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Neuroendocrine Neoplasms

9

Introduction

Primary mediastinal neuroendocrine neoplasms as they are referred to in this chapter encompass several tumors that do not necessarily share the same histogenesis, biologic behavior, or treatment modalities. In addition, some of these tumors may in turn occur as ectopically placed tissues that may be deposited in the mediastinal compartment. In some of these cases, the embryologic development may be the clue to their occurrence. Nevertheless, this group of tumors ranges from benign tumors to the overtly high-grade malignant tumors. Basically, the group of tumors that more often present as mediastinal tumors are:

- Neuroendocrine carcinomas:
  - Well-differentiated neuroendocrine carcinoma (carcinoid tumor)
  - Moderately differentiated neuroendocrine carcinoma (atypical carcinoid)
  - Poorly differentiated neuroendocrine carcinoma (small cell carcinoma and large cell neuroendocrine carcinoma)
- Paragangliomas
- Parathyroid tumors:
  - Parathyroid adenoma
  - Parathyroid carcinoma
- Thyroid tumors:
  - Intrathoracic goiter
  - Thyroid carcinoma

In practice, these tumors represent only a small percentage of the mediastinal tumors and may account for no more than 10% of primary mediastinal neoplasms. Mediastinal neuroendocrine carcinomas are by far the most common tumors in this family of neoplasms and the ones that deserve special attention as these tumors may follow a more aggressive course.

In general, previously published series of mediastinal tumors do not account for much of the occurrence of neuroendocrine tumors. In 1968, Oldham and colleagues [1] reported 164 cases of mediastinal tumors and cysts without documenting any neuroendocrine carcinoma (carcinoid tumor) and thyroid or parathyroid tumors. In 1971, Wychulis and colleagues [2] documented a 40-year experience by describing 1029 mediastinal tumors, which encompassed the years 1929–1968. The authors documented 56 cases of intrathoracic goiter but no parathyroid tumors or neuroendocrine carcinomas (carcinoid tumor). Interestingly, more recent reports of mediastinal tumors in general have not been able to document a considerable number of cases of neuroendocrine tumors. Blegvad and colleagues [3], in a report of 129 mediastinal tumors, were able to document only 2 cases of neuroendocrine carcinomas, 1 paraganglioma, and 31 intrathoracic goiters. Important to mention is the fact that cases of carcinoma arising in intrathoracic goiters have been described [4]. Adkins and colleagues [5] also presented similar experience documenting 38 cases of mediastinal tumors, encountering only 2 patients with "carcinoid" tumors of thymic origin. However, in general terms, these reports clearly point out that, in general practice, the presence of neuroendocrine tumors, whether they are carcinomas, paragangliomas, or parathyroid tumors, is rare.

Neuroendocrine Carcinomas

Although there is general agreement that the credit for the recognition of neuroendocrine carcinomas (carcinoid tumors) in the mediastinum should be given to Rosai and Higa [6], who in 1972 described eight of these tumors in the mediastinum, it is also important to highlight that in 1963, Pachter and Lattes [7], in a description of uncommon mediastinal tumors, also described four cases, one of which was what the authors called "mediastinal bronchial-type" adenoma, clearly alluding to similar tumors that have already been described in the bronchus, and which at that time were coded as "adenomas," currently regarded as well-differentiated neuroendocrine carcinomas (carcinoid tumor).

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Since Rosai and Higa's [6] description, several reviews and reports on the subject have been presented [8–12]. Some of these reports have been on the histopathologic spectrum, while others have been on the classification of these tumors. However, in most of the series presented, it appears that when these tumors are in the mediastinal compartment, they may show a more aggressive course.

Needless to say, mediastinal neuroendocrine neoplasms, namely, neuroendocrine carcinomas, just like their counterparts in other anatomic areas continue to be the subject of study, controversy, and further analysis.

Clinical Features

The spectrum of clinical syndromes or conditions that have been associated with neuroendocrine carcinomas (carcinoid tumors) is extensive. Conditions such as Cushing's syndrome, polyarthropathy, proximal myopathy, peripheral neuropathy, hyperparathyroidism, Eaton-Lambert syndrome, hypertrophic osteoarthropathy, parathyroid adenoma, cutaneous hyperpigmentation, pericarditis, secretion of ACTH, ADH, parathormone, calcitonin, beta-lipoprotein, serotonin, and multiple endocrine neoplasia (MEN) type I and II [13–34] are among the most commonly reported associations. It has been estimated that about half of all neuroendocrine carcinomas of the thymus are functionally active or associated with MEN syndrome. It is important to highlight that there is not a strong association between thymic neuroendocrine carcinomas and myasthenia gravis or carcinoid syndrome. However, of all previous associations between neuroendocrine carcinomas and other syndromes, it appears that the most important one or at least the most consistent one is the association with MEN syndrome, which in turn may also play a role in the outcome of these patients.

Multiple endocrine neoplasia, type I, or Wermer's syndrome is an autosomal dominant disease that is characterized by the presence of neoplasms that commonly involve parathyroid, pancreas, and pituitary. However, other anatomic structures such as thyroid and adrenal gland may also be involved. In these patients, common manifestations would include hyperparathyroidism or the presence of Zollinger-Ellison syndrome. Rosai and colleagues [13] are also credited for highlighting the association of thymic neuroendocrine carcinomas with multiple endocrine adenomatosis (MEA) after describing three adult patients with such association. The three patients followed a fatal course. In one patient, surgical exploration of the neck revealed the presence of chief cell hyperplasia in three parathyroid glands. At autopsy, adenomatous changes involving pancreas, thyroid, and adrenal were identified. In a second patient, pituitary and parathyroid adenomas were the anatomic structures involved, while in the third patient, symptoms of hyperparathyroidism were identified. Based on the illustrations provided in that report, it is possible that all three mediastinal tumors correspond to what is today considered a moderately differentiated neuroendocrine carcinoma (atypical carcinoid). Interestingly, Rosai and colleagues [13] alluded to the presence of MEN in several cases prior to their report. However, the pathology of the mediastinal lesions is unclear in those cases as they were coded by different names. Nevertheless, it is possible that, using today's nomenclature, some of those lesions may fall into what is known now as neuroendocrine carcinoma, well or moderately differentiated (carcinoid and atypical carcinoid). Important to note is the possible familial occurrence of multiple endocrine adenomatosis or MEN. Manes and Taylor [14] documented a familial case in which parathyroid hyperplasia was the salient feature and in which one member of the family had simultaneous occurrence of parathyroid hyperplasia and thymic neuroendocrine carcinoma. The histology of the thymic tumor appears to have been of the well-differentiated type, with spindle cell morphology. Although MEN type I appears to be more commonly associated with thymic neuroendocrine carcinomas, Marchevsky and Dikman [16] documented a case of a 60-year-old woman with thymic neuroendocrine carcinoma associated with parathyroid hyperplasia, medullary carcinoma of the thyroid, and adrenal neuroma, which the authors interpreted as an incomplete Sipple's syndrome or MEN type II. Based on the illustrations provided of the thymic tumor, it appears to have been of the well-differentiated type (carcinoid tumor). In a separate study analyzing patients diagnosed with MEN type I, Teh and colleagues [35] found 204 patients from 9 Australian and Malaysian MEN type I families. Of those, ten patients had an anterior mediastinal lesion from six unrelated kindreds. Interestingly, in all kindreds, linkage analysis was performed confirming linkage to the MEN type I locus in chromosome 11q13.

Unfortunately, there are not enough series of cases of thymic neuroendocrine carcinomas from where to draw extensive experience. In 1984, Wick and Scheithauer [36] reported a series of 12 patients with thymic neuroendocrine carcinomas in which the patients' ages ranged from 28 to 78 years; 11 patients were men, and 5 of these patients had an associated endocrinopathy. In a previous report, Wick and colleagues [37] had reported seven patients with thymic neuroendocrine carcinomas occurring in five men and two women between the ages of 27 and 67 years. In this group of patients, one patient had an islet cell carcinoma of the pancreas and one other patient had parathyroid hyperplasia. Also in 1996, de Montpreville and colleagues [38] reported patients with thymic neuroendocrine carcinomas occurring in 11 men and 3 women between the ages of 35 and 71 years. Interestingly, in this group of patients, one patient had an associated endocrinopathy, one patient had von Reckinghausen disease, and one other patient had severe

psychosis. Similarly, Economopoulos and colleagues [39] reported seven patients with thymic neuroendocrine carcinoma in which none of the patients had an associated endocrinopathy, and the majority of the patients were men (six patients) with ages ranging between 36 and 70 years. In a more exhausting review of mediastinal tumors, Wang and coworkers [40] encountered eight cases of thymic neuroendocrine carcinomas out of 162 patients. In this group, six patients were men and two were women between the ages of 32 and 68 years. Interestingly, only two patients had an associated Cushing's syndrome. More recently, Cardillo and coworkers [41] collected 19 patients with primary neuroendocrine tumors of the thymus over a period of 24 years, with similar demographic features as those previously described in terms of gender and age distribution. Nine of the 19 patients had an associated paraneoplastic syndrome, which was not further specified. Furthermore, Cardillo and coworkers [42] reported their experience with 35 cases accumulated from 5 different institutions. In this particular group of patients, 14 patients had an associated paraneoplastic syndrome. Neary and coworkers [43], in a more direct approach to the association of paraneoplastic syndromes associated with neuroendocrine thymic tumors, reported 12 patients with ACTH-producing thymic tumors. The patients' ages varied from 7 to 51 years (4 patients were children), and 11 of these patients presented with classic Cushing's syndrome at a median age of 21 years. The authors concluded that thymic ACTH-producing neuroendocrine tumor is an aggressive disease, particularly in young patients.

In our experience with 80 cases [44] that we had the opportunity to evaluate, we encountered that the tumor appears to be more common in men in a proportion of approximately 2:1; the age in these patients can be wide, ranging from as young as 16 years to older patients over 90 years of age, with a mean age of 58 years. Most of the tumors, however, appear to be more common in the sixth decade of life among men and in the fourth decade of life for women. Even though in about 28% of the patients the mediastinal mass was found during a routine chest radiograph, about 22% of these patients had an associated endocrinopathy, which included 6% of patients in whom Cushing's syndrome was determined to be associated with the tumor at the time of diagnosis. In addition, another 26% of patients presented with various symptoms, which include chest pain, weight loss, shortness of breath, and superior vena cava syndrome. Interestingly, when compared the age distribution between men and women, there appears to be a slight difference in the appearance of the tumor at certain age. For instance, the tumor appears to be more common in younger women in their 30s, while the tumor in men appears to be more common in their 50s. These demographic and clinical findings are depicted in Figs. 9.1, 9.2, 9.3, and 9.4.

One important issue that needs highlighting is the importance of assessing these neoplasms for what they represent, which essentially is a low- or intermediate-grade carcinoma. For instance, in the report of eight "atypical carcinoid tumors of the thymus" by Valli and coworkers [45], the authors encountered that in four cases in which

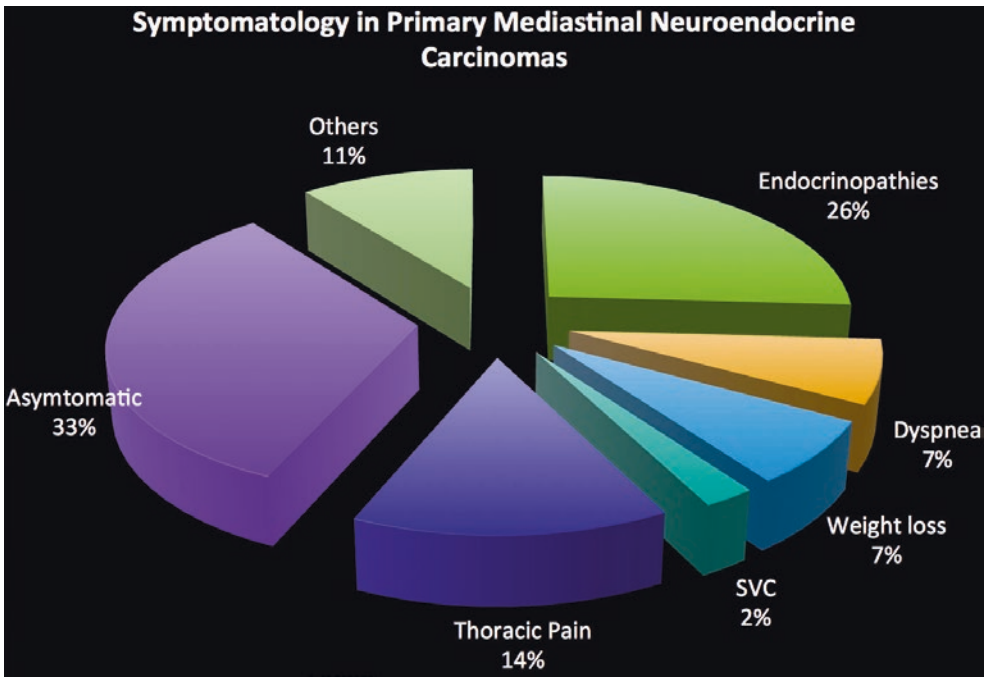


Fig. 9.1 Clinical symptomatology of patients with thymic neuroendocrine carcinomas

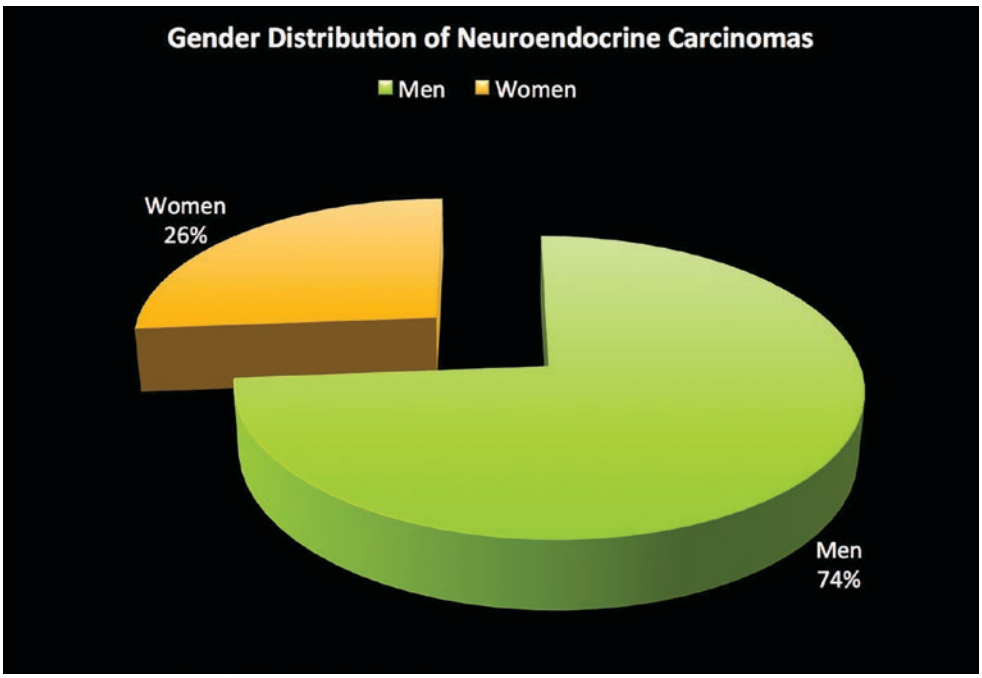


Fig. 9.2 Gender distribution of thymic neuroendocrine carcinomas

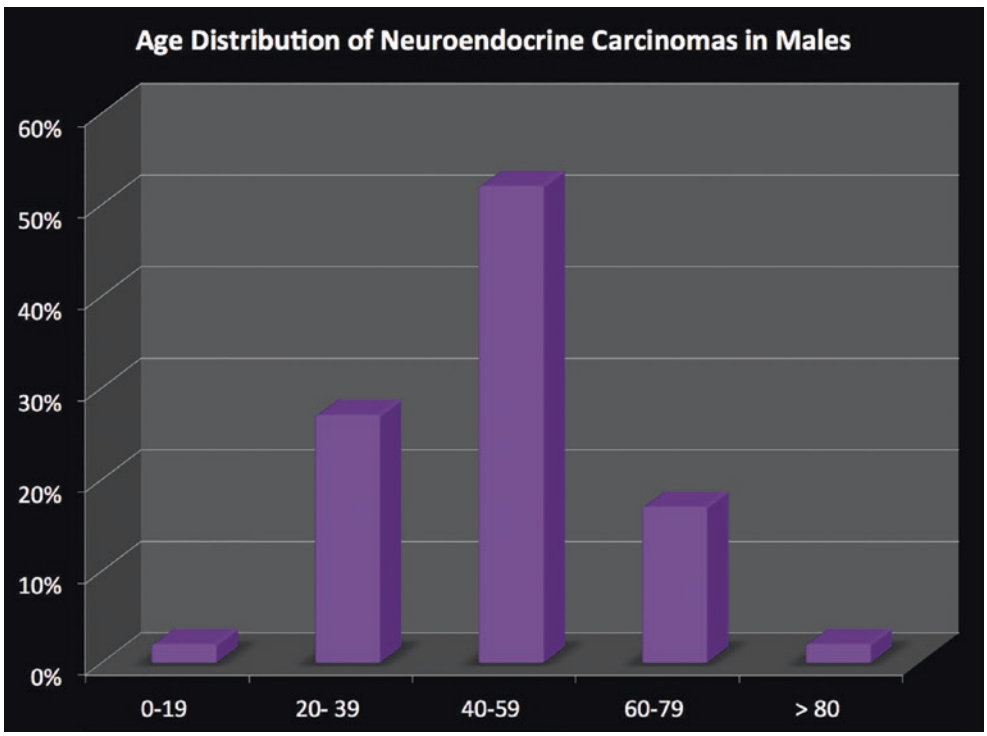


Fig. 9.3 Age distribution of thymic neuroendocrine carcinomas in men

they have follow-up information, even though the authors used the Masaoka staging schema of thymoma, which is clearly inappropriate for these tumors, recurrence and metastatic disease were documented, and three of these four patients died with widespread metastatic disease. In the 19 cases reported by Cardillo and coworkers [41], even though, once again, using an inappropriate schema for staging, the authors stated that the prognosis of these

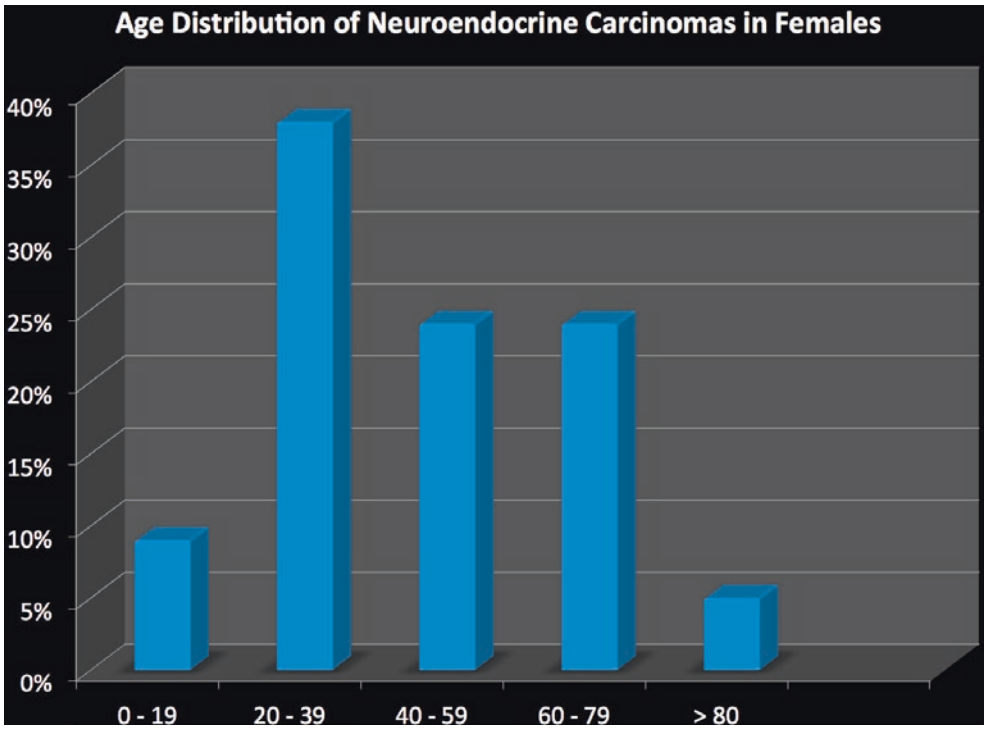


Fig. 9.4 Age distribution of thymic neuroendocrine carcinomas in women

tumors is related to grading, presence of paraneoplastic syndromes, and staging. The same authors [42] in a multicenter experience with 35 cases concluded that size (>7 cm) and proliferation index (ki-67 > 10%) are statistically significant and added a similar statement as in their manuscript with 19 cases that histology, paraneoplastic syndrome, staging, evidence of metastatic disease, and postoperative radiotherapy also impact prognosis. De Montpreville and coworkers [38], in their report of 14 cases, concluded that these tumors should be considered thymic neuroendocrine carcinomas because of their malignant behavior and added that complete surgical resection offers the best hope for a long-term survival. In our experience with 80 cases, we observed after a mean follow-up of 8.6 years that the overall survival for these patients was 28% at 5 years and 10% at 10 years. When further analyzed by histologic grading of the tumor, 32% of patients with low-grade carcinomas (carcinoid tumor) died of tumor, while 48% of patients with intermediate-grade carcinoma (atypical carcinoid) died of tumor in a period of time up to 11 years. In addition, 90% of patients with high-grade carcinoma died of tumor in a period of time up to 7 years. Recurrences were documented in 18 of the 80 patients studied as was metastatic disease to lymph nodes, lungs, bone, chest wall, and liver. Based on the above experience and with the perspective offered by others, it is difficult to argue against the preferred and more accurate terminology of thymic neuroendocrine carcinoma, rather than the ambiguous terminology of neuroendocrine tumor.

Classification

Although the classification of neuroendocrine carcinomas of the thymus appears to be similar to that of lung in terms of names or designations to the different categories of these tumors, there are important subtleties that are important to keep in mind as the criteria for diagnosis of each one of the specific categories of these tumors in the thymus are somewhat different from those in the lung. Interestingly, in the WHO publication of 1999 on the histological typing of tumors of the thymus [46], despite the fact that in a more forward vision of these tumors in the thymus the authors incorporated in parenthesis the term "carcinoma," the definition regarding mitotic activity in the "carcinoid tumor" or well-differentiated neuroendocrine carcinoma was that "mitotic activity is low and necrosis is scanty or absent." However, when the definition of "atypical carcinoid" was presented, not only was the definition regarding the mitotic count stated as "$2 \times 10/2mm^2$," but the designation of carcinoma was also missing, therefore, leading to argue the following: what is the meaning of "mitotic activity low"? In reality, there is only one digit smaller than 2 and that is 1 (of course the absence of value will be 0), but even riskier is the fact that the author left the interpretation of well-differentiated neuroendocrine carcinoma for both low-grade and intermediate-grade tumors. In addition, it is stated that the proportion of "atypical carcinoids" is higher than that of pulmonary carcinoids. That may also be another inaccuracy, as when seen in larger numbers as in the series

presented with 80 cases [44], the proportion of low-grade tumors against intermediate-grade tumors (carcinoid versus atypical carcinoid) were not even in a proportion of 2:1. Those numbers are depicted in Fig. 9.5. Such an assessment clearly underrepresents the true nature of these neoplasms and leads to erroneous interpretations and possible treatment options. Unfortunately, such assessment without further analysis was also repeated in the 2004 WHO publication [47] in which these tumors (low and intermediate) were under the designation of "well-differentiated neuroendocrine carcinomas." One would argue that, after such a misrepresentation, the new version of the WHO 2015 [48] would shed more light into the spectrum of two important and yet prognostically different neoplasms. However, in the new version of the WHO 2015 [48], these neoplasms are presented under the heading of thymic neuroendocrine tumors (carcinoid and atypical carcinoid), and it is stated that terms such as well-differentiated neuroendocrine carcinoma are not recommended. Here, it is important to highlight key issues regarding that warning. Indeed, the use of the term well-differentiated neuroendocrine carcinoma should be abandoned when it implies that it represents two different neoplasms, carcinoid and atypical carcinoid; however, it is unclear whether the authors of the WHO meant not to use the term "carcinoma" at all, which would be very much a contradiction to almost everything that has been recorded in more recent literature. Needless to say, such preferential organization was made without conducting a specific clinicopathological study of their own nor citing a specific publication dealing with that specific categorization of tumors. Furthermore, the WHO authors state that the mitotic activity for the low-grade tumor (carcinoid tumor) should be of <2 per 2 mm^2, basically promoting the same criteria that have been put forward with similar tumors in the lung. Regarding that particular topic, the mitotic count issue of low-grade carcinomas (carcinoid tumor) of the lung has been questioned more recently. Tsuta and coworkers [49], in a study of low- and intermediate-grade neuroendocrine carcinomas of the lung (carcinoid and atypical carcinoid) specifically on the issue of mitotic count, analyzed 80 patients and counted mitotic figures using different modalities, which included random count, hot spot count, and the evaluation of the whole section; however, more important was the demonstration that the mitotic count of fewer than 2 mitotic figures per 10 high-power fields is likely incorrect, as it does not provide any meaningful or statistically significant survival prognosis for patients with these tumors. As a matter of fact, when each case was individualized to correlate mitotic count with the 5-year RFS (recurrence-free survival), the results were 0 mitosis, 95.1%; 1 mitosis, 87.5%; 2 mitosis, 75%; and 3 mitosis, 100%. Therefore, the authors had to reset to 3 mitotic figures per 10 high-power fields for the low-grade tumors while 4 to 10 mitotic figures for the intermediate-grade carcinomas. Once these cutoffs were reset, the results clearly show a difference for the 5-year RFS of 93.1% and 0%, respectively (p = 0.002). In addition, when the count was on hot spots, the 5-year RFS for tumors with 0–1 mitosis × 10 hpf, 2–10 mitosis × 10 hpf, and more than 11 mitosis × 10 hpf were 95.5%, 94.6%, and 75.2%, respectively. Furthermore, when each case was individualized and correlated with mitotic counts, the 5-year RFS showed 0 mito-

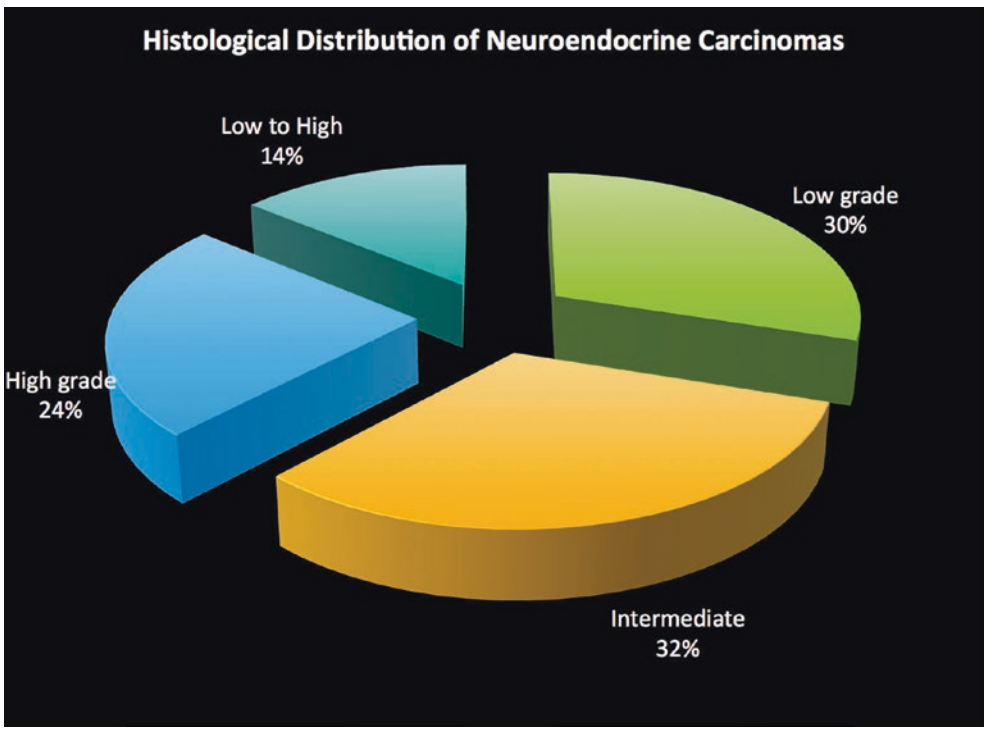


Fig. 9.5 Histological distribution of neuroendocrine carcinomas

sis, 100%; 1 mitosis, 90%; 2 mitosis, 100%; and 3 mitosis, 100%. Thus, the cutoff had to be resetted? to low-grade tumor 0–3 mitosis and intermediate-grade tumor to 4 or more mitotic figure × 10 hpf. Then the 5-year RFS showed 97.4% and 83.4%, respectively. This is similar to our reported experience with 80 thymic neuroendocrine carcinomas in which the mitotic count of 0–3 was assigned to low-grade neuroendocrine carcinoma and 4–10 mitosis × 10 hpf for intermediate-grade neuroendocrine carcinomas. Based on these data, it is likely that not only the WHO is incorrect in their assumption of the number of mitotic figures for the pulmonary low-grade neuroendocrine carcinomas, but also most definitely it is incorrect for the thymic low-grade neuroendocrine carcinomas. Tables 9.1 and 9.2 depict the subtle differences not only in specific nomenclature but also in diagnostic criteria.

In our experience, which up to now remains the largest series of these tumors presented in the literature, a novel classification system with specific histopathological definitions was presented [44]. The study was composed of an analysis of 80 patients with primary thymic neuroendocrine carcinomas ranging from low to intermediate to poorly differentiated carcinomas. In this study, all the different tumor differentiations were observed. Of the 80 cases studied, 29 corresponded to the low-grade tumors, 36 to the intermediate-grade tumors, and 15 to the high-grade tumors. The criteria for diagnosis and inclusion into any of these specific categories as well as its specific nomenclature are as follows:

- Low-grade neuroendocrine carcinoma (well-differentiated neuroendocrine carcinoma, grade I neuroendocrine carcinoma, carcinoid tumor).
  - Predominantly organoid pattern.
  - Small focus of necrosis (punctuate necrosis) may be seen.
  - Mild cytologic atypia.
  - Up to 3 mitotic figures × 10 high-power fields.
  - Vascular invasion may be seen.
- Intermediate-grade neuroendocrine carcinoma (moderately differentiated neuroendocrine carcinoma, grade II neuroendocrine carcinoma, atypical carcinoid).
  - Organoid and diffuse growth pattern.
  - Extensive comedonecrosis or frank necrosis.
  - Moderate cytologic atypia.
  - 4 to 10 mitotic figures × 10 high-power fields.
  - Vascular invasion may be seen.
- High-grade neuroendocrine carcinoma (poorly differentiated neuroendocrine carcinoma, grade III neuroendocrine carcinoma, small cell carcinoma, or large cell neuroendocrine carcinoma).
  - Diffuse growth pattern (loss of organoid pattern).
  - Extensive necrosis.
  - Marked cytologic atypia.
  - >10 mitotic figures per 10 high-power fields.
  - Vascular invasion may be seen.

Table 9.1 Classification schemas for thymic neuroendocrine carcinomas

Moran-Suster[a]	WHO 1999φ	WHO 2004λ	WHO 2015π
Low-grade NE Ca	Classic carcinoid	Well-diff. NE Ca	Typical carcinoid
Intermediate-grade NE Ca	Atypical carcinoid	Well-diff. NE Ca	Atypical carcinoid
High-grade NE Ca	Poorly diff. NE Ca	Poorly diff. NE Ca	Large cell NE carcinoma Small cell carcinoma

φ not based on any clinicopathological study
λ not based on any clinicopathological study
π not based on any clinicopathological study
NE neuroendocrine, *Ca* carcinoma, *Diff* differentiated
[a]Based on a clinicopathological correlation of 80 cases

Table 9.2 Histopathological criteria for the diagnosis of thymic neuroendocrine carcinomas

Feature	Moran-Suster	WHO 1999	WHO 2004	WHO 2015
	Low grade	*Classic carcinoid*	*Well-diff. NE Ca*	*Typical carcinoid*
Mitosis	Up to 3 × 10 hpf	Low	<2 × 10 hpf	<2 × 10 hpf
Necrosis	Small foci	Scanty	No necrosis	No necrosis
Growth pattern	Organoid	Not mentioned	Not mentioned	Not mentioned
	Intermediate grade	*Atypical carcinoid*	*Well-diff. NE Ca*	*Atypical carcinoid*
Mitosis	4–10 × 10 hpf	2–10 × 10 hpf	2–10 × 10 hpf	2–10 hpf
Necrosis	Extensive	Foci of necrosis	Present	Present
Growth pattern	Organoid and diffuse	Not mentioned	Not mentioned	Not mentioned
	High grade	*Poorly diff. Ca*	*Poorly diff. NE Ca*	*Large cell* *Small cell*
Mitosis	>10 × 10 hpf	Not mentioned	>10 × 10 hpf	>10 × 10 hpf
Necrosis	Extensive	Not mentioned	Not mentioned	Frequent
Growth pattern	Diffuse	Not mentioned	Not mentioned	Not mentioned

It is also important to highlight that this stratification and classification of neuroendocrine tumors is based on tumor resections and not on biopsy material. In daily practice, it is more common to have only a mediastinoscopic biopsy available for review. Thus, one is confronted with obvious limitations to provide a specific subclassification of these tumors. In such a situation, as we often do with similar tumors in the lung, the most important separation is with the high-grade tumors such as small cell carcinoma or large cell neuroendocrine carcinoma, which may be followed and treated differently than the lower-grade tumors. Also important to highlight is the possibility of encountering tumors that may show features ranging from low-grade to high-grade histology. In these cases, it is important to assess such histology, which in turn illustrates the limitations that one may encounter with small mediastinoscopic biopsies.

Staging

Due to the rarity of these tumors as primary thymic neoplasms, a more specific staging system has not been officially promoted. Thus, this leaves the staging of these tumors to various schemas that in the majority of the cases have been presented for other more common thymic tumors. However, it is important to highlight that neuroendocrine neoplasms, namely, thymic neuroendocrine carcinomas, are most likely to behave as conventional non-neuroendocrine carcinomas than as thymomas; therefore, the use of schemas proposed for thymomas is likely to show inconsistencies regarding staging and clinical behavior for these tumors. Even though there have been some attempts to use staging for neuroendocrine carcinomas of the thymus, these schemas have lacked universal agreement, and, in some of them, the usefulness has been hampered due to its lack of clarity. For instance, Fukai and coworkers [50] presented a tentative TNM schema and concluded that distant metastasis is the most important prognostic factor, leaving T and N as associated features without any specific clinical impact. Due to these shortcomings, the Masaoka or the Koga-modified Masaoka staging proposal has been used in many cases. However, it is highly important to note that those staging systems were proposed for thymomas and not for thymic carcinoma or neuroendocrine carcinoma, which represent different clinicopathological entities. The fact that these tumors have the potential to spread to lymph nodes, lung, bone, or organs below the diaphragm or above the thoracic inlet [44] should provide a sense of the need to use a more appropriate staging system than the one proposed for thymomas. Therefore, in view of the similar biological behavior of conventional thymic carcinoma to neuroendocrine carcinoma in terms of metastatic spread, we consider that the application of the Weissferdt-Moran [51] proposed staging should be applied not only to conventional thymic carcinoma but also to thymic neuroendocrine carcinoma. A recent review on the topic of staging for thymic tumors addressing these specific issues has been presented in which a comparison of the different schemas is analyzed, with the main emphasis that those schemas presented for thymomas are inadequate for thymic carcinomas or neuroendocrine carcinomas [52]. A comparison of the different schemas for the staging of thymic carcinomas is presented in the chapter on Staging of thymic epithelial neoplasms [Chap. 6].

An illustrative view of the different stages for thymic neuroendocrine carcinoma is presented in Figs. 9.6a–c, 9.7a–c, and 9.8a, b.

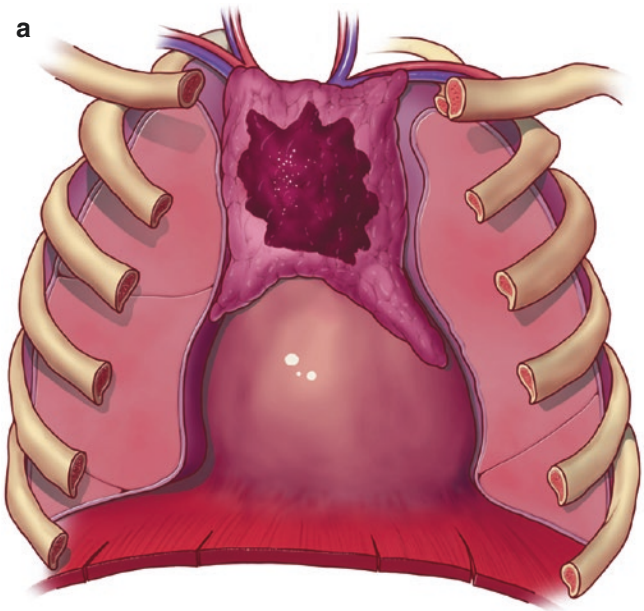
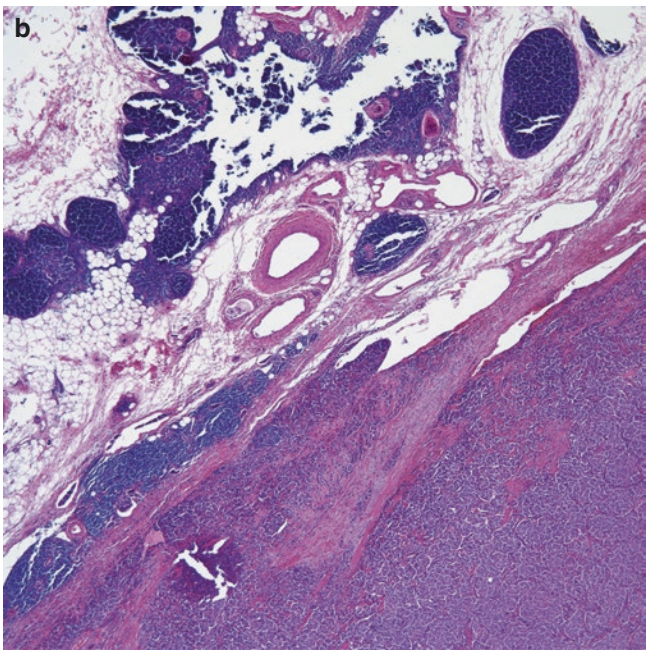


Fig. 9.6 (**a**) Thymic neuroendocrine carcinoma stage I – tumor is confined to the mediastinal compartment (**a**: Copyright © 2016 with permission from Dr. Kalhor and Moran)



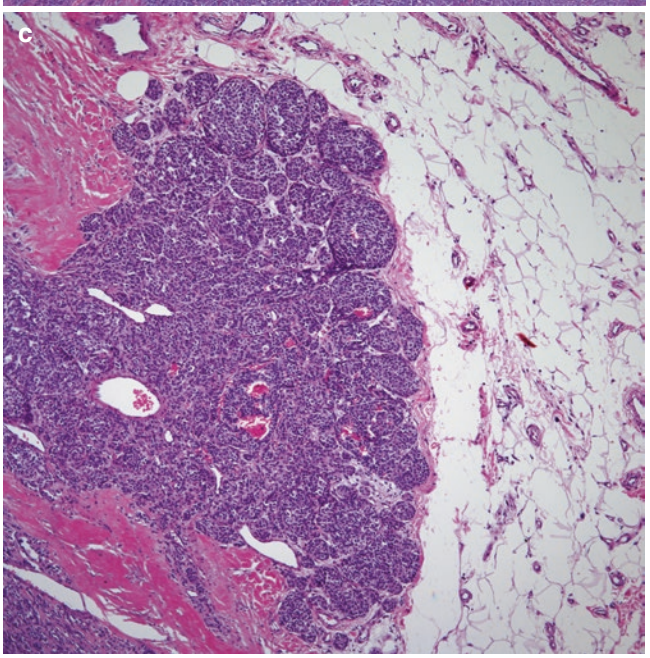
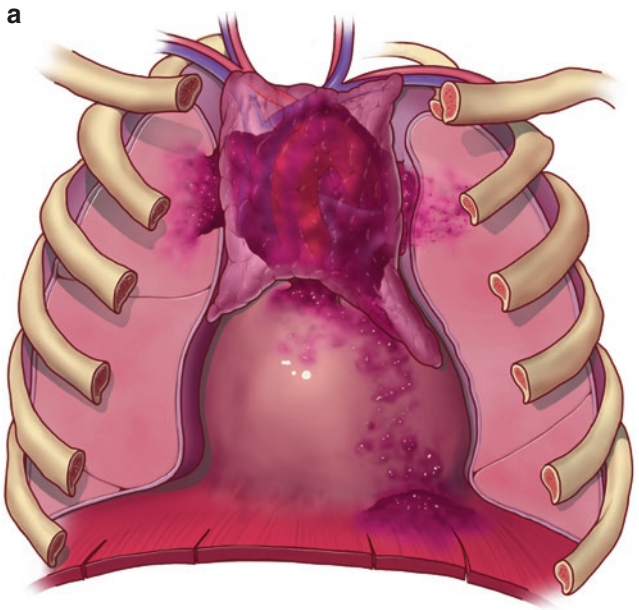


Fig. 9.6 (continued) (**b**) Tumor involves the thymic gland; (**c**) tumor infiltrates into adipose tissue



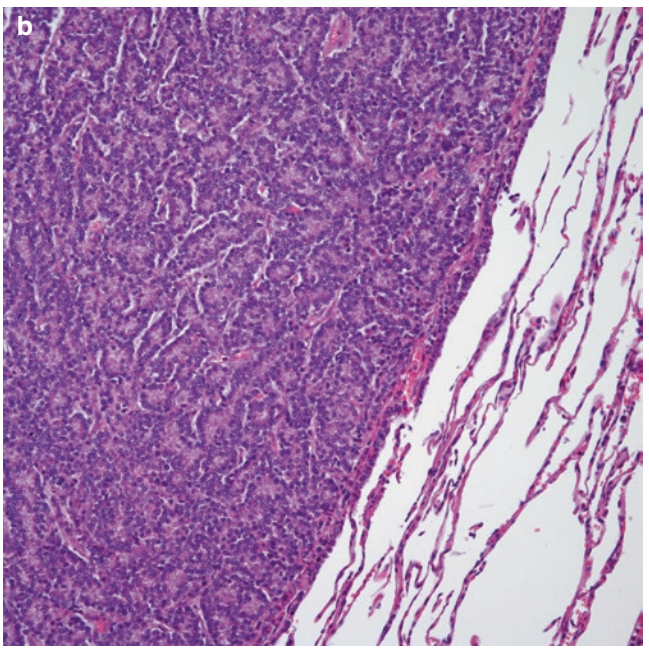
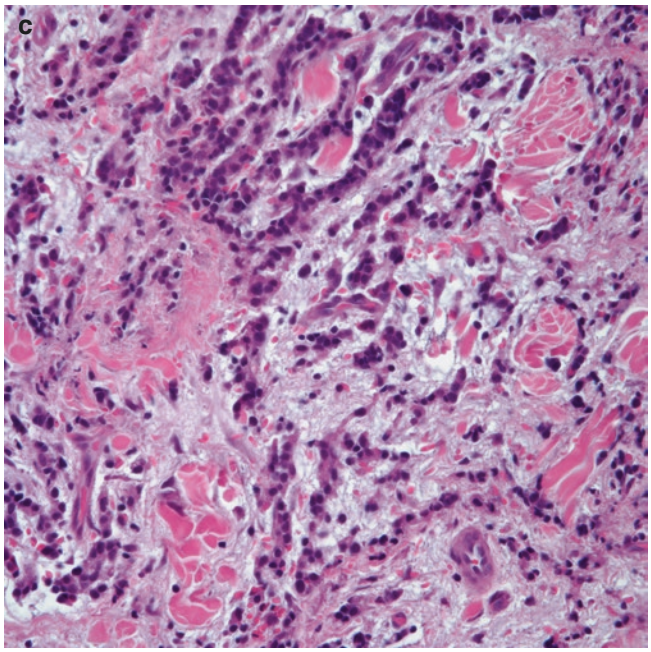


Fig. 9.7 (**a**) Neuroendocrine carcinoma stage II – tumor extends outside of the mediastinal compartment but remains within the thoracic cavity; (**b**) tumors involves lung parenchyma (**a**: Copyright © 2016 with permission from Dr. Kalhor and Moran)



Pathological Features

Gross Features

The macroscopic features of thymic neuroendocrine carcinomas, either low or intermediate grade, are rather non-specific. These tumors are commonly described as large, soft, and light brown in color. The tumor may measure from a couple of centimeters in greatest diameter to tumors over 15 cm in greatest dimension (Fig. 9.9). The cut surface of these tumors may show a homogeneous rubbery surface, while the presence of areas of hemorrhage and necrosis should alert of the possibility of an intermediate-grade neoplasm. These areas not only need to be documented but also carefully sampled, as the presence of necrosis is part of the criteria for upgrading a neoplasm.

Fig. 9.7 (continued) (**c**) Tumor involves diaphragm

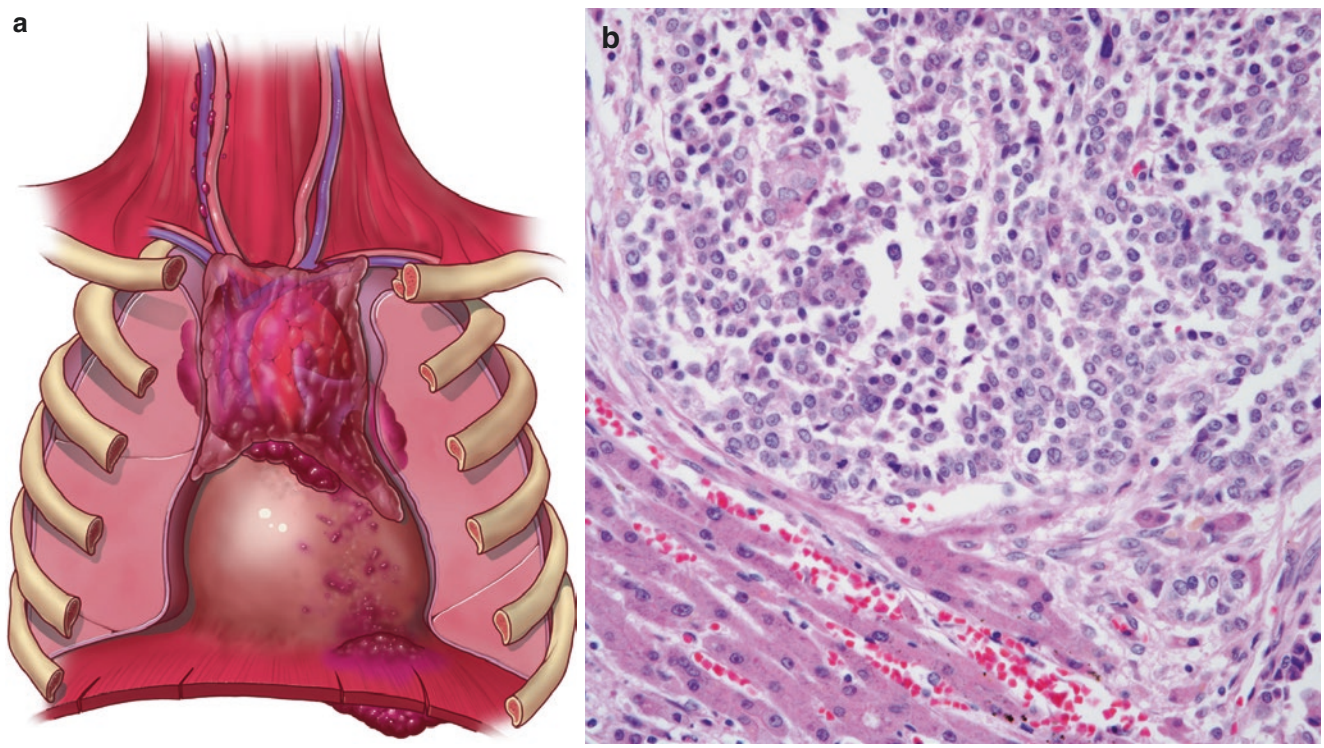


Fig. 9.8 (**a**) Neuroendocrine carcinoma stage III – the tumor extends above the thoracic inlet or below the diaphragm; (**b**) metastatic NE carcinoma in the liver. (**a**: Copyright © 2016 with permission from Dr. Kalhor and Moran)

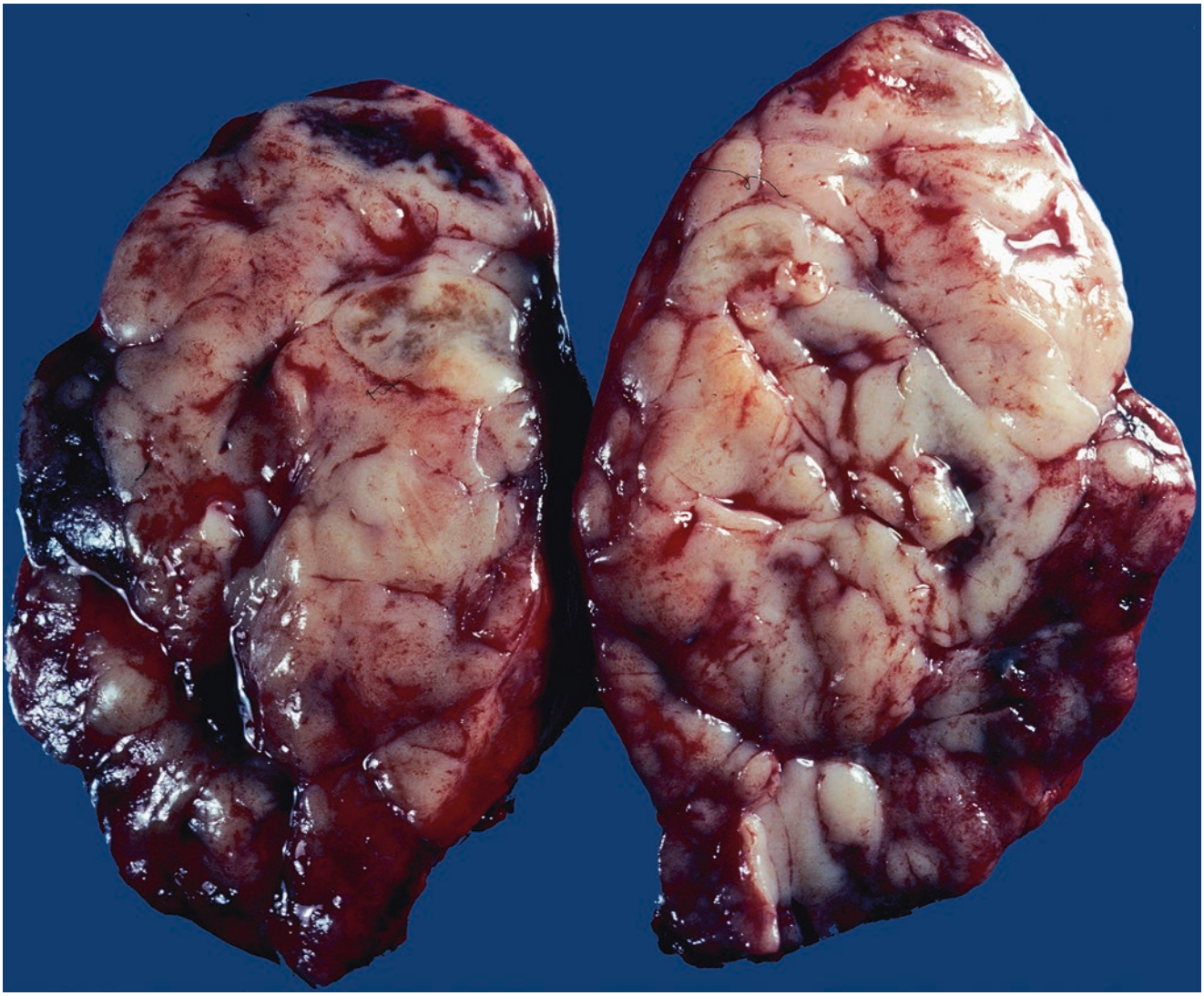


Fig. 9.9 Thymic neuroendocrine carcinoma showing a fleshy homogeneous light brown cut surface

Histopathological Features

The histopathological features ascribed to these tumors have been well presented in the literature, and the basic histopathological features are similar to those tumors in other organ systems such as lung and gastrointestinal tract. Therefore, due to this similarity, it is important to keep in mind the possibility of metastatic disease, as in reality there is not a single histopathological hallmark to separate thymic neuroendocrine carcinomas from those of other anatomic areas. This separation is often performed on clinical and radiological grounds after a good clinical evaluation of these patients.

Low- and Intermediate-Grade Neuroendocrine Carcinomas

Thymic neuroendocrine carcinomas have been the subject of numerous publications either as case reports or small series of cases in which emphasis has been given not only to the morphological aspects of the tumors but also to specific associations of the neuroendocrine neoplasm with other types of histology, or emphasizing a specific clinical feature with the histology of the tumor [53–62]. For instance, Paties and coworkers and Kuo [63, 64] both documented a case in a 62- and 56-year-old men with a mediastinal neoplasm. The authors

coded these cases as "multidirectional carcinoma of the thymus with neuroendocrine and sarcomatoid components and carcinoid syndrome." Also, Mizuno and coworkers [65] documented a 60-year-old man with the coexistence of what the authors called "thymic carcinoid and thymoma."

In general, the histopathological features of these tumors include the presence of prominent "organoid" or nested growth pattern in which these nests are surrounded by a delicate fibrovascular septa. In some tumors, the tumor cells may be arranged in cords or ribbons with little intervening stroma. The presence of rosettes may be a common finding in some cases, while in other cases this feature may be subtler and not so easily identified. At higher magnification, the tumor cells are round to oval with moderate amount of cytoplasm and round nuclei with coarse chromatin (Figs. 9.10, 9.11, 9.12, 9.13, 9.14, 9.15, 9.16, 9.17, 9.18, 9.19, 9.20, 9.21, and 9.22). The degree of cellular atypia in the low-grade tumors is rather mild, even though cells with more prominent nucleoli, sporadic mitotic figures, and focal punctuate necrosis may be seen in these tumors (Figs. 9.23 and 9.24). Even though

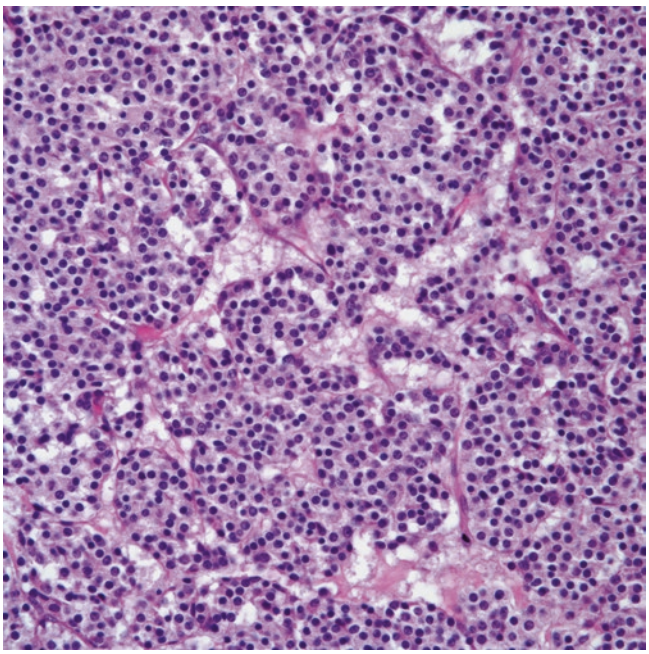


Fig. 9.11 Low-grade neuroendocrine carcinoma showing a fairly homogeneous cellular proliferation with only mild nuclear atypia and absent mitotic activity

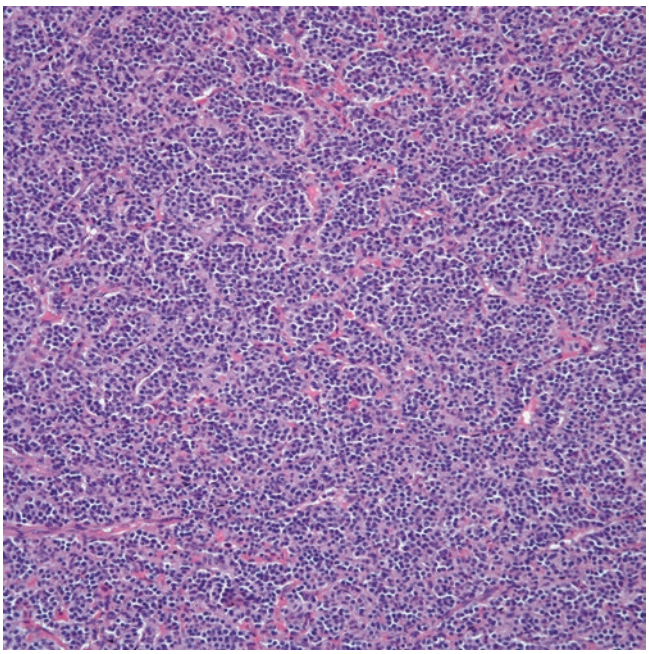


Fig. 9.10 Low-grade neuroendocrine carcinoma showing a well-organized "organoid" growth pattern

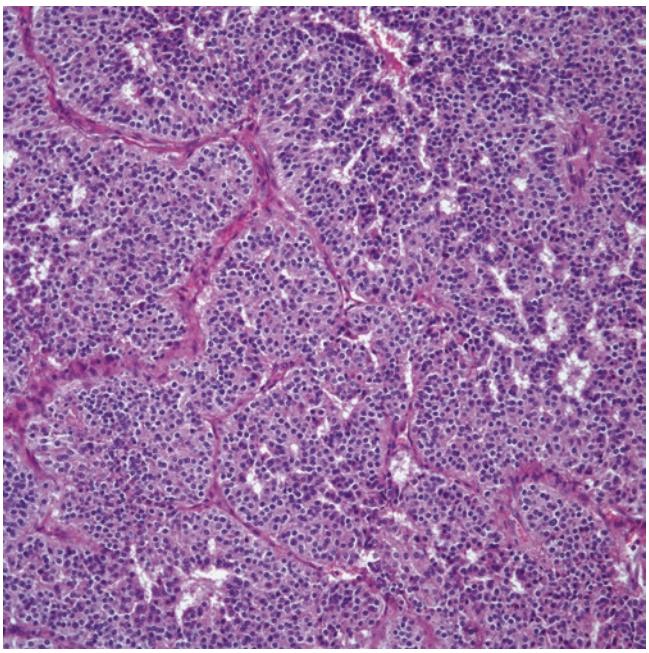


Fig. 9.12 Low-grade neuroendocrine carcinoma showing a nested pattern with a fairly discrete fibroconnective tissue separating tumor nests

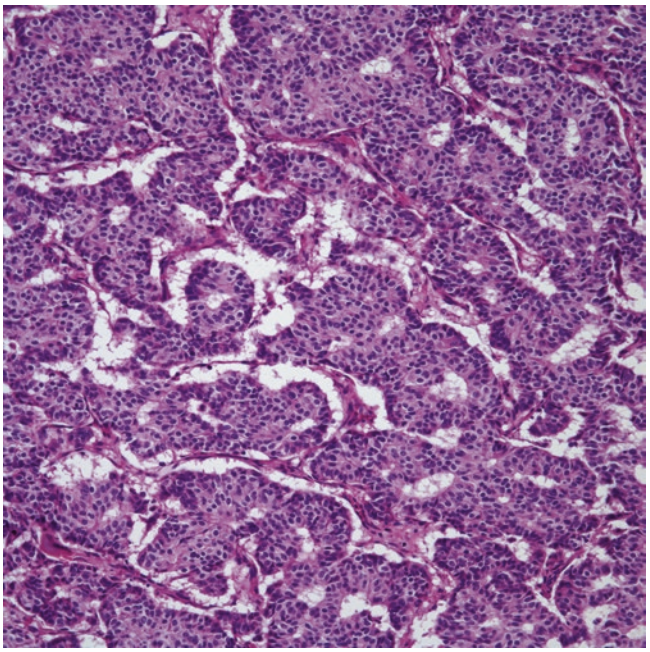


Fig. 9.13 Low-grade neuroendocrine carcinoma showing an organoid pattern with pseudoglandular areas

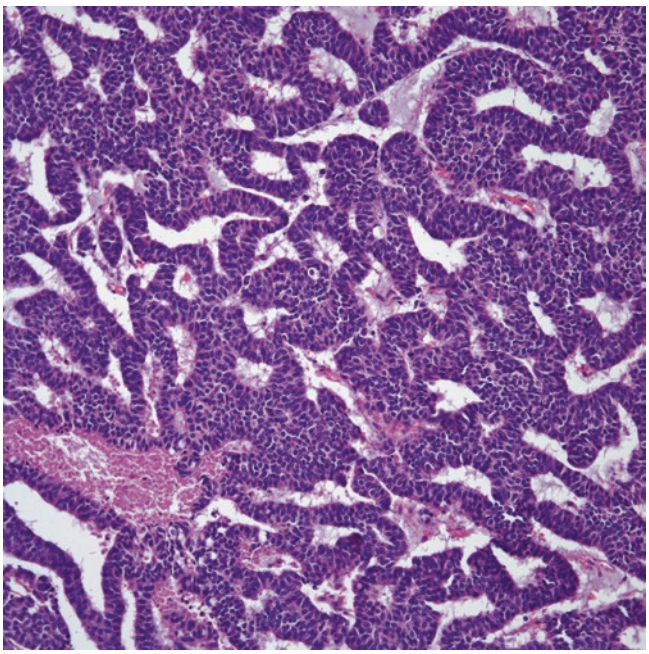


Fig. 9.15 Low-grade neuroendocrine carcinoma showing a more glandular appearance

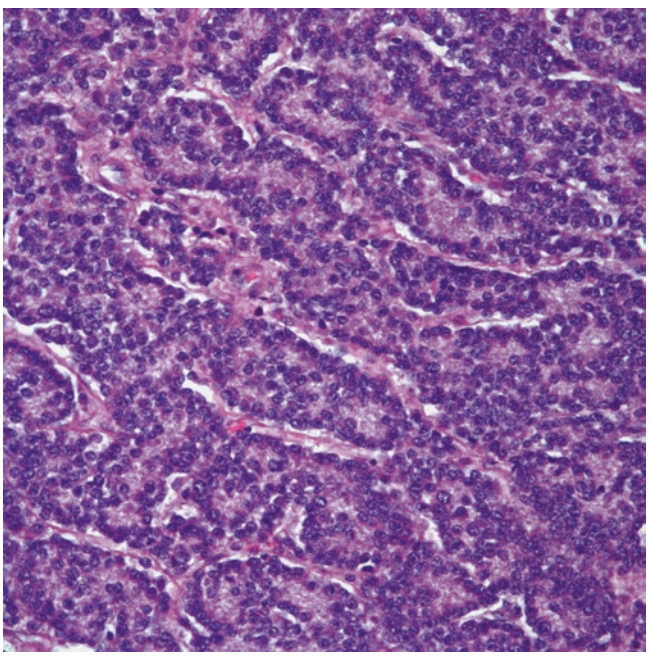


Fig. 9.14 Low-grade neuroendocrine carcinoma showing ribbons of tumor cells

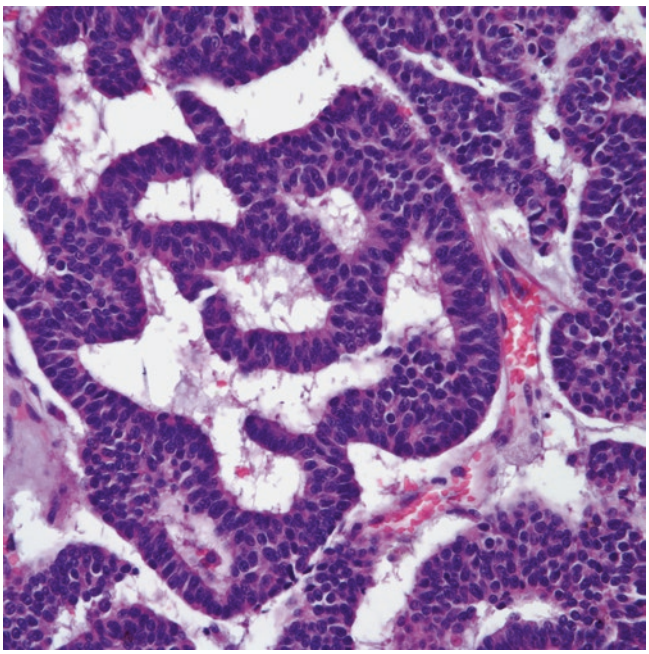


Fig. 9.16 Higher magnification of a low-grade neuroendocrine carcinoma with a glandular appearance

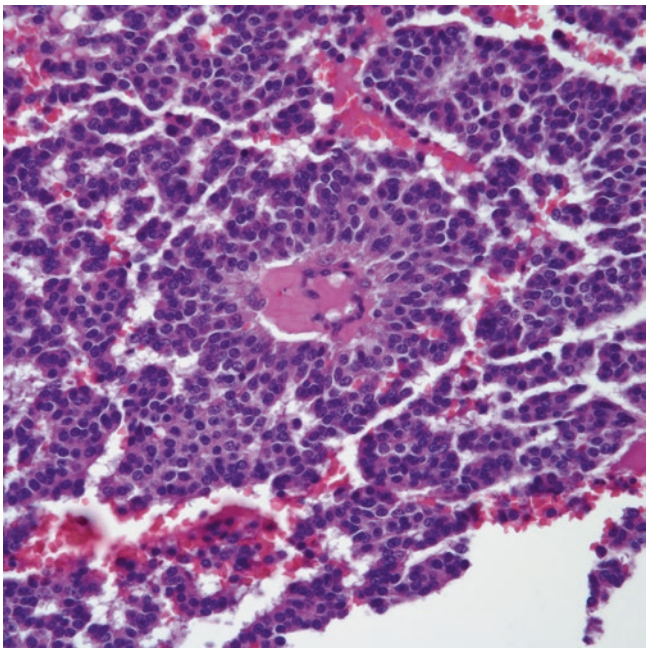


Fig. 9.17 Low-grade neuroendocrine carcinoma showing rosettes

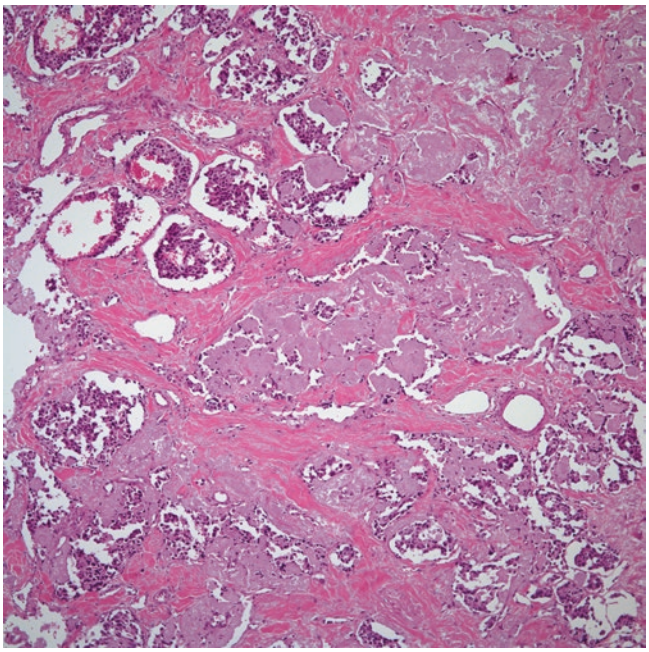


Fig. 9.19 Low-grade neuroendocrine carcinoma with amyloid-like areas

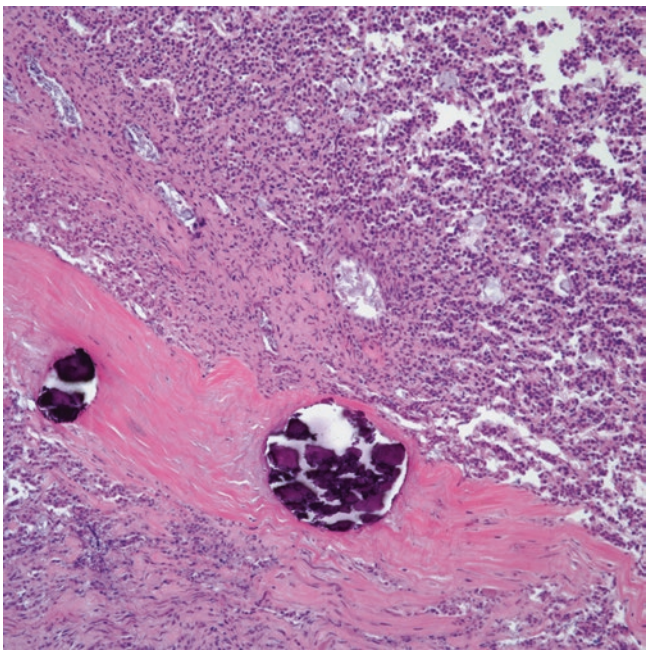


Fig. 9.18 Calcifications present in a low-grade neuroendocrine carcinoma

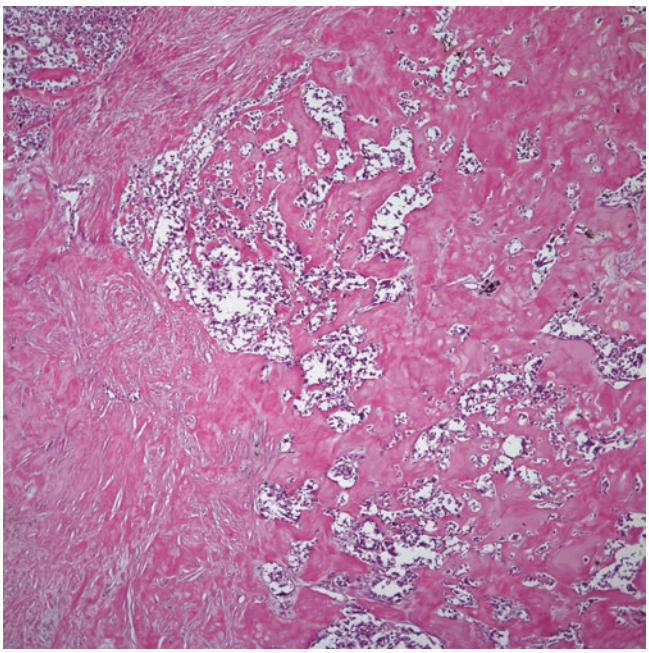


Fig. 9.20 Amyloid-like areas in a low-grade neuroendocrine carcinoma, which is not more than hyalinized fibroconnective tissue

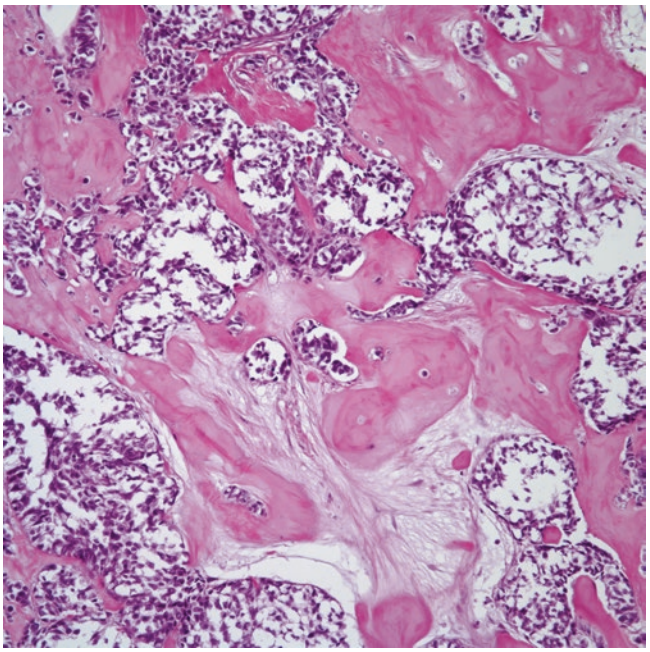


Fig. 9.21 Extensive hyalinization in neuroendocrine carcinoma can pose a challenge in diagnosis

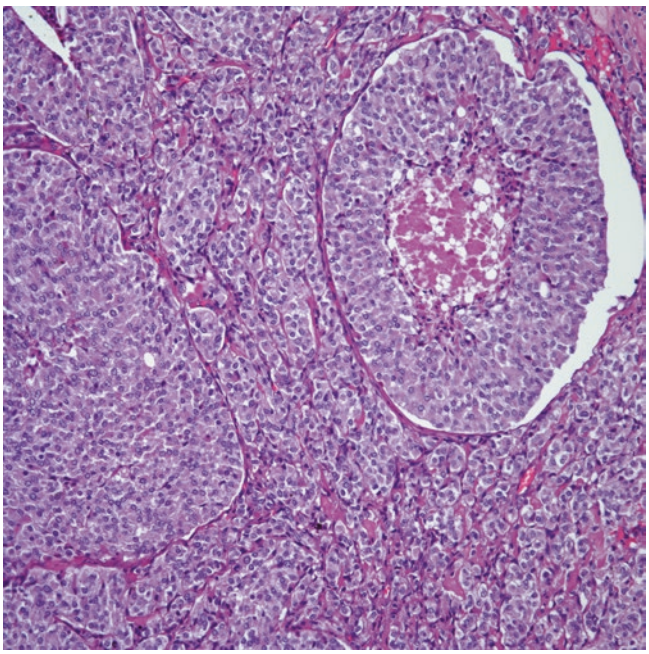


Fig. 9.23 Low-grade neuroendocrine carcinoma with a microscopic focus of necrosis

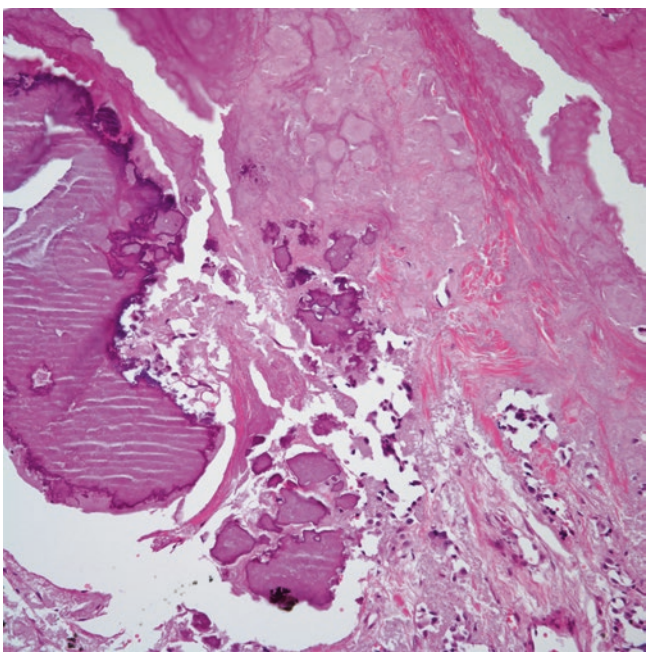


Fig. 9.22 Extensive hyalinization and calcification in a neuroendocrine carcinoma

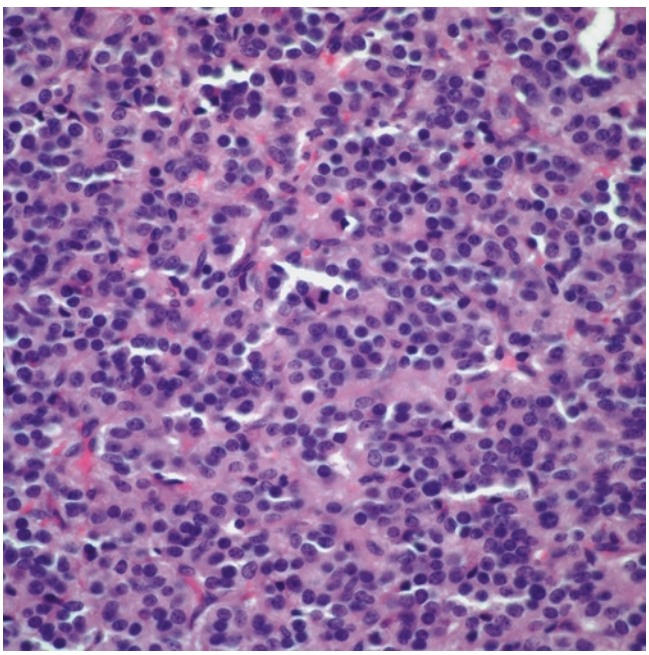


Fig. 9.24 Low-grade neuroendocrine carcinoma showing scattered mitotic figures

similar features may be seen in intermediate-grade tumors, the pattern of growth may be a mixed type in which one can observe the presence of a well-defined nested growth pattern admixed with extensive areas of diffuse, sheetlike growth pattern. The cytological features of these tumors show more pronounced nuclear atypia, and the presence of nucleoli is easier to identify than in the low-grade tumors. However, one important clue to the diagnosis is in the low power view of these tumors, as the presence of areas of comedo-like necrosis is apparent in most of these tumors. As stated in the section on classification of these tumors, the presence of necrosis and mitotic activity in the ranged of 4–10 ×10 hpf should make the classification of these tumors easier (Figs. 9.25, 9.26, 9.27, 9.28, 9.29, 9.30, 9.31, 9.32, 9.33, and 9.34).

In addition, series of different histopathological growth pattern have been described or amplified regarding neuroendocrine carcinoma of the thymus [66–74]. Some of these growth patterns may pose a challenge in the diagnosis and are discussed below.

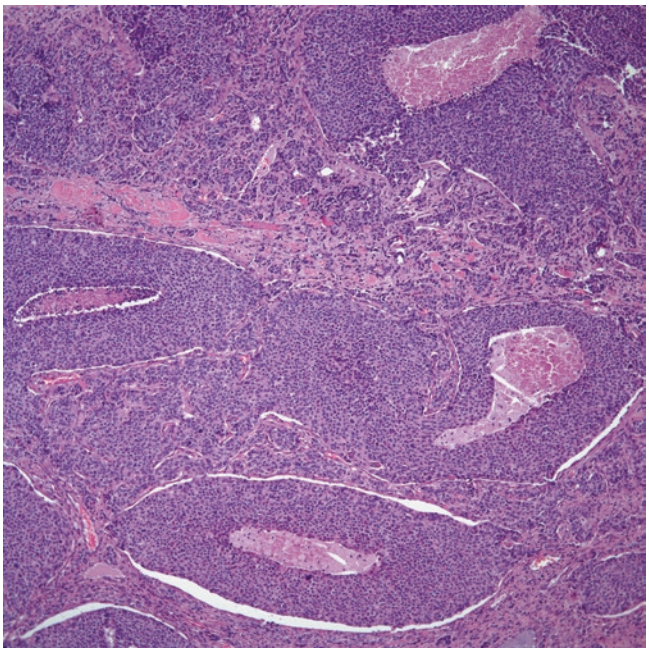


Fig. 9.25 Intermediate-grade neuroendocrine carcinoma showing obvious areas of comedonecrosis

Mucinous

This specific variant is rather unusual as the tumors are characterized by the presence of extensive pools of mucin in which the neoplastic cells are floating within this stroma (Figs. 9.35, 9.36, and 9.37). The neoplastic cells may be arranged in clusters with similar cytologic features as those that have been described in garden-variety cases. In some areas, the tumor may show more solid cellular proliferation in which the tumor may appear as forming glands with a cribriform appearance. Mitotic activity is possible in these cases and may help in properly classifying these tumors.

Angiomatoid

The hallmark of this particular variant is the presence of multiple cystically dilated spaces filled with blood, which at low power magnification resembled a vascular neoplasm. However, upon closer inspection, the cystically dilated spaces are not lined by endothelial cells but rather by neoplastic neuroendocrine cells (Figs. 9.38, 9.39, 9.40, and 9.41).

Pigmented (Melanocytic)

The presence of melanin pigment associated with neuroendocrine carcinomas may be focal or extensive and may also be seen in any type of growth pattern. When the pigment is

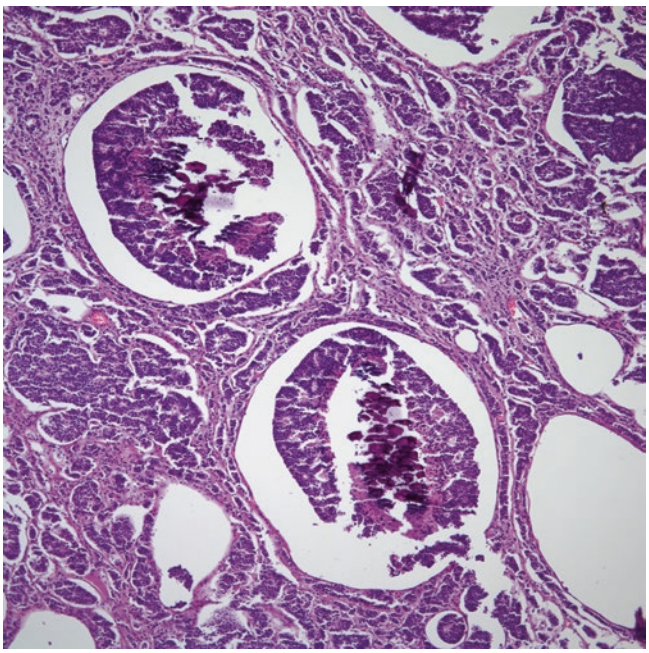


Fig. 9.26 Intermediate-grade neuroendocrine carcinoma showing comedonecrosis and calcifications

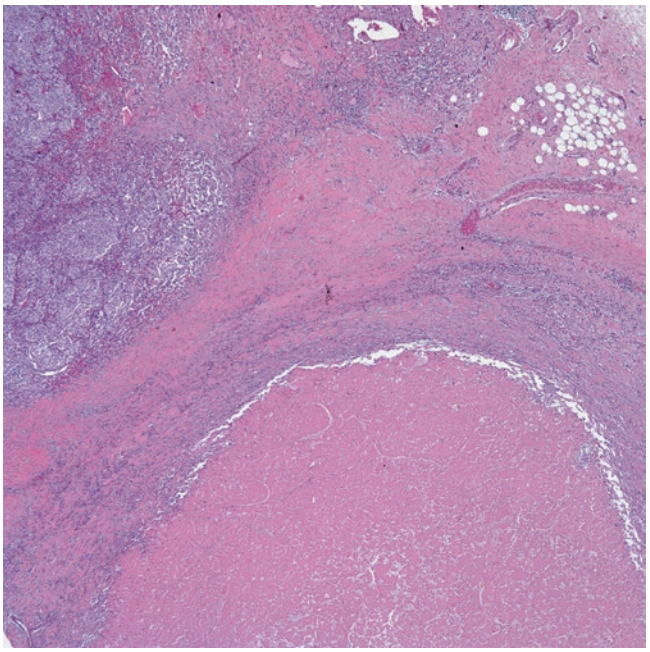


Fig. 9.27 Intermediate-grade neuroendocrine carcinoma showing more extensive areas of necrosis

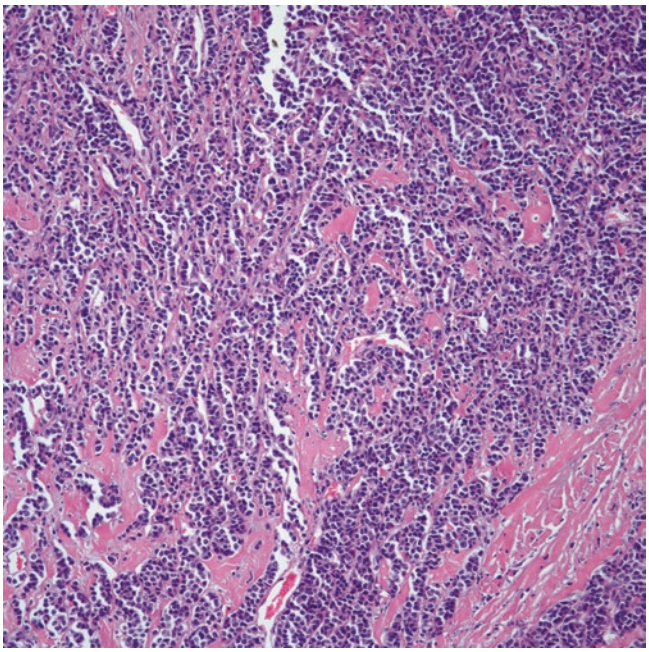


Fig. 9.29 Intermediate-grade neuroendocrine carcinoma showing cords of neoplastic cells

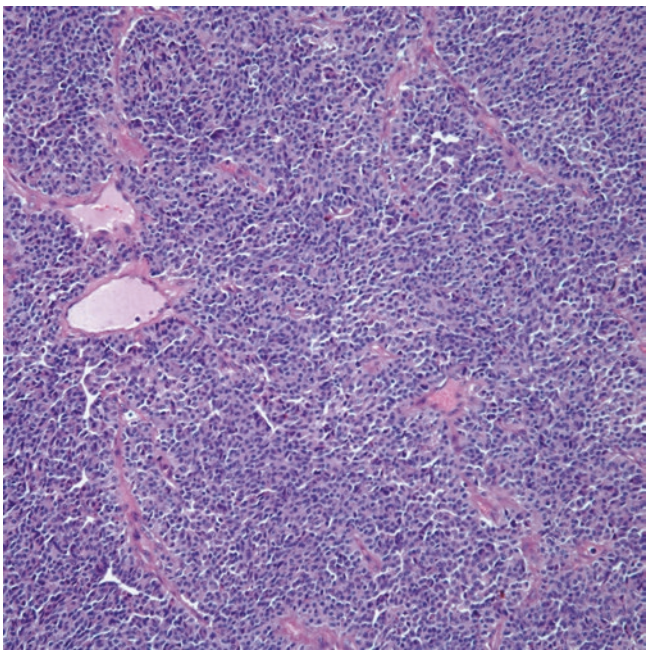


Fig. 9.28 Intermediate-grade neuroendocrine carcinoma showing a more diffuse growth pattern

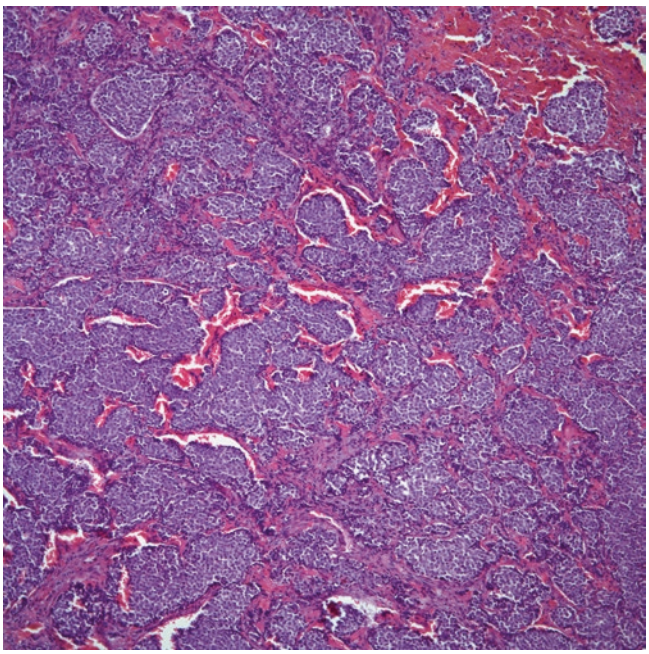


Fig. 9.30 In some areas a more subtle nested pattern may be seen in intermediate-grade neuroendocrine carcinomas

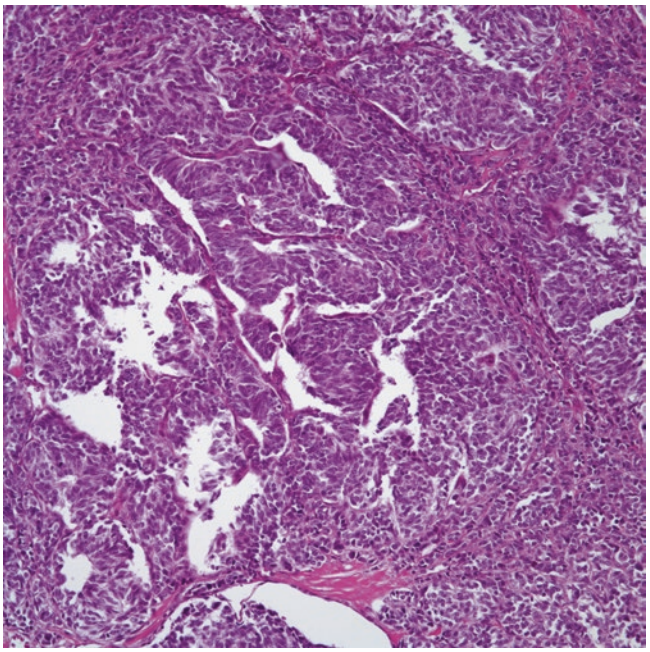


Fig. 9.31 Intermediate-grade neuroendocrine carcinoma showing a more solid growth pattern

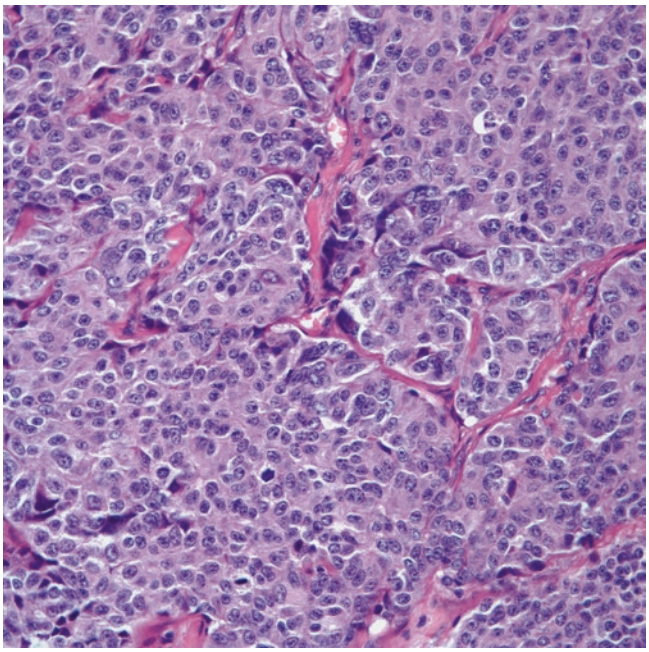


Fig. 9.33 Intermediate-grade neuroendocrine carcinoma showing nuclear atypia and easily identifiable mitotic figures

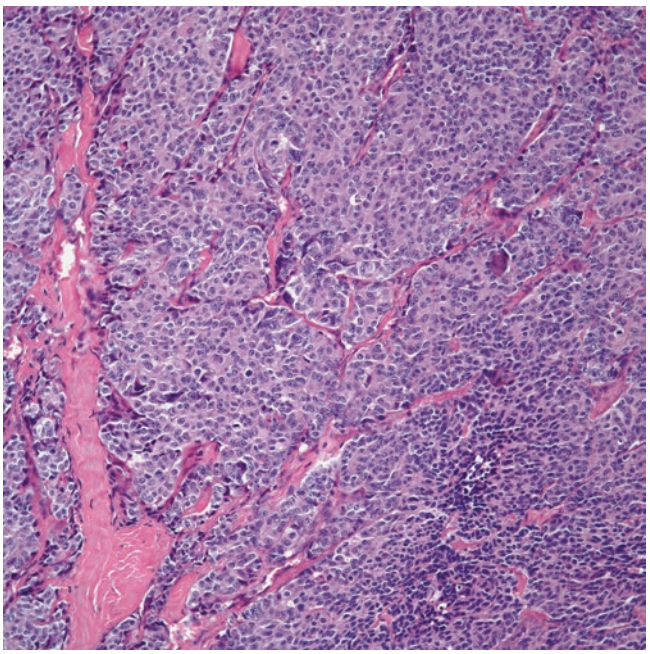


Fig. 9.32 Intermediate-grade neuroendocrine carcinoma showing moderate cellular atypia and mitotic activity

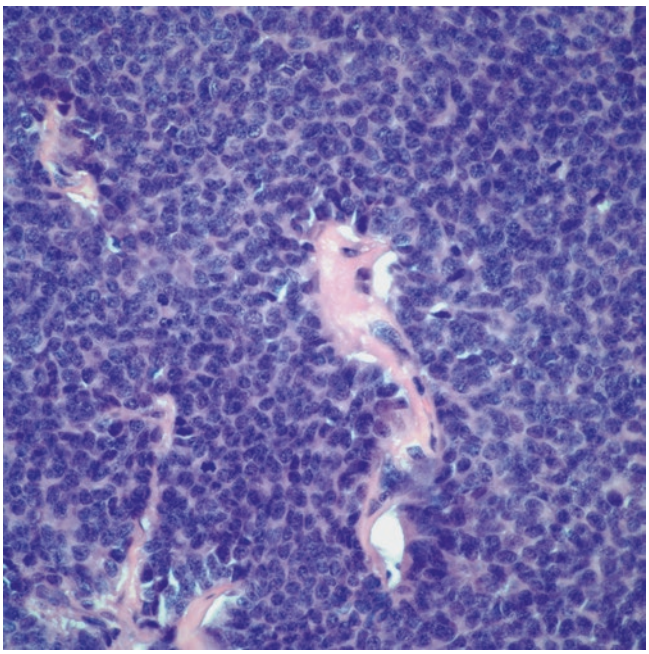


Fig. 9.34 Intermediate-grade neuroendocrine carcinoma showing a solid growth pattern with nuclear atypia and mitotic activity

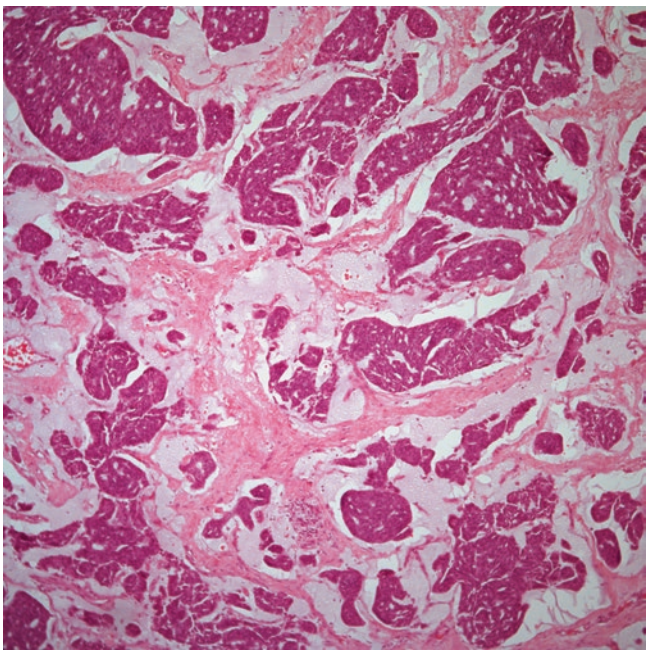


Fig. 9.35 Low power view of a mucinous neuroendocrine carcinoma

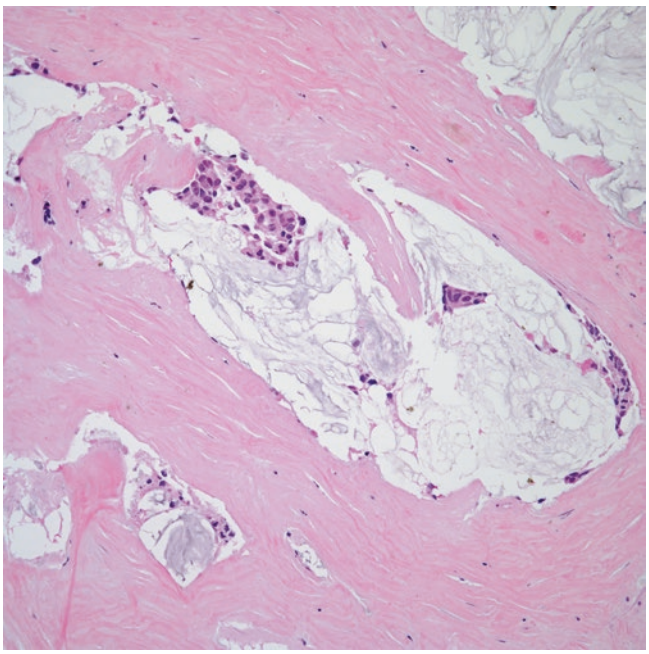


Fig. 9.37 Extensive pools of mucin in neuroendocrine carcinoma

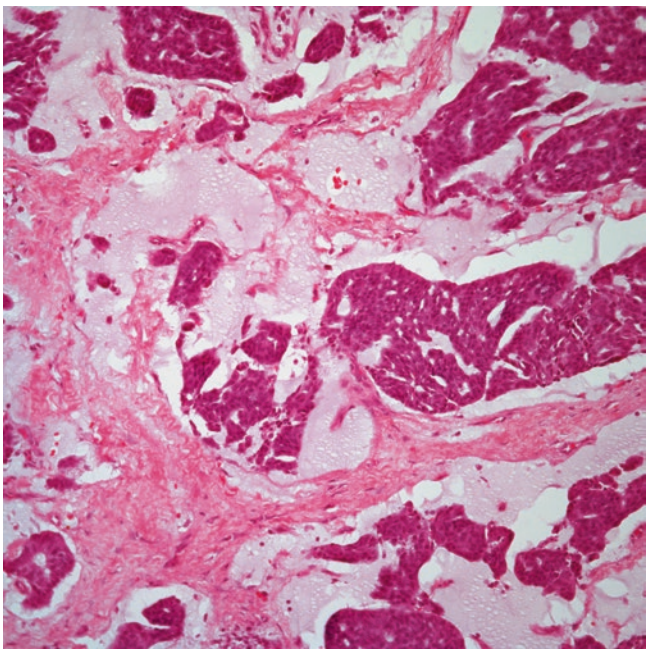


Fig. 9.36 Mucinous neuroendocrine carcinoma showing pools of mucoid material

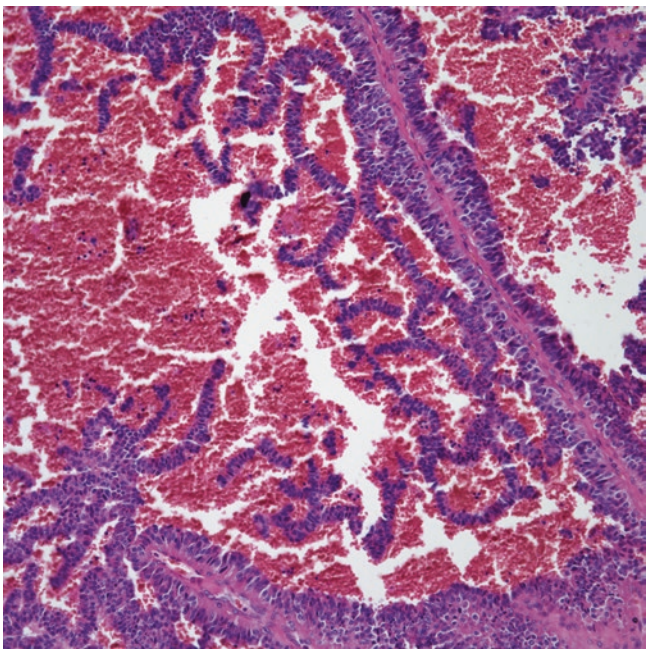


Fig. 9.38 Low power view of an angiectatic neuroendocrine carcinoma

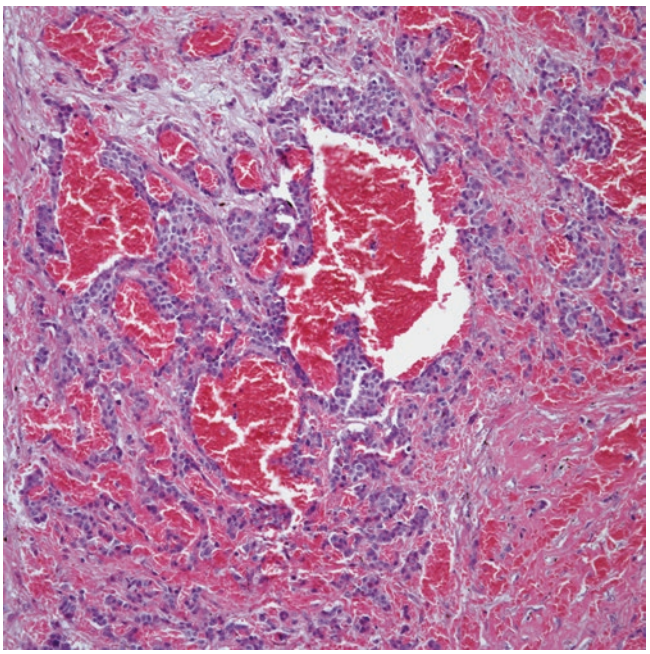


Fig. 9.39 Angiectatic neuroendocrine carcinoma showing areas mimicking a vascular neoplasm

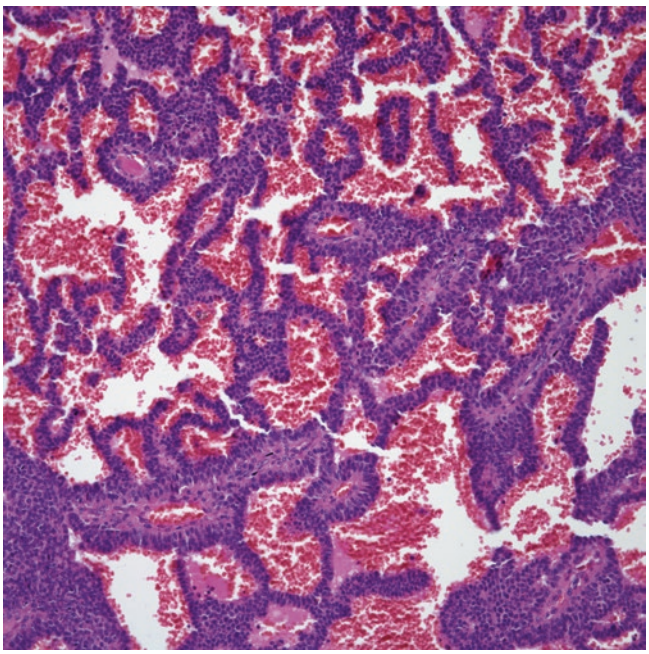


Fig. 9.41 Vascular-like spaces in an angiectatic neuroendocrine carcinoma

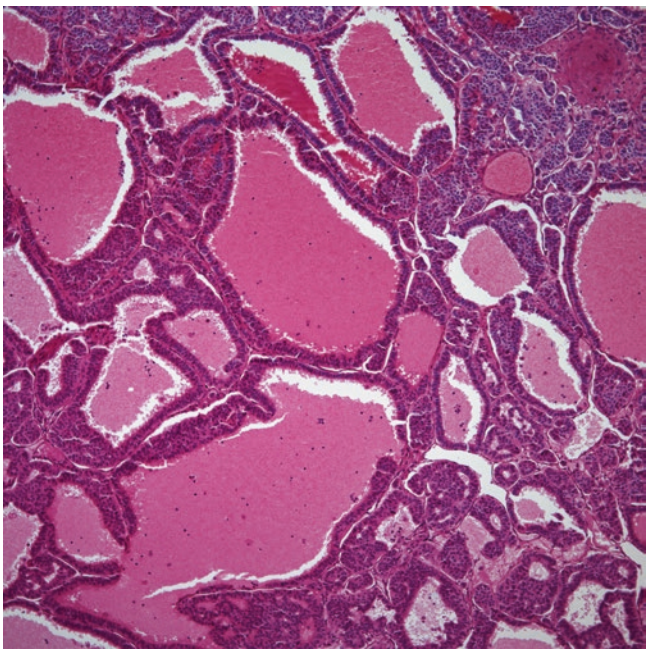


Fig. 9.40 Angiectatic neuroendocrine carcinoma showing dilated spaces occupied by acellular material

extensive, the tumor may resemble other neoplasms, namely, melanoma, in which the presence of pigment is much more common. However, in that setting, the use of immunohistochemistry may be of aid in identifying the true nature of the neoplasm (Fig. 9.42).

Spindle Cell

Neuroendocrine carcinomas may show a distinct growth pattern composed predominantly or exclusively of fusiform cells with elongated nuclei and scant to moderate amounts of cytoplasm. The tumor may also show a subtle hemangiopericytic growth pattern or in some areas a nested growth pattern composed of small nests populated by spindle cells (Figs. 9.43, 9.44, 9.45, 9.46, 9.47, and 9.48).

Oncocytic

The presence of oncocytic changes in neuroendocrine carcinomas may vary from focal change to tumors composed almost exclusively of an oncocytic neoplastic cellular proliferation. The basic growth pattern may show ribbons of neoplastic cells with presence of rosettes, or the tumor may show a nested growth pattern. However, the cell composition is that

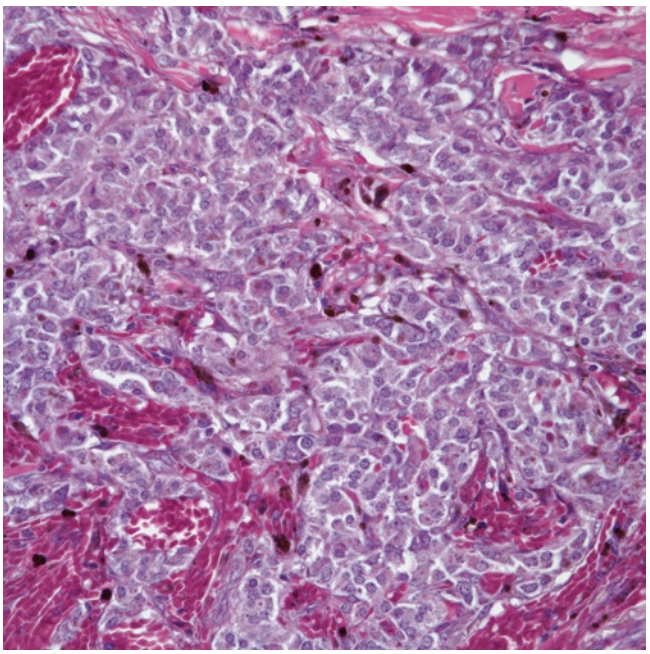


Fig. 9.42 Neuroendocrine carcinoma showing areas of melanin pigment

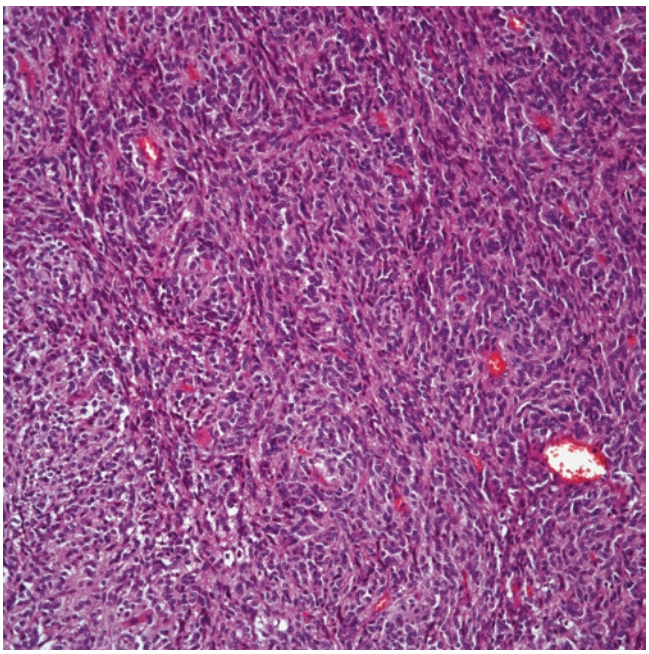


Fig. 9.44 Solid spindle cell growth pattern in a neuroendocrine carcinoma

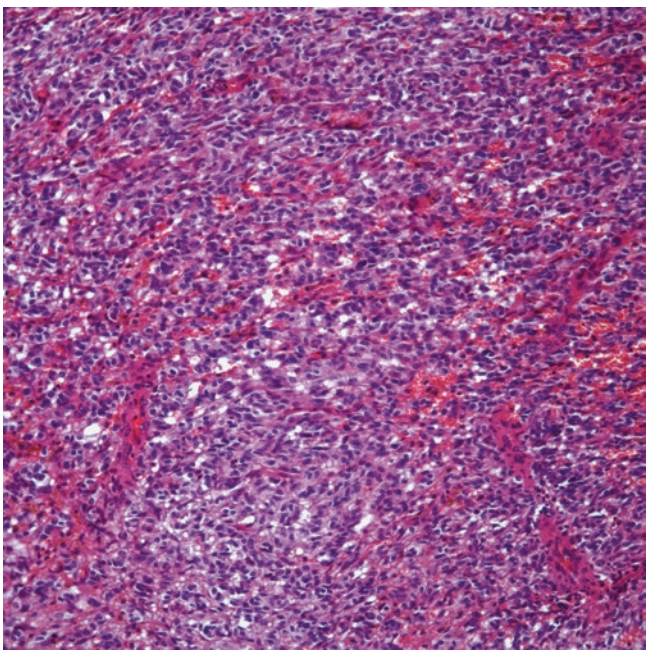


Fig. 9.43 Low power view of a neuroendocrine carcinoma with a spindle cell growth pattern

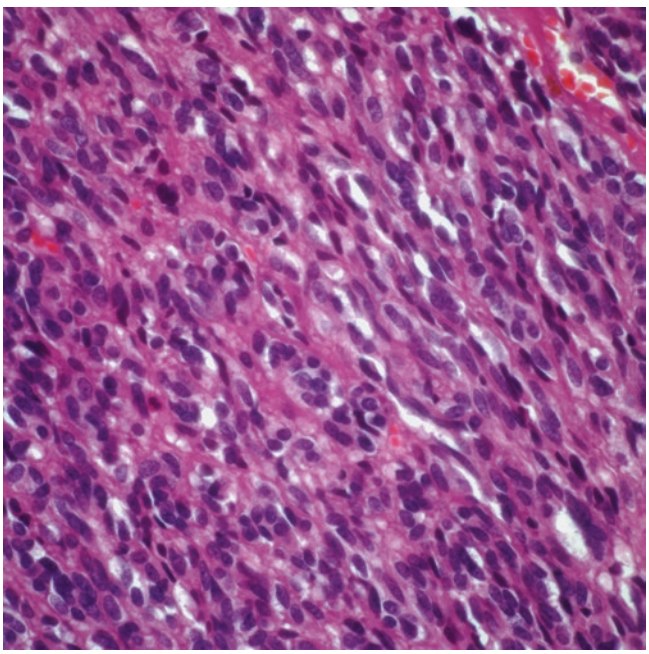


Fig. 9.45 Higher magnification of the spindle cells showing mild nuclear atypia and no mitotic activity

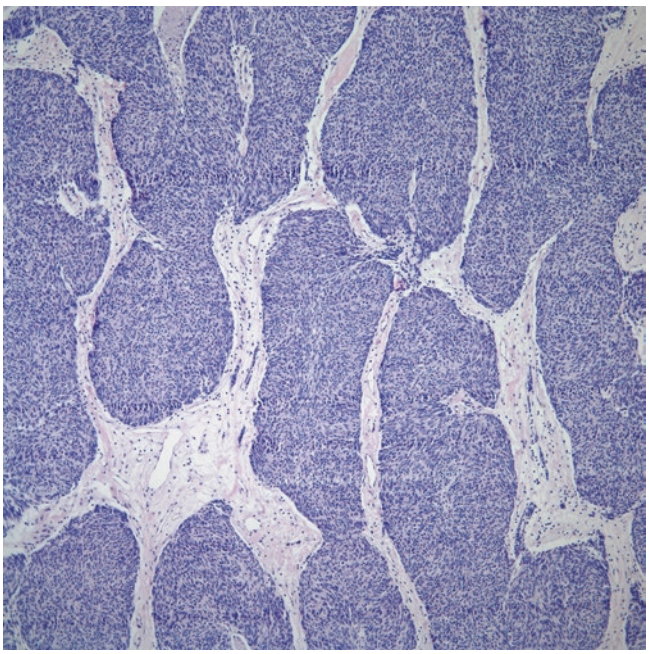


Fig. 9.46 Intermediate-grade neuroendocrine carcinoma with a spindle cell growth pattern

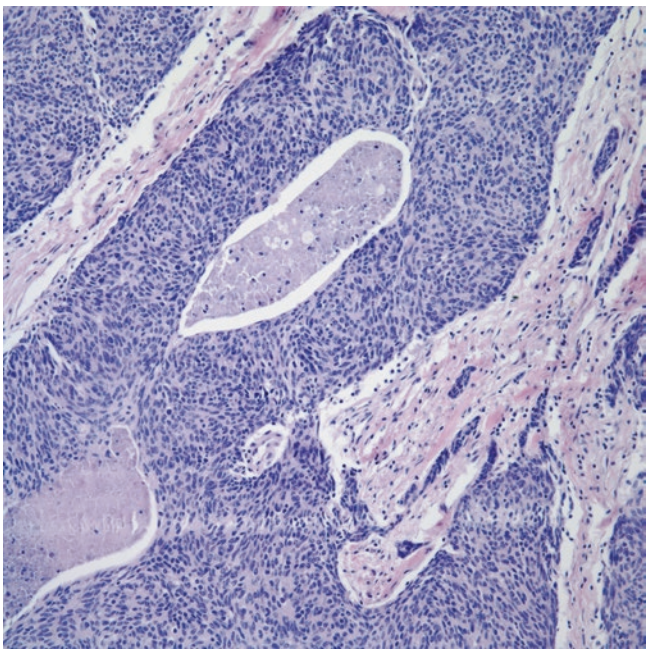


Fig. 9.47 Focal area of comedonecrosis in an intermediate-grade neuroendocrine carcinoma with spindle cell morphology

of relatively larger cells with ample eosinophilic cytoplasm, round to oval nuclei, and in some cells prominent nucleoli may be seen. In this type of neuroendocrine carcinoma, one may be able to identify more nuclear atypia than in the non-oncocytic tumors (Figs. 9.49, 9.50, 9.51, and 9.52).

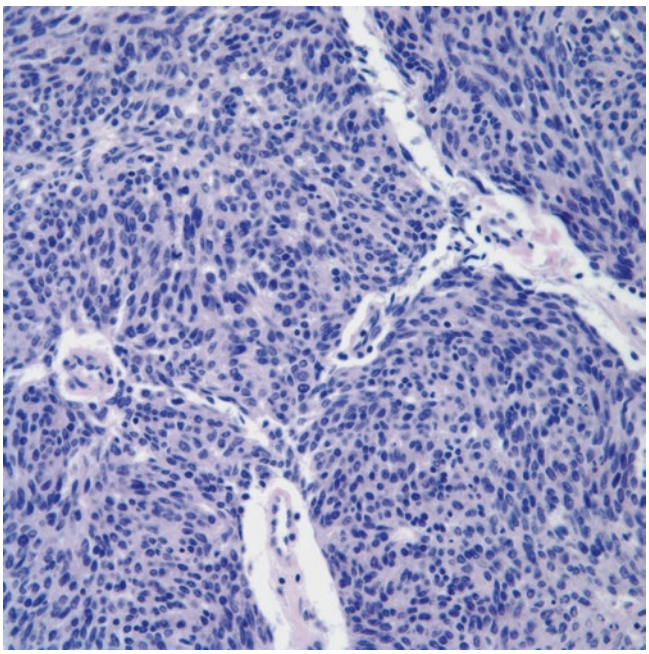


Fig. 9.48 Intermediate-grade spindle cell neuroendocrine carcinoma showing mitotic activity

Cystic

This represents a rather unusual occurrence as the tumor may show predominantly cystic changes similar to those described in multilocular thymic cyst. However, in the walls of the cyst, one can identify the presence of a neuroendocrine neoplastic cellular proliferation, which focally can extend to the surface epithelium lining the cystic structures. These tumoral areas may be focal in some cystic areas, while in others areas the tumor may be more obvious (Figs. 9.53, 9.54, 9.55, and 9.56).

Combined (Low, Intermediate, and High Grade)

Tumors showing transitions between low- and high-grade neuroendocrine carcinomas are unusual but represent a distinct type of malignancy, which may become apparent only after complete resection of the mediastinal tumor. In these cases, low- and intermediate-grade neuroendocrine carcinomas (carcinoid or atypical tumor) are clearly identifiable, while in other areas the tumor is more compatible with a small cell carcinoma. Areas of transition between those two tumors may be observed (Figs. 9.57, 9.58, 9.59, and 9.60)

High-Grade Neuroendocrine Carcinomas

Essentially, there are two types of mediastinal high-grade neuroendocrine carcinomas: small cell carcinoma and large cell neuroendocrine carcinoma [75–77]. In the former, the diagnosis is essentially done on morphological grounds, as the criteria used for these tumors in the thymus are the same as that in the pulmonary small cell carcinomas. However, great care must be taken when

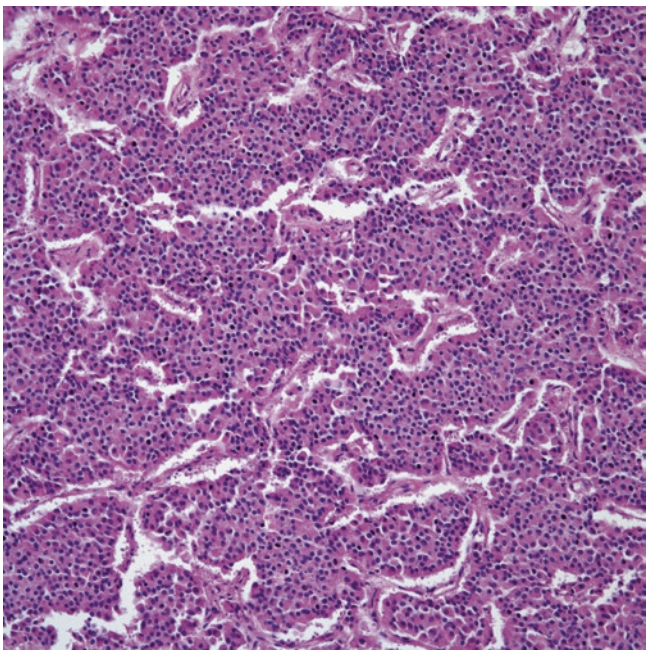


Fig. 9.49 Low power view of an oncocytic neuroendocrine carcinoma

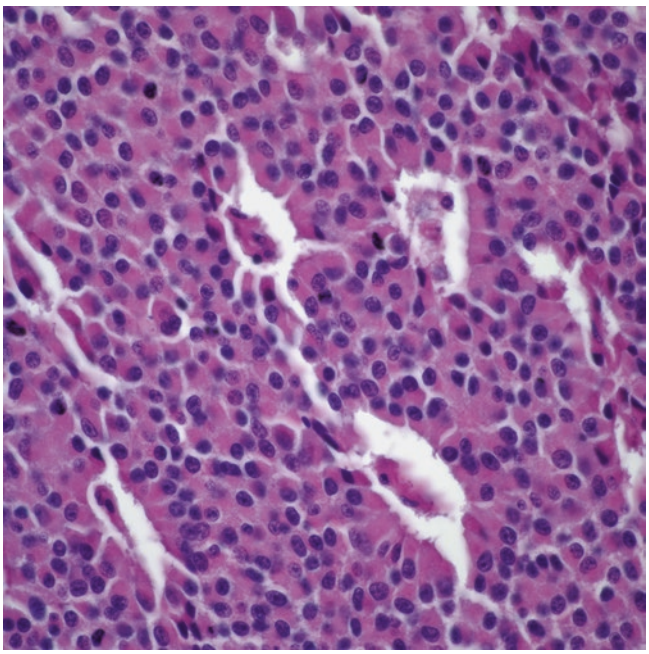


Fig. 9.51 Mitotic activity and nuclear atypia may be seen also in oncocytic neuroendocrine carcinomas

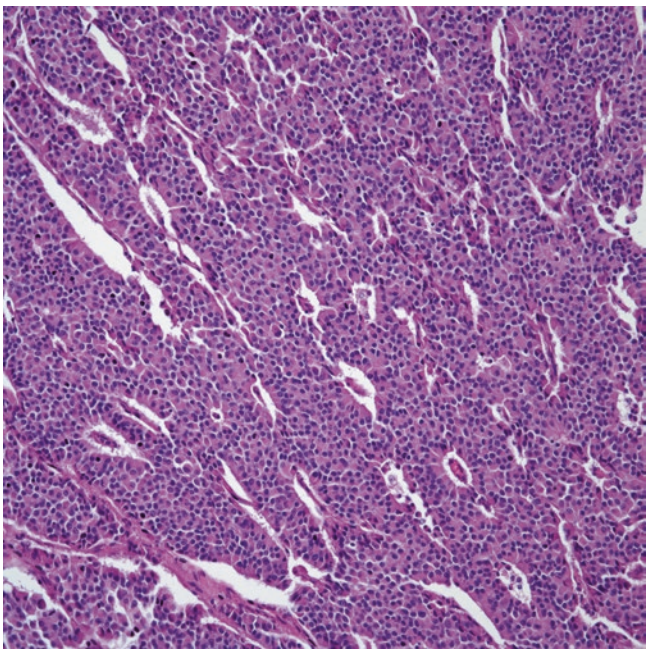


Fig. 9.50 Diffuse and focal glandular areas in an oncocytic neuroendocrine carcinoma

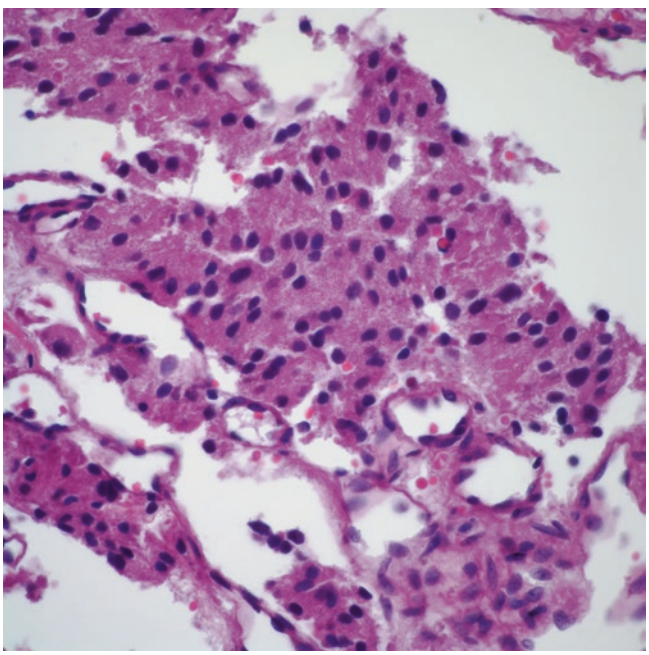


Fig. 9.52 Higher magnification of an oncocytic neuroendocrine carcinoma; note the granular cytoplasm

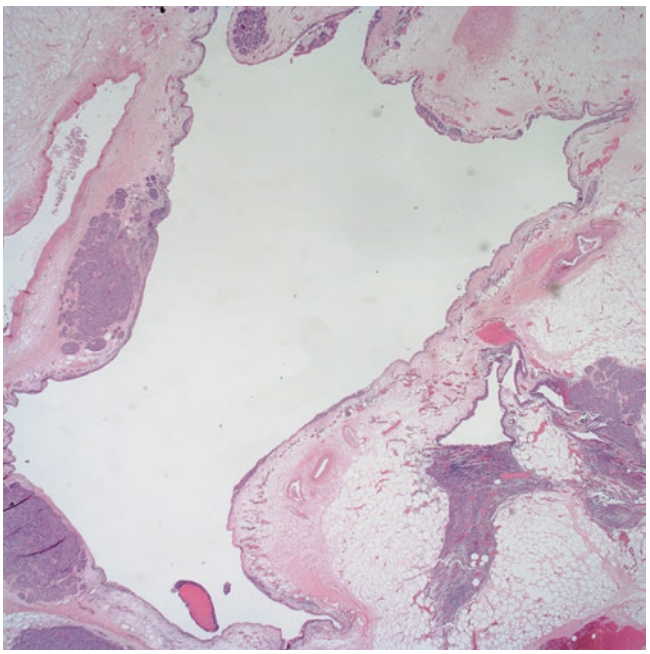


Fig. 9.53 Low power view of a cystic neuroendocrine carcinoma mimicking multilocular thymic cyst

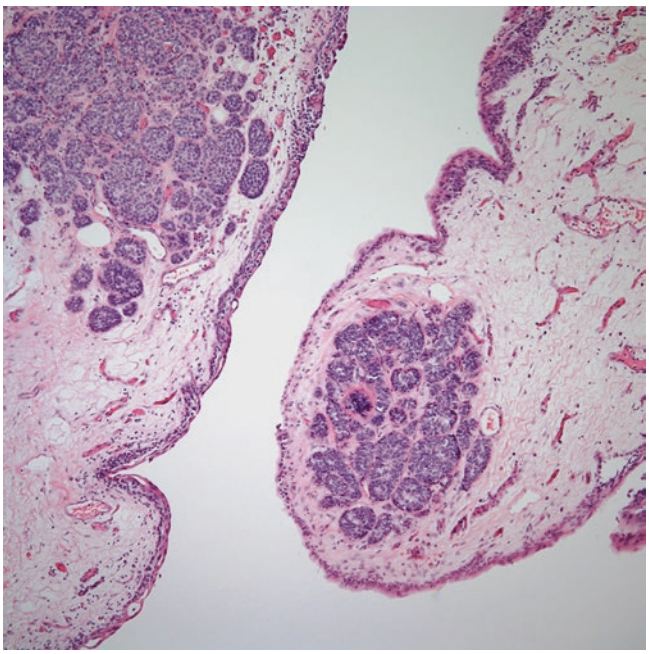


Fig. 9.55 Closer view of the cystic walls containing neoplastic cells

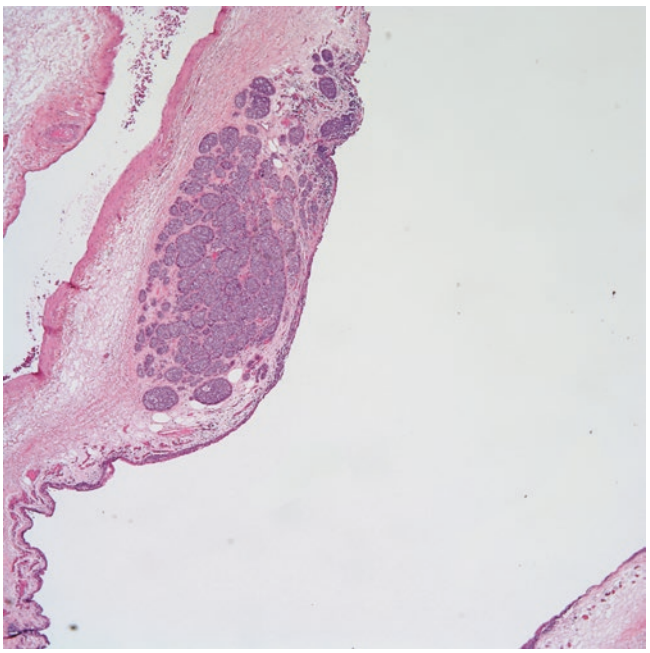


Fig. 9.54 Cystic neuroendocrine carcinoma showing the neoplastic cellular proliferation in the walls of the cyst

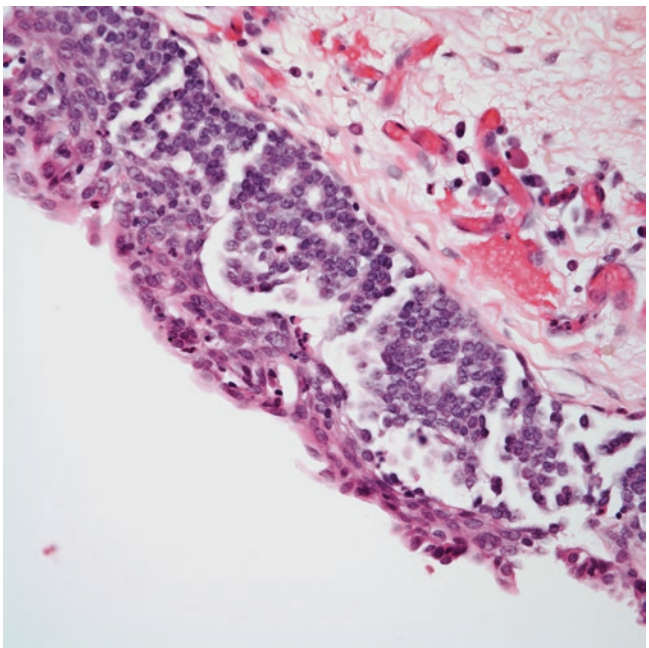


Fig. 9.56 Cystic neuroendocrine carcinoma; note the subtle neoplastic cellular proliferation just underneath the cyst lining

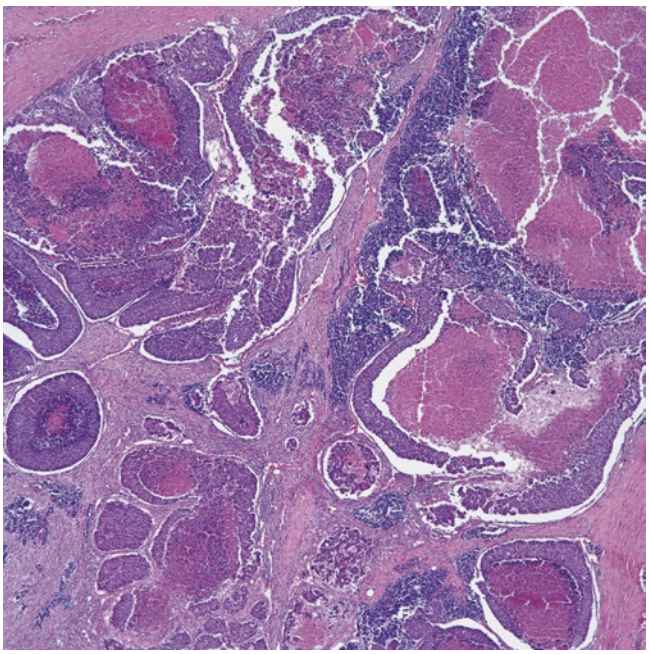


Fig. 9.57 Low power view of a high-grade neuroendocrine carcinoma. The necrosis is obvious

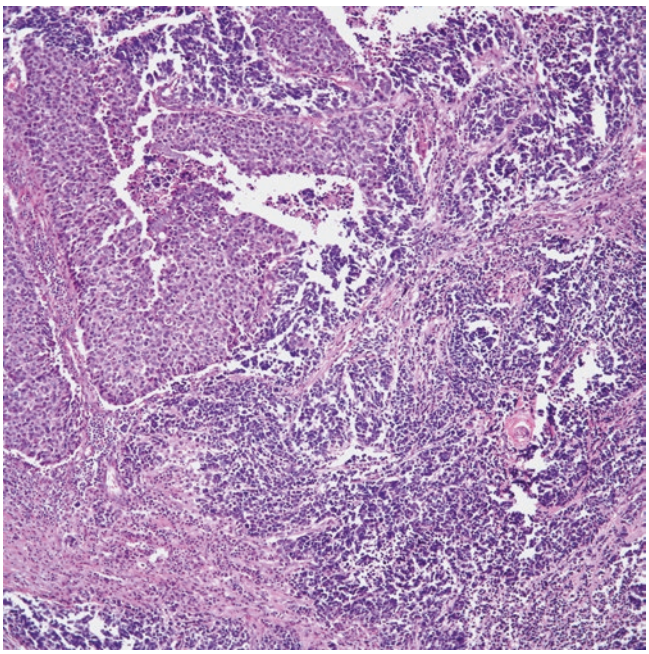


Fig. 9.59 Easily identifiable components of an intermediate-grade and a high-grade neuroendocrine carcinoma

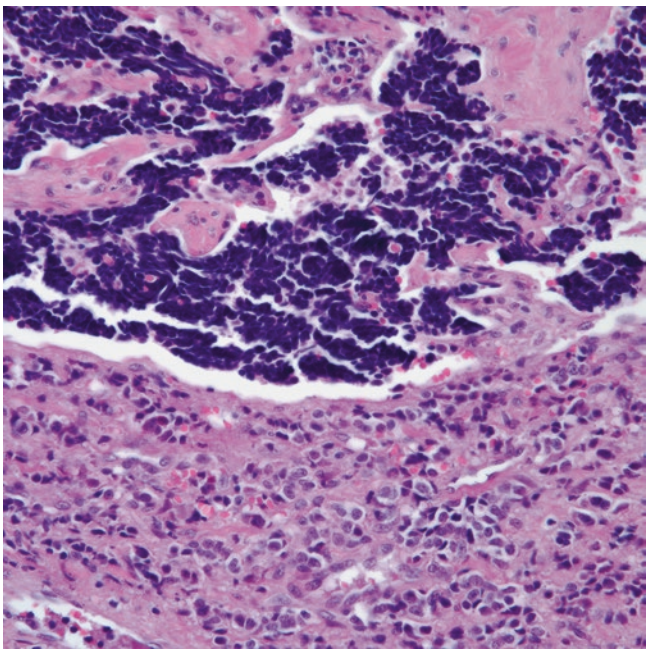


Fig. 9.58 Transitional areas of low- to high-grade neuroendocrine carcinoma (small cell carcinoma)

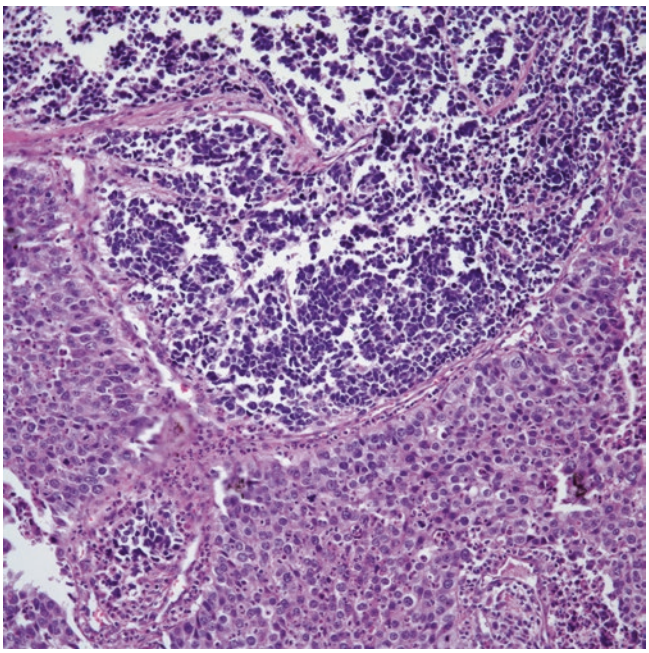


Fig. 9.60 High-grade neuroendocrine carcinoma, small cell type admixed with an intermediate-grade neuroendocrine carcinoma

diagnosing primary thymic small cell carcinoma, as it is not uncommon for a primary lung carcinoma to present with mediastinal involvement. Even though similar warning can be applied to large cell neuroendocrine carcinoma of the thymus, in this particular tumor two different aspects must be carefully analyzed. One is the fact that these tumors must have a neuroendocrine pattern that also shows neuroendocrine differentiation using neuroendocrine markers or electron microscopy. The second aspect may be more complicated as thymic non-neuroendocrine carcinomas may also show areas of positive staining using neuroendocrine markers. However, in these tumors, the growth pattern is not a neuroendocrine growth pattern. Thus, such positive staining should not be construed as specific for the diagnosis of large cell neuroendocrine carcinoma. It is important to highlight that high-grade neuroendocrine carcinomas within the thoracic cavity are much more common in the lung than in the mediastinum, so that every attempt should be made to clinically rule out that possibility. Ultimately, the diagnosis of either one of these tumors lies on the radiological evidence of the absence of tumor in the lung.

Histologically, small cell carcinoma may show extensive areas of necrosis with a rather small neoplastic cellular proliferation composed of cells with round nuclei and finely dispersed chromatin and absence of nucleoli. High mitotic count and apoptotic cells are easily identified. Molding of the nuclei is commonly seen, while the so-called Azzopardi phenomenon may be seen in some cases (Figs. 9.61 and 9.62). On the contrary, large cell neuroendocrine carcinoma by definition is a non-small cell carcinoma with a neuroendocrine growth pattern (ribbon, rosettes, etc.) composed of a neoplastic cellular proliferation of larger cells with round to oval nuclei and prominent nucleoli. Extensive areas of necrosis may be present, and the mitotic activity in these tumors is high. However, the current diagnostic criteria require the presence of positive staining using neuroendocrine markers (chromogranin, synaptophysin, CD56).

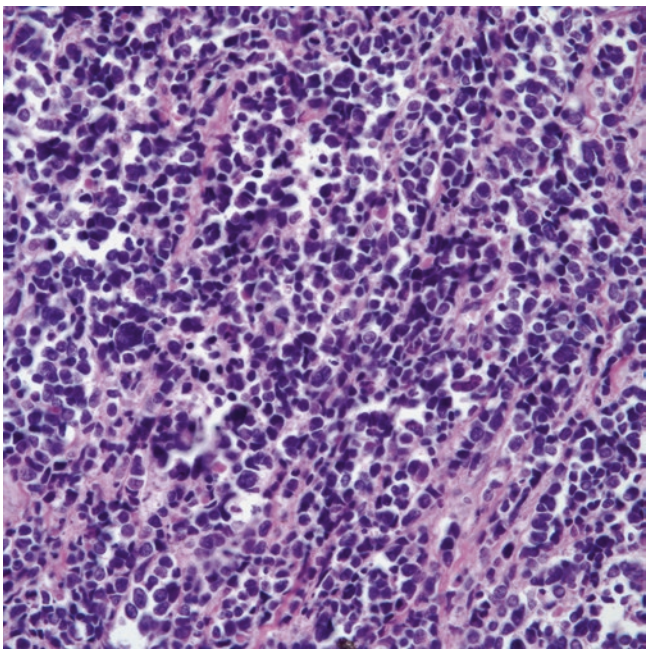


Fig. 9.61 High-grade neuroendocrine carcinoma, small cell type

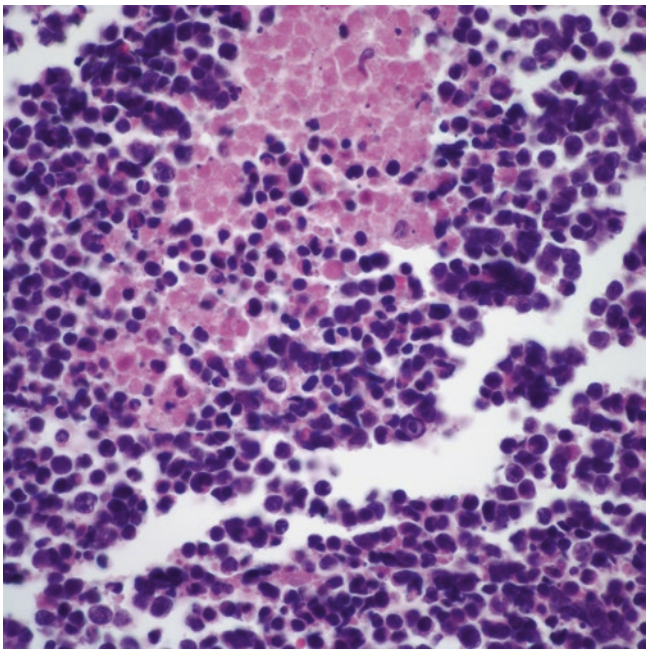


Fig. 9.62 Closer view of a high-grade neuroendocrine carcinoma (small cell carcinoma); note the presence of necrosis and molding

Immunohistochemical Features

Table 9.3 depicts some of the most commonly used immunohistochemical stains in the diagnosis of mediastinal neuroendocrine neoplasms. Specific studies on thymic neuroendocrine carcinomas with large series of cases are lacking. However,

Table 9.3 Commonly used immunohistochemical stains in the diagnosis of mediastinal neuroendocrine neoplasm

Antibody	NE carcinoma	Paraganglioma	Parathyroid adenoma
Chromogranin	Positive	Positive	Positive
Synaptophysin	Positive	Positive	Positive
CD-56	Positive	Positive	Positive
S-100 protein	Positive	Positive	*Negative*
Keratin	Positive	*Negative*	Positive
GATA3	*Negative*	Positive	*Negative*
TTF-1	Positive	*Negative*	*Negative*
Parathyroid hormone	*Negative*	*Negative*	Positive
Histochemical studies			
PAS	*Negative*	*Negative*	Positive
D-PAS	*Negative*	*Negative*	*Negative*
Mucicarmine	Positive in some cases extracellular	*Negative*	*Negative*

the use of immunohistochemistry to aid in the diagnosis of these tumors is well recognized in the literature, and there are several series of cases on this particular topic [44, 78–83]. Essentially, the use of conventional neuroendocrine markers such as chromogranin, synaptophysin, and CD-56 has been shown to aid in the diagnosis. Also important to highlight is that, in unusual cases, calcitonin may also show positive staining in these tumors [80]. In our experience with 40 cases of low- and intermediate-grade neuroendocrine carcinomas of the thymus, we were able to observe that low molecular weight keratin (CAM5.2) stained 100% of the tumors while broad-spectrum keratin stained 88% of them. In addition, chromogranin stained 75%, synaptophysin 72%, and Leu-7 68%. It is important to highlight that only 60% of the cases showed positive staining for both chromogranin and synaptophysin, thus arguing for performing a complete panel rather than just selected immunostains. More recently, in an attempt to separate thymic neuroendocrine tumors, namely, carcinoid and paraganglioma [83], a study of 46 cases was performed which not only used the conventional neuroendocrine markers but also other relatively new markers such as thyroid transcription factor (TTF-1); napsin A, and GATA-3 were added for evaluation. We reported that neuroendocrine carcinoma (carcinoid tumor) showed 100% staining for pan-cytokeratin, while chromogranin A and synaptophysin showed positive staining in 92 and 88%, respectively (Fig. 9.63a–c). Interestingly, TTF-1 was seen positive in 17% of thymic neuroendocrine carcinoma (Fig. 9.63d), while GATA-3 and napsin A were negative in all the cases. In a different study [81], we also attempted to determine the use of polyclonal PAX-8 and TTF-1 to separate thymic from pulmonary neuroendocrine carcinomas. We observed that pulmonary neuroendocrine carcinomas showed polyclonal PAX-8 expression in 8% of the tumors, while TTF-1 was seen positive in 76% of these tumors. On the contrary, thymic neuroendocrine carcinomas showed 32% positive staining for polyclonal PAX-8 and 8% positive staining for TTF-1.

Based on the collected experience with these tumors and their immunohistochemical profile, the use of neuroendocrine markers such as chromogranin and synaptophysin offers a good yield of positivity. The use of other stains such as TTF-1 and polyclonal PAX-8 offers a limited value in the diagnostic aid for these neoplasms. Important to highlight is the use of keratin, either pan-cytokeratin or low molecular weight keratin CAM5.2, which can help in separating these tumors from other neuroendocrine neoplasms that have a different biological behavior, namely, paragangliomas.

One important stain that has generated popularity is the use of Ki67 proliferative marker as an aid in the grading of neuroendocrine carcinomas. Even though it is an important stain, the use of that immunostain to properly grade these tumors may have some limitations. For instance, if the use of the marker is to determine grading of the tumor before resection, then it may prove complicated, as the marker would have to be used in a biopsy specimen, which may not necessarily be representative of the entire tumor. That is especially problematic for mediastinal tumors, which may be larger tumors. Thus, in this setting, the use of the marker may have limitations. On the other hand, if the use of the marker is left for resections, then once again their use may have limitations as the histological evaluation of these tumors in terms of mitotic count, and the presence of necrosis should be easily performed by light microscopy, delegating the use of Ki67 to a lesser importance. More important is the fact that there is not a single study addressing such a feature in thymic neuroendocrine carcinomas. Therefore, any conclusion on that topic would have to be extrapolated from tumors either of lung or gastrointestinal origin, and that may prove not necessarily correct. One other important issue is where to draw the lower and upper limit of the nuclear labeling. It is perhaps safe to assume that low-grade tumors should have <5% of nuclear labeling while high-grade tumors will have easily a nuclear labeling of 90–100%. However, determining the proper labeling range for intermediate-grade tumors may prove more complicated, thus the importance of an accurate histopathological assessment. Important to mention is the fact that even though the use of Ki-67 in the assessment of neuroendocrine carcinomas is

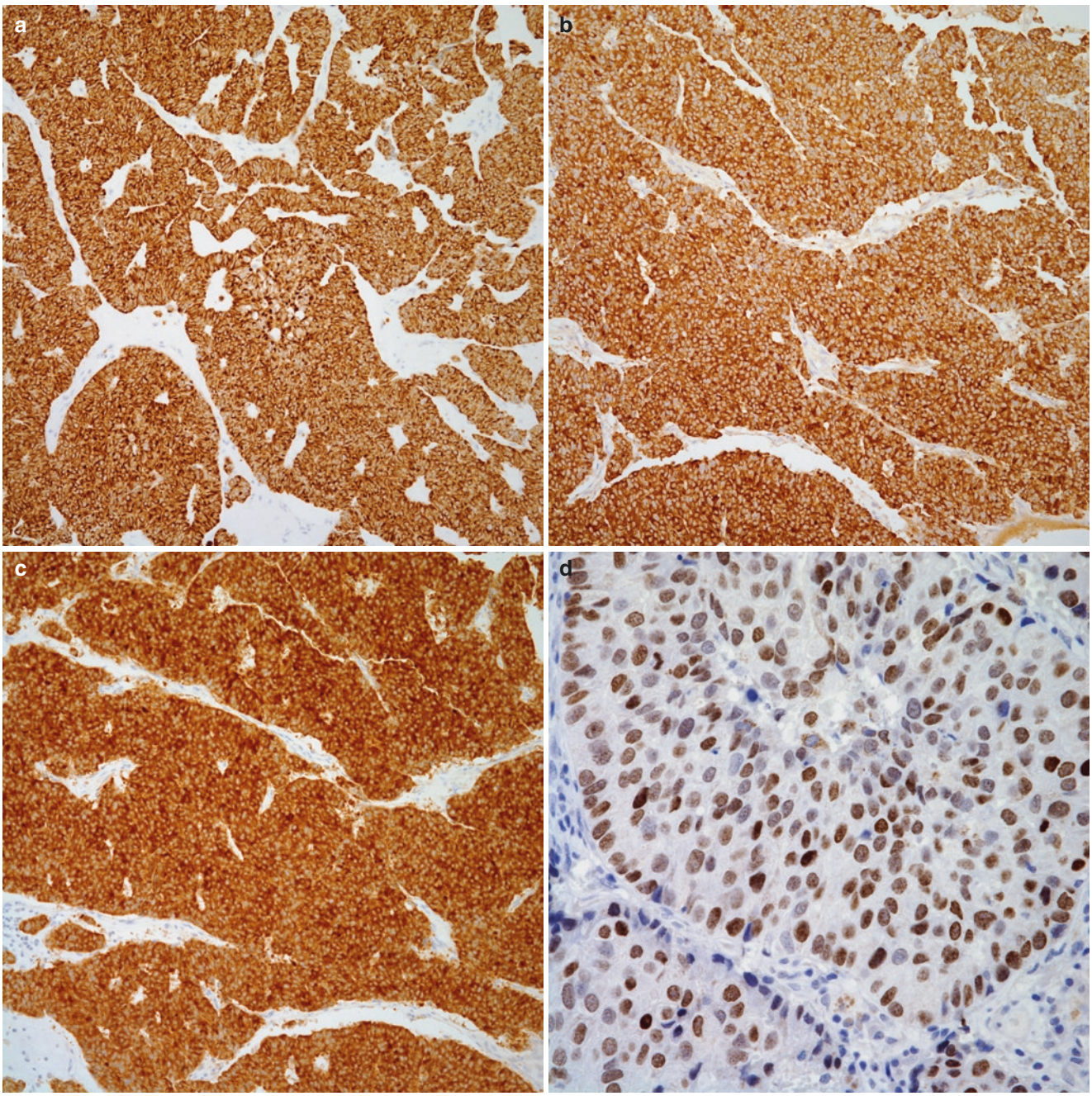


Fig. 9.63 (**a**) positive staining for keratin in a low-grade neuroendocrine carcinoma; (**b**) positive chromogranin stain; (**c**) positive staining for synaptophysin; (**d**) positive nuclear staining for TTF-1

important, the morphological appraisal of the presence of necrosis in these tumors cannot be underestimated, and this assessment can be easily performed by light microscopy. The presence of necrosis plays an important role in the grading of these neoplasms.

It is important to highlight that the use of neuroendocrine markers, such as those that have been mentioned for low- and intermediate-grade tumors, is not needed for the diagnosis of high-grade neuroendocrine carcinomas, except in the setting of the diagnosis of large cell neuroendocrine carcinoma, which requires such positive staining for final diagnosis. For the diagnosis of small cell carcinoma, the presence or absence of positive or negative staining for neuroendocrine markers should not be used as a discriminatory feature. However, if the consideration is another neoplasm, then their use may be appropriate. Table 9.3 depicts some of the most common antibodies used in daily practice for the diagnosis of neuroendocrine neoplasms.

Other Ancillary Studies

In today's practice, the use of immunohistochemistry is widespread in diagnostic surgical pathology in general. Nevertheless, there are other modalities that have been employed with some success and which potentially can be used as either diagnostic tools, or for pure academic curiosity. For instance, Kujari and coworkers [84] evaluated 23 carcinoid tumors by flow cytometry; they concluded that DNA aneuploidy is common in human carcinoid tumors, and may occur in tumors secreting biogenic amines. Fetissof and coworkers [85] evaluated the presence of probable intermediate filaments, which were accompanied by neurosecretory granules, and correlated these findings with a Grimelius histochemical stain. Similarly, Levine and Rosai [72] reported the use of electron microscopy in spindle cell "carcinoid" as a way to aid in the separation of these tumors from spindle cell thymomas. Kay and Wilson [86] reported a thymic ACTH-secreting tumor in which the authors performed electron microscopy, concluding that neurosecretory granules were easily identified in the tumor cells, and added that these granules were similar to those present in similar tumors in the lung. Essentially, the use of histochemical stains like Grimelius or the use of ultrastructural studies can also aid in the diagnosis of neuroendocrine carcinomas, as the presence of neurosecretory granules is rather characteristic in those tumors. However, in current practice the use of those ancillary studies is not as common as it used to be.

Differential Diagnosis

The differential diagnosis of thymic neuroendocrine carcinomas may include a diversity of conditions based on the type and growth pattern of the neuroendocrine carcinoma. However, more important in the assessment of neuroendocrine carcinomas is defining the primary site, as these tumors share similar histopathological features with those tumors arising in the gastrointestinal or pulmonary region. Often, establishing a good clinical and radiological correlation will lead to a more accurate interpretation regarding origin of the neoplasm. Therefore, whether it is a low-, intermediate-, or high-grade neuroendocrine carcinoma, establishing a good clinical and radiological correlation is highly recommended in order to determine a primary site, as such features not only determine prognosis but also lead to possible different treatment options.

From the histopathological point of view, the most important and difficult differential diagnosis is with paraganglioma and ectopic parathyroid adenoma. Both of these tumors may pose a significant problem in a small mediastinoscopic biopsy, and both of these tumors may also show positive staining for neuroendocrine markers. In this setting, if the suspicion is high, then the use of additional immunohistochemical stains such as keratins and parathyroid hormone immunostains may provide important information regarding the true nature of the neoplasm. Paragangliomas are likely to show negative staining for keratin, while parathyroid adenomas are likely to show positive staining for parathyroid hormone. In addition, the clinical information on disturbances in the metabolism of calcium and phosphorous will be relevant information that is generally correlated with parathyroid adenomas. In cases in which the histology of the neuroendocrine carcinoma is that of spindle cells, then spindle cell thymoma becomes an important tumor to exclude. In this setting, the use of neuroendocrine markers should lead to the correct interpretation. In cases in which the tumor shows mucinous component, a metastatic neoplasm from gastrointestinal origin should be carefully considered and properly excluded on clinical and radiological grounds. The use of other immunohistochemical markers such as CDX2 may also provide some additional aid in defining the site of origin of the tumor. When the tumors show prominent oncocytic features, important consideration would include an ectopic or metastatic thyroid carcinoma. Once again, the use of appropriate immunostains such as thyroglobulin, calcitonin, or monoclonal PAX-8 should lead to the correct interpretation.

In short, the differential diagnosis of thymic neuroendocrine carcinomas can be separated into (a) tumors that shared similar immunohistochemical profile and are primary thymic neoplasms, (b) primary thymic tumors that may show similar histopathological features but with different immunohistochemical phenotype, and (c) tumors that may share histological and immunohistochemical features but their primary site is outside of the mediastinal compartment. In all these settings, establishing a close

clinical and radiological correlation coupled with proper assessment of the histopathological features of the tumor supported by a proper immunohistochemical profile should lead more often to a more appropriate interpretation.

Paraganglioma

Extra-adrenal paragangliomas are tumors of ubiquitous distribution that have been described in many unusual anatomic areas such as the cauda equine and bladder. In the mediastinum, paragangliomas have been described in either anterior or posterior mediastinal locations [87–108].

Clinical Features

In one of the earlier reports of "intrathoracic pheochromocytoma," Phillips [90] described a single case of a 39-year-old man who presented with cardiac palpitation, throbbing in the head, polyuria, nocturia, and high blood pressure, and stated that a review of the literature had disclosed only 11 other cases in which the adrenal gland was not involved. He also alluded to the finding of chromaffin cells along the entire length of the autonomic nervous system in nests in the autonomic ganglions (paraganglions) or independently as chromaffin bodies (adrenal gland and Zuckerkandl's organ). In 1950, Lattes [91] described four cases of what the author called nonchromaffin paraganglioma of ganglion nodosum, carotid body, and aortic arch bodies, and asserted previous views that these tumors are not part of chromaffin paraganglionic system, and that they belong to an entirely different system. Marshall and Horn [92] studied 19 carotid and jugular body tumors and alluded to prior cases as far back as 1762. Green and Bassett [93] described what the authors called "intrathoracic pheochromocytoma" and accounted for 12 previous cases, of which 9 occurred in men and 3 in women between the ages of 8 and 64 years, with the average age being 30 years. Tama and coworkers [94] described a similar case in a 66-year-old man who presented with superior vena cava obstruction; however, the authors designated this neoplasm as a "chemodectoma of the mediastinum." Pachter in 1963 [95] described eight additional cases under the designation "mediastinal nonchromaffin paraganglioma." The tumors occurred in six women and two men between the ages of 27 and 68 years (average 46.5 years). Six of these patients were asymptomatic, and two others had non-specific symptoms; three of the cases described were incidental findings at autopsy. None of the tumors had clinical or laboratory evidence of hormonal activity, and all the tumors were in the anterior mediastinum. One important issue that is worth mentioning in the cases described by Pacther is that, in one of these cases, the patient had three separate tumors, similar to the case with multiple localizations also described by Lacquet and coworkers [99] in a 31-year-old woman. These cases highlight the issue of the care that must be exercised in rendering these cases as synchronous or metachronous tumors rather than metastatic disease. Olson and Salyer described four cases of their own in three men and one woman between the ages of 16 and 35 years. The authors stated that local recurrence or metastasis could not be predicted on histologic grounds and in their review of the literature concluded that the incidence of metastasis varies and depends on the length of the follow-up. In the cases reviewed by the authors, seven patients were known to have died of disease, with an average survival time of 6 years; four patients lived 8 years or longer. In addition to previous reports on thoracic paragangliomas, there have been cases in which the tumors from the outset have been described as "malignant." Enquist, Victor, and Odze, respectively [96, 97, 105], described three different male patients between the ages of 20 and 59 years, who presented with metastatic disease to the humerus, rib, and chest wall and whose main tumor was either in the anterior or posterior mediastinum. It is also important to recognize that, clinically, extra-adrenal paragangliomas may be associated with other neoplasms including pulmonary chondromas and gastric smooth muscle tumors, which is also known as Carney triad [103, 107]. In our experience with 16 mediastinal paragangliomas [89], the patients were ten men and six women between the ages of 16 and 69 years (mean: 42.5 years); 12 tumors were located in the posterior mediastinum, while 3 tumors were in the anterior mediastinum. In one case, a definitive location was not defined. Follow-up information obtained in 12 patients ranged from 1 to 168 months (mean: 84.5 months). Nine patients (75%) remained alive and well; however, metastatic disease to the bone marrow, lymph node, lung, and pelvis was documented as far as 14 years after initial diagnosis. It was concluded that the only parameter that correlates with aggressive behavior for these tumors is the extent of circumscription and/or local infiltration of the tumor at initial resection. No clinical or histological features were possible to associate with the behavior of these neoplasms; thus, close follow-up is highly recommended for patients with these tumors.

More recently, succinate dehydrogenase (SDH) has been studied in the evaluation of hereditary paragangliomas. Essentially, four subunits are evaluated in this setting, A, B, C, and D, which are the subunits that encode the mitochondrial enzyme succinate dehydrogenase (SDH) [109]. For mediastinal paragangliomas, Sato and coworkers [110] described a 69-year-old Japanese woman with a posterior mediastinal paraganglioma and a novel mutation (P236S) in

the SDH subunit B gene (SDHB). The authors stated the relevance of such mutation, as it may be associated with an aggressive behavior. Also, Garibaldi and coworkers [111] reported on a 55-year-old man with hereditary paraganglioma syndrome associated with SDHD gene mutations. The patient is described as having multiple extra-adrenal paragangliomas, including one in the mediastinal para-aortic area. Prodanov and associates [112] also reported on an 8-year-old girl with history of catecholamine excess-related symptoms with a malignant mediastinal paraganglioma associated with SDHB mutations. The authors stated that SDHB mutations in paragangliomas have a higher risk of malignancy.

Pathological Features

Gross Features

These tumors are either well-localized or ill-defined with local invasion into adjacent structures. They are soft, irregular, and tan to brown in color, which at cut surface may show focal areas of hemorrhage; otherwise, the surface is smooth (Fig. 9.64). The tumor also varies in size from a couple of centimeters to tumors over 10 cm in greatest dimension.

Histological Features

These tumors are characterized by a nesting pattern (so-called Zellballen), which is composed of islands of large cells with eosinophilic cytoplasm with round to oval nuclei; some cells may also have prominent nucleoli (Figs. 9.65, 9.66, 9.67, 9.68, 9.69, 9.70, and 9.71). Closer view of these tumors shows areas of prominent cellular pleomorphism, which are characterized by the presence of larger "bizarre" cells with macronuclei and prominent nucleoli (Figs. 9.72, 9.73, and 9.74). Even though mitotic figures may be present, they are scattered despite the prominent cellular pleomorphism that some tumors may have. The tumor also shows the presence of prominent ectatic vessels separating the islands of tumor cells. Even though these tumors show essentially a fairly similar growth pattern, some cases may show some unusual features that may pose a challenge in the evaluation of these

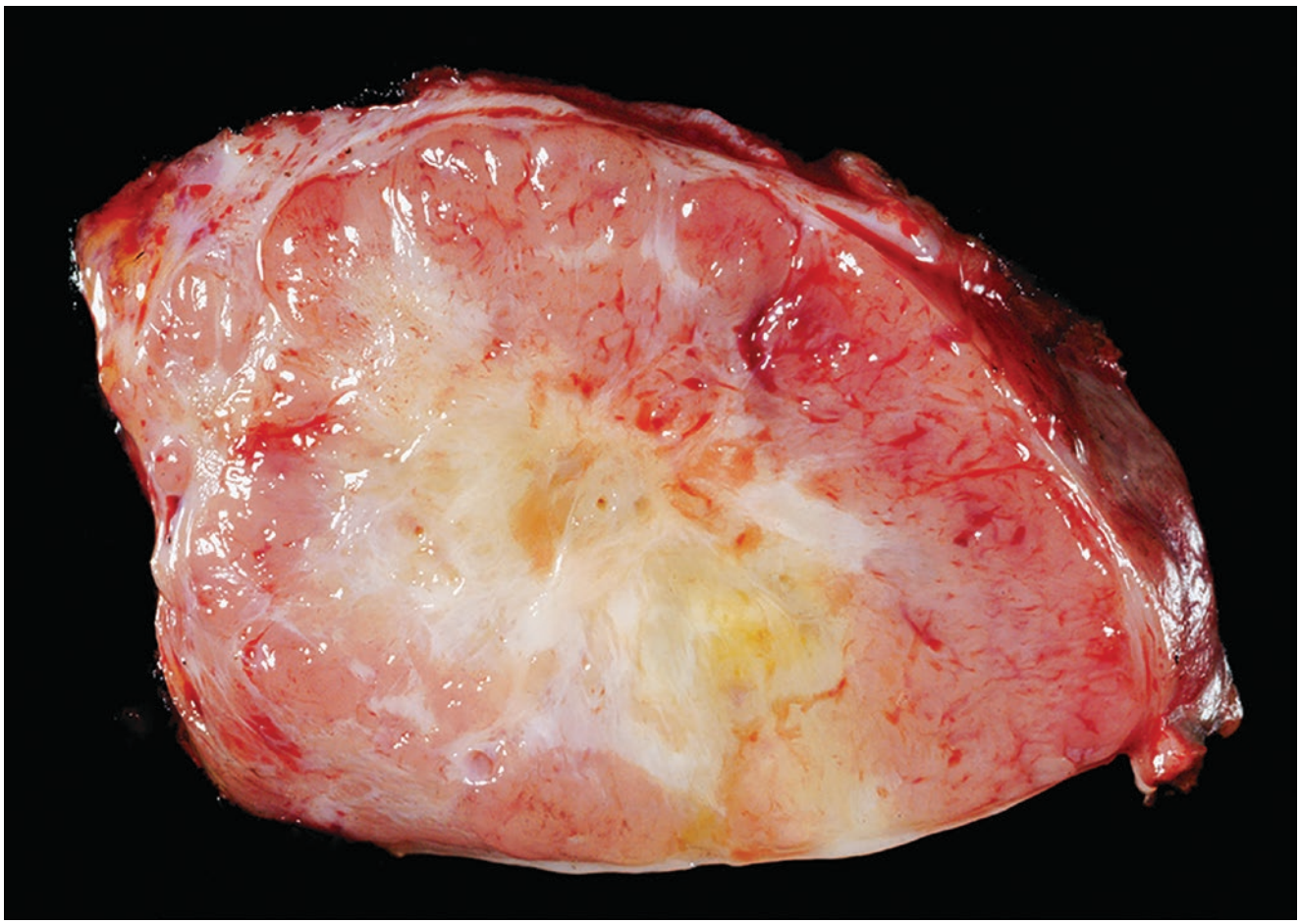


Fig. 9.64 Mediastinal paraganglioma showing a fleshy homogeneous cut surface. The tumor does not show areas of necrosis

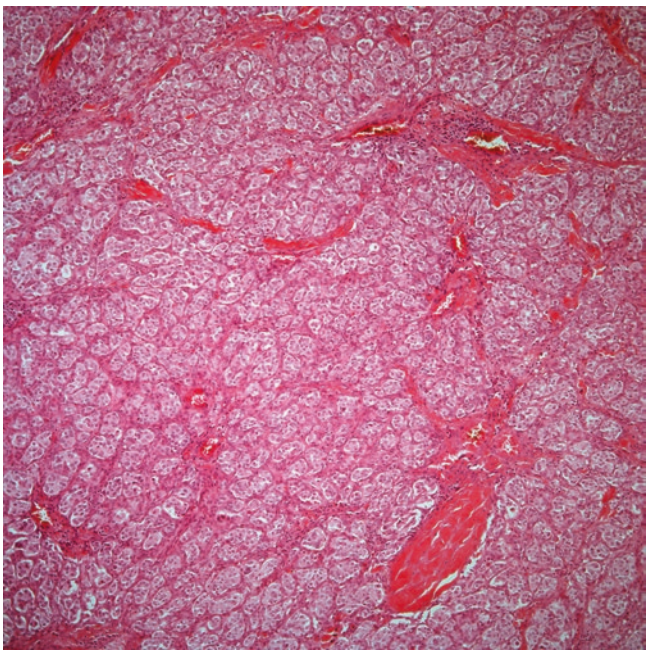


Fig. 9.65 Low power view of a paraganglioma showing the classic so-called zellballen

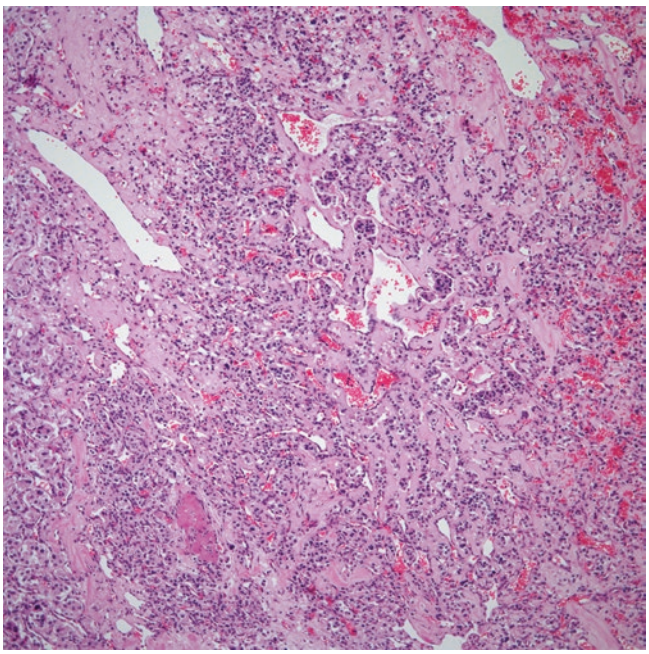


Fig. 9.67 Paraganglioma showing prominent ectatic vessels

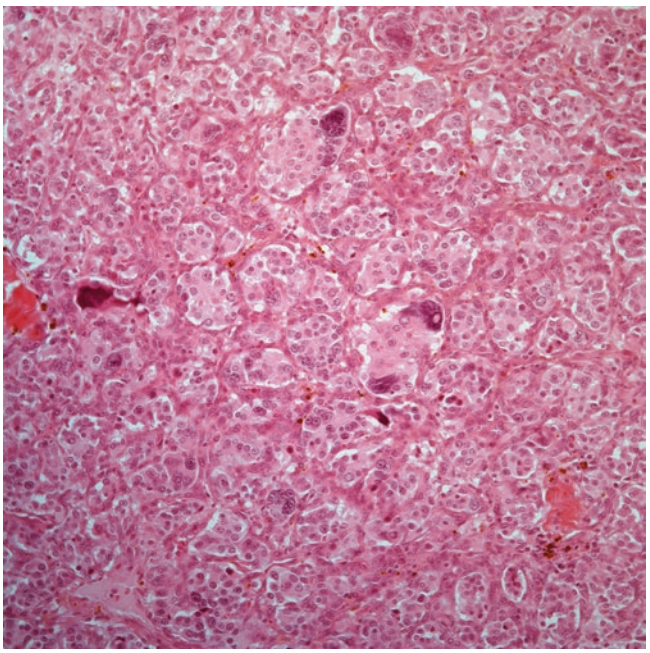


Fig. 9.66 Intermediate magnification of a paraganglioma showing the classic nested growth pattern and easily identifiable nuclear atypia

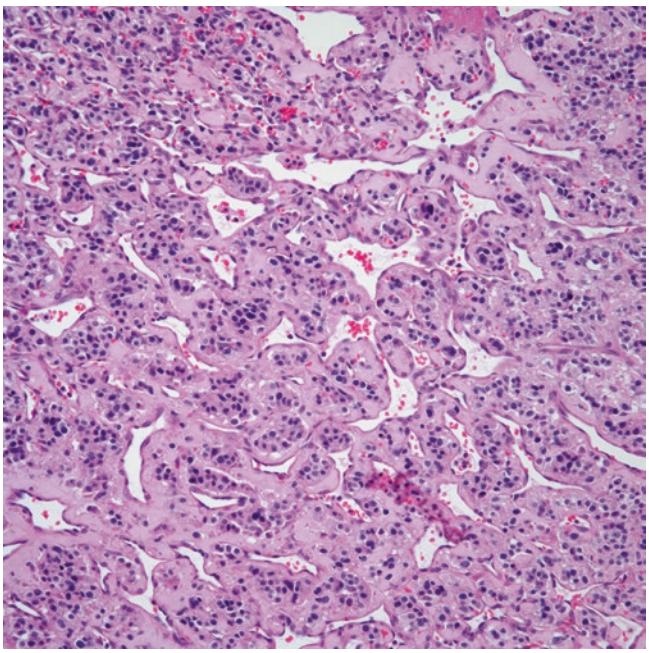


Fig. 9.68 Paraganglioma with an HPC-like growth vascular proliferation

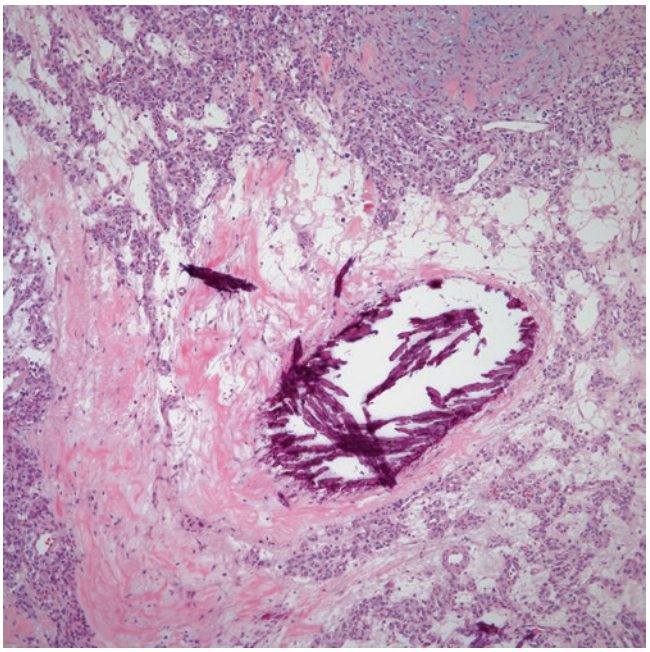


Fig. 9.69 Paraganglioma with extensive calcification

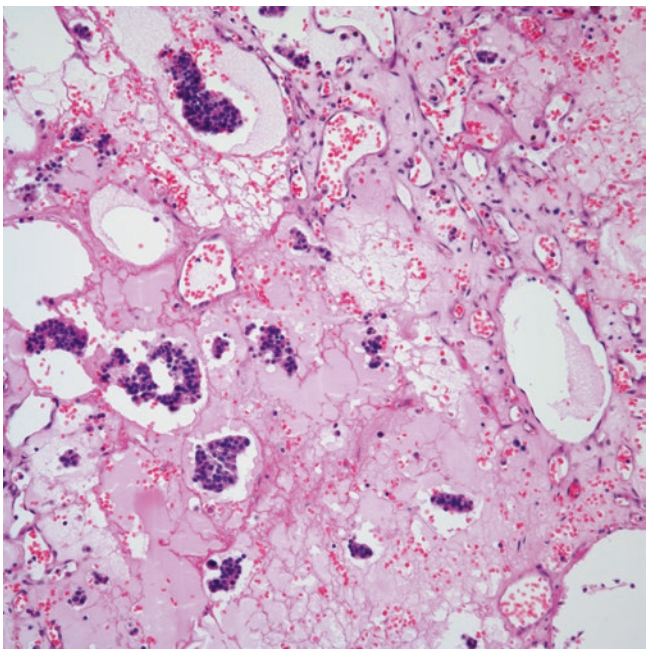


Fig. 9.71 Paraganglioma with extensive hyalinization and only clusters of neuroendocrine cells

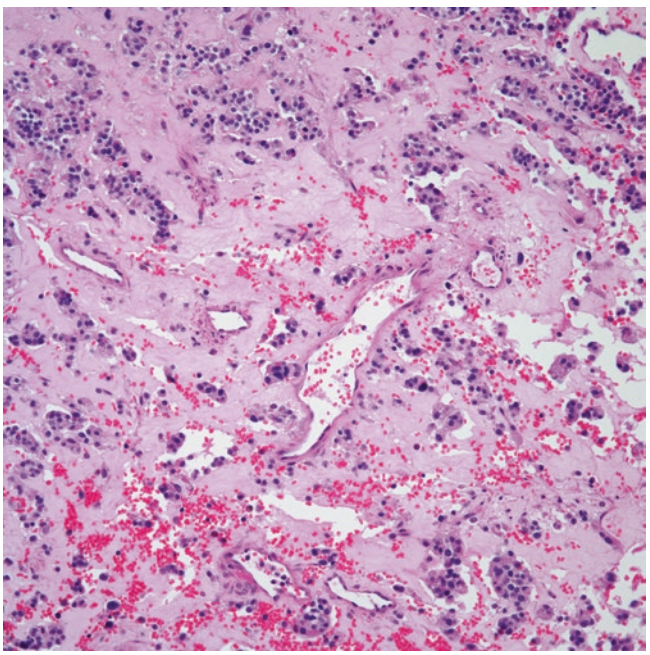


Fig. 9.70 Paraganglioma with more extensive areas of hyalinization

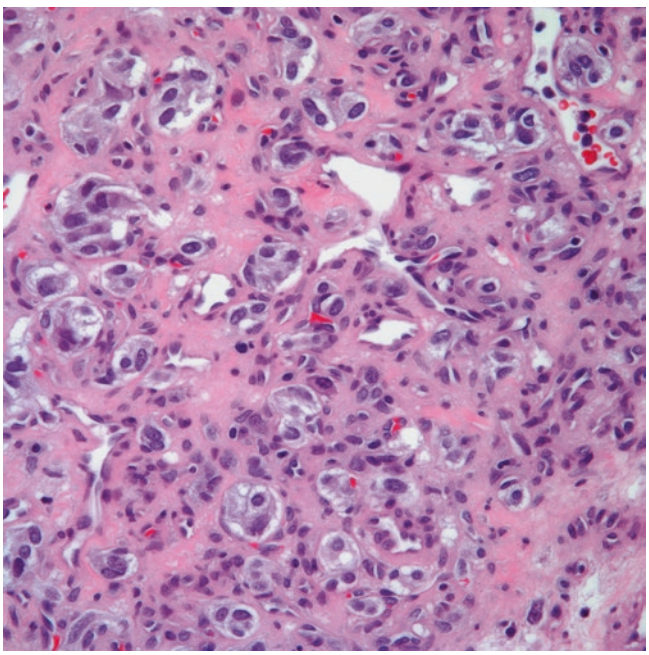


Fig. 9.72 Closer view of a paraganglioma showing nests of neuroendocrine cells with absent of nuclear atypia or mitotic activity

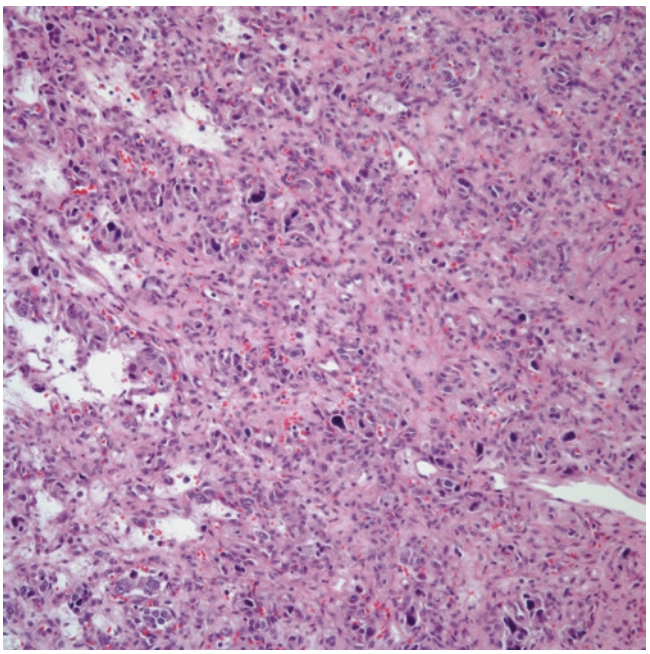


Fig. 9.73 Paraganglioma with easily identifiable cells with macronuclei

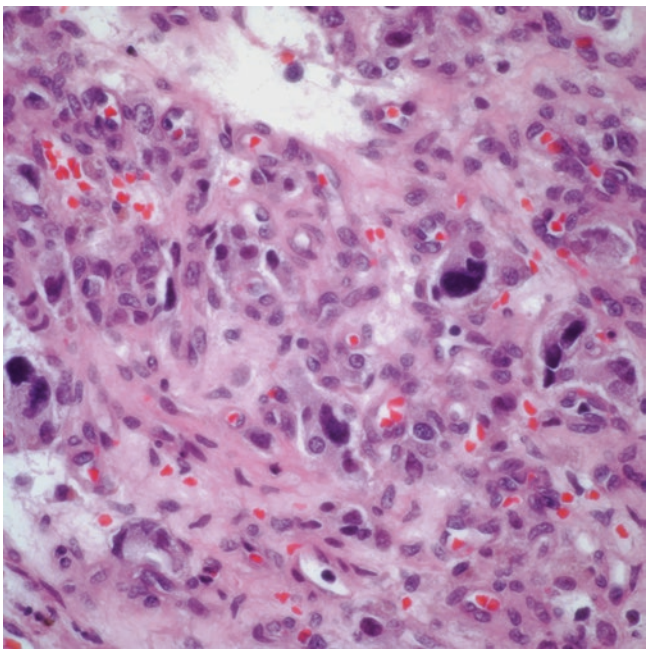


Fig. 9.74 Closer view of a paraganglioma showing bizarre cells with macronuclei

tumors. The presence of spindle cells (Figs. 9.75, 9.76, and 9.77) in which the tumor cells are arranged in a subtle storiform growth pattern may pose a challenge in the definitive diagnosis of these tumors. Also, tumors showing extensive areas of sclerosis (hyalinization) (Figs. 9.78, 9.79, and 9.80) have been described [108]. In addition, an unusual cystic variant of paraganglioma has been described [113]. From the cytologic standpoint, the tumor cells may show a striking granular appearance (Figs. 9.81 and 9.82), oncocytic changes (Figs. 9.83 and 9.84), clear cell cytoplasm (Fig. 9.85), and melanin pigment.

Immunohistochemical Features

By definition, paragangliomas are neuroendocrine neoplasms that may show positive staining for the conventional purported neuroendocrine markers, which include chromogranin, synaptophysin, and CD-56. In addition, S-100 protein may show positive staining in the sustentacular cells, which may be more prominent in those surrounding the epithelioid round cell areas rather than in the spindle cell component that may be present in these tumors. Also, other stains that have shown to be positive in these tumors, even though in a small number of cases, include Leu-enkephalin and neurofilament protein. One important feature with paragangliomas is the negative staining for these tumors with keratin. In a more recent study [83], we identified that paragangliomas may also show positive staining for GATA-3 in approximately 50% of the cases, while the tumors are also negative for TTF-1 and Napsyn, which may also aid in differentiating these tumors from neuroendocrine carcinomas (carcinoid tumors) (Fig. 9.86a–d).

Other Ancillary Studies

The use of ultrastructural studies may also help in the diagnosis of these tumors as the fine ultrastructural features of paragangliomas may show the presence of neurosecretory granules. However, the separation of neuroendocrine carcinomas and paragangliomas solely on ultrastructural grounds may prove to be very difficult as both tumors may show the presence of neurosecretory granules. Grimellius histochemical stain in paragangliomas may also show positive staining in tumor cells. The tumor is negative for PAS with and without diastase.

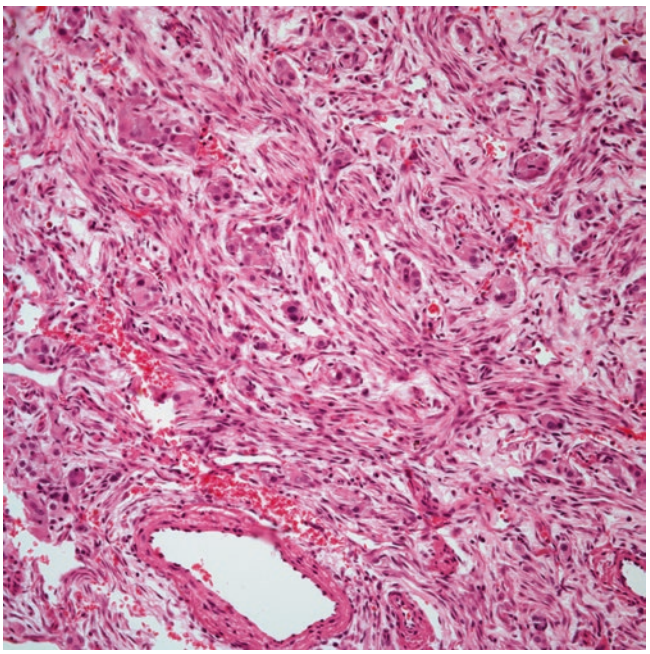


Fig. 9.75 Paraganglioma showing a mixture of round and spindle cells

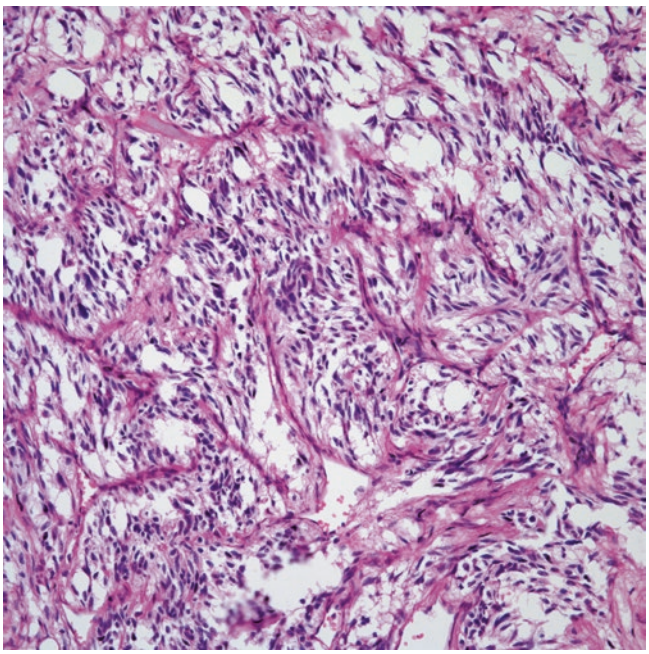


Fig. 9.77 Spindle cell paraganglioma

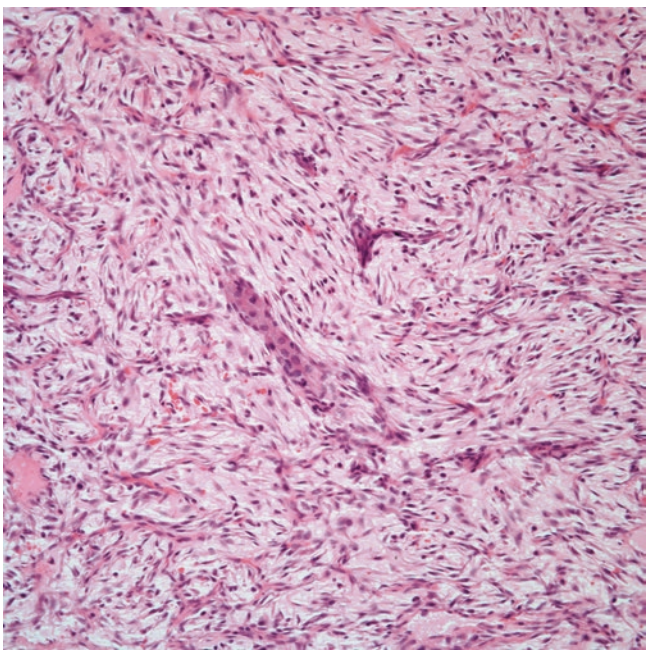


Fig. 9.76 Predominantly spindle cell paraganglioma with only focal round cell component

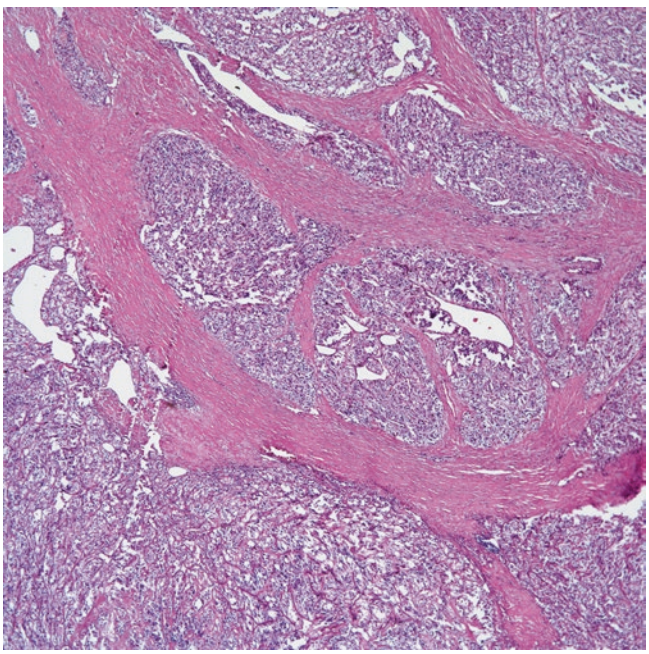


Fig. 9.78 Paraganglioma with extensive areas of thick fibrous bands

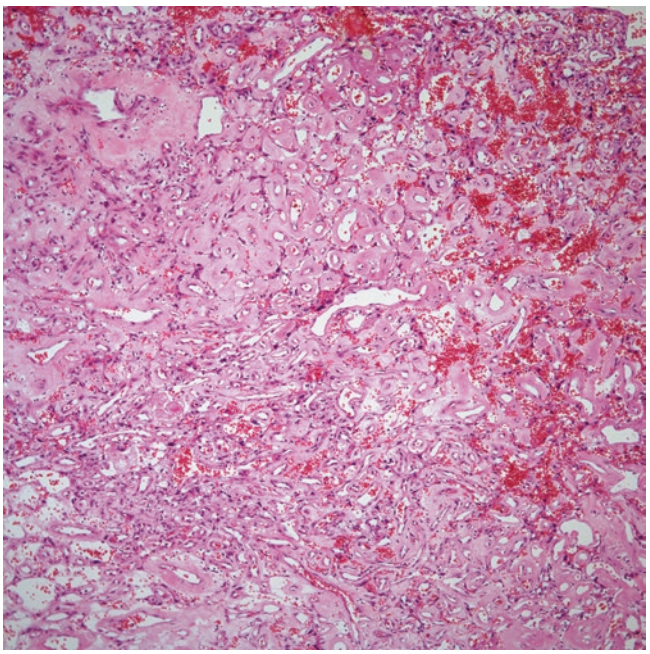


Fig. 9.79 Paraganglioma with extensive vascularity and hyalinization

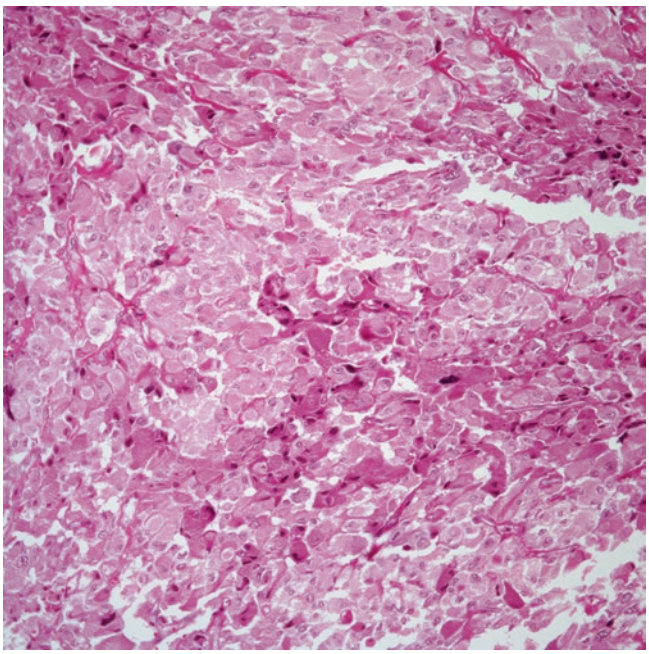


Fig. 9.81 Low power view of a paraganglioma with prominent granular cells

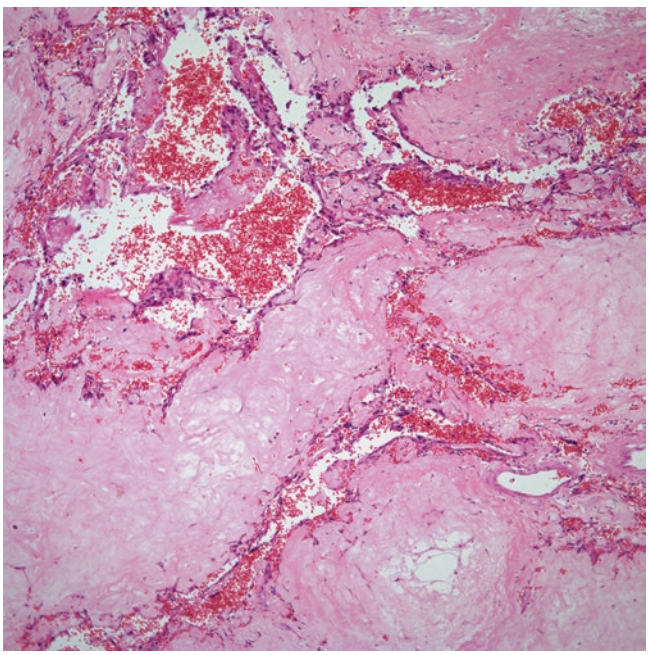


Fig. 9.80 Paraganglioma with extensive hyalinization

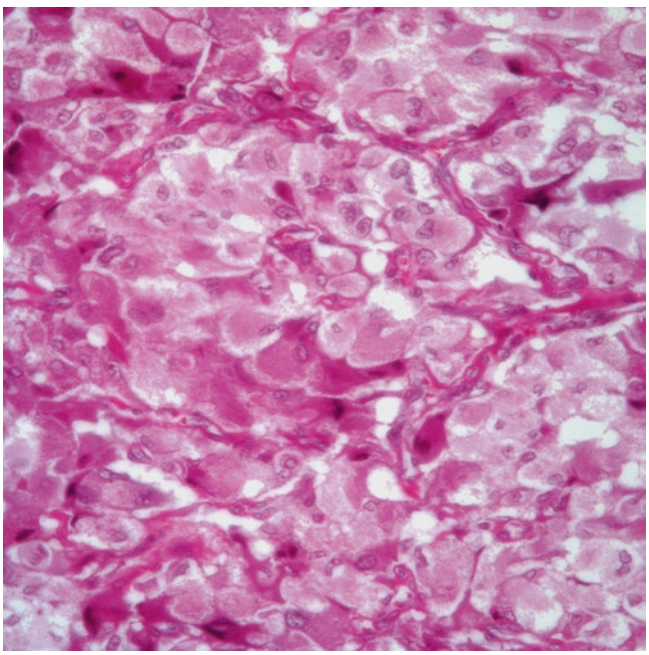


Fig. 9.82 Higher magnification of a granular cell paraganglioma; note the presence of ample granular cytoplasm of the cells

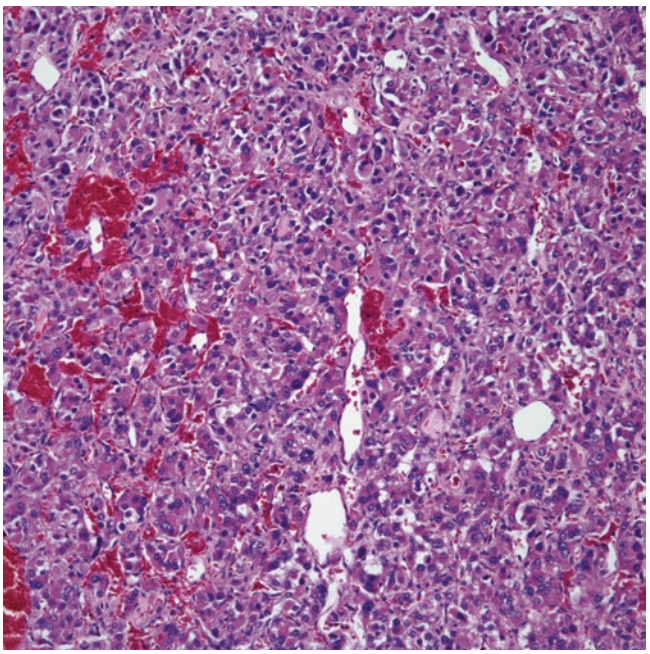


Fig. 9.83 Low power view of an oncocytic paraganglioma

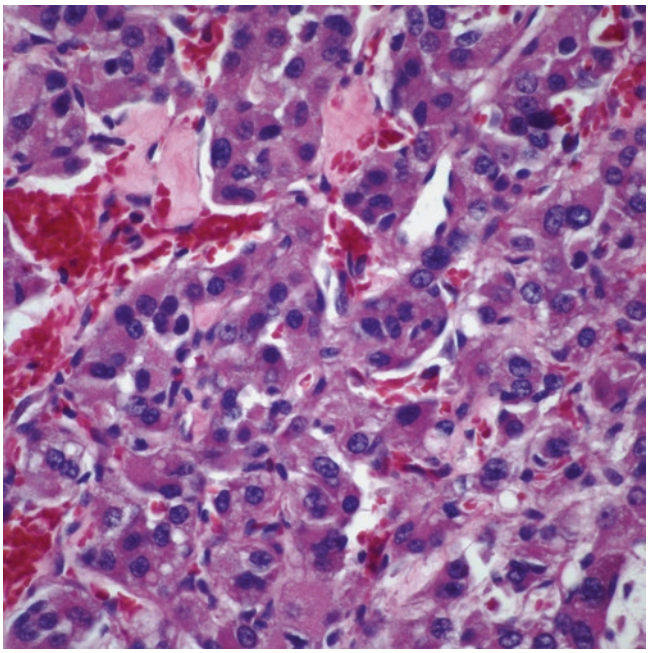


Fig. 9.84 Higher magnification of an oncocytic paraganglioma

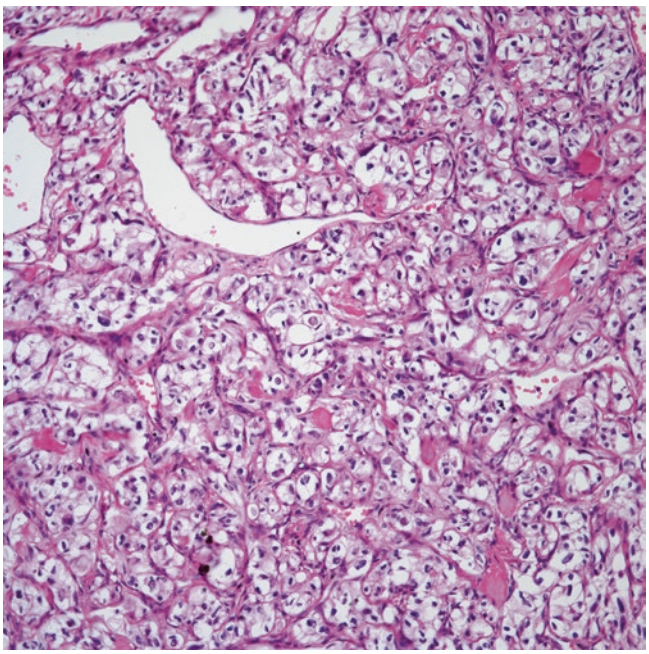


Fig. 9.85 Paraganglioma with prominent clear cell change

Differential Diagnosis

By far, the most important differential diagnosis is separating paragangliomas from neuroendocrine carcinomas and ectopic parathyroid adenomas or carcinoma. In this setting, the use of immunohistochemical stains – mainly the use of keratin coupled with neuroendocrine markers (chromogranin, synaptophysin, and CD-56) – may lead to the correct interpretation, as paragangliomas may show positive staining for neuroendocrine markers but negative staining for keratin and parathyroid hormone.

One other important consideration in the differential diagnosis of these tumors is the evaluation of multicentricity, as these tumors may be present in different locations from where normal paraganglia may exist, and yet the tumor should not be interpreted as metastatic in nature but rather synchronous or metachronous tumors.

On morphological grounds, the tumor that may mimic some of the growth pattern seen in paragangliomas is alveolar soft part sarcoma [114]. Alveolar soft part sarcoma has been described in the mediastinum; however, the tumor will

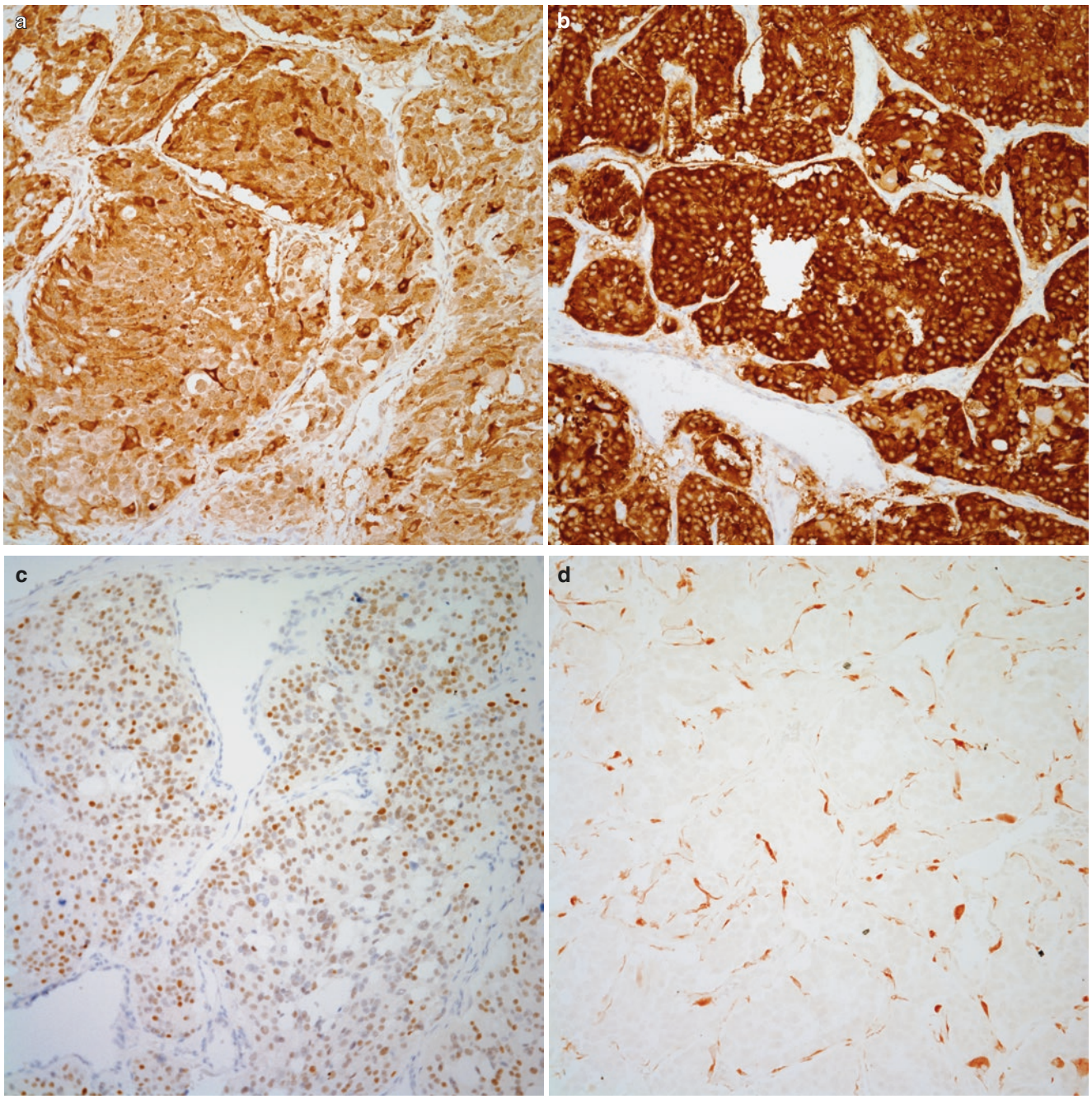


Fig. 9.86 (**a**) paraganglioma showing positive staining for chromogranin; (**b**) positive staining for synaptophysin; (**c**) positive nuclear staining for GATA3; (**d**) positive staining in sustentacular cells for S-100 protein

show negative staining for neuroendocrine markers. Other possible neoplasms that may enter in the differential diagnosis include metastatic renal cell carcinoma and other carcinomas that may have an organoid growth pattern. However, in this context, the use of keratin stain will lead to the correct interpretation.

Parathyroid Tumors

The presence of primary parathyroid tumors in the mediastinal compartment is a rare occurrence and represents a small percentage of these tumors when compared to other mediastinal neuroendocrine neoplasms such as carcinomas (carcinoid tumors) and paragangliomas. Even though parathyroid tumors were described in the mediastinum for more than a century, still these tumors are rare in daily practice and when present may pose a real problem in interpretation.

A possible explanation to account for these tumors may be the embryological development of the parathyroid glands and thymus. Parathyroid glands are formed from the dorsal diverticula of the endothelial cells of the third and fourth pharyngeal pouches. The pair from the fourth pouch is located on each side of the tunica propria of the medial surface of the lateral thyroid lobes at the level of the cricoid cartilage. On the other hand, the pair from the third pouch migrates caudally to the lower border of the thyroid gland. Regarding the primitive thymus, it arises as ventral and medial prolongations on either side from the third pharyngeal pouch. Some additional portions are derived from smaller invaginations of the fourth branchial pouch. The atrophy of the connecting ducts is followed by caudal migration of these cells to form the thoracic thymus [115]. Interestingly, the presence of parathyroid tissue in the thymus appears to be much more common in inferior animals such as rats, rabbits, and hedgehogs. Brewer [115] reported what appears to be one of the earliest observations of this phenomenon in humans in the USA, accounting for four autopsy cases in which the author was able to find two cases of heterotopia of parathyroid in thoracic thymus and two cases of parathyroid nodules in cervical thymus. On the other hand, some authors have actually questioned the name "parathyroid" as it suggests that the glands exist only in a limited area near the thyroid gland [116].

Clinical Features

The hallmark of patients with either parathyroid adenomas or carcinomas in the mediastinum is that of hyperparathyroidism. In 1941, Cope [116] documented his experience with 60 patients with hyperparathyroidism in whom 11 cases of parathyroid adenomas were found in the anterior mediastinum and 5 in the posterior mediastinum. The author estimated that hyperparathyroidism may be secondary to enlarged parathyroid glands in the mediastinum in more than 10% of the cases. Bauer and Federman [117] provide a detailed account of a particular patient who appears to have been one of the earliest cases diagnosed in the USA with hyperparathyroidism secondary to an anterior mediastinal parathyroid adenoma. In 1963, Pachter and Lattes [7] reported their experience with three mediastinal parathyroid tumors. Of the three cases reported, one was a functional parathyroid adenoma in which the patient had symptoms of nephrolithiasis and osteitis cystica. The parathyroid carcinoma was a nonfunctional tumor in which the patient presented with chest pain and no hormonal symptoms, while the additional parathyroid adenoma was an incidental finding during an autopsy procedure. Hardy and associates [118] documented a case in which the patient had four normal cervical parathyroids with an additional large functioning "fifth parathyroid" intrathoracic adenoma. In 1970, Nathaniels and associates [119] reviewed once again the subject of intrathoracic parathyroid tumors and documented that, out of 400 patients treated for hyperparathyroidism, 84 of the parathyroid tumors were located in the mediastinum, 67 in the anterior, and 17 in the posterior mediastinum. Interestingly, the authors also documented that, of the 94 normal parathyroid glands identified in the right neck, 19–20% were located within the thymic capsule in the lower neck or in the substance of the thymus in the anterior mediastinum. Important to mention is the fact that parathyroid cysts similar to those described in the neck have also been described in the mediastinum. Thacker and associates [120] documented a single case of a 46-year-old man with no symptoms of hyperparathyroidism and also provided an account of nine previous cases reported in the literature dating back to 1925. However, Margolis and associates [121] documented a similar case of a mediastinal parathyroid cyst in a 40-year-old man who had metabolic abnormalities, while Simkin [122] documented a 52-year-old man with hyperparathyroidism in association with a mediastinal parathyroid cyst. Eventually, numerous publications on the topic of mediastinal parathyroid cyst have been published in the literature on patients presenting with a diversity of symptoms, while others do not show any symptoms of functioning parathyroid tumor [123–128]. Scholz and associates [129] also documented a 43-year period of time with approximately 1000 patients with hyperparathyroidism. The authors documented 14 cases of mediastinal parathyroid tumors, which were found after one or more cervical explorations. Of the 14 mediastinal tumors, 13 were adenomas and 1 carcinoma; two of the cases were findings at autopsy. Interestingly, the authors also documented five patients in whom abnormalities (hyperplasia or adenoma) in one or more parathyroid glands in the neck were identified. In addition, five patients had a total of five para-

thyroids including one in the mediastinum. In 1979, Wang and associates [130], in what appears to be the third review from the same institution, presented six additional cases of what the authors called hyperfunctioning supernumerary parathyroid glands, of which four of the patients have mediastinal tumors. Russell and associates [131] described their experience, also in what appears to be the second review from the same institution, with 38 mediastinal tumors requiring mediastinotomy for removal. Except for one of these patients, all had previous parathyroid exploration, while the authors described that "almost all" had significant complications of primary parathyroidism.

In general, regarding the occurrence of parathyroid tumors in the mediastinum, in a review of 285 patients treated surgically for hyperparathyroidism, 22% of the tumors were present in the mediastinum, and 38% of the patients required reoperation for persistent or recurrent hyperparathyroidism. The location of these tumors was more common in the anterior mediastinum at a ratio of approximately 4:1 [132]. Similar findings were also documented by Conn and associates [133], who reviewed 573 patients who had been explored for primary hyperparathyroidism and in whom parathyroid tissue was found in the mediastinum in approximately 11%. In a report more focused toward parathyroid adenomas, Roslyn and Mulder [134] encountered 26 out of 262 patients with persistent primary hyperparathyroidism. Six of these 26 patients had mediastinal parathyroid adenomas. Similar cases of fifth parathyroid adenoma after surgical exploration of the neck have also been documented [135].

Contrary to cases of mediastinal parathyroid adenomas, reports on mediastinal parathyroid carcinomas have been also presented in the literature; almost all of them reported as single case reports [136–140]. Just the same as with the cases reported as adenomas, patients with mediastinal parathyroid carcinomas may also present with functional and nonfunctional tumors. However, it is important to highlight that some metabolic abnormalities have also been associated with other tumors that are not of parathyroid origin. Yoshiike and associates [141] documented a 54-year-old man with a thymic squamous cell carcinoma producing parathyroid hormone-related protein and CYFRA 21-1. Also, Hsiao and associates [142] documented a patient with primary mediastinal B-cell lymphoma secreting parathyroid hormone-related protein who presented with superior vena cava syndrome and hypercalcemia. More recently, we have documented our experience with 17 patients with primary parathyroid tumors [143]. The tumors were equally distributed in both genders as nine tumors were in women and eight in men. All the tumors were located in the anterior mediastinum, and all patients had disturbances in the metabolism. One patient had previous history of neck exploration and secondary hyperparathyroidism due to polycystic kidney disease. One case was encountered at autopsy.

From the radiological point of view, patients with either parathyroid adenoma or parathyroid carcinoma may present with large mediastinal masses, which in turn may be either solid or cystic [144, 145]. However, the definitive diagnosis lies on the histopathological evaluation of the tumor.

Regarding the treatment and prognosis of parathyroid mediastinal tumors, it is linked to the histological type. For those tumors with the histological characteristics of adenoma, complete surgical resection may be the only therapy needed, while for parathyroid carcinoma, not only may the resection be more extensive due to the infiltrative manner of these tumors in the mediastinum, but, in addition, the patients may also be candidates for additional medical treatment with close follow-up.

Pathological Features

Gross Features

The description of most parathyroid adenomas is that of a well-circumscribed tumor mass, which at cut surface shows a homogeneous light brown color. The tumors do not show areas of hemorrhage or necrosis. However, in the macroscopic description of cases in which the histology is that of carcinoma, the tumors may show a more infiltrative nature by compromising more extensive areas within the mediastinum or involve adjacent structures such as the pericardium or mediastinal pleura. In these tumors, areas of hemorrhage or necrosis may be apparent. The size of these tumors varies, and small tumors of about 2 cm as well as large tumor of over 15 cm with large weight have been described (Fig. 9.87).

Histopathological Features

The histopathological features of parathyroid tumors can be subdivided in those seen in (A) parathyroid cyst, (B) parathyroid adenomas, and (C) parathyroid carcinomas. The different morphological patterns would show distinctive characteristics that make them amenable for appropriate interpretation.

Mediastinal parathyroid cyst would show a unilocular cystic structure lined by flatten epithelium and thick wall, which may show inflammatory reaction and underlying adipose tissue. Higher magnification of the walls of the cyst will disclose the presence of a cellular proliferation that may be

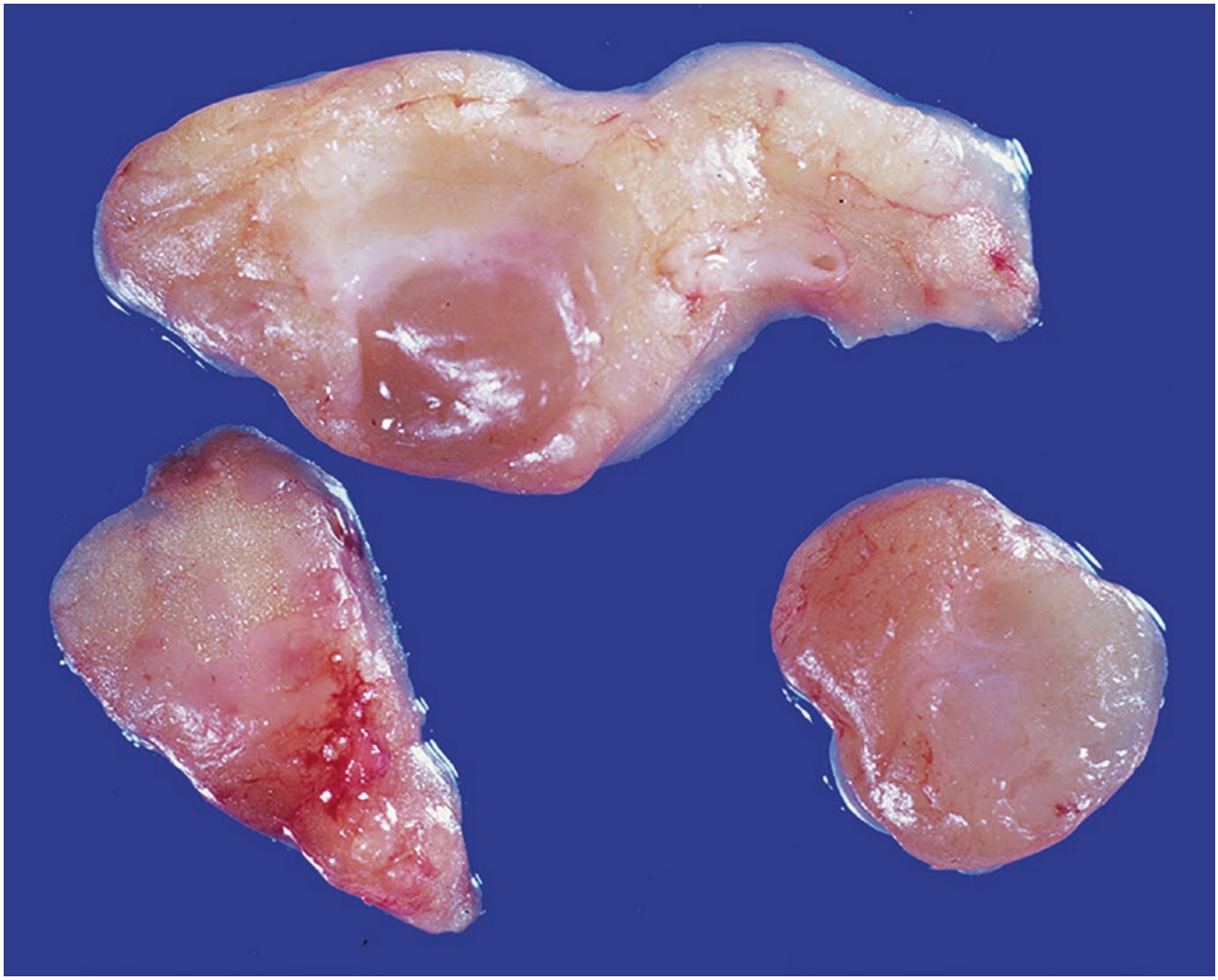


Fig. 9.87 Mediastinal parathyroid adenoma showing a light brown color with the absence of necrosis or hemorrhage

present in sheets of cells or in a subtle nested growth pattern (Fig. 9.88a, b). The cells may show a mixture of oncocytic cells with clear cells (chief cells). This cellular proliferation may extend in varying proportions in the walls of the cystic structures. Areas of necrosis and hemorrhage are generally not present nor are cellular atypia or mitotic activity.

Mediastinal parathyroid adenomas may be further separated in tumors with predominant oncocytic proliferation, chief cells, or a mixture of both. In predominantly oncocytic tumor, the cellular proliferation may be arranged in two forms. One is a more solid cellular proliferation with an organoid growth pattern composed of medium size, oval to polygonal cells with moderate amounts of eosinophilic cytoplasm, round to oval centrally placed nuclei, and in many cells with prominent nucleoli. The other unusual growth pattern is that of a pseudoglandular appearance with similar cytological features as those seen in the solid growth pattern. The presence of areas with numerous pyknotic cells is common. On the other hand, the tumors may be composed predominantly of chief cells in which the tumor cells are arranged in sheets of round to polygonal cells with clear cytoplasm, round to oval nuclei, and inconspicuous nucleoli (Figs. 9.89, 9.90, 9.91, 9.92, 9.93, 9.94, 9.95, 9.96, 9.97, 9.98, and 9.99). Microscopic cystic changes may be seen in both of these growth patterns. Even though the presence of mitotic activity is generally absent, in some cases,

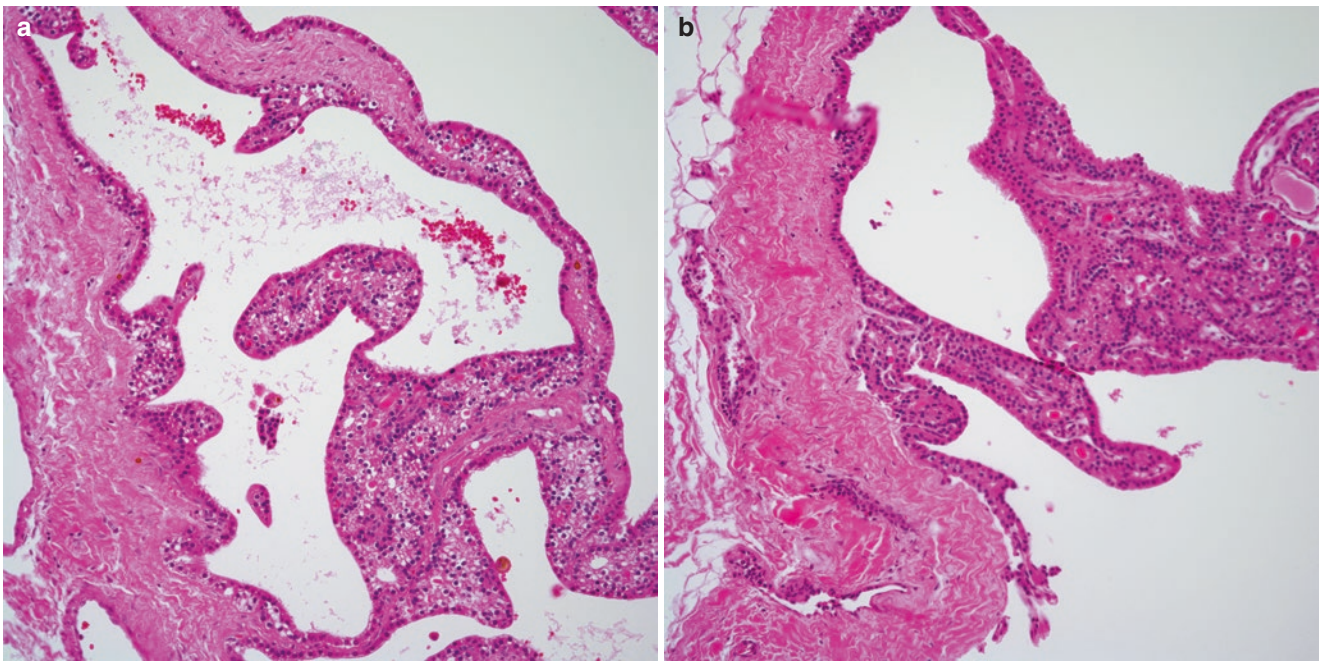


Fig. 9.88 (**a**) Mediastinal parathyroid cyst; note the cystic nature of the tumor; (**b**) mediastinal parathyroid cyst showing a proliferation of neuroendocrine cells

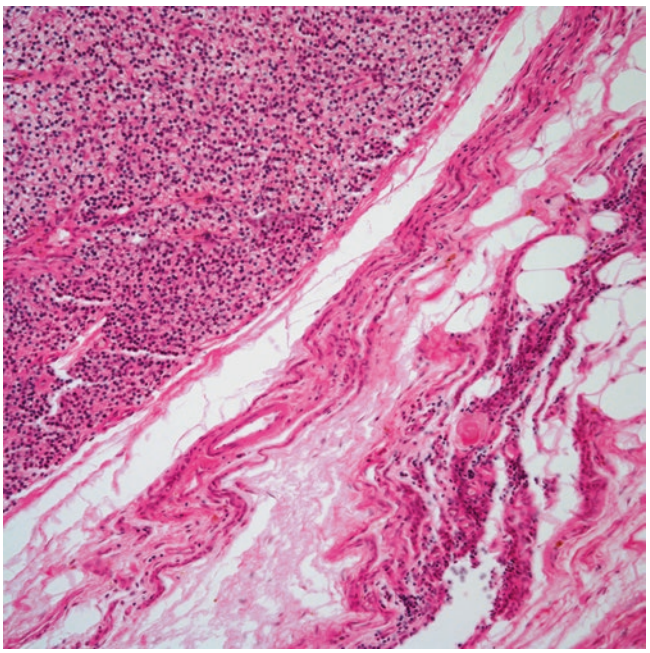


Fig. 9.89 Mediastinal parathyroid adenoma; note the presence of residual thymus in the periphery (Hassall's corpuscle)

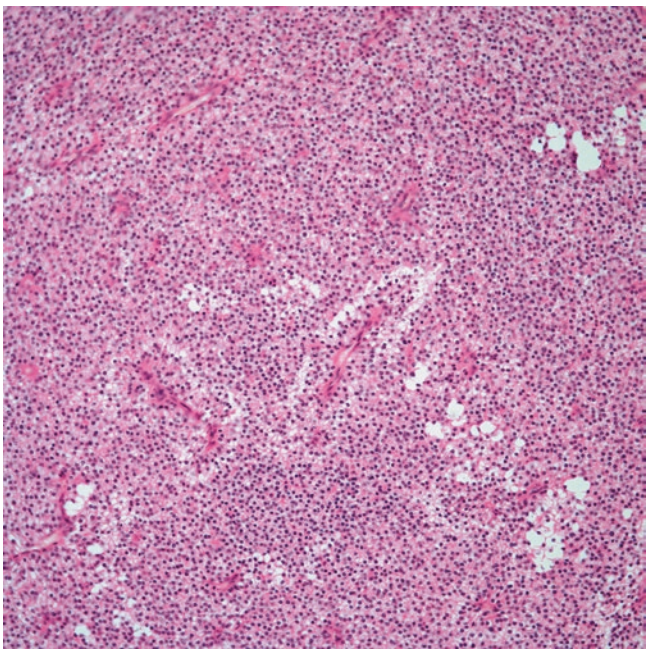


Fig. 9.90 Mediastinal parathyroid adenoma composed predominantly of chief cells

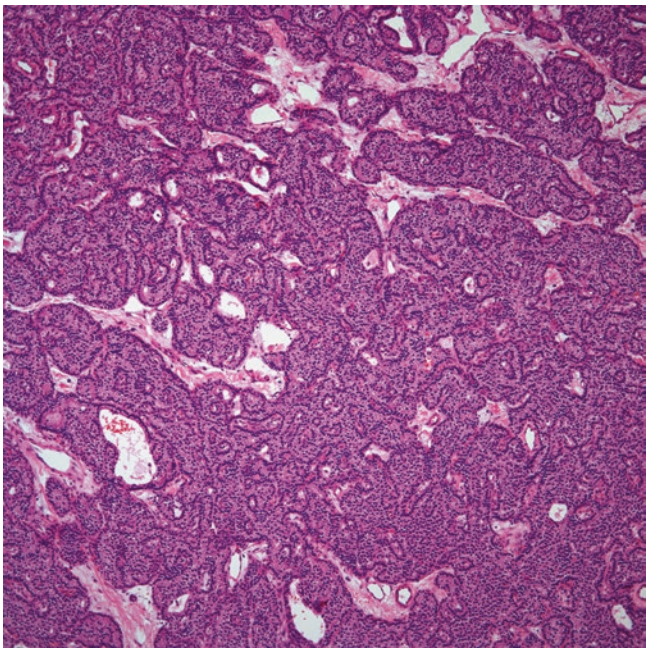


Fig. 9.91 Mediastinal parathyroid adenoma composed predominantly of chief cells in a pseudoglandular growth pattern

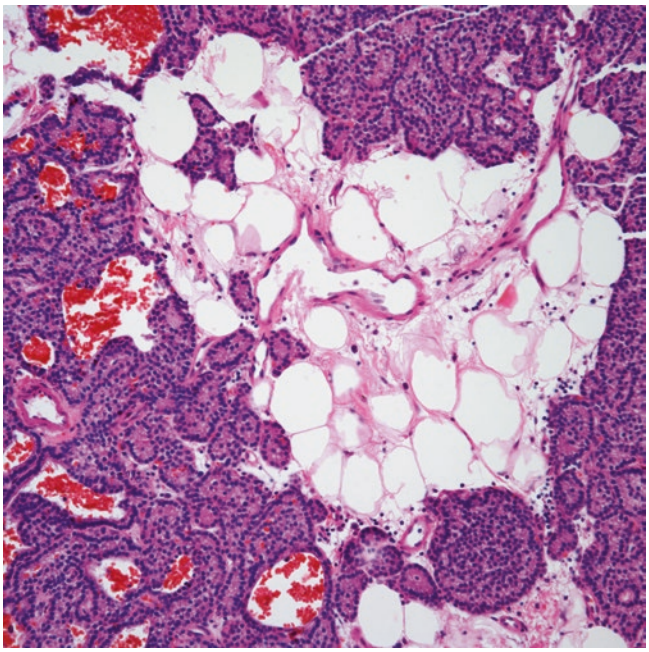


Fig. 9.93 Mediastinal parathyroid adenoma showing focal areas of adipose tissue

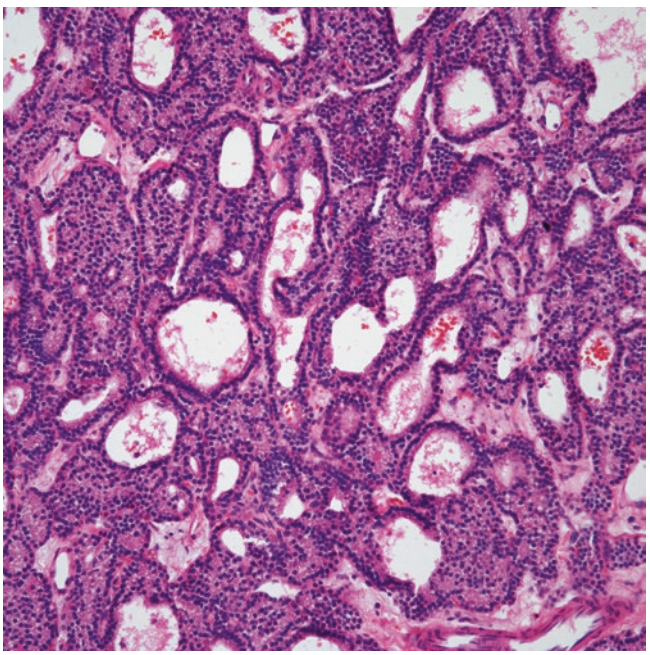


Fig. 9.92 Higher magnification showing a homogeneous cellular proliferation with absence of nuclear atypia or mitotic activity

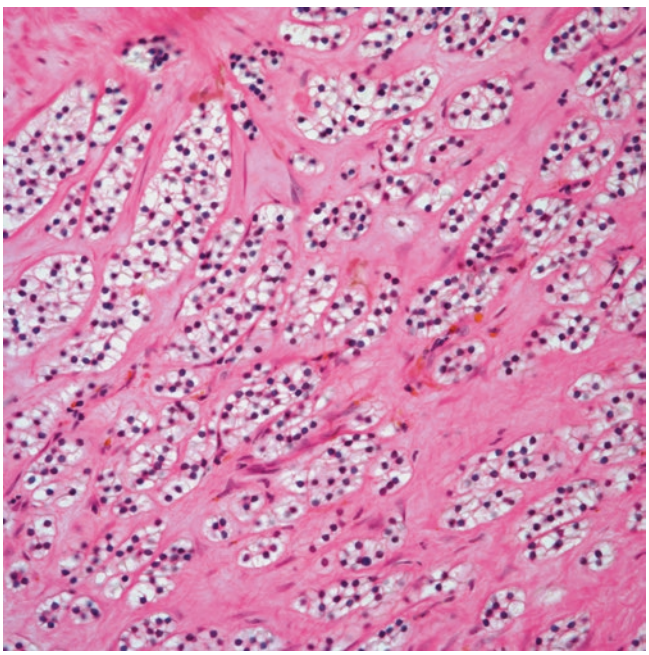


Fig. 9.94 Mediastinal parathyroid adenoma showing cords of clear cells (chief cells) dissecting fibroconnective tissue

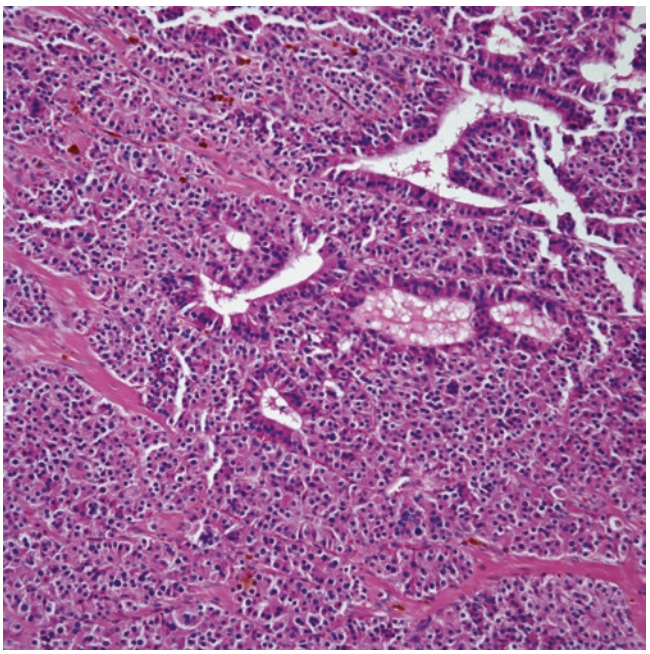


Fig. 9.95 Mediastinal parathyroid adenoma showing diffuse and glandular components

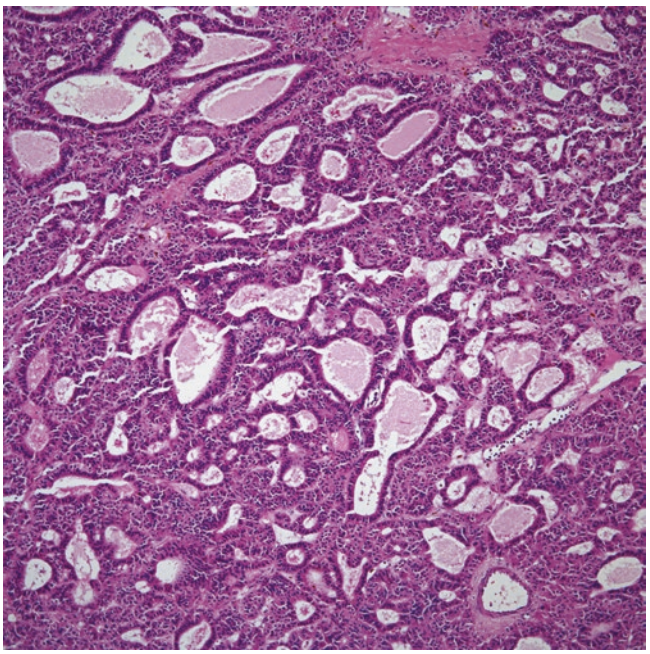


Fig. 9.96 Mediastinal parathyroid adenoma showing glandular like areas similar to those seen in angiectatic neuroendocrine carcinoma

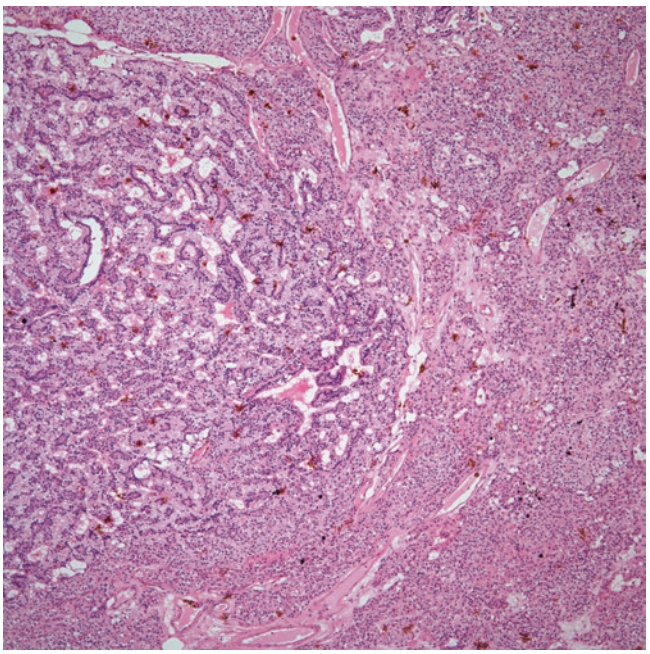


Fig. 9.97 Mediastinal parathyroid adenoma showing a mixture of components one diffuse and the other more glandular

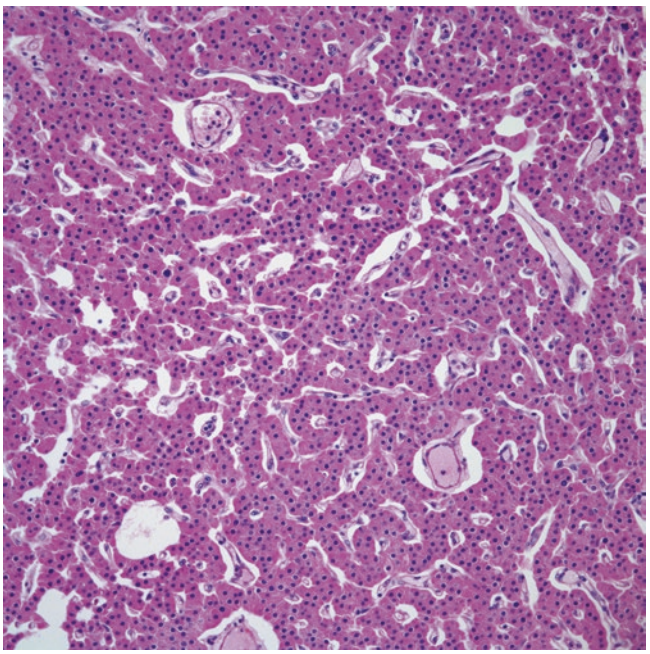


Fig. 9.98 Oncocytic mediastinal parathyroid adenoma. Note the absence of nuclear atypia

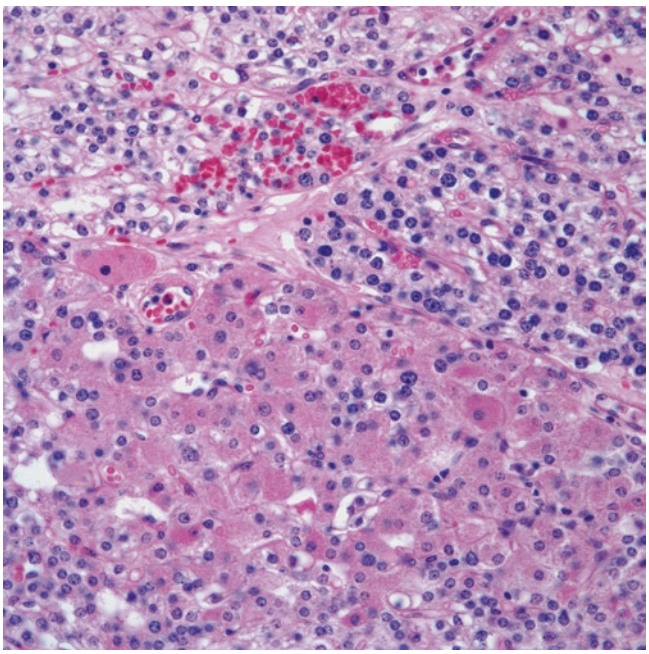


Fig. 9.99 Mediastinal parathyroid adenoma showing a mixture of chief and oncocytic cells

rare mitotic figures may be present. One additional feature that is important to recognize is the presence of extensive areas of sclerosis that are present in either oncocytic or chief cells predominant tumors (Fig. 9.100a–c). In addition, some tumors may show the presence of a combination of oncocytic and chief cell components with similar characteristics as those seen when one of those cell types predominate.

One important parathyroid tumor that has also been described in the mediastinum is parathyroid lipoadenoma [146]. Hargreaves and Wright described such a lesion in the posterior mediastinum. The tumor is characterized by the presence of areas of adipose tissue and parathyroid tissue, which can be arranged in acini, tubules, or simple aggregates. The adipose component may make up to 70% of the tumor mass.

The histopathological features of mediastinal parathyroid carcinoma are similar to those described for those tumors when they occur in the neck. Mainly, the tumor may show a more infiltrative growth pattern with ill-defined borders, presence of fibrous septa of varying thickness, necrosis, and increase mitotic activity. The tumors usually show the presence of a cellular proliferation composed of round to oval cells with oxyphilic and clear cells. Nuclear pleomorphism may be mild, and presence of nucleoli may not be apparent (Fig. 9.101a–c).

Ancillary Studies

The use of histochemical stains in the evaluation of parathyroid tumors may prove to be very useful when compared to other endocrine tumors that may enter in the differential diagnosis of these tumors. Periodic acid-Schiff may show the presence of glycogen in tumors that are composed of chief cells (Fig. 9.102). This particular histochemical stain may not be very useful in tumors that are composed predominantly of oncocytic cells. Mucicarmine is essentially negative in these tumors. Immunohistochemical stains are also of value in the evaluation of parathyroid tumors; however, care must be exercised, as other endocrine tumors may also share similar immunohistochemical phenotypes. Parathyroid tumor may show positive staining for chromogranin, synaptophysin, low molecular weight keratin, neuron-specific enolase, and parathyroid hormone. Because of this immunohistochemical profile, it is highly important to properly analyze these tumors, as other tumors with different clinical behavior may also share similar immunohistochemical features. In addition, the ultrastructural features of these tumors may also disclose the presence of neurosecretory granules that may be indistinguishable from those seen in other endocrine neoplasms.

Differential Diagnosis

By far the most important differential diagnosis of parathyroid tumors is with mediastinal neuroendocrine carcinoma (carcinoid and atypical carcinoid) and paragangliomas. When the parathyroid tumor is composed predominantly of chief cells, it may be slightly easier to reach the appropriate interpretation as neuroendocrine carcinomas with prominent clear cell changes are unusual. In addition, the presence of strong parathyroid hormone immunohistochemical stain may prove useful. In cases in which the tumors shows predominant oncocytic component, the morphological interpretation may be a bit more complicated, as oncocytic neuroendocrine carcinomas are not that unusual. The interpretation may get more complicated when the tumor shows an angiomatoid growth pattern that has been described in both tumors. It is highly important in these cases not only to have a thorough morphological evaluation of the tumor but also to perform a complete immunohistochemical panel that includes parathyroid hormone.

The separation of parathyroid tumor from paragangliomas may be slightly easier if the correct material is available for interpretation. The presence of macronuclei and nuclear atypia with bizarre cells is by far more common in paragan-

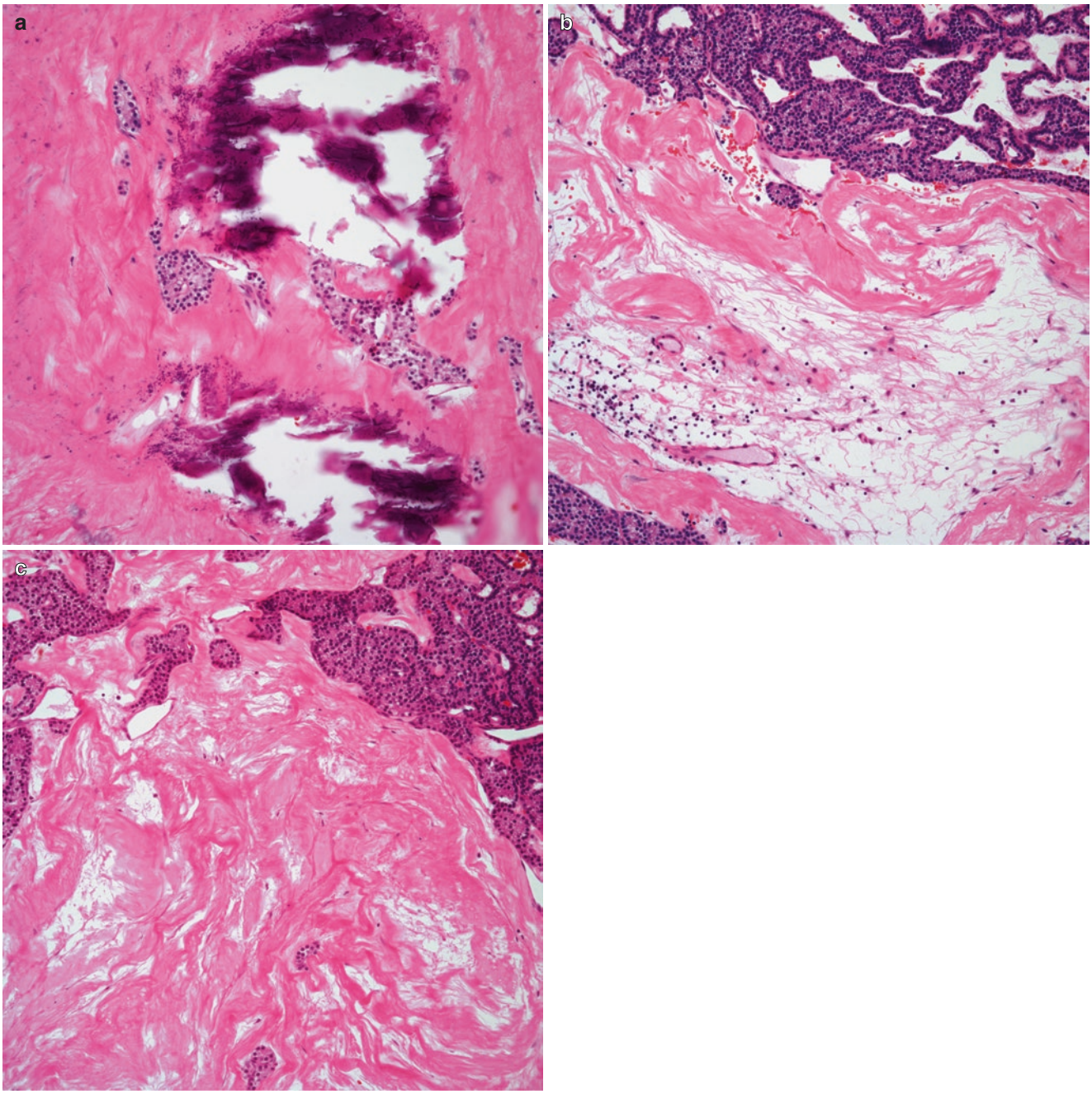


Fig. 9.100 (**a**) Mediastinal parathyroid adenoma with extensive calcification; (**b**) mediastinal parathyroid adenoma showing areas of hyalinization; (**c**) mediastinal parathyroid adenoma with extensive areas of hyalinization

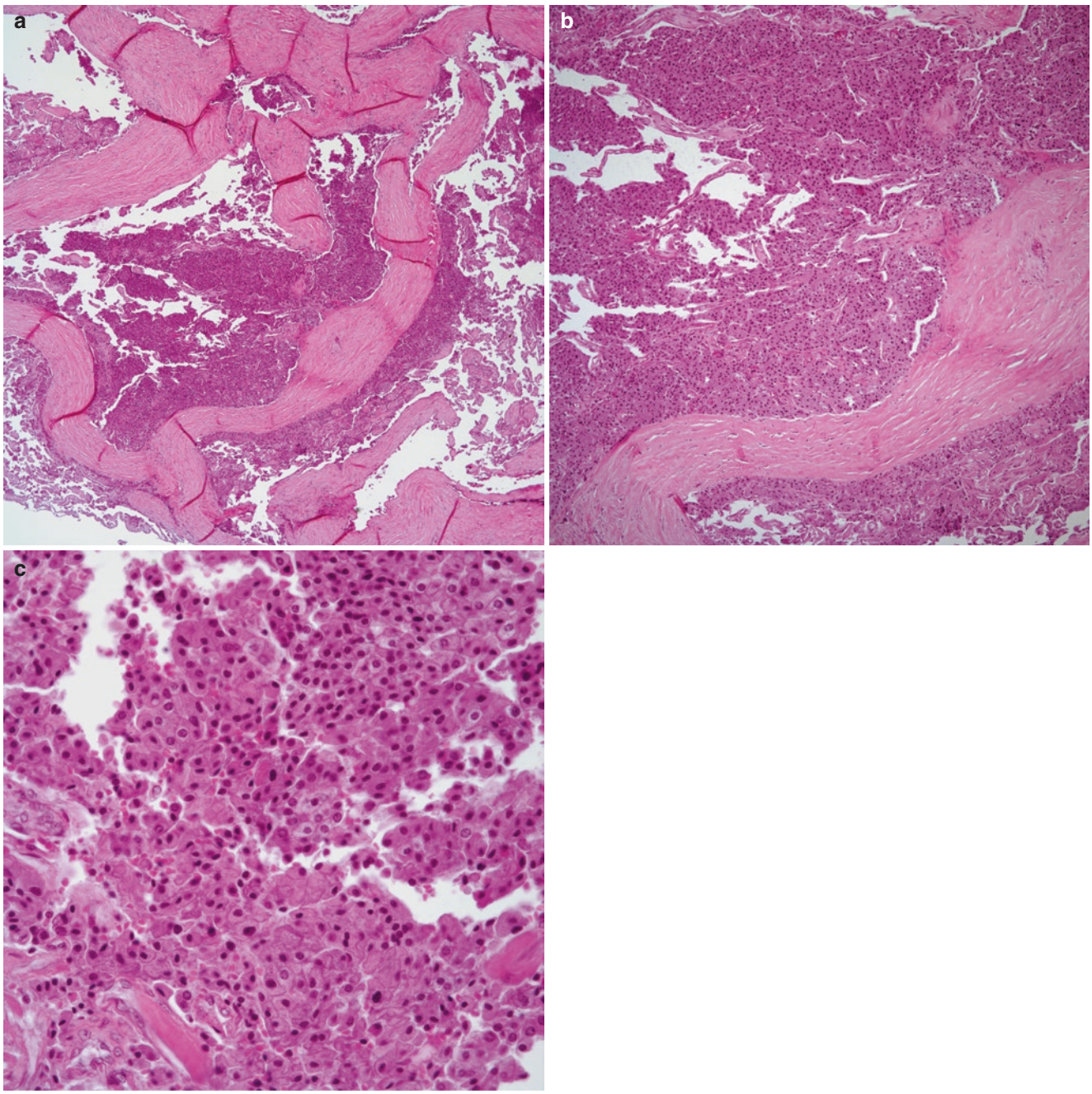


Fig. 9.101 (**a**) Mediastinal parathyroid carcinoma showing thick fibrous bands and a more infiltrate growth pattern; (**b**) Note the tick fibrous bands separating the neoplastic cellular proliferation; (**c**) higher magnification showing cellular and nuclear atypia

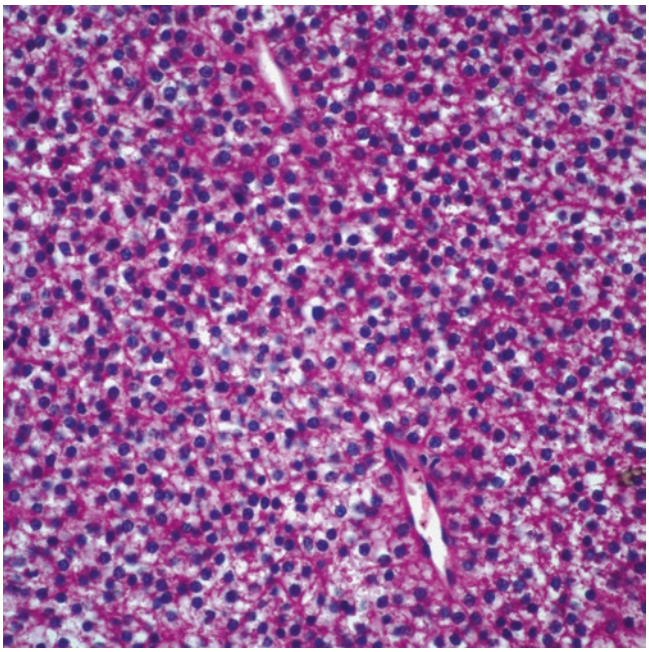


Fig. 9.102 Periodic acid-Schiff (PAS) in a parathyroid adenoma showing abundant glycogen deposition in tumor cells

gliomas than parathyroid tumors. In addition, the presence of positive staining for keratin may be of help in separating the two tumors.

Finally, the separation between mediastinal parathyroid adenoma and parathyroid carcinoma is similar to the histopathological approach for these tumors when they occur in the neck. Mainly, the features of ill-defined tumors with infiltrative borders, necrosis, increased mitotic activity, and fibrous bands of different thickness are more commonly seen in carcinomas.

Thyroid Tumors

Even though the presence of thyroid tumors within the mediastinal compartment may not necessarily belong to the conventional group of neuroendocrine tumors, it is presented in this section, as the thyroid itself is an endocrine gland, thus raising the possibility of developing either benign or malignant tumors of thyroid origin within the mediastinal compartment. Furthermore, the presence of thyroid tissue or thyroid tumors within the mediastinal compartment has been recognized widely in the literature. This occurrence has been reported under different designations including retrosternal, substernal, intrathoracic, and mediastinal [147–155]. Even though the majority of thyroid neoplasms within the mediastinum appear to be of the benign type, mainly represented by mediastinal goiters, it is the definition of what constitutes mediastinal goiter that has been discussed for many years and what at the end determines the incidence of these tumors in the mediastinal cavity. There appears to be at least four definitions regarding mediastinal goiters: (1) any portion of the thyroid below the thoracic inlet, (2) thyroid reaching the level of the aortic arch, (3) thyroid reaching the level of T4 on imaging, and (4) 50% or more of the thyroid below the thoracic inlet. Currently, the last definition of mediastinal goiter is the one that appears more accepted. However, it is essential to recognize that the existence of thyroid in the mediastinal compartment regardless of its definition may be seen in two different forms: (a) primary mediastinal goiter in which there is no connection between the mediastinal thyroid tissue and the cervical thyroid, and (2) secondary mediastinal goiter in which there is a connection between the mediastinal component and the cervical thyroid. By far, the most common is the secondary mediastinal goiter, as true primary mediastinal goiter appears to be a rare occurrence. The possible explanation to account for these two distinct occurrences may be based on the embryological development of the thyroid gland. The true or primary mediastinal goiter may result from autonomic growth of germinal nuclei of the thyroglossal duct, while the secondary mediastinal goiter may develop from the cervical thyroid that becomes disconnected from it. In view of the different definitions of mediastinal goiter, it is difficult to be exact regarding their true incidence; however, it has been estimated that it may vary from 5 to 20%. Erbil and associates [150] reported their experience with substernal goiters and calculated that they occur in approximately 6.4% of the patients. The authors reviewed 2650 patients with thyroid gland disorders between 1990 and 2003, identifying 170 patients (6.4%) with substernal goiter. Raffaelli and associates [149], in a study of substernal goiters using the criteria of 50% or more of the thyroid gland below the thoracic inlet, identified 355 patients out of 2263 patients who underwent thyroidectomy, which represents 15.7% of patients with substernal goiter. Huins and associates [153] reviewed the literature of the subject, and, after analyzing cumulative data of more than 22000 patients with goiter, the authors estimated that retrosternal extension occurs in approximately 6.28% of patients. On the contrary, the occurrence of true "primary" mediastinal goiters appears to be much more uncommon, with estimates of

approximately 1% of all mediastinal goiters. One important issue that needs to be highlighted is the fact that malignant thyroid neoplasm may arise in the mediastinum. However, it is very difficult to determine the incidence of thyroid carcinomas developing in a substernal goiter, not only because, in general terms, such development in a cervical thyroid is not common and it is difficult to estimate but also because mediastinal goiters are far less common. Thus, the presence of malignancies developing within an otherwise substernal goiter likely represents an unusual phenomenon. Rios and associates [156] studied 672 patients with multinodular goiters and identified 59 patients with an associated malignancy. Papillary microcarcinomas were the most common malignancies associated in 37 of the 59 patients. The authors stated that the risk factors for carcinoma associated with multinodular goiters include family history of thyroid pathology and history of radiation to the neck among others. Nevertheless, the occurrence of thyroid carcinomas within the mediastinal compartment has been recorded in the literature [4, 157–160]. Similar to the cases described as substernal goiters, the cases described of thyroid carcinoma also followed the same characteristics, as some develop in the background of a substernal goiter, while a minority of cases develop as de novo in possible ectopic thyroid tissue with no connection with the cervical thyroid.

Clinical Features

Based on different reviews that have been presented on substernal goiters or thyroid carcinomas arising in a mediastinal compartment, it appears that the majority of these patients are adult women. In some studies, it has been estimated that these tumors are more common in women in a proportion of 7:1 against men. Clinically, patients may present completely asymptomatic or with a diversity of symptoms, which would include palpable neck mass, dysphagia, dyspnea, hoarseness, cough, chest pain, and hyperthyroidism. Interestingly, in some reviews, a thyroid mass has been present in approximately 88% of patients with substernal goiter. Diagnostic imaging is important to determine the presence of a mediastinal involvement, and the use of chest films or chest CT appears to provide good results. Another procedure that has been performed in some patients is thyroid scintigraphy.

Anatomically, the tumors may be in the anterior or posterior mediastinum. However, the anterior mediastinum is much more common, with some estimates at more than 90% of the tumors in that location. The treatment of choice for these tumors is complete surgical resection of the mediastinal tumor, and the prognosis is excellent for those lesions that are in the spectrum of mediastinal goiters. Because there are not meaningful series of cases of thyroid carcinomas developing in the mediastinal compartment, it is difficult to determine the behavior of those tumors while occurring in the mediastinal compartment. However, it is logical to expect that small papillary carcinomas developing in the background of large mediastinal goiters should also have a good prognosis.

Histopathological Features

The diagnosis of these lesions should not pose a problem in interpretation, and these are often diagnosed as substernal goiter, mediastinal goiter, mediastinal colloid goiter, or nodular hyperplasia. The morphological features present in mediastinal goiters are essentially similar to those described in the cervical thyroid, namely, the presence of distended thyroid follicles with or without colloid, and in areas separated in a nodular pattern by fibroconnective tissue (Figs. 9.103 and 9.104a, b). These tumors do not show much in terms of cytologic atypia or increased mitotic figures.

In cases in which carcinoma is present, the histology of these tumors is also similar to that occurring in cervical thyroid. Papillary thyroid carcinoma appears to be probably the most common histology.

Immunohistochemical Features and Other Ancillary Studies

The use of immunohistochemistry in the diagnosis of mediastinal goiter is essentially limited as, in reality, there is no need for it as the morphological features of the lesion are sufficient enough to make an unequivocal diagnosis. However, in cases in which there may be a malignant neoplasm associated, then the use of immunohistochemical studies such as thyroglobulin, calcitonin, or PAX-8 may be of aid in the diagnosis. Similarly, the use of histochemical stains such as PAS with or without diastase, mucicarmine, and the use of ultrastructural studies have very limited use in the diagnosis of these tumors.

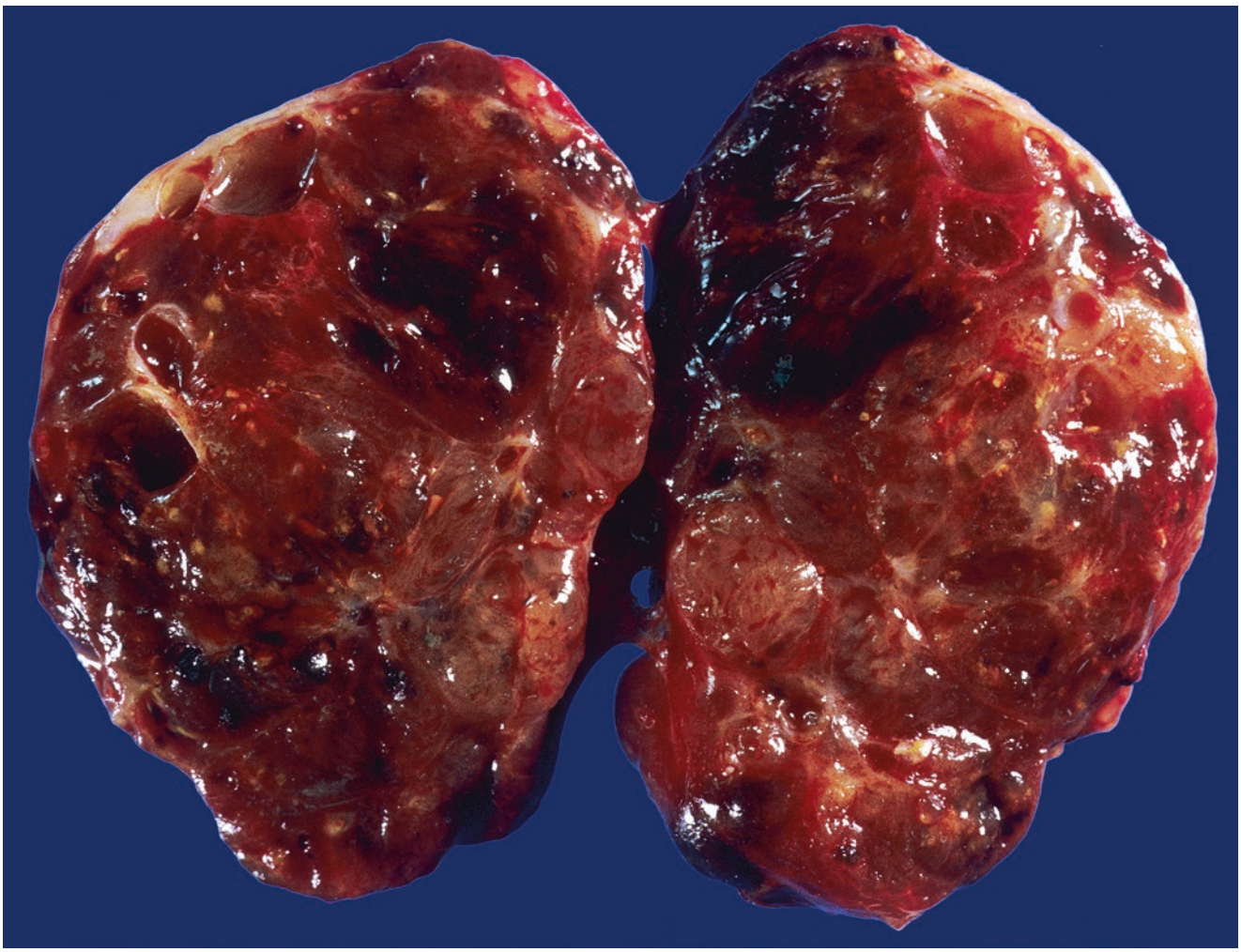


Fig. 9.103 Mediastinal goiter; note the presence a fleshy nodular tumor. Focal areas of hemorrhage are present

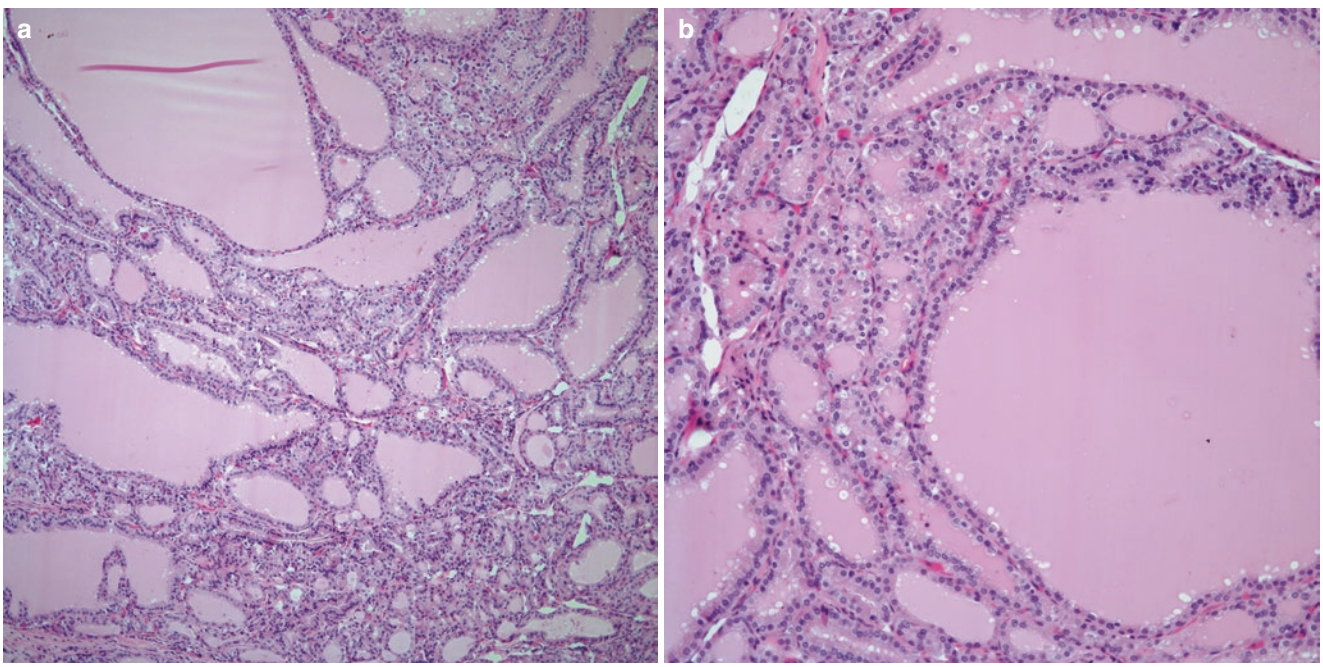


Fig. 9.104 (**a**) Low power view of a mediastinal goiter showing dilated thyroid follicles; (**b**) closer magnification showing thyroid follicles filled with colloid

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