRD)-associated malignant schwannoma. The authors encountered that 40% of these patients had evidence of neurofibromatosis on physical examination, with a median age of 32 years in those with associated von Recklinghausen's disease (VRD), while those without it had a median age of 48 years. The tumor appeared to affect both genders equally in patients without VRD, while in those patients with VRD, the tumor was more frequent in females. The clinical course in both groups follows multiple local recurrences even though such occurrences had more aggressive course in patients with VRD. In addition, the authors noted that 8.5% of patients developed malignant schwannoma in an area of prior radiation. Follow-up information provided in this study shows that patients with VRD have shorter survival than those without VRD. In a different study on long-term follow-up of von Recklinghausen neurofibromatosis, Sorensen and colleagues [117] followed 212 affected patients and families; they encountered that survival rates were diminished in relatives with neurofibromatosis, worse in probands and worst in female probands. The authors concluded that patients with severe neurofibromatosis requiring hospital admission often have a poor prognosis. Of interest in this study is the association of different types of tumors in these patients. According to the table presented, four cases were classified as neurofibrosarcomas, one as neuromyxoma, one as acoustic neuroma, two as sarcoma fusocellular, one as fibrosarcoma, and one as fibromyxosarcoma, among many other epithelial and mesenchymal tumors.

As documented by Sordillo and colleagues [116], Ducatman and Scheithauer [118] analyzed 109 patients with neurofibrosarcoma in the period from 1912 to 1981, also documenting 12 patients in whom the tumor arose from an area previously irradiated. Seven of these 12 patients had evidence of neurofibromatosis. The authors determined that the latency period between the radiation and the occurrence of the tumor was 15.6 years (range 5–26 years). More recently, in a study of 75 cases of intrathoracic peripheral nerve sheath tumors, Boland and colleagues [50] found only five cases of MPNST, four of those tumors in a pleuropulmonary location and one in the anterior mediastinum. Based on these publications, it is likely that the occurrence of MPNST in the mediastinal location represents less than 1% of all tumors. However, the clinical history of von Recklinghausen neurofibromatosis and a posterior mediastinal mass should alert to the possibility of MPNST, especially when there is a history of previous radiation in that area.

As it has been noted with other posterior mediastinal tumors, these patients may be completely asymptomatic or have other non-specific symptoms related to the compression of the tumor in adjacent structures.

Pathological Features

Macroscopically, MPNST are usually larger tumors of more than 5–8 cm in greatest dimension. Even though a nerve may be grossly identified, in many cases that feature may not be possible to observe. The tumors are round to ovoid, solid, tan in color, and usually will show areas of hemorrhage and/or necrosis (Fig. 11.58). Cystic changes may also be present in some tumors, while in others that are heavily pigmented, dark areas may be observed.

Histologically, the tumors are characterized by the presence of a spindle cell proliferation that may be arranged in interlacing fascicles. The tumor may display several growth patterns including a "herringbone" pattern that commonly is ascribed to fibrosarcomas; thus, earlier publications use such nomenclature. However, for the most part, the spindle cellular proliferation is solid, which in some areas may show nuclear palisading and tactoid differentiation. Areas of hyalinization, necrosis, and/or hemorrhage are commonly encountered. At higher magnification, the malignant cells have a wavy appearance with a comma-shaped nuclei, easily identifiable mitotic activity, apoptotic cells, and cellular pleomorphism. One important feature commonly seen in MPNST is the presence of perivascular hyalinization (Figs. 11.59, 11.60, 11.61, 11.62, 11.63, 11.64, 11.65, 11.66, and 11.67). In addition, the tumors may show focal areas of muscle, cartilage, and bone elements.

Important variants of MPNST that have been described include epithelioid [119], pigmented [120–123], malignant Triton tumor [124–127], glandular [128], and tumors with small round cells type and pleomorphic spindle cell sarcomatous areas [129].

Epithelioid PMNST

These tumors are characterized by the presence of a cellular neoplasm composed of large epithelioid, round to oval cells with abundant amounts of cytoplasm, round nuclei, and prominent nucleoli. The tumor may have a subtle nodular appearance and also the presence of focal myxoid areas. Nuclear atypia and mitotic activity are commonly seen (Figs. 11.68, 11.69, and 11.70).

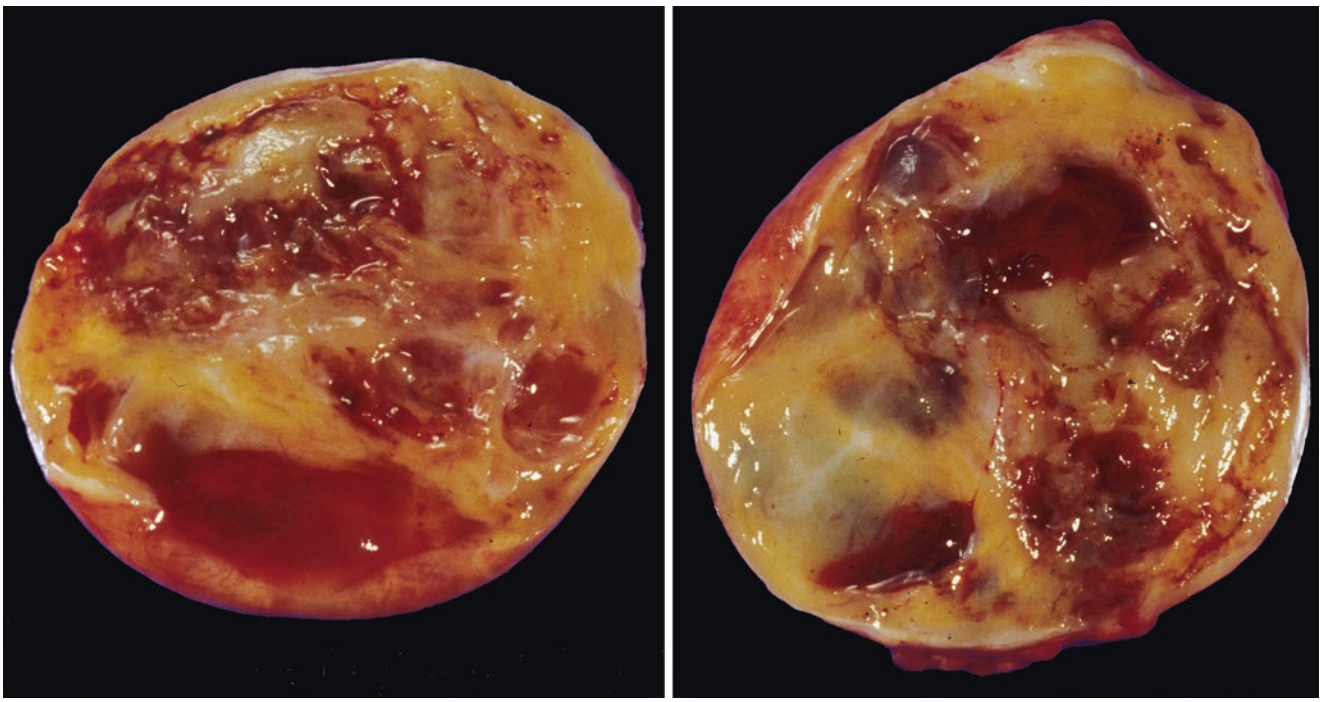

Fig. 11.58 Gross illustration of a MPNST showing a round to oval tumor with focal areas of necrosis and hemorrhage

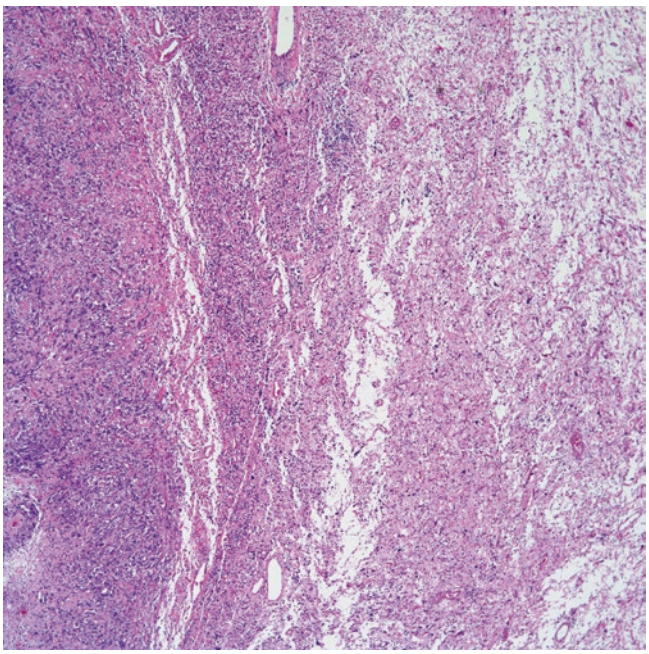

Fig. 11.59 Low power view of a MPNST developing from a neurofibroma. Note the transitional areas from low cellular (neurofibroma) to high cellular areas MPNST

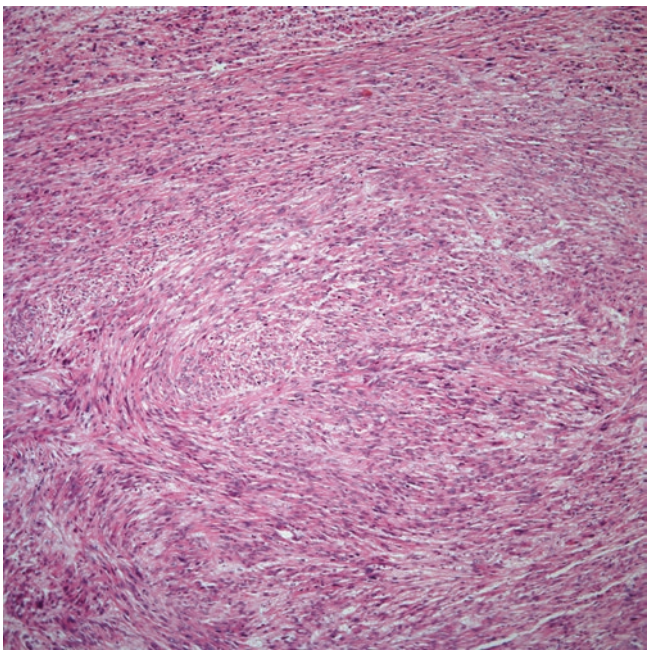

Fig. 11.60 MPNST showing a fascicular growth pattern composed of spindle cells

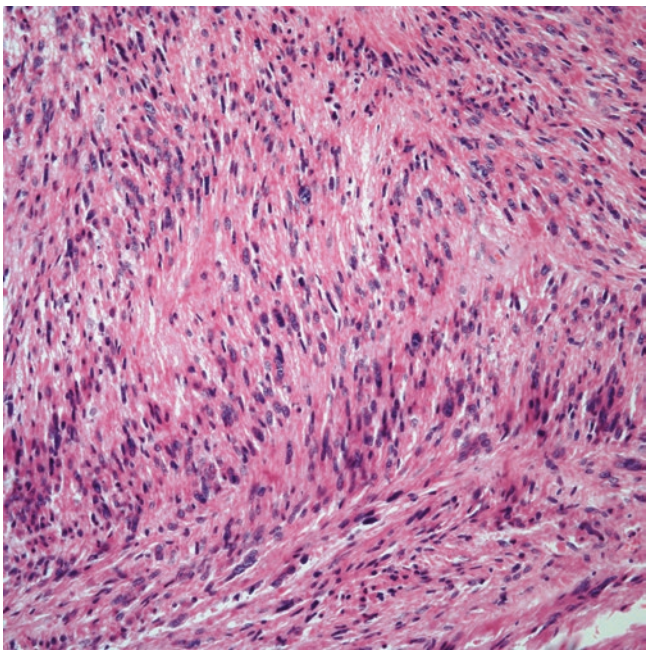

Fig. 11.61 MPNST showing focal and subtle areas in which there is a hint of nuclear palisading

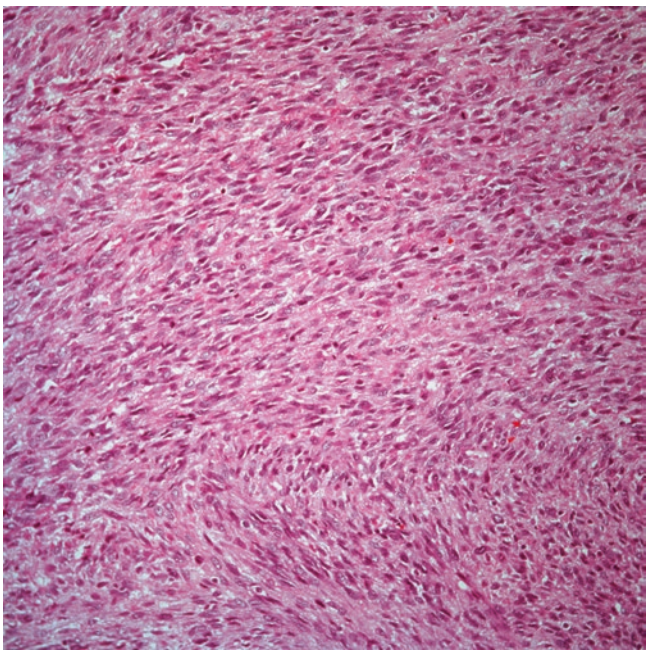

Fig. 11.63 MPNST showing solid areas of atypical spindle cells

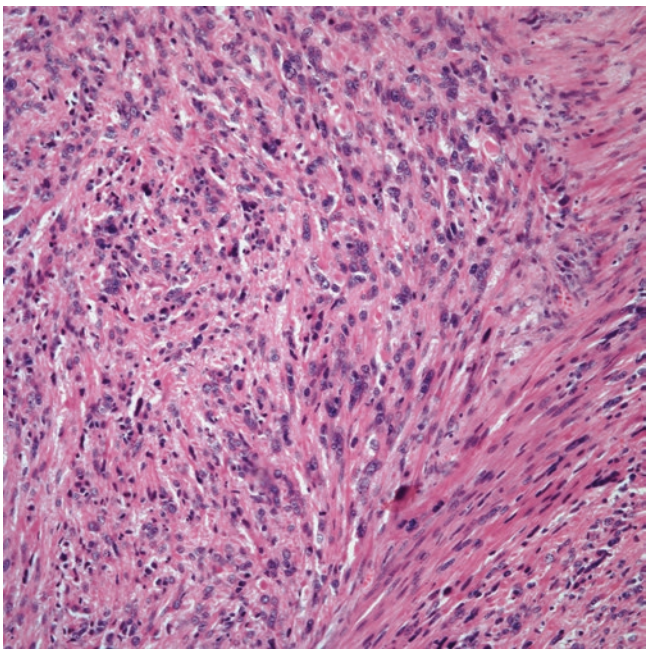

Fig. 11.62 Intermediate magnification of MPNST showing nuclear atypia and apoptotic cells

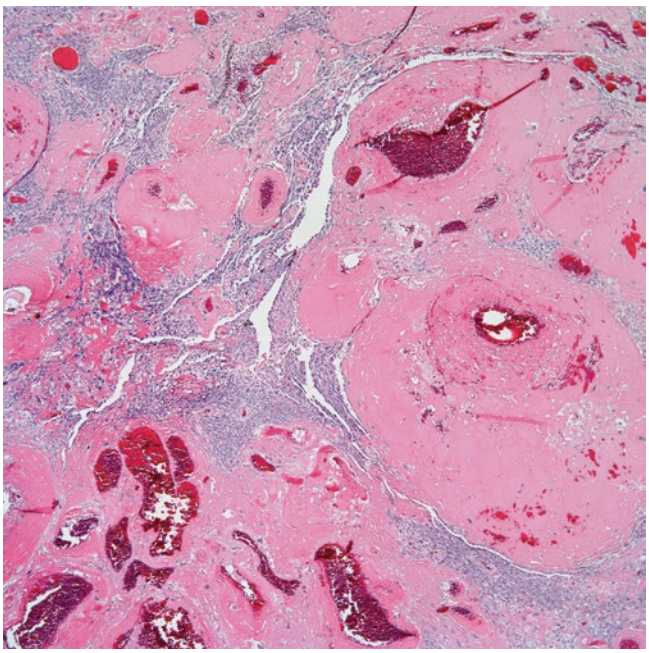

Fig. 11.64 MPNST showing extensive hyalinization of blood vessels

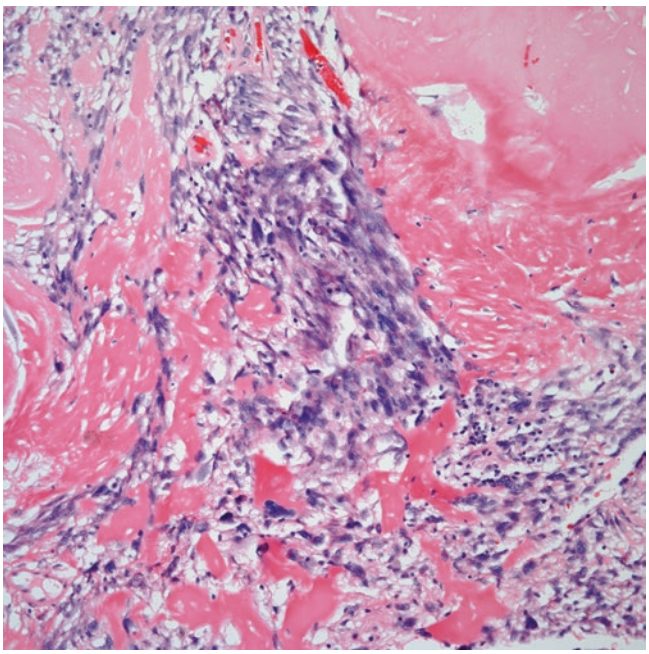

Fig. 11.65 MPNST showing focal areas of extensive hyalinization

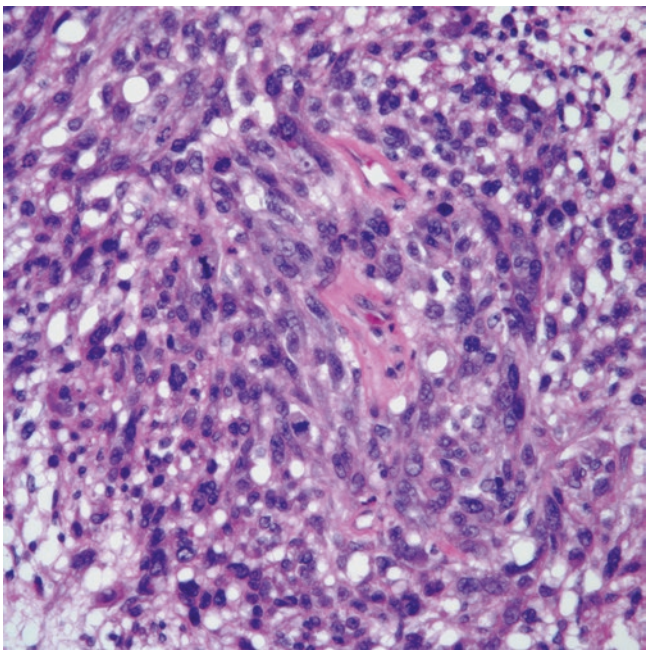

Fig. 11.67 MPNST showing nuclear atypia and increase mitotic activity

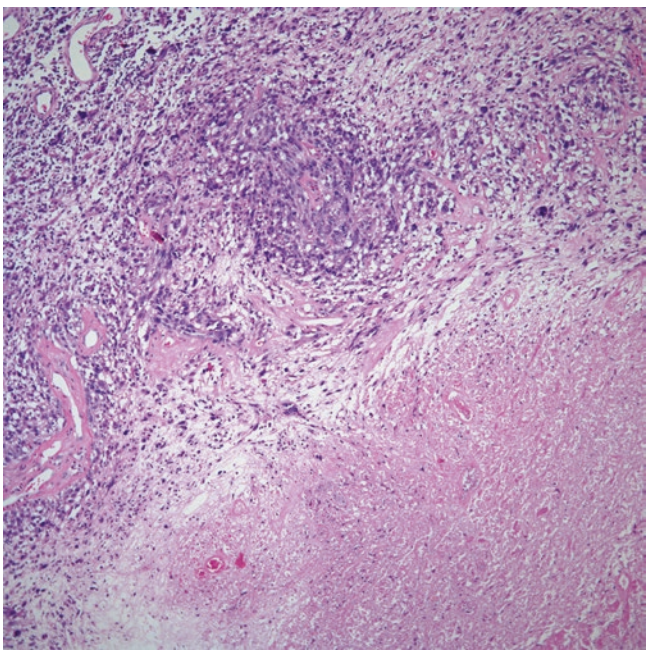

Fig. 11.66 MPNST showing malignant spindle cells and areas of necrosis

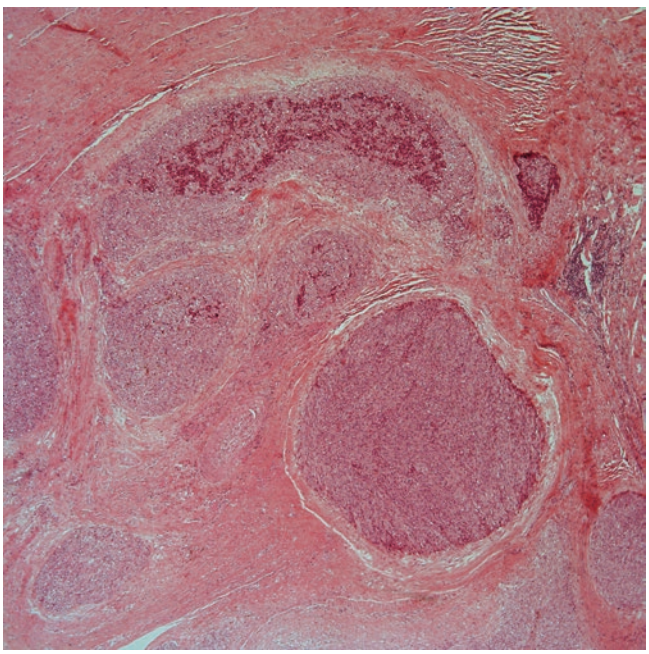

Fig. 11.68 Low power view of an epithelioid MPNST. Note the nodular growth pattern of the tumor

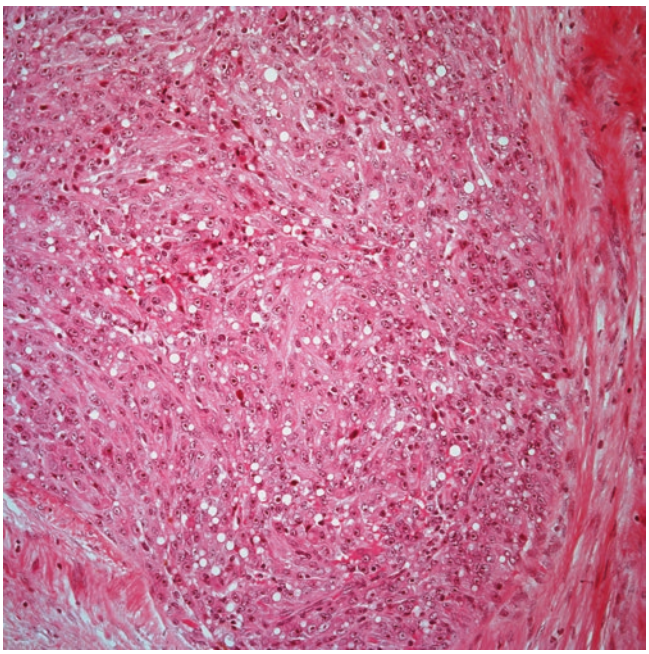

Fig. 11.69 Epithelioid MPNST showing oval cells with prominent nucleoli

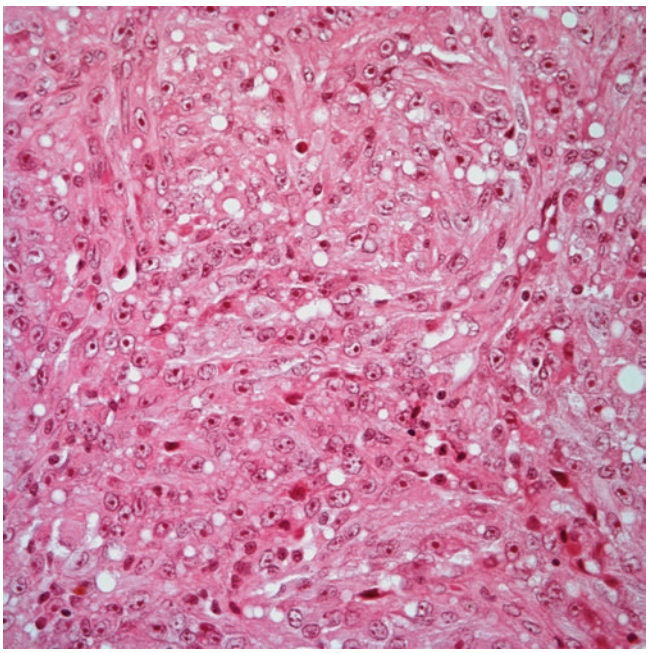

Fig. 11.70 Higher magnification of an epithelioid MPNST showing slightly elongated cells with round to oval nuclei and prominent nucleoli

Pigmented MPNST

The basic histological features are similar to those described with conventional cases or those with epithelioid morphology. However, the tumor is characterized by the presence of melanin pigment, which can be present in subtle form or in easily identifiable dark pigment on low power evaluation of the tumor. In cases in which the tumor shows more subtle pigmented areas, the melanin is present in intracytoplasmic cells that may be in groups or alternating with cells without melanin pigment. However, in some cases, the presence of melanin is extensive, which can easily obscure the true nature of the neoplasm and raise the possibility of malignant melanoma (Figs. 11.71 and 11.72). Tumoral areas containing psammoma bodies may be seen in some tumors. In the reported series of 40 cases by Torres-Mora and colleagues [122], 3 of the 40 cases were in mediastinal location. However, in general, the authors documented local recurrences in 35% of cases and metastases in 44%. In a period spanning from 1 to 300 months, seven patients had died of tumor.

MPNST with Rhabdomyosarcomatous Differentiation: "Malignant Triton Tumor"

The basic histological features of a MPNST are the presence of a solid spindle cell proliferation with areas of focal palisading of the nuclei, cellular and nuclear atypia, mitotic activity, perivascular hyalinization, and areas of necrosis and/or hemorrhage. However, associated with this spindle cell proliferation, one can identify the presence of larger cells with moderate amounts of eosinophilic cytoplasm and nuclei displaced toward the periphery, representing the rhabdomyoblastic differentiation (Figs. 11.73, 11.74, and 11.75). This tumor has been described in the anterior and posterior mediastinum. In addition, malignant Triton tumors with glandular differentiation, although uncommon, can also pose a significant problem in diagnosis. These tumors, in addition to showing the conventional neural and rhabdomyoblastic differentiation, also show the presence of a glandular component, which can be either focal or extensive. The glands are formed by columnar epithelium with well-formed lumen, and these glands can be of different sizes. The glands are haphazardly embedded in the spindle cell component (Figs. 11.76, 11.77, and 11.78).

Glandular MPNST

These tumors are characterized by the presence of haphazard glandular structures composed of low cuboidal to tall columnar cells lining the glandular elements. The glands are of different sizes and shapes and may contain intraluminal mucinous material. These glandular elements are separated by the spindle cell proliferation as described in conventional cases of MPNST. The presence of the glandular component may be focal or more prominent in some cases (Figs. 11.79, 11.80, and 11.81). Contrary to glandular Triton tumor, in this particular growth, the tumor does not show rhabdomyoblastic differentiation. In addition, the glandular component to some extent is histopathologically somewhat different. However, the differentiation of these

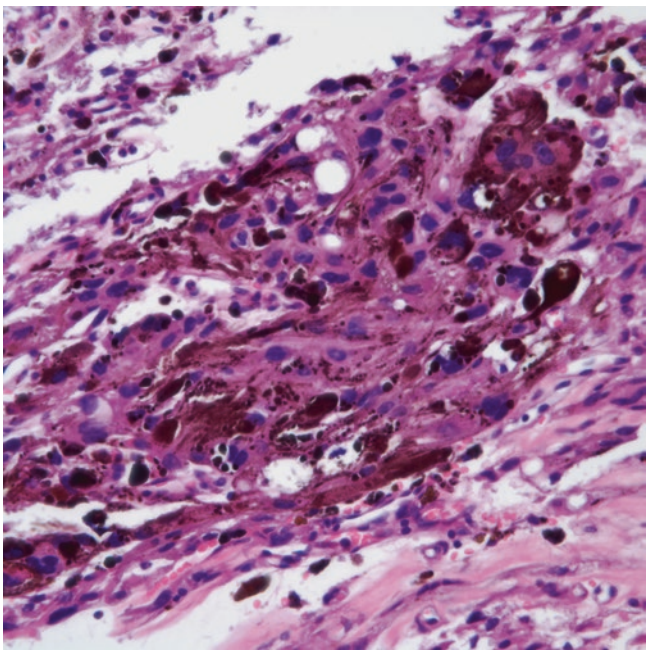

Fig. 11.71 Pigmented MPNST showing extensive areas of melanin pigment. Note the presence of spindle cells admixed with the pigment

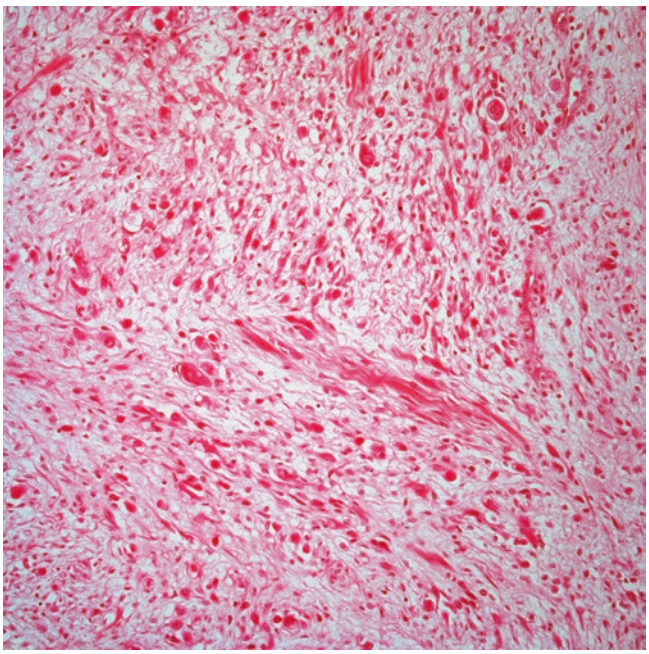

Fig. 11.73 MPNST with areas of rhabdomyoblastic differentiation (Triton Tumor). Note the presence of scattered rhabdomyoblastic cells

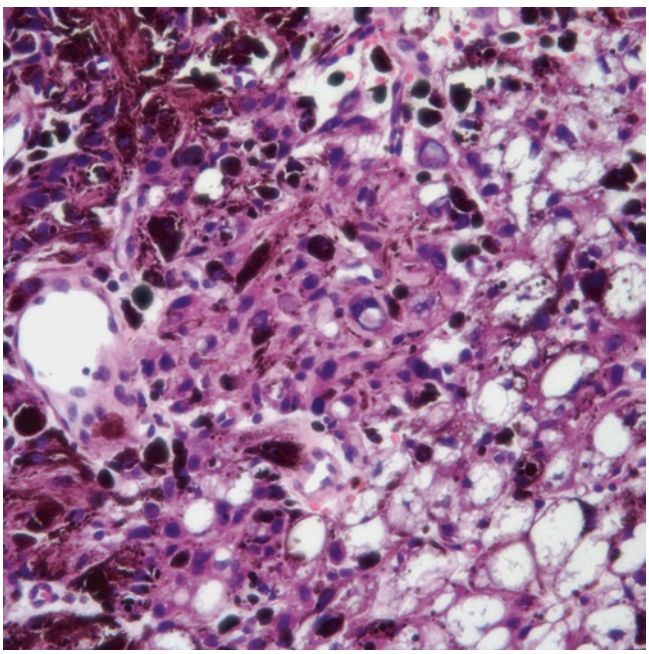

Fig. 11.72 Pigmented MPNST showing malignant cells with nuclear vacuolization and marked nuclear atypia. Note the presence of extensive melanin pigment deposition

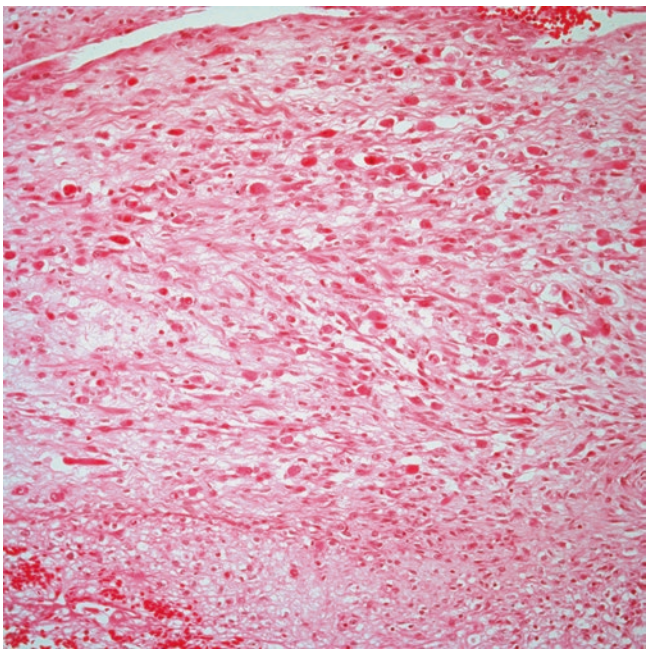

Fig. 11.74 Malignant Triton Tumor showing two distinct populations of cells. The larger cells representing rhabdomyoblasts

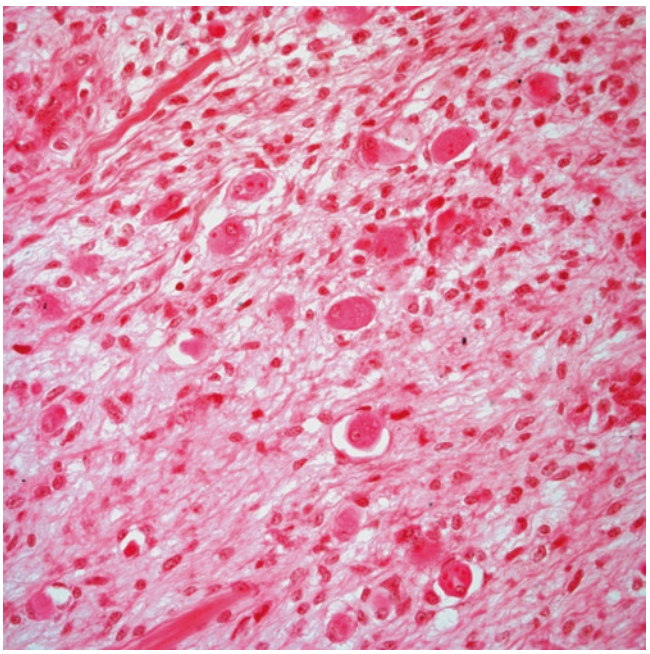

Fig. 11.75 Higher magnification of a Triton tumor showing the presence of rhabdomyoblasts separated by spindle neural component

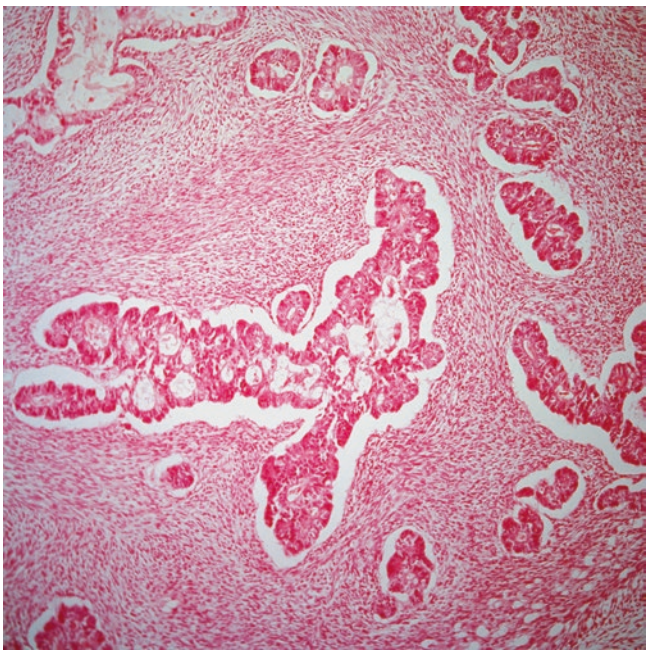

Fig. 11.77 Glandular Triton tumor showing closer view of the glandular component, mimicking adenocarcinomatous component

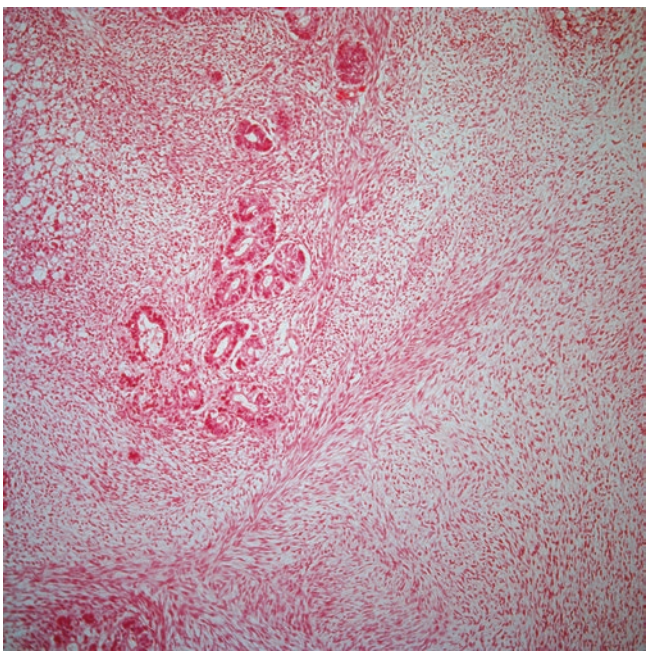

Fig. 11.76 Glandular Triton tumor showing well-defined glandular component embedded in spindle cells

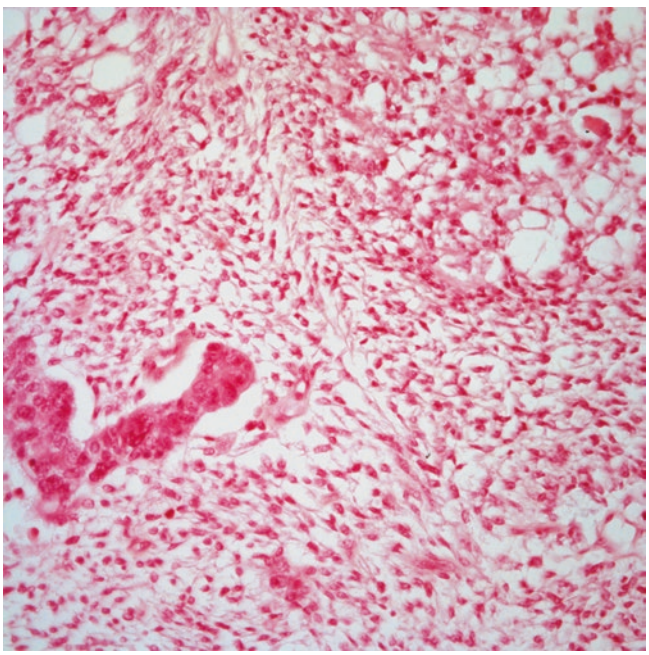

Fig. 11.78 Higher magnification of a glandular Triton tumor showing the three components -glands, neural, and rhabdomyoblastic differentiation

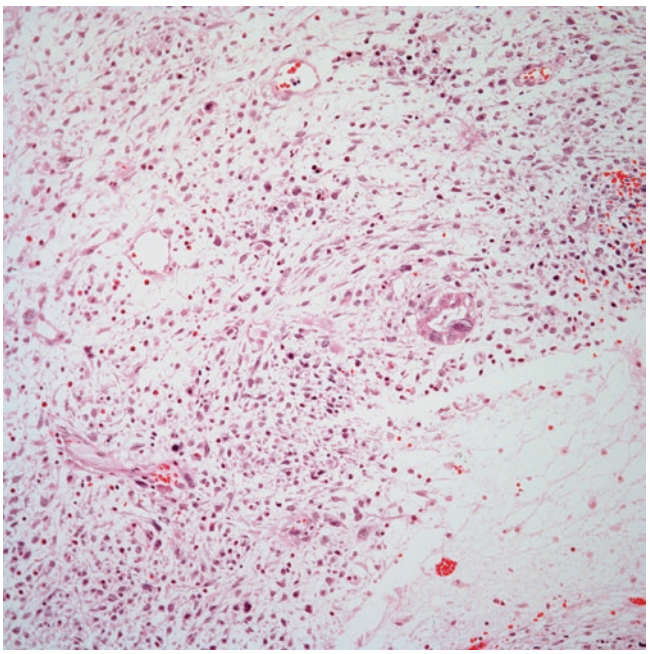

Fig. 11.79 Glandular MPNST showing predominantly neural component with only a focal area of glandular component

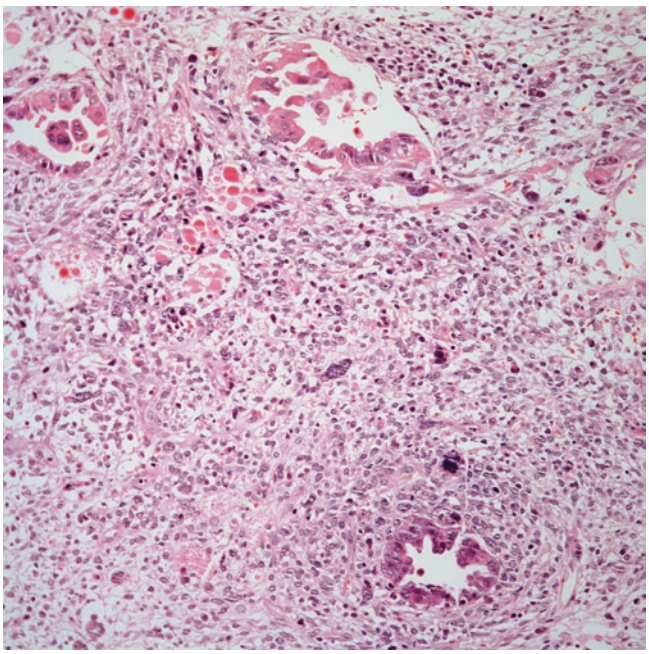

Fig. 11.81 Glandular MPNST showing the glandular component, which is composed of small glands with cylindrical type of epithelium. The neural component shows some epithelioid features

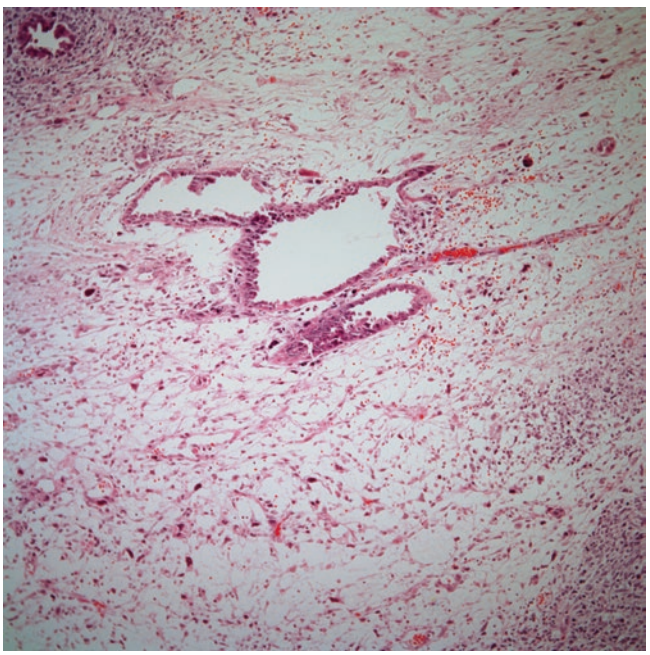

Fig. 11.80 Glandular MPNST in which the glandular component is more obvious

two tumors is based on the presence or absence of rhabdomyoblastic differentiation.

MPNST with Sarcomatous Areas and Small Round Cells

This growth pattern in MPNST is unusual and is characterized by the presence of the basic histological features of MPNST; however, the tumor also shows areas composed of small cells that can be arranged in tubular-like structures, and in some cases with rosette formation. In addition, in some areas the tumor may also show the presence of larger cells with ample cytoplasm and pleomorphic cells.

Immunohistochemical, Ultrastructural, and Molecular Features

The essential work-up of MPNST is done by ruling out other malignant spindle cell tumors that may show similar morphological features. Furthermore, the use of S-100 protein, even though helpful, may show negative results in about 50% of cases. Therefore, the use of other immunohistochemical markers to properly rule out other spindle cell sarcomas is recommended. Other immunostains that may show positive staining and yet are not specific include NSE, vimentin,

and neurofilament protein (NFP). The problem may be much more complicated when these tumors show different growth patterns. For instance, in a series of pigmented MPNST, the tumors in addition to S-100 positivity have also shown positive staining for Melan A, HMB45, and tyrosinase [122], which has led some authors to suggest a different name for these tumors: "malignant melanotic schwannian tumors." For tumors with glandular elements, the glandular structures will show positive staining for epithelial markers such as keratin and EMA. Also, in cases with rhabdomyoblastic differentiation, the tumor may show positive staining for MyoD, myoglobin, desmin, and/or caldesmon.

Ultrastructure studies often may show the presence of abundant rER, well-developed Golgi apparatus, microtubules, lysosomes, and cell processes coated with lamina. All these features suggest Schwannian differentiation. At the molecular level, NF1 mutation may be present in some cases, while some other cases may show PTEN overexpression.

Differential Diagnosis

The differential diagnosis of MPNST will include other spindle cell sarcomas of non-neural origin such as leiomyosarcoma, rhabdomyosarcoma, and solitary fibrous tumor. Also important to include is the benign schwannoma in the differential diagnosis. In cases in which the tumor shows extensive pigmented areas, the most difficult differential diagnosis is with malignant melanoma. In cases in which the tumor shows an epithelioid morphology, the most important differential diagnosis is with carcinoma or melanoma, while in cases in which the tumor shows glandular component, the most important differential diagnosis is with carcinosarcoma.

In tumors of non-neural origin such as leiomyosarcoma and rhabdomyosarcoma, the presence of positive staining for desmin, MyoD, myoglobin, and/or caldesmon will lead to the correct interpretation. However, it is also important to know that malignant triton tumor may also show rhabdomyoblastic differentiation. Leiomyosarcomas will unlikely show positive staining for S-100 protein, and the same applies for pure rhabdomyosarcomas. In the setting of epithelioid MPNST, if the consideration is carcinoma, the use of epithelial markers such as keratins and EMA would lead to the correct interpretation. In cases of pigmented MPNST, the interpretation of immunohistochemistry may be much more difficult, as it has been stated that pigmented MPNST may also show positive staining for markers such as Melan A and HMB45. In such cases, the use of electron microscopy may be of aid. Glandular MPNST may be confused with carcinosarcomas; however, by definition, carcinosarcomas should show the presence of malignant epithelial component (squamous cell carcinoma or adenocarcinoma) in addition to the malignant mesenchymal component. Perhaps the most important differential in many cases is with a cellular schwannoma. In this setting, the presence of necrosis and/or hemorrhage and high mitotic activity would lead to a more correct interpretation. Because solitary fibrous tumor is much more common in the thoracic location and because of its stated wide spectrum of growth patterns, this tumor should be very carefully included in the differential diagnosis. In this setting, the use of CD34 and STAT6 would be of great aid in ruling in or out such a possibility.

In essence, the diagnosis of MPNST may be facilitated using good clinical information such as the clinical diagnosis of von Recklinghausen's disease, a reasonable biopsy, the use of a wide panel of immunohistochemical stains, and the use if necessary of ultrastructural studies. The global interpretation of these findings would be of great help in arriving at a proper diagnosis.

Peripheral Neuroectodermal Tumor (PNET)/ Extraskeletal Ewing Sarcoma

For consistency, the term PNET will be used in this section to refer to this entire category, of course noting that often both of these tumors are considered in the same spectrum. However, throughout history, many other names have been used to describe this particular tumor including neuroepithelioma, small round cells tumor of thoracopulmonary region, Askin Tumor, and malignant small round cell tumor.

It is very likely that the existence of these peripheral neuroectodermal tumors had been recognized more than a century ago. However, the specific designation of PNET had not been properly recognized in the literature [130]. However, it was not until the mid-1970s that Nesbitt and Vidone [131] and Seemayer and colleagues [132] documented similar tumors as the one described by Stout in 1918 in the peripheral soft tissues. The case described by Nesbitt and Vidone [131] was in a 6-year-old boy with a sciatic nerve tumor, which the authors designated as "primitive neuroectodermal tumor (Neuroblastoma)." The authors acknowledged that few similar tumors had been reported in the literature and considered that these tumors are best classified as "primitive neuroectodermal neoplasms." Also in 1975, Angervall and Enzinger [133] reported 39 cases of a "small, round, or oval cell sarcoma" of soft tissue, histologically indistinguishable from Ewing sarcoma of the bone. Interestingly, the authors stated "it is impossible to prove or disprove whether the tumors described as Ewing's sarcoma share similar histogenesis."

Despite the fact that the existence of these tumors in the soft tissue was becoming more evident, the occurrence of these tumors in the thoracic cavity had not been properly determined, even though early publications alluding to the occurrence of similar tumors in the paravertebral region had

been mentioned. Tefft and colleagues [134] described the radiographic features of five children with what the authors described as "unusual histologic characteristics" and designated these tumors as "paravertebral round cell tumors." However, it was not until Askin in 1979 [135] reported 20 cases in children and adolescents of a malignant tumor that the authors coined as "malignant small cell tumor of the thoracopulmonary region," which subsequently also became known as "Askin tumor." The tumors described were more common in female patients, and the tumor originated from the soft tissues of the chest wall or the peripheral lung. The median survival in these patients was 8 months. Interestingly, ultrastructural studies performed in some of these cases suggested a "neuroepithelial derivation"; however, the authors concluded that the histogenesis remained uncertain. Perhaps more important to mention is that in 1979, the basis to separate Ewing sarcoma from this new entity – "small round cell tumor of the thoracopulmonary region"– was the presence of PAS positive material in the tumor cells (negative in all the cases reported by Askin). In 1989, Marina and colleagues [136] reported 26 cases of what the authors called "peripheral primitive neuroectodermal tumor (peripheral neuroepithelioma) in children." Of these 26 cases, 6 were located in the chest wall, similar to those described by Askin [135]; the remaining cases were in different soft tissue locations. All the patients were children and young adolescents, and, after a median follow-up of 109 months, 9 of the 26 reported patients were alive. Interestingly, in a report of ten of these tumors, Llombart-Bosch and colleagues [137] described a mean age of 32.6 of the patients reported, with a male predominance. In a different report of 54 patients, Kushner and coworkers [138] described patients ranging in ages from 1 to 81 years, with a median of 17 years; of the 54 cases described, 25 were in the thoracopulmonary region while the remaining were in different soft tissue locations. The authors also stated that radiation therapy induced tumor shrinking but was not curative. The progression-free survival in 43 patients with localized tumor was 25% at 24 months, while patients with localized tumor who had complete surgical resection within 3 months of diagnosis had significant longer progression-free survival. The authors also concluded that the possible way to treat these patients is with complete surgical resection, radiation therapy, and chemotherapy.

In general, the occurrence of PNET in the lung or mediastinum is rather rare [139–143]. In the mediastinal compartment, all the tumors described have been in adults and in either anterior or posterior mediastinal location. The patients have presented with diverse clinical findings including superior vena cava compression. Even though one can only assume that the clinical course in the mediastinal location is similar to that described in other locations, due to the limited number of cases described in the literature, it is impossible to come to meaningful conclusions about PNET in the mediastinal compartment.

Pathological Features

Macroscopically, the tumors in the anterior or posterior mediastinal compartment may reach a size of over 10 cm in greatest dimension. The tumors are ill-defined and may involve adjacent structures. The tumors are light tan in color with areas of hemorrhage and/or necrosis.

Histologically, the tumors are characterized by a uniform cellular proliferation composed of small, round to oval cells, with small round nuclei and inconspicuous nucleoli. The neoplastic cells contain scant eosinophilic cytoplasm. Even though the tumors may show different growth patterns, usually the neoplastic cellular proliferation may be arranged in sheets or cords of neoplastic cells. The presence of pseudorosettes or rosettes of the Homer-Wright type may be seen in these tumors, but their presence is not always found. Mitotic activity is variable in these tumors and may be increased in some tumors, while in others it appears more subdued. Areas of necrosis and/or hemorrhage are easily identified in these tumors, and their presence is also variable and depends on the type of material available for evaluation (Figs. 11.82, 11.83, 11.84, 11.85, 11.86, and 11.87).

Histochemical, Immunohistochemical, Ultrastructural, and Molecular Features

At the initial publication of these tumors in the thoracopulmonary region, Askin and coworkers [135] discussed extensively the absence of PAS material in these tumors and used such feature to separate PNET from Ewing sarcoma. However, focal positive reaction for PAS may be seen in some cases. Other histochemical stains including mucicarmine are generally negative. The use of immunohistochemical stains, although important, may also have some limitations; even though the tumor appears to commonly express CD99 and focally synaptophysin, chromogranin, and CD56, these immunohistochemical stains may also show positive staining in other tumors that are not related to PNET, and that may mimic its morphology. Other immunostains that have shown positive staining include S-100 protein, NSE, and HNK-1. On the other hand, the tumor is commonly negative for muscle and epithelial markers as well as other markers including HMB-45, MelanA, and Sox-10. Ultrastructurally, PNET may show the presence of interdigitating processes, primitive intercellular attachments, and membrane bound granules. However, in current practice, the use of molecular analysis may prove to aid further in the diagnosis. Ambros and coworkers in 1991 [144] reported what the authors considered the specific expression of MIC2 gene in Ewing sarcoma and PNET as evidence for a common histogenesis for both tumors. In addition, Selleri

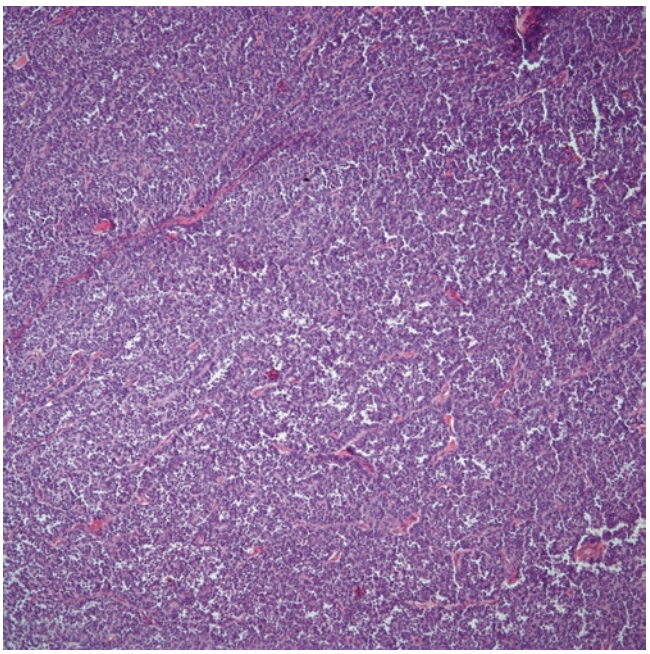

Fig. 11.82 Low power view of a PNET showing a solid neoplastic cellular proliferation

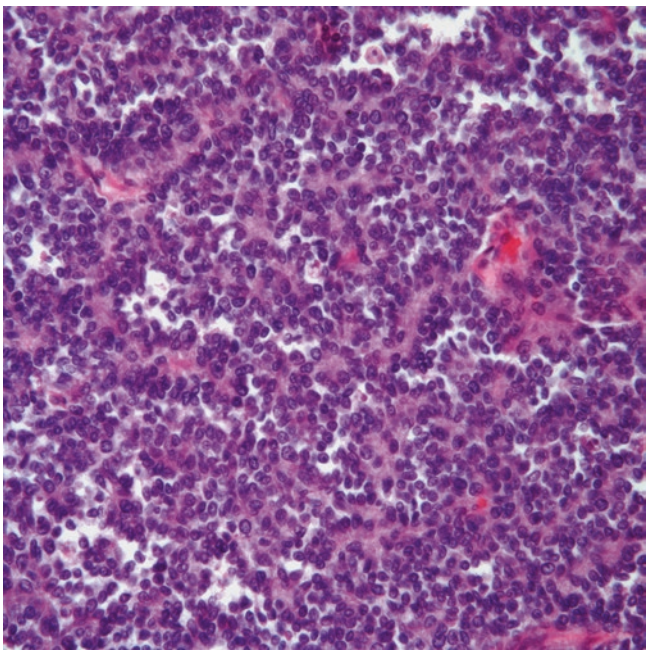

Fig. 11.84 Higher magnification of a PNET showing pseudorosettes. The tumor is composed of small cells with round to val nuclei and inconspicuous nucleoli. No mitotic activity is present

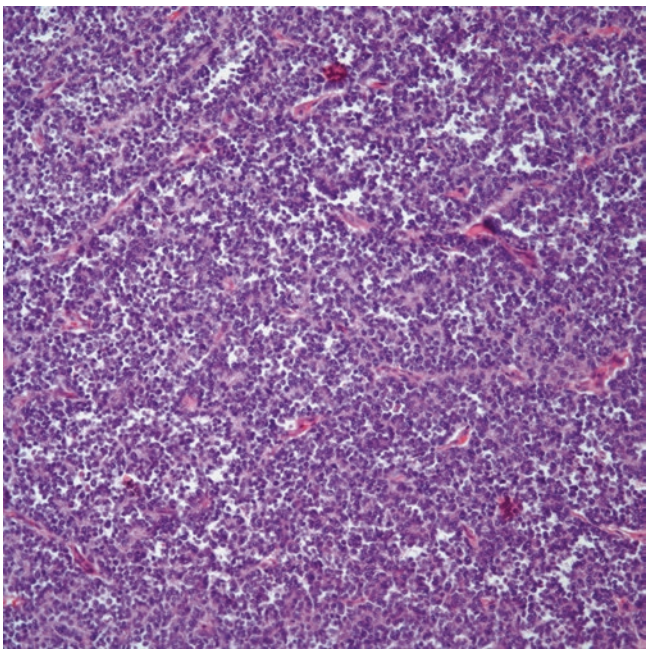

Fig. 11.83 PNET showing numerous pseudorosettes. Note the fairly homogeneous cellular proliferation

and coworkers [145] analyzed the molecular localization of the t(11;22)(q24;q12) translocation, which essentially occurs in Ewing sarcoma and PNET. Turc-Carel and coworkers [146] encountered similar findings in a study of 85 cases in which the authors identified similar translocation in Ewing sarcoma.

Differential Diagnosis

The differential diagnosis of PNET in the mediastinal compartment will include not only tumors within the ranged of "small round cells neoplasms" but also other tumors that potentially mimic PNET in the mediastinum. By far, since these tumors occur predominantly in young patients, the consideration of rhabdomyosarcoma and neuroblastoma is highly important. In cases of rhabdomyosarcoma, the use of muscle markers will lead to a correct interpretation as PNET invariably show negative staining for those antibodies. In cases of neuroblastoma, mainly in the poorly differentiated tumors in which there is absence of neutrophil, the diagnosis can be much more difficult, as neuroblastomas may also show positive staining for CD99. However, in this setting in the difficult cases, the molecular analysis and the identification of the common translocation will lead to a correct interpretation. One important consideration will include a tumor that may occur in the pleural region and that may pose a significant challenge – desmoplastic small round cell tumor (DSRCT). This latter neoplastic process also occurs in young patients and may present as a thoracic bulky mass. In addition, the tumor may also show similar immunohistochemical profile as PNET. However, it is important to mention that DSRCT may show positive staining for desmin, keratin, EMA, and WT1, while about 20% of the cases show positive staining for CD99. Molecular analysis of DSRCT shows that site on chromosome 11 is WT1, while for Ewing sarcoma it is FLI1 gene, thus the translocation for Ewing sarcoma t(11;22)(q24;q12) and that of DSRCT t(11;12)(q13;q12)

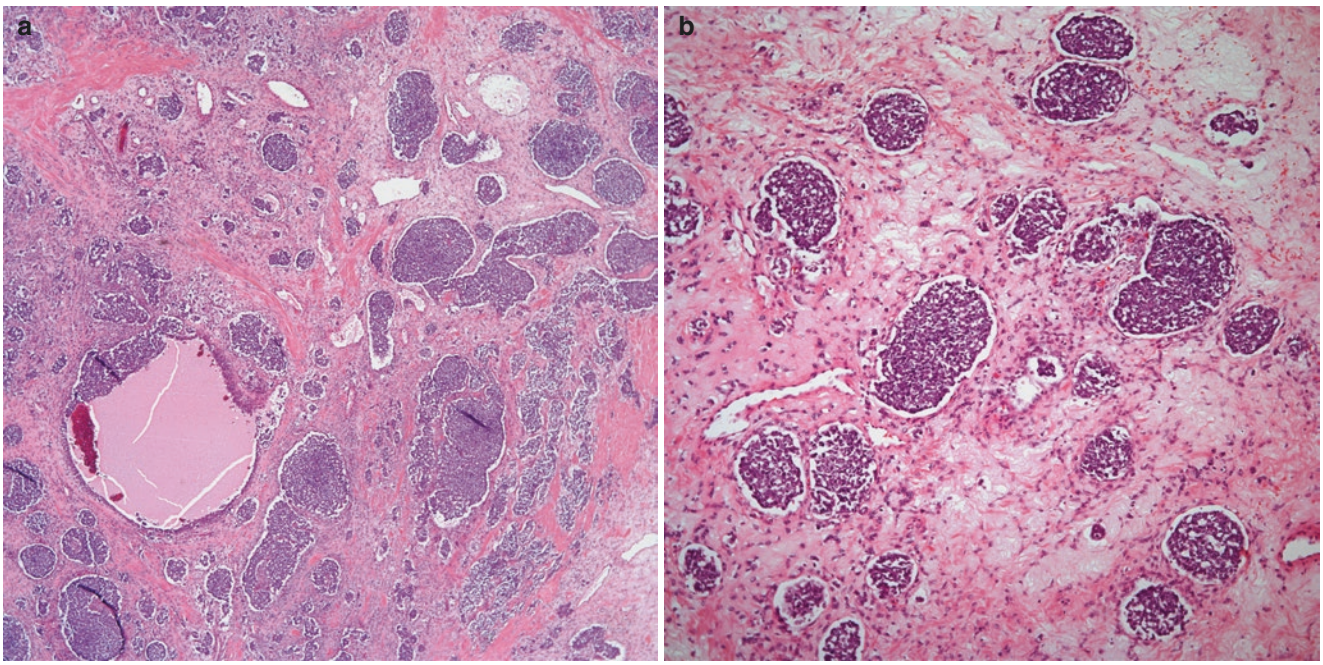

Fig. 11.85 (**a**) PNET showing a pseudo-alveolar growth pattern composed of nests of tumor cells. (**b**) Higher magnification showing lymphatic permeation by tumor and in other areas retraction of the fibroconnective tissue

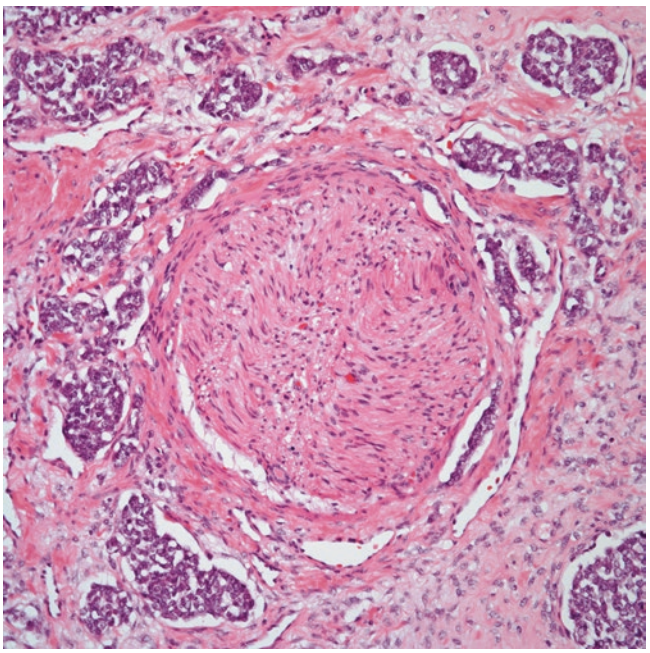

Fig. 11.86 PNET showing perineural invasion

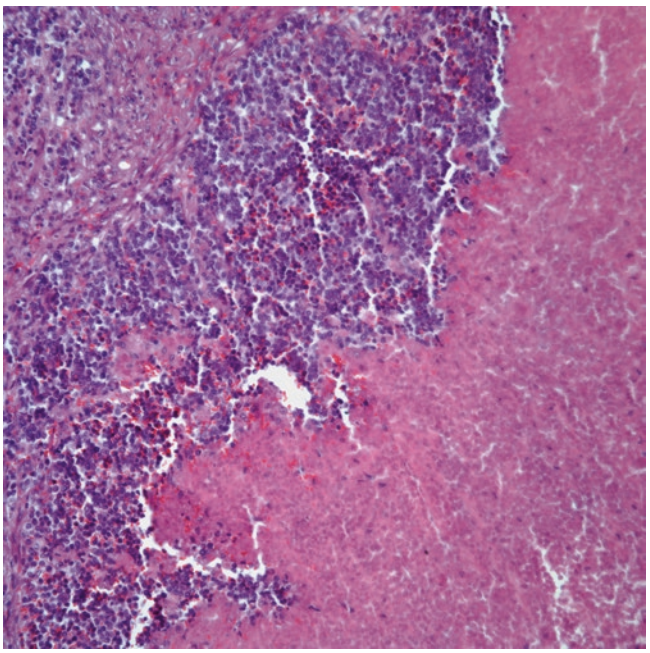

Fig. 11.87 PNET showing extensive necrosis

[147]. Even though this tumor in large resections may show histopathological features, which may aid in the diagnosis such as the presence of extensive desmoplasia, the challenge in small biopsies cannot be overemphasized.

Pigmented Neuroectodermal Tumor of Infancy (Melanotic Progonoma, Retinal Anlage Tumor)

This tumor is a very rare occurrence in the mediastinal region [148]. The tumor is commonly observed in infants during the first year of life and anatomically affects more often the head and neck area with preference for the maxillary region [149]. However, the tumor has been reported in numerous other locations. The only case that has been published of this particular tumor in the mediastinal region is credited to Misugi and coworkers [148], who, in 1965, described a 7-month-old child with a posterior mediastinal mass. The child underwent a right posterolateral thoracotomy with initial partial resection of a tumor that extended from the right costovertebral sulcus to the left, across the thoracic spine, posterior to the aorta and from the level of D4 to the esophageal hiatus. The tumor was described as compressing the trachea and right stem bronchus, displacing the heart anteriorly, and the esophagus to the left. Due to the initial unresectability of the tumor, the child received radiation therapy with subsequent further thoracotomy, and the authors provided a follow-up of 6 months in which the child remained alive. Even though in general terms, this tumor is considered benign, the tumor can be aggressive, and in a small proportion of patients, it may metastasize. However, it is difficult to determine whether these tumors in the mediastinal location will follow an indolent or aggressive clinical behavior. It is possible that the initial treatment of these tumors in the mediastinum should have the goal of complete surgical resection whenever possible. Important to highlight is that due to the infrequent occurrence of these tumors in the mediastinum, a more precise clinical behavior is not possible.

Pathological Features

In the report by Misugi [148], even though the mass was initially incompletely resected, the resected tumor mass measured 7 cm in greatest dimension and weighed 65 grs; the tumor was slightly lobulated, grayish-black, and solid.

Histologically, the tumor shows similar features as those tumors in the more conventional location, namely, the presence of extensive areas of fibrous tissue with a neoplastic cellular proliferation composed of cuboidal cells, while in other areas, the tumors cells appear more undifferentiated. The neoplastic cells may be arranged in small clusters, while in other areas, the tumor cells appear to be forming small glandular structures with a subtle alveolar growth pattern. In addition, one of the most important features is the occurrence of pigmented cells, which can be seen in the glandular-like areas in the cluster of neoplastic cells. The cells appear to be rather small, with round nuclei, and inconspicuous nucleoli (Figs. 11.88, 11.89, 11.90, 11.91, and 11.92). Mitotic activity is not high, but, in some cases, mitotic activity can be easily identified. Areas of necrosis and hemorrhage are usually not common.

Immunohistochemical, Ultrastructural, and Molecular Features

The use of immunohistochemical stains plays an important role in the diagnosis of these tumors, as these tumors may also show some features that may be seen in other small round cell neoplasms. However, in general terms, as the name (retinal anlage tumor) implies, this particular neoplasm shows similar immunohistochemical phenotype as the normal retina, namely, the presence of positive staining for keratin as well as for S-100 protein. In general, the tumor does not show positive staining for muscle marker, mainly desmin, Myo D, Myoglobin, smooth muscle actin, or caldesmon. The ultrastructural findings in the case described by Misugi and coworkers [148] showed two different types of pigmented cells: (1) large spindle cells with abundant cytoplasm, well-developed granular endoplasmic reticulum, and prominent Golgi complex; and (2) small cells filled with numerous pigment granules of varying electron density. More recently, Barnes and coworkers [150] reported a case in which by molecular means, the authors identified that the tumor showed a germline mutation of CDKN2A and a novel RPL1-C19MC fusion.

Differential Diagnosis

By far the most important differential diagnosis will be with other small round cell tumors of infancy. The histopathological features of retinal anlage tumors may be confused with rhabdomyosarcomas, and, in this setting, the use of immunohistochemical stains for muscle markers, including desmin, myoglobin, MyoD, and caldesmon, would lead to the correct interpretation. One other important differential diagnosis would be with neuroblastoma, as the tumor also occurs in infants and young children. In this setting, the positive staining using keratin and S-100 protein will lead to the interpretation of retinal anlage tumor. Even though the age group for the occurrence of melanoma is highly unusual, the histology of the tumor – mainly the presence of pigment – may mimic melanoma. One other tumor to consider, even though it would be unusual in young children, is the desmoplastic small round cell tumor. This latter tumor not only may show a small round cell tumor but also will show extensive areas of hyalinization and fibrous tissue, somewhat similar to that display of the retinal anlage tumor. However, even though desmoplastic small round cell tumor may show in some cases positive staining for S-100 protein, it may also show positive staining for desmin and negative staining for keratin.

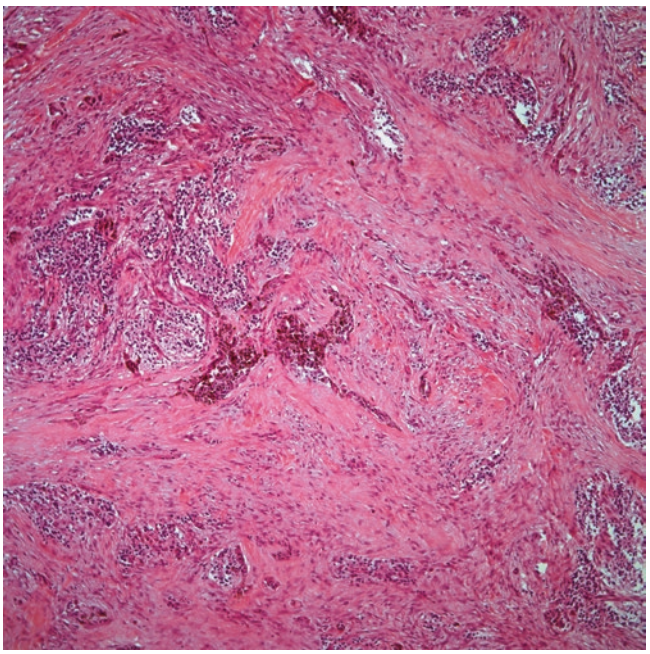

Fig. 11.88 Retinal anlage tumor showing extensive areas of fibrosis. Note the presence of a small tumor cells admixed with focal areas of pigmented cells

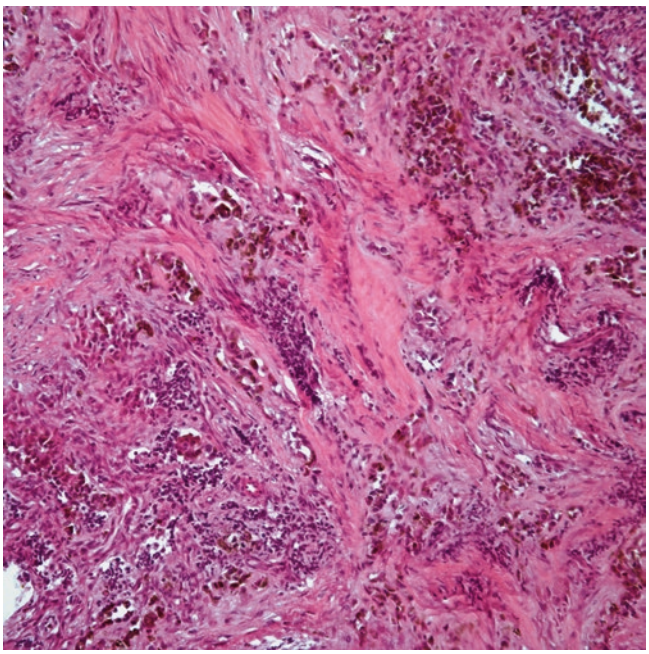

Fig. 11.90 Retinal anlage tumor showing areas of obvious pigmented cells

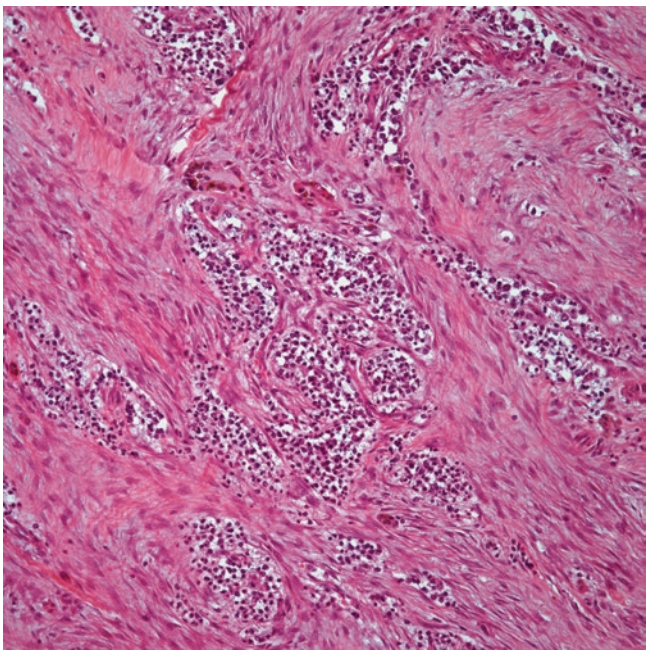

Fig. 11.89 In some areas the presence of pigmented cells in retinal anlage tumor may be focal

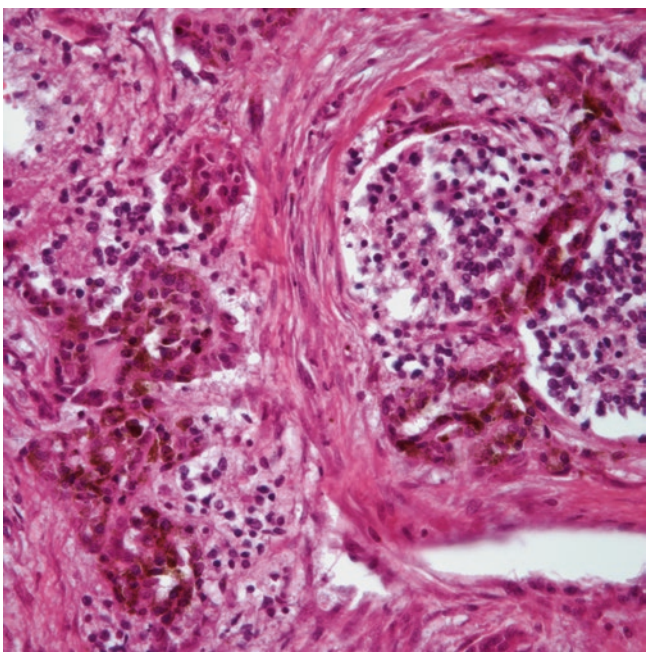

Fig. 11.91 Dual cellular proliferation – one composed of small cells with no pigment while others are arranged in a glandular appearance with cuboidal cells and melanin pigment

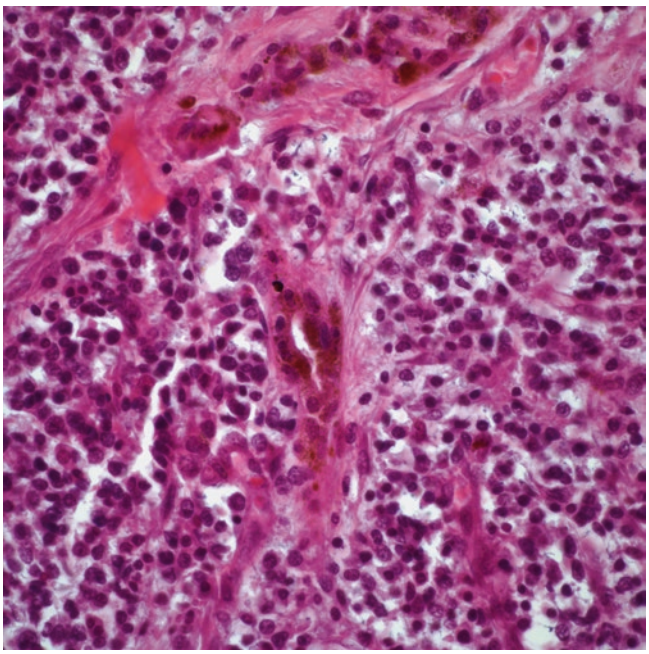

Fig. 11.92 High power view of a retinal anlage tumor showing small pigmented glands admixed with a cellular proliferation composed of small cells. Mitotic activity is not present

Ependymoma

The occurrence of these tumors in the mediastinal region is rare, but it has been well documented in the literature [151–153]. It is possible that Doglioni and coworkers [152] are the ones who first reported a primary ependymoma occurring in the mediastinal region. The authors reported a 51-year-old asymptomatic woman with a posterior mediastinal tumor. Thoracotomy was performed, and the tumor did not show any connection with nerve trunks. The patient died 4 months after surgical resection due to complications. The case described by Nobles and coworkers [151] was that of a 35-year-old woman who presented with chest pain, diaphoresis, and lightheadedness. The tumor was located in the posterior mediastinum with no continuity with the spinal canal. Surgical resection of the tumor was performed. The authors did not document specific follow-up for this patient. Wilson and Moran [153] reported three additional cases; the three patients were women between 36 and 71 years of age (mean age, 50 years). Clinically, the patients presented with nonspecific symptoms, and their tumors were located in the posterior mediastinum without any connection to the spinal canal. Surgical resection took place in all these patients. Interestingly, in one of the cases reported, lymph node metastasis was documented; however, after a follow-up (mean, 64 months), none of the patients had recurrence of disease or metastasis.

Based on the reported cases, it appears that these tumors have a predilection for the posterior mediastinum, in middle-aged women who may present with non-specific symptoms or asymptomatic. In addition, it appears that complete surgical resection is the best alternative for long-term survival despite the presence in some cases of lymph node metastasis.

Pathologic Features

Macroscopically, the tumors appear to range in size from 5 to 9 cm in greatest diameter. The tumors have been described as tan in color, solid but some have shown cystic changes. Areas of necrosis and/or hemorrhage may be seen.

Histologically, the tumors are characterized by the presence of a solid, uniform cellular proliferation with mild to moderate atypia. The neoplastic cells are round to oval with round nuclei and inconspicuous nucleoli, and stipple to vesicular chromatin. The cells may be arranged in interanastomosing ependymal tubules, presence of pseudorosettes, with true ependymal rosettes and canals with ciliated cells. In some areas, the tumor may show a pseudopapillary configuration with occasional psammoma bodies. Mitotic activity is variable and may range from one to five mitotic figures per high-power field. Areas of necrosis and/or hemorrhage may also be variable from focal to extensive (Figs. 11.93, 11.94, 11.95, 11.96, 11.97, 11.98, 11.99, 11.100, 11.101, and 11.102).

Immunohistochemical and Ultrastructural Features

Mediastinal ependymomas, like their counterpart in the central nervous system, will show similar immunophenotype. The tumors are positive for glial fibrillary acid protein (GFAP) while negative for S-100 protein, chromogranin, synaptophysin, and HMB-45. Some tumors may show focal weakly positive stain for keratin. Ultrastructurally, in the cases described by Wilson [153], the tumors showed the presence of multipart junctional complexes, intracytoplasmic lumina containing microvilli, and occasional apical cilia. Ciliary basal bodies were also present, while no neurosecretory granules or premelanosomes were identified.

Differential Diagnosis

The most important differential diagnosis is with metastatic ependymoma; however, in this setting a proper clinical history should lead to the correct interpretation. Once that is clear, the tumor may be confused with schwannoma, neuroendocrine carcinoma, or melanoma. In these cases, the use of immunohistochemical stains will be of aid as none of those tumors will show positive staining for GFAP, while some of these tumors will show positive staining for S-100 protein, epithelial, and/or neuroendocrine markers.

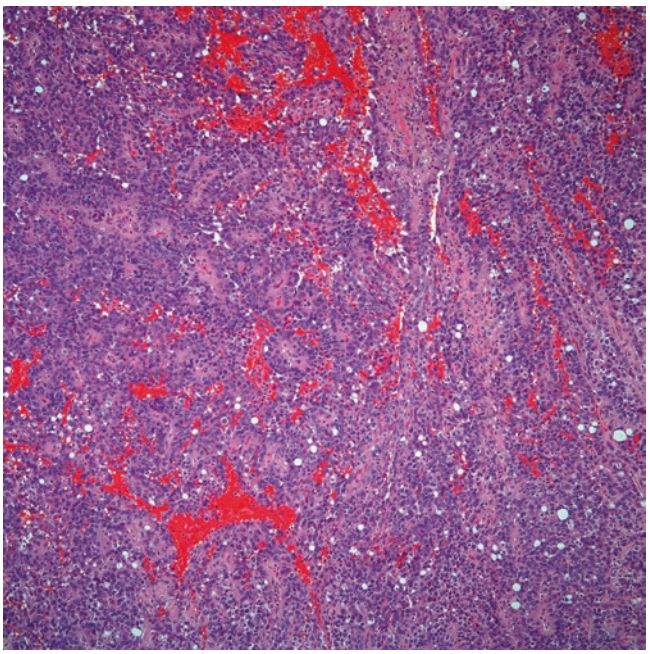

Fig. 11.93 Low power view of a mediastinal ependymoma showing a rather solid cellular proliferation with rosette formation

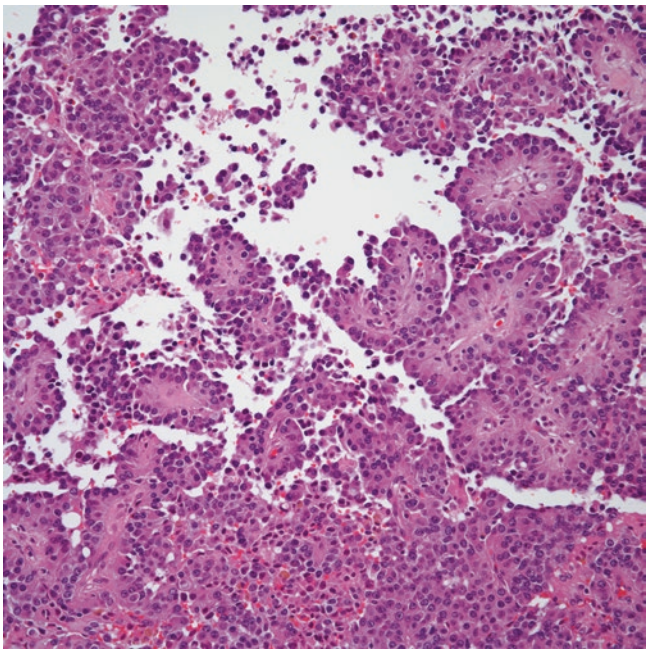

Fig. 11.95 Mediastinal ependymoma with prominent rosette formation giving the appearance of a papillary neoplasm

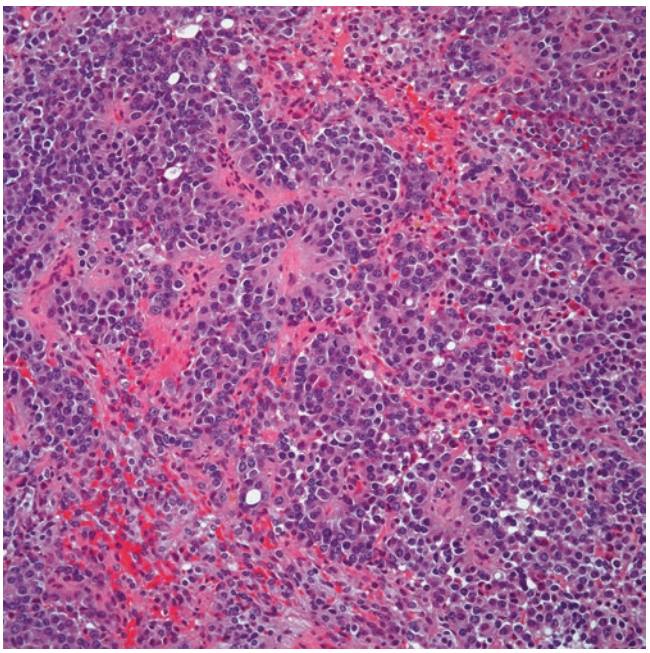

Fig. 11.94 Mediastinal ependymoma showing rosettes and pseudorosettes

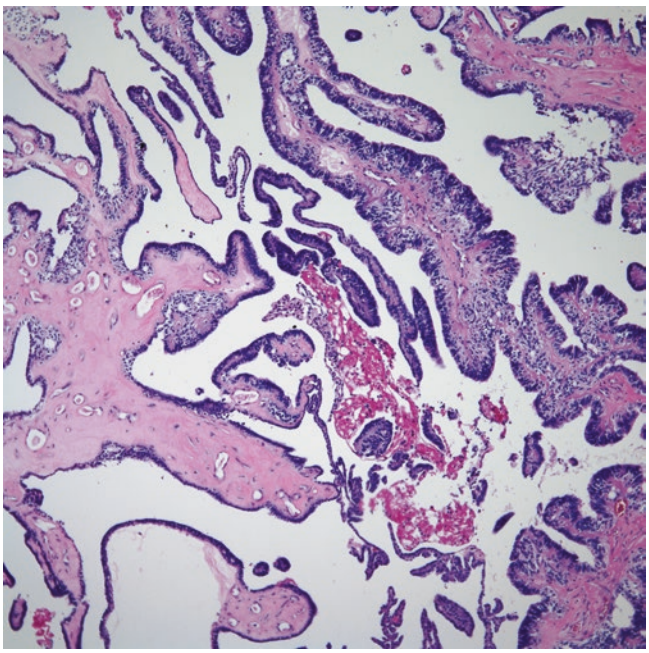

Fig. 11.96 Ependymoma with prominent papillary growth pattern

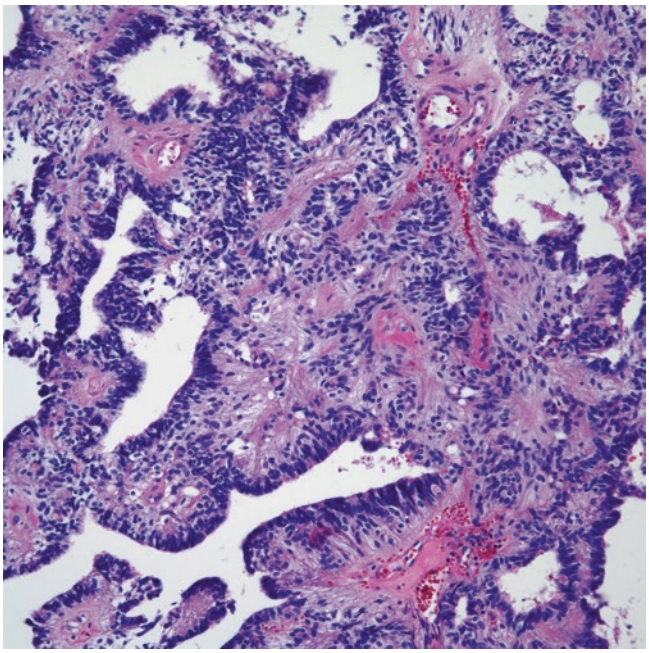

Fig. 11.97 Ependymoma with solid and papillary features

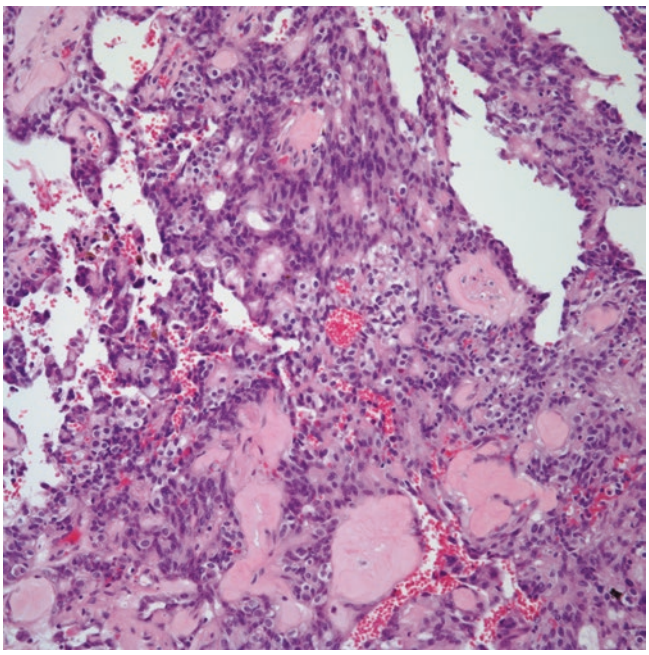

Fig. 11.99 Ependymoma with areas of hyalinization

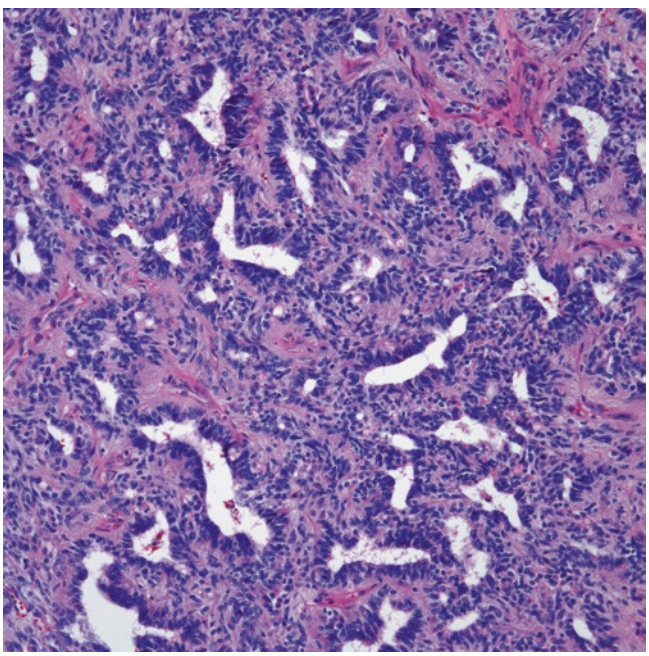

Fig. 11.98 Ependymoma with pseudo-glandular formation

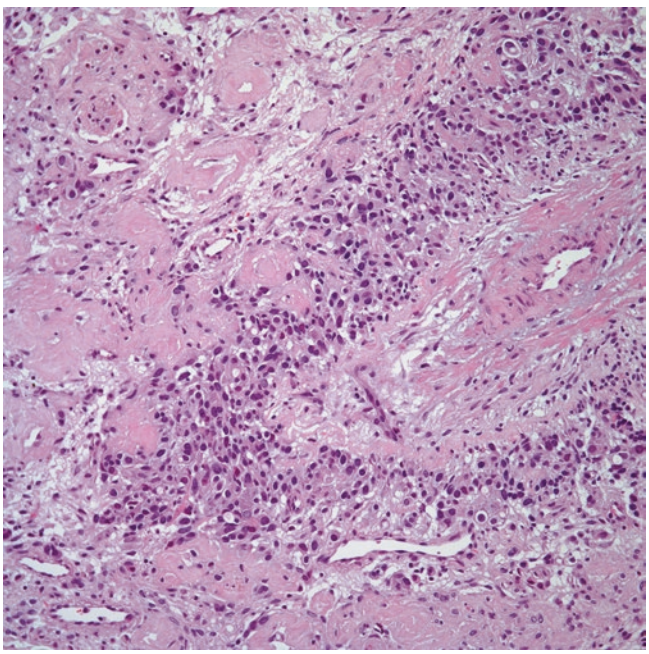

Fig. 11.100 Extensive hyalinization in blood vessels in a mediastinal ependymoma

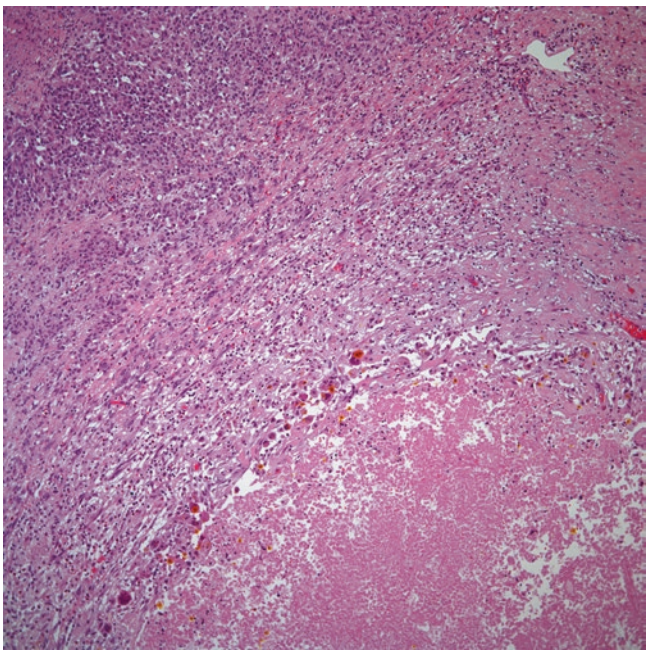

Fig. 11.101 Ependymoma with areas of necrosis

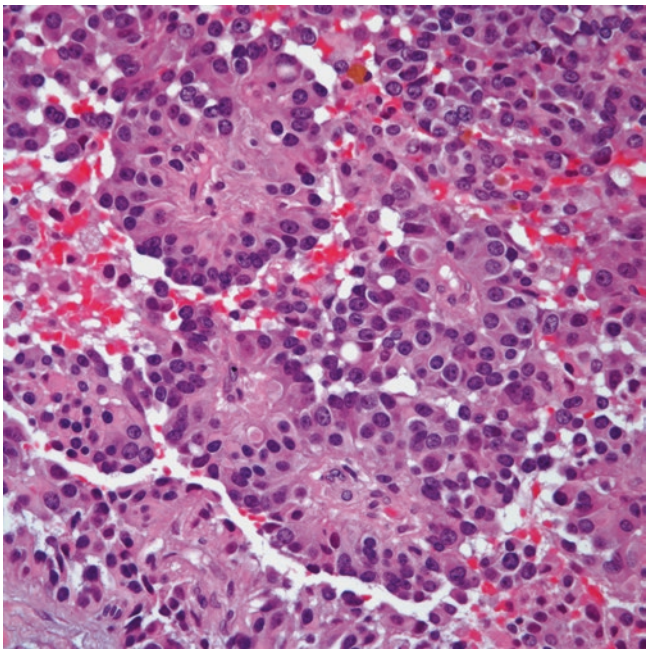

Fig. 11.102 High power magnification of a mediastinal ependymoma showing rosettes. Note the absence of mark cellular atypia or mitotic activity

Meningioma

This is another neural tumor of unusual occurrence in the mediastinal compartment, even though the knowledge of the occurrence of these tumors in the mediastinal compartment dates back more than 30 years. In 1979, Wilson and coworkers [154] reported a case in a patient with Horner's syndrome and absence of intracranial tumor. Since then, the tumor has been reported mainly as case reports [155–159]. Palimento and Picchio [155] reported a case in a 45-year-old woman who presented with spontaneous pneumothorax. A CT scan showed the presence of a left paravertebral mass. Surgical resection took place, and the patient was alive and well 1-month postsurgical resection. Interestingly, despite the description of increase mitotic activity, the diagnosis of malignant or atypical was not provided in this case. Yang and coworkers [157] reported a case of a 41-year-old woman who presented with chest distress and cough and, who on CT scan, showed the presence of an anterior mediastinal mass. Surgical resection of the mass was undertaken followed by radiation therapy. Follow-up after 7 months showed no evidence of tumor recurrence. Even though the authors labeled this tumor as "malignant meningioma" in which focal necrosis was described, the authors did not provide any histological description of mitotic activity. Mogi and coworkers [158] described an anterior mediastinal meningioma in a 64-year-old man who presented with thoracic pain. In this particular case, the tumor appeared to infiltrate lung parenchyma, and, histologically, the tumor showed focal necrosis and mitotic activity of four mitotic figures per 10 hpf. Based on the overall features of this neoplasm, the authors labeled the meningioma as "atypical." Follow-up provided showed the patients alive and well 12 months postsurgical resection. More recently, Lu and associates [159] described a posterior mediastinal meningioma in a 42-year-old man who presented with dysphagia. Surgical resection of the tumor was performed, and the histological description provided was that of a tumor without mitotic activity or necrosis. Follow-up provided stated that the patient was without evidence of recurrence of metastatic disease 24 months postsurgical resection.

Based on the cases reported, it appears that mediastinal meningiomas are tumors that may occur in the anterior or posterior mediastinum. The tumors described have been in adult individuals with diverse symptomatology. Histologically, the tumors may range from the conventional meningioma to the atypical or malignant tumor. Surgical resection appears to be the treatment of choice for these tumors, and, even though the follow-up in the cases described was not long enough, well-documented metastatic disease has not been reported.

Pathological Features

Macroscopically, the tumor may reach a size of more than 10 cm in greatest dimension and infiltrate adjacent organs. The tumor is solid, tan to yellowish with a homogeneous surface. Areas of necrosis and/or hemorrhage may be present.

Histologically, similar to its counterparts in the CNS, the tumor may show the conventional features of epithelioid or spindle cell proliferation; in some cases, one can observe both of these components. In tumors in which the predominant cells are the epithelioid-like cellular proliferation, the tumor is arranged in whorls with scattered presence of

psammoma bodies. In focal areas, the tumor may show the presence of foamy macrophages entrapped within the neoplastic cells. When the tumor is composed of spindle cells, the growth pattern may mimic other spindle cell neoplasms. The tumor is arranged in a subtle storiform growth pattern in which the spindle cell bundles are separated by thin fibrocollagenous material with ectatic hyalinized blood vessels. Even in tumors which are predominantly spindle, there may be focal areas in which the tumor shows round cells and focal calcifications (Figs. 11.103, 11.104, 11.105, 11.106, 11.107, and 11.108). In general, conventional meningiomas do not show mitotic activity, necrosis, or hemorrhage. The presence of any necrosis and mitotic activity are features to upgrade the tumor to an atypical or malignant meningioma (Figs. 11.109, 11.110, and 11.111).

Immunohistochemical and Molecular Features

The immunohistochemical features of mediastinal meningiomas are similar to those described for CNS meningiomas or pulmonary meningiomas. Essentially, the tumor may show positive staining for EMA and vimentin. In some cases, CD34 and keratin have been reported to show positive staining in tumor cells. In addition, some tumor may also show positive staining for estrogen receptors. However, in general, the tumor is negative for keratin 5/6, STAT6, P40, P63, and other muscle and vascular markers. Recently, a study of pleuropulmonary meningiomas comparing to those of the CNS, suggested a common histogenesis for these tumors, as some of these tumors show loss of the NF2 gene on chromosome 22 [160]. Such findings suggest that all these tumors arise from the same precursor cell. Even though mediastinal meningiomas have not been investigated for the loss of the NF2 gene, it is possible that the findings would be similar, thus providing further explanation for the occurrence of these tumors in the thoracic cavity.

Differential Diagnosis

By far the most important interpretation would be that of a primary versus a metastatic meningioma. In this setting, obtaining an unequivocal history of previous CNS tumor is highly important in order to arrive at a more definitive interpretation. Other tumors that enter in the differential diagnosis of meningiomas would depend not only on the histology of the tumor but also on the location of the tumor. For instance, tumors that occur in the anterior mediastinum may be easily confused with thymoma. Thymomas are well-known neoplasms that show high versatility in tumor growth and pattern, and some thymomas may show areas that can easily mimic the transitional meningioma, while some tumors showing spindle cells and desmoplastic features may be confused with spindle cell meningiomas. However, if thymoma is a consideration, the use of immunohistochemical stains may aid, as it is known that thymomas are generally negative for EMA and positive for keratin 5/6. Another tumor that may enter in the differential diagnosis, mainly in tumors composed of epithelioid cells (transitional meningiomas), would be a neuroendocrine carcinoma (carcinoid tumor). In this setting, once again the use of immunohistochemical stains such as keratin and neuroendocrine markers should lead to the correct interpretation. Tumors composed of spindle cells, whether in the anterior or posterior mediastinum, can mimic solitary fibrous tumor. In this setting, the use of STAT6 should lead to the correct interpretation.

Malignant Granular Tumor

This tumor is of unusual occurrence in the mediastinum; however, it has been reported [161–164]. Interestingly, the majority of reported cases have been in adult individuals and in the posterior mediastinum. Clinically, the patients reported have either been asymptomatic or with non-specific symptoms, and their tumor has been found during radiographic studies. It appears that surgical resection has been performed in those cases reported, and, in at least one, patient recurrence and death were documented, while in a different patient metastatic disease to the liver was documented. It is likely that these tumors in the mediastinal locations may follow the same clinical behavior as those malignant granular cell tumors of the soft tissues.

Pathological Features

Macroscopically, these tumors have been reported to reach more than 10 cm in greatest dimension. They are tan to yellow in color, solid, and necrosis may or may not be present.

Histologically, the tumor shows a malignant cellular proliferation composed of large cells with ample granular eosinophilic cytoplasm, round nuclei, and prominent nucleoli. Cellular pleomorphism and mitotic activity are easily identifiable, while areas of necrosis may be variable from focal to extensive areas. The neoplastic cellular proliferation is arranged in sheets of cells without any particular growth pattern (Figs. 11.112, 11.113, 11.114, and 11.115).

Immunohistochemical Features

Malignant granular cell tumors are essentially positive for S-100 protein and NSE. Other immunohistochemical stains that have shown positive staining in tumor cells include CD56 and Vimentin. However, the tumor is negative for muscle markers including desmin, caldesmon, MyoD, myoglobin, and smooth muscle actin. In addition, epithelial markers such as keratin and EMA are negative in these tumors. The tumor is negative for HMB45 and Melan A.

Differential Diagnosis

The differential diagnosis of malignant granular cell tumor may encompass different tumors of different histogenesis,

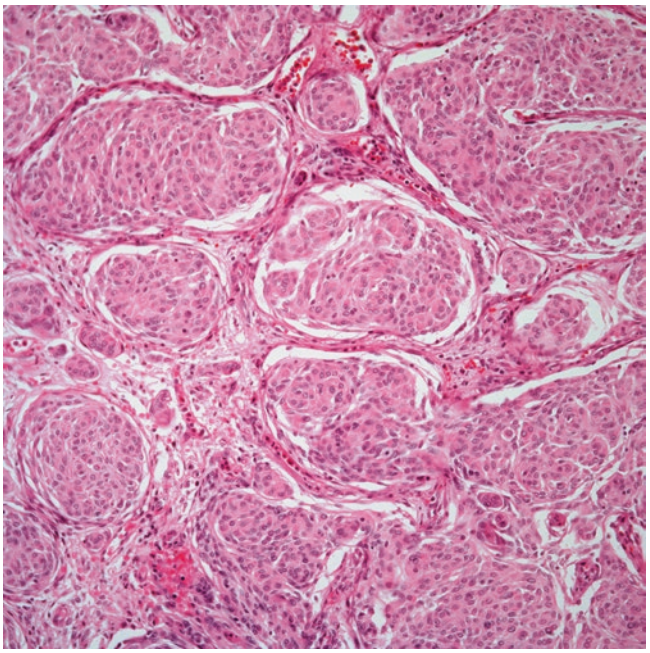

Fig. 11.103 Low power view of a mediastinal meningioma showing the classic whorling pattern

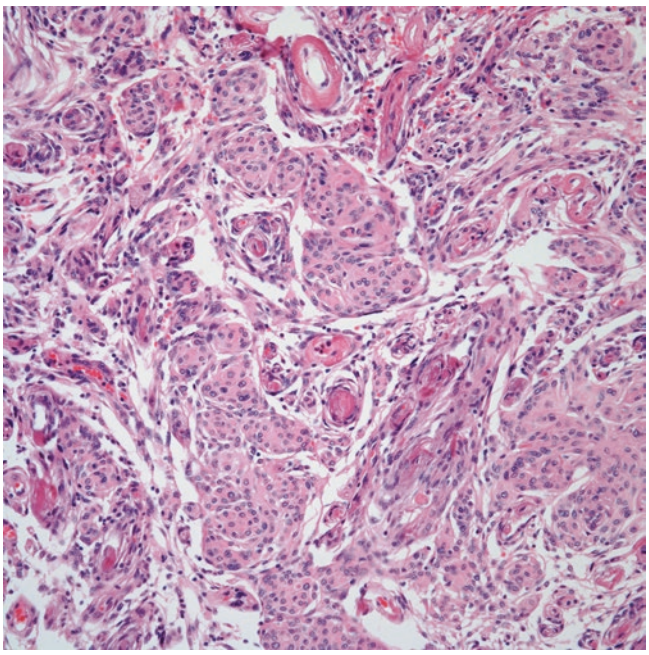

Fig. 11.105 Mediastinal meningioma showing numerous hyalinized ectatic vessels

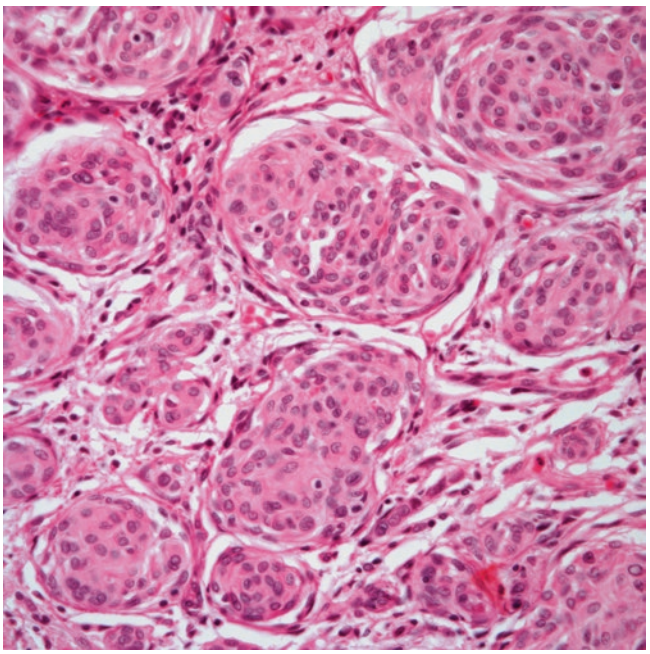

Fig. 11.104 Closer view showing whorls of cells arranged in small nests and separated by thin fibroconnective tissue. No mitotic activity is present

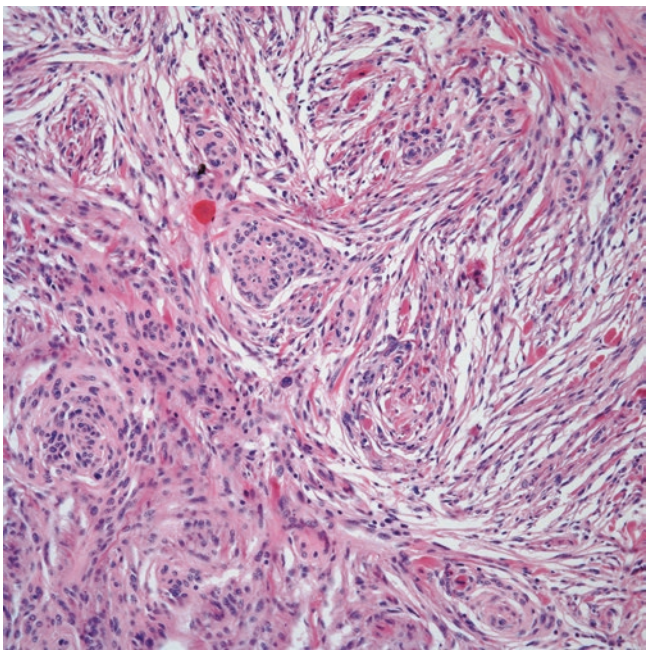

Fig. 11.106 Meningioma with features of both transitional (epithelioid cells) and fibroblastic (spindle cells)

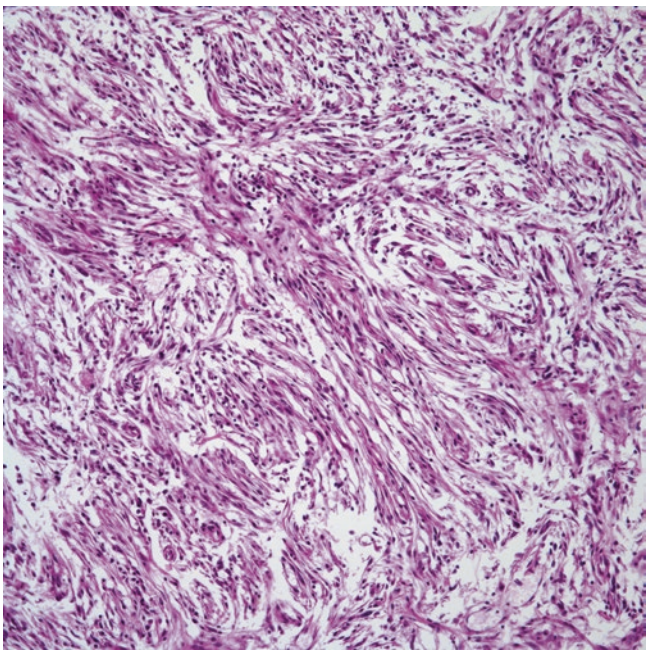

Fig. 11.107 Predominantly fibroblastic meningioma composed of fascicles of spindle cells

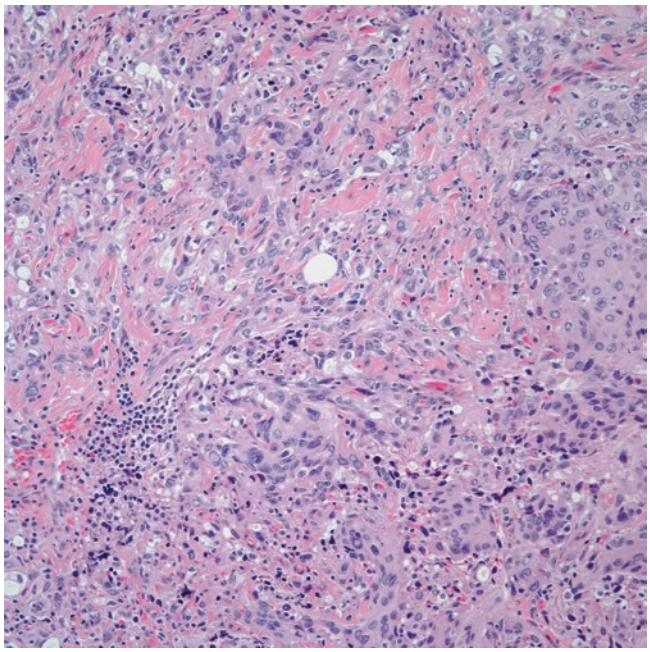

Fig. 11.109 Malignant meningioma showing nuclear atypia

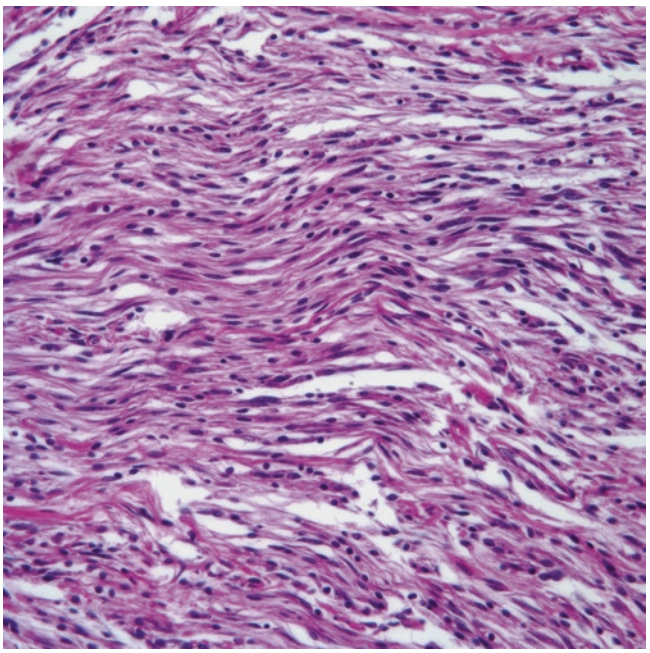

Fig. 11.108 Higher magnification of a fibroblastic meningioma showing spindle cells with lack of nuclear atypia or mitotic activity

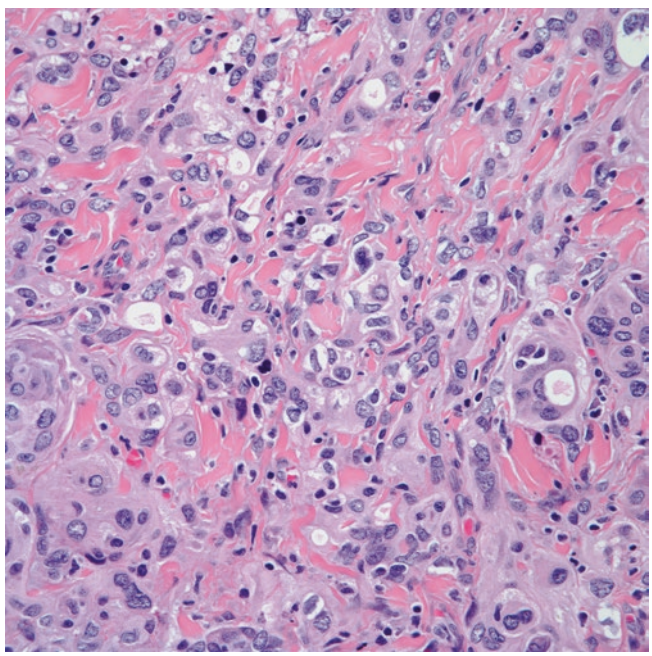

Fig. 11.110 Malignant meningioma showing mitotic activity

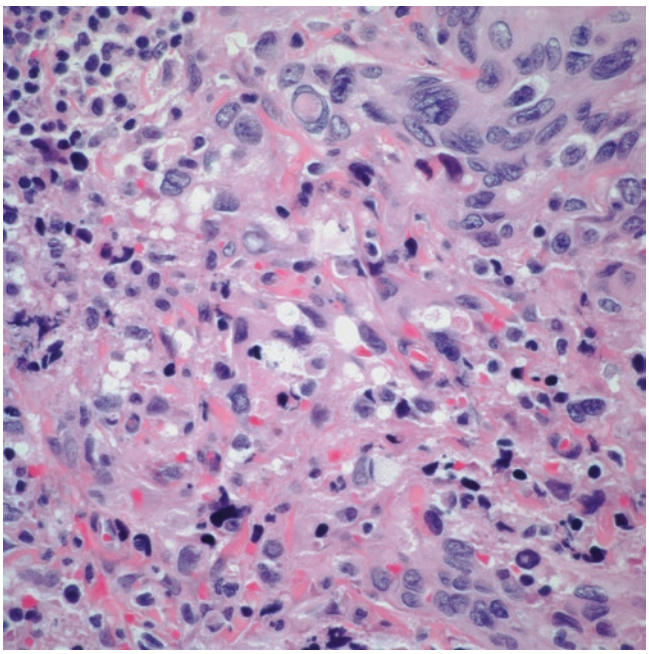

Fig. 11.111 Nuclear atypia with intranuclear inclusion and mitotic activity in a malignant meningioma

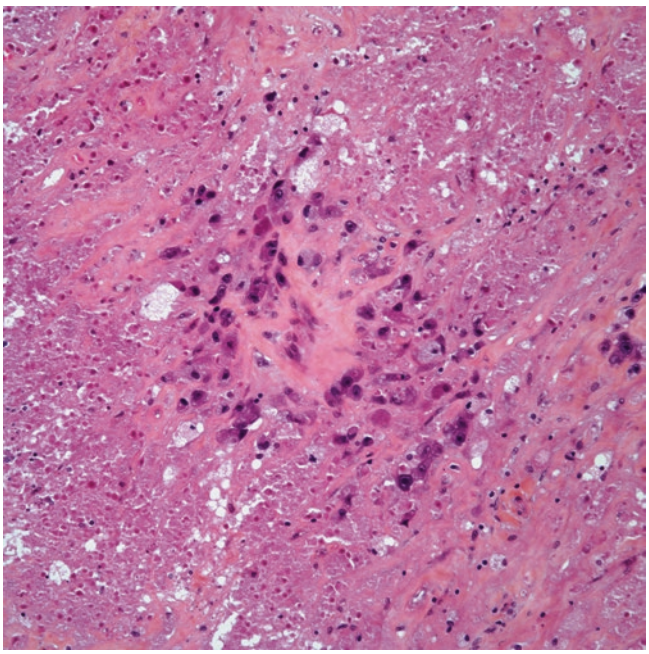

Fig. 11.113 Extensive areas of necrosis with only focal areas of viable tumor in malignant granular cell tumor

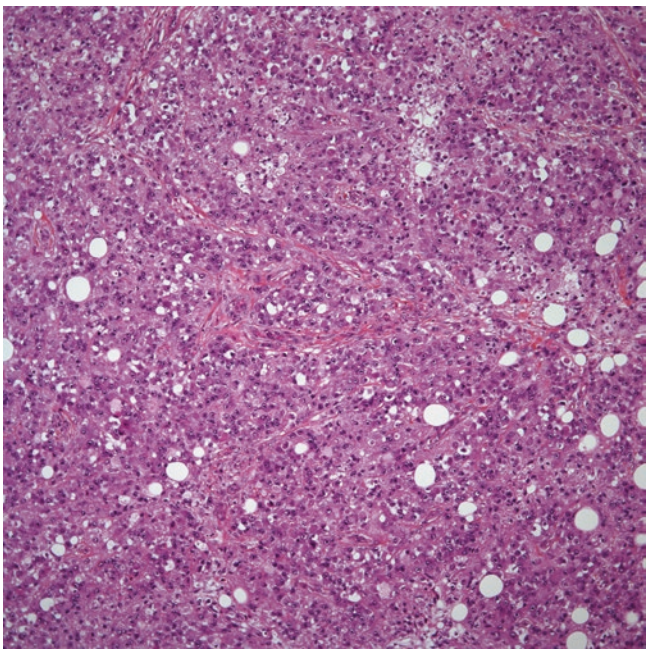

Fig. 11.112 Malignant granular cell tumor showing sheets of malignant cells

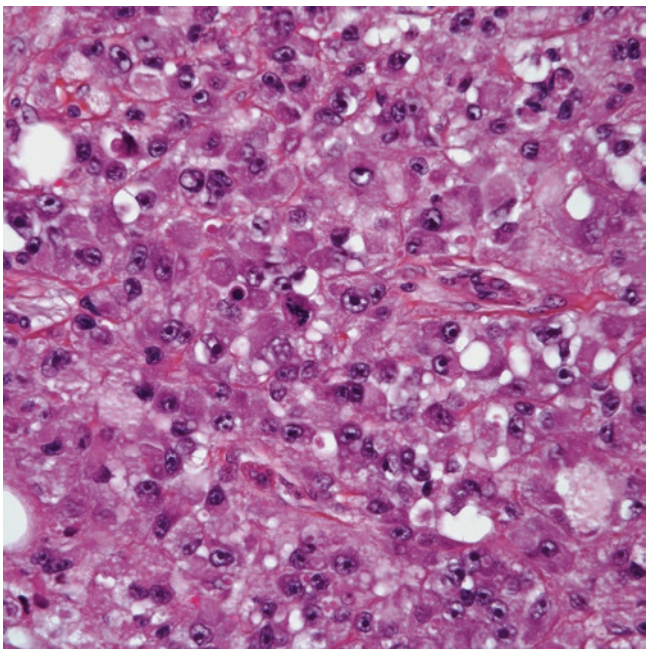

Fig. 11.114 Nuclear atypia and mitotic activity in malignant granular cell tumor

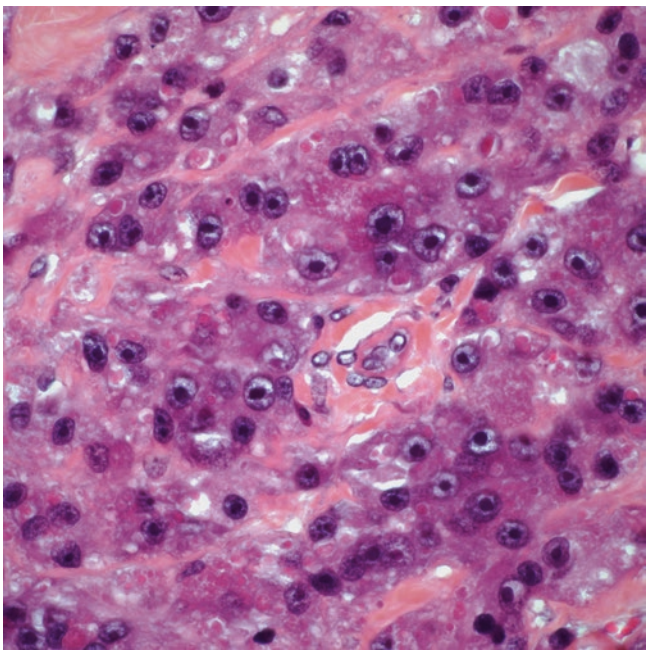

Fig. 11.115 High power view of a malignant granular cell tumor showing cells with granular eosinophilic cytoplasm, round to oval nuclei, and prominent nucleoli

mainly when the tumor occurs in the mediastinal region. Poorly differentiated carcinoma and melanoma would be the leading differential diagnosis. In the former, the negative staining in tumor cells for epithelial markers such as keratins or EMA should alert against that possibility. In the setting of melanoma, the issue may be more challenging, as both tumors will show positive staining for S-100 protein. Granular cell tumor would show negative staining for HMB-45 and Melan A. In addition, negative clinical history of previous cutaneous melanoma and the characteristic cellular features of the tumor, mainly the presence of abundant granular cytoplasm, would be helpful. Ultimately, the ultrastructural features of both tumors are different, and the presence or absence of pre-melanosomes should lead to the correct interpretation.

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