Chapter 10
Primitive Mediastinal Germ Cell Tumors: An Update

Andrea Ronchi, Federica Zito Marino, Gaetano Facchini, Marina Accardo, and Renato Franco

General Features

Mediastinal germ cell tumors (MGCTs) are a group of mediastinal neoplasms that are morphologically characterized by the presence of neoplastic cells similar to germ cells or by the formation of embryonal or adnexal tissues. According to the 2015 WHO classification, MGCTs consist of *seminomatous* and *non-seminomatous* type. The former includes only classical seminoma. Spermatocytic seminoma, a variant of seminoma observed in the testis, has never been described in the mediastinum. The latter includes embryonal carcinoma, yolk sac carcinoma, choriocarcinoma, and teratoma [1]. MGCTs are sometimes composed by two or more histotypes coexisting in the same neoplasm and are referred as *mixed MGCTs* [1]. MGCTs are rare, affect all age groups, and represent up to 16% of all mediastinal neoplasms in adults and 19–25% in pediatric population (<18 years) [2]. The frequency of every single histological type of MGCTs is widely variable according to age and sex of patients. Teratoma is by far the most

A. Ronchi · F. Z. Marino · M. Accardo · R. Franco (✉)
Pathology Unit, Department of Mental and Physic Health and Preventive Medicine, Università della Campania 'Luigi Vanvitelli', Naples, Italy
e-mail: a.ronchi@unicampania.it; federicazito.marino@libero.it; marina.accardo@unicampania.it; renato.franco@unicampania.it

G. Facchini
Urogenital Oncology, Istituto dei Tumori 'Fondazione G. Pascale', Naples, Italy
e-mail: g.facchini@istitutotumori.na.it

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common MGCTs in the prepuberal patients regardless of the sex, as pure form or mixed form, especially in combination with yolk sac carcinoma [3]. In postpubertal patients, the distribution of MGCT histotypes depends on sex: in females, teratoma represents up to 90% of all MGCTs, while in males the distribution is more equilibrated, and the most common forms include teratoma, seminoma, mixed tumors, and yolk sac carcinoma [3]. Epidemiological distribution of MGCTs is represented in Fig. 10.1. Mixed MGCTs account for 16% of all MGCTs and occur almost exclusively in male patients [4]. In pediatric population, the most frequent combination is by far mature or immature teratoma and yolk sac tumor (see Fig. 10.2). In adult population there is a greater morphological variability, and the most frequent components are teratoma (immature more frequent then mature) and embryonal carcinoma. However all the other histotypes may be observed in various combinations [3].

The etiology of MGCTs is substantially unknown. In the same way, it is substantially unknown why the mediastinum is a preferential site for the development of neoplasms classically located in the gonads. According to the classical hypothesis, these neoplasms derive from a wrong midline migration of germ cells during the embryogenesis [5]. The thymus would be particularly prepared to accommodate the germ cells due to the expression of KIT ligands, involved in proliferation and survival of primordial germ cells [6]. Non-seminomatous MGCTs are more common in Klinefelter's syndrome [7]. Although pathogenesis of MGCTs is still substantially unknown, genetic analysis has provided an improved understanding of the biological substrate of these neoplasms. Gains of chromosome arm 12p and aneuploidy are almost constantly observed in gonadal and mediastinal GCTs [8]. Chromosome 12 abnormalities have been demonstrated in 96% of mediastinal seminoma specimens, with 87% resulting in 12p overexpression [8]. There are limited data on the genetic alterations responsible of non-seminomatous GCTs. The most common chromosomal abnormality is an increased copy number of chromosome 12p usually in the form of an isochromosome [9, 10]. A recent study based on whole-exome and transcriptome sequencing analysis showed that primary somatic features of GCTs include highly recurrent chromosome arm-level amplifications, reciprocal deletions, and K-RAS mutations [11].

MGCTs remain clinically asymptomatic for a long time and are often accidentally noticed during radiological examinations performed for other causes. Presenting symptoms are related to the compression of the adjacent anatomical structures and include dyspnea, cough, hoarseness, and chest pain. If the neoplasm reaches large dimension, it may cause mediastinal syndrome. Paraneoplastic symptoms are very rare, but some cases of presumed paraneoplastic encephalitis have been reported [12].

Serum tumor markers are frequently elevated in MGCTs and play an important role for both diagnostic and management purposes. The serum markers most commonly elevated in patients with MGCTs are αFP, β-hCG, and LDH. In particular, αFP is never elevated in patients with pure seminoma, while it is frequently elevated in non-seminomatous GCTs (10–20% in stage I, 20–40% in low-volume stage II,

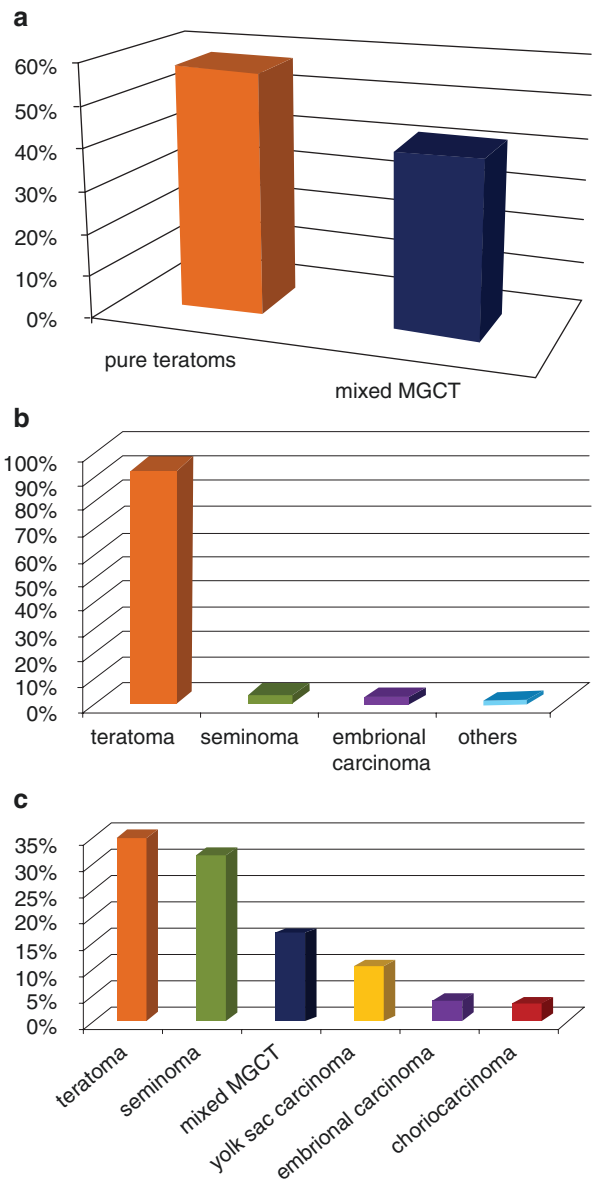

Fig. 10.1 Relative frequencies of MGCTs in clinical subsets. (**a**) Prepuberal patients regardless of the sex. (**b**) Postpubertal female patients. (**c**) Postpubertal male patients [1]

40–60% in advanced disease) [13]. Almost all patients with pure embryonal carcinoma or mixed MGCT with a component of embryonal carcinoma present elevated serum αFP. β-hCG may be elevated in both pure seminoma (15–20% in advanced disease) and non-seminomatous GCTs (10–20% in stage I, 20–30% in low-volume stage II, 40% in advanced disease) [13]. LDH is elevated in 40–60% of

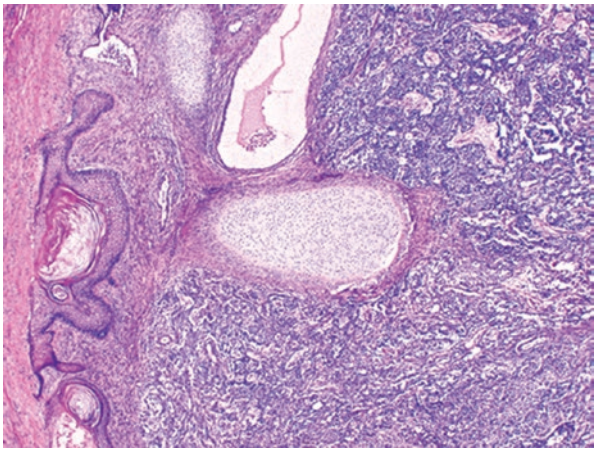

Fig. 10.2 Mixed mediastinal germ cell neoplasm constituted by mature teratoma (on the left) and yolk sac tumor (on the right)

patients with GCTs regardless of the histological type. Caution must be however placed in the interpretation of serum markers, because numerous neoplastic and non-neoplastic conditions can determine their increase. The International Germ Cell Cancer Collaborative Group (IGCCCG) system recommends the use of serum tumor markers to stratify the risk and monitor the treatment of patients with non-seminomatous GSTs but not for patients with seminoma [14].

MGCTs are on average chemo- and radiosensitive neoplasms, so the treatment is primarily based on neoadjuvant chemotherapy and radiotherapy, followed by surgical consolidation in selected cases with residual mediastinal mass. The sample available for primary diagnosis is therefore almost always represented by incisional biopsy or cytology (see Fig. 10.3). As teratoma is not much chemosensitive, it's a frequent event in the case of mixed MGCTs, after chemotherapy, the observation only of the teratomatous component in the primary mass. In the same way, metastasis from mixed MGCTs frequently shows just a teratomatous morphology. This is sometimes observed even in case of pure MGCT; in these instances, a misunderstood primary diagnosis of mixed tumor or a post-therapy differentiation is hypothesized [15].

Patients affected by MGCTs do not present a higher risk of gonadal germ cell tumors, but an association with hematological malignancies has been reported [16, 17]. Prognosis is strictly related to histological type: seminomatous MGCTs have a long-time survival rate of about 90%, whereas non-seminomatous types have a 5-year survival rate of about 45% [18]. MGCTs have a worse prognosis than gonadal counterparts [18]. Non-seminomatous histology, primary mediastinal location, presence of non-pulmonary visceral metastases, and elevated beta-hCG are independent prognostic factors for shorter survival [18].

In rare instances a somatic-type solid malignancy may develop in the context of a MGCT. This event seems to be more frequent in MGCTs than in gonadal counterparts. The majority of cases is observed in adult males, mainly in the setting of pure teratoma or mixed MGCT. Somatic malignancies include sarcomas (mainly embryonal

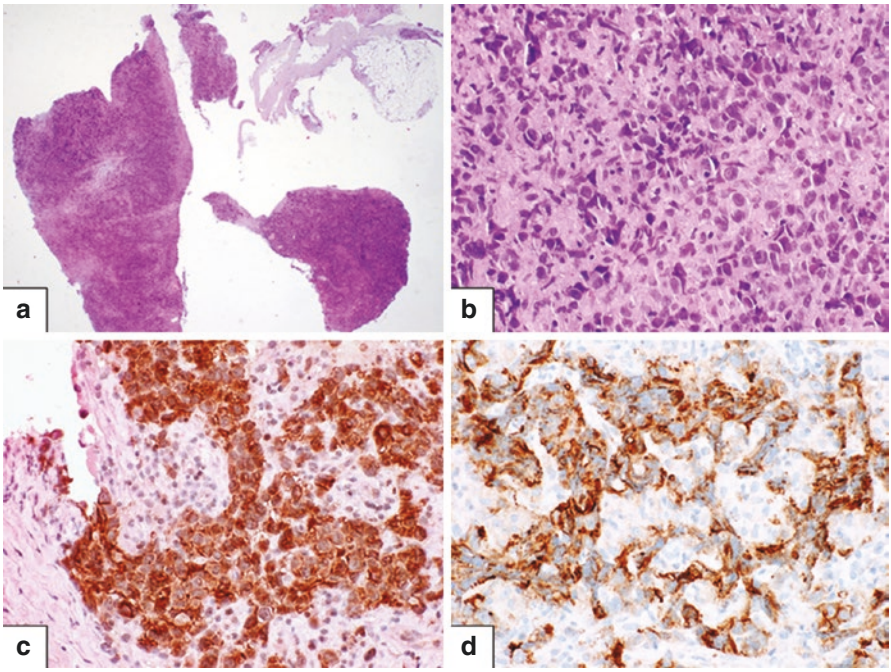

Fig. 10.3 Biopsy sample of a mediastinal seminoma constituted by small fragments (**a**). These samples are often subject of intraoperative examination for rapid on-site evaluation (ROSE) of adequacy. An adequate sample should allow the recognition of morphological features of the neoplastic population and the realization of a sufficient immunohistochemical panel. This example shows large cells with indistinct borders and roundish nuclei (**b**). Immunohistochemically, the cells are positive for CD117 (**c**) and PLAP (**d**)

rhabdomyosarcoma, angiosarcoma, leiomyosarcoma, and neuroblastoma) and carcinomas (mainly intestinal-type adenocarcinoma). The occurrence of a somatic malignancy makes the prognosis worse with a median survival of 9months [18]. A particular type of somatic malignancies associated with MGCTs is represented by hematological malignancies. About 1% of patients (almost exclusively young male patients) affected by MGCTs develop a hematological malignancy clonally related to the germ cell neoplasm [16]. The hematological disorders may develop either in the context of the mediastinal neoplasm or in lymphatic organs or in bone marrow and include acute leukemias, histiocytic sarcoma, myelodysplastic syndromes, myeloproliferative disorders, and mastocytosis [16]. The pathogenetic correlation between MGCTs and hematological disorders is poorly understood. It is hypothesized that hematological neoplasm origins from the differentiation of a primordial germ cell or from an area of intratumoral extramedullary hematopoiesis [19]. Interestingly, this peculiar association has been observed only in mediastinal neoplasms, while it never occurs in the gonadal counterparts. The underlying MGCT is constituted by yolk sac tumor or mixed MGCT in the large majority of cases [20].

Seminoma

Mediastinal seminoma occurs in the anterior mediastinum and represents 3–4% of all mediastinal neoplasms [21]. It is the second most common MGCT in postpubertal male patient after teratoma, corresponding to 32% of cases in this setting, while it is rare in prepuberal patients regardless of the sex and in postpubertal female patients [1]. Most cases present as localized mass at the time of primary diagnosis, but about 40% of patients subsequently develops distant metastasis [18]. The most frequent sites of metastasis include lymph nodes, lung, pleura, brain, liver, adrenal glands, and bones [21]. Macroscopically, mediastinal seminoma is a well-circumscribed mass with a vaguely lobulated, tan-gray or pink cut surface. Tumor size is quite variable, ranging from 1 to 20 cm [22]. Histological features of mediastinal seminoma are the same as gonadal counterparts (see Fig. 10.4). Architectural pattern is mainly lobular, with incomplete thin fibrous septa delimitating irregular neoplastic nodules, but it may include cellular sheets, cords, and strands. The neoplastic population is composed by large, round to polygonal cells with well-represented clear to lightly eosinophilic cytoplasm and roundish, centrally located, nucleus with one or more prominent nucleoli. A lymphoid infiltrate is a common finding, and it is mainly constituted by small mature lymphocytes with a variable number of plasma cells and eosinophils. This infiltrate is more often present in the thickening of the fibrous septa but may be intermingled with the neoplastic cells. In some circumstances the neoplastic population can be obscured or replaced by an extensive fibrotic reaction. In such cases an extensive sampling of the mass is mandatory to find the residual neoplastic component. Some scattered syncytiotrophoblastic cells can be present, especially in cases with the rise of B-hCG. These cells have to be distinguished from multinucleated giant cells of a possible granulomatous reaction, which is often present. Cytological samples of mediastinal seminoma are characterized by a dispersed cell population constituted by large cells with round

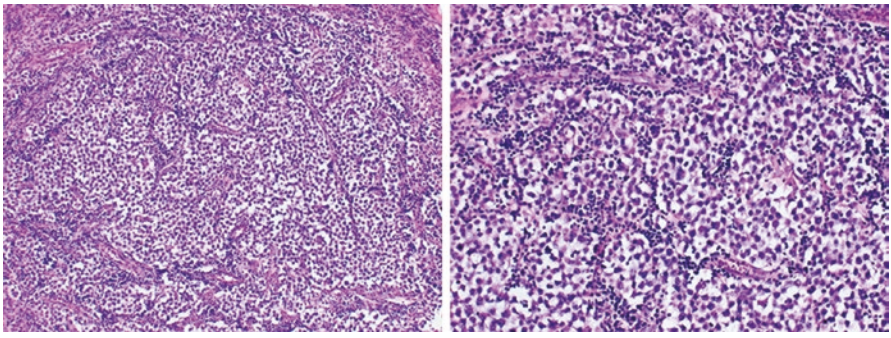

Fig. 10.4 Morphological features of seminoma. The neoplastic population is arranged in irregular nests partially demarcated by thin fibrous septa containing small lymphocytes. Neoplastic cells are large elements with slightly eosinophilic cytoplasm, roundish nuclei with one or more prominent nucleoli

Table 10.1 Immunohistochemical findings of MGCTs

Histotype	CK	αFP	βhCG	CD117	PLAP	CD30	OCT4	SALL4	Glypican 3
SE	Neg[a]	Neg	Neg[b]	Pos	Pos	Neg	Pos	Pos	Neg
EC	Pos	Neg	Neg[b]	Neg	Neg	Pos	Pos	Pos	Neg
YSC	Pos	Pos	Neg[b]	Neg	Pos	Neg	Neg	Pos	Pos
PT	Pos	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg
CHC	Pos	Neg	Pos	Neg	Neg	Neg	Neg	Pos[c]	Pos/Neg

MGCTs mediastinal germ cell tumors, *SE* seminoma, *EC* embryonal carcinoma, *YSC* yolk sac tumor, *PT* pure teratoma, *CHC* choriocarcinoma
[a]Dot-like positivity can be observed
[b]Syncytiotrophoblastic cells are positive, if present
[c]Positive in mononuclear trophoblastic cells

nuclei, finely granular chromatin and one or more nucleoli. The background is classically described as "tigroid," because of the presence of variable numbers of lymphocytes and plasma cell; epithelioid histiocytes are a possible feature [23]. Immunohistochemically, seminoma shows positivity for PLAP, OCT4, SALL4, and c-kit (CD117). β-hCG is negative but can be positive in syncytiotrophoblastic cells, if present. Although keratins are usually negative, a dot-like staining pattern can be observed; αFP and CD30 are negative [1]. Immunohistochemical features of MGCTs are summarized in Table 10.1.

Embryonal Carcinoma

Mediastinal embryonal carcinoma occurs in the anterior mediastinum and is a rare neoplasm, representing about 2% of all MGCTs [2]. Most of cases affect young adult males, while it is very rare in females and in children [2]. Most cases are at least locally advanced at the time of the diagnosis. Infiltration of the lung and distant metastasis are common events. The most common metastasis locations include the lung, liver, brain, and bones, while lymph node metastases are uncommon [2]. Macroscopically, embryonal carcinoma is a large mass, often with signs of infiltration of adjacent mediastinal soft tissue or lung parenchyma. The cut surface is generally gray or white frequently with large areas of necrosis and hemorrhages. Histologically, embryonal carcinoma presents a variable architectural pattern. A solid, undifferentiated pattern is a common finding, but glandular or papillary patterns are usually at least focally present. These "epithelial" features are important for differential diagnosis from seminoma, and a wide sampling of the neoplasm is consequently mandatory. Coagulative necrosis is variably present, as large irregular areas or microscopic multiple foci. The neoplastic cells are large and polygonal, with indistinct cellular borders. A columnar shape may sometimes be evident. Cytoplasms are more often amphophilic but may be basophilic, eosinophilic, or clear. Nuclei are large and roundish with vesicular chromatin and evident eosinophilic nucleoli (see Fig. 10.5). Some scattered syncytiotrophoblastic cells can be present, while

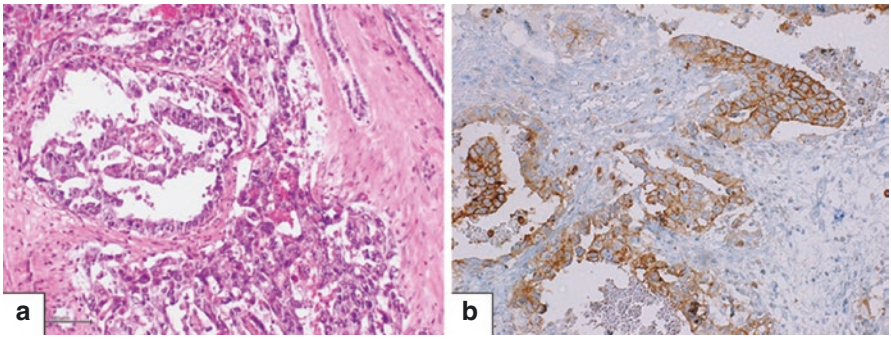

Fig. 10.5 Embryonal carcinoma. (**a**) Neoplastic population is arranged in irregular, poorly formed pseudoglandular elements. Hemorrhagic microspots are evident. Neoplastic cells show large and atypical nuclei with vesicular chromatin and evident nucleoli. Mitotic figures are present. (**b**) CD30 immunostain

granulomatous reaction is rare. Cytological samples of embryonal carcinoma usually show a highly cellular population arranged in sheets or tridimensional clusters. The cells are large and pleomorphic with large nuclei and evident nucleoli. Necrotic debris may be present. The cytological features may be different to differentiate from a poorly differentiated carcinoma of other histogenesis, and immunohistochemical study is mandatory. Immunohistochemically, embryonal carcinoma stains positive for OCT4, low-molecular-weight keratins, and CD30. CD30 is positive in about 85–100% of cases and is an important treatment target for biological therapy, but its expression can be lost during the chemotherapy [24]. αFP is usually negative but can be positive in single cells or small cellular clusters in a minority of cases; B-hCB is negative but can be positive in scattered syncytiotrophoblastic cells; CD117 expression is infrequent, but some cases have been reported [25].

Yolk Sac Tumor

Yolk sac tumor occurs in the anterior mediastinum and is one of the most common MGCTs, with an incidence depending on age and sex of patients [1]. In prepuberal population, YST is the most common malignant MGCTs and the second most common MGCT after teratoma. In adult population, YST represents about 10% of all MGCTs in male patients, while it is very rare in female patients [26]. Almost all cases are at least locally advanced disease at the time of primary diagnosis, with extension to the adjacent fat tissue and lung parenchyma [27]. Distant metastases are relatively frequent, and the most common localizations include the lung, lymph nodes, liver, bone, and brain [2]. Macroscopically, YST is a large mass with a whitish cut surface often presenting gelatinous areas. Hemorrhagic areas and necrosis are relatively frequent, especially in cases removed after neoadjuvant treatment. Histological features of YST are quite variable and include several possible architectural patterns which

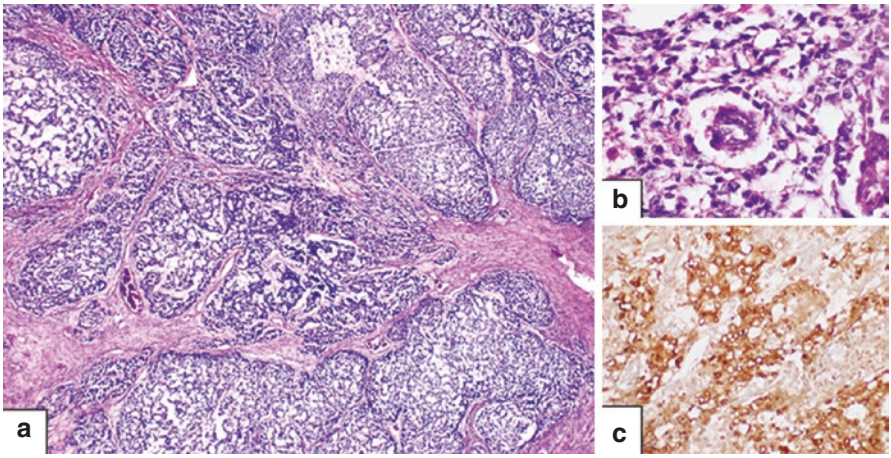

Fig. 10.6 Yolk sac tumor. (**a**) Prominent reticular/microcystic architectural pattern. (**b**) Schiller-Duval body. (**c**) αFP immunostain

often coexist in the same tumor. Most common patterns include reticular/microcystic and pseudopapillary/endodermal sinus. The reticular or microcystic variant is characterized by small cystic spaces and a loose network of irregular channels. Pseudopapillary/endodermal sinus variant shows pseudopapillary structures with the presence of Schiller-Duval bodies. These latter are glomeruloid structures consisting of a roundish cavity circumscribed by germ cells containing a central small vessel covered by another layer of germ cells (see Fig. 10.6). Schiller-Duval bodies are present in about 50% of cases and are almost pathognomonic of YST. Other architectural patterns include glandular, myxomatous, hepatoid, enteric, and solid. The neoplastic cells are medium- or large-sized cells with moderate to abundant cytoplasm and roundish nucleus with irregular chromatin pattern and prominent nucleolus. Nuclear atypias are variably present and more often are focal. Some scattered syncytiotrophoblastic cells can be present, while granulomatous reaction is rare. Cytological samples of YST consist of aggregates of large cells with clumped chromatin and small nucleolus. Debris and metachromatic material are usually present in the background, while lymphocytes are not present. Immunohistochemically, YSTs are positive for cytokeratins (in most cases with a dot-like staining pattern), SALL4, and glypican 3 [28, 29]. The majority of cases are positive for αFP and PLAP. Immunostaining for CD117 and CD30 is variable and most often negative [30].

Teratoma

Teratoma is a germ cell neoplasm characterized by the formation of variable somatic tissues derived from two or three germ layers [1]. Teratoma occurs in anterior and posterior mediastinum and is the most common extragonadal germ cell tumor in

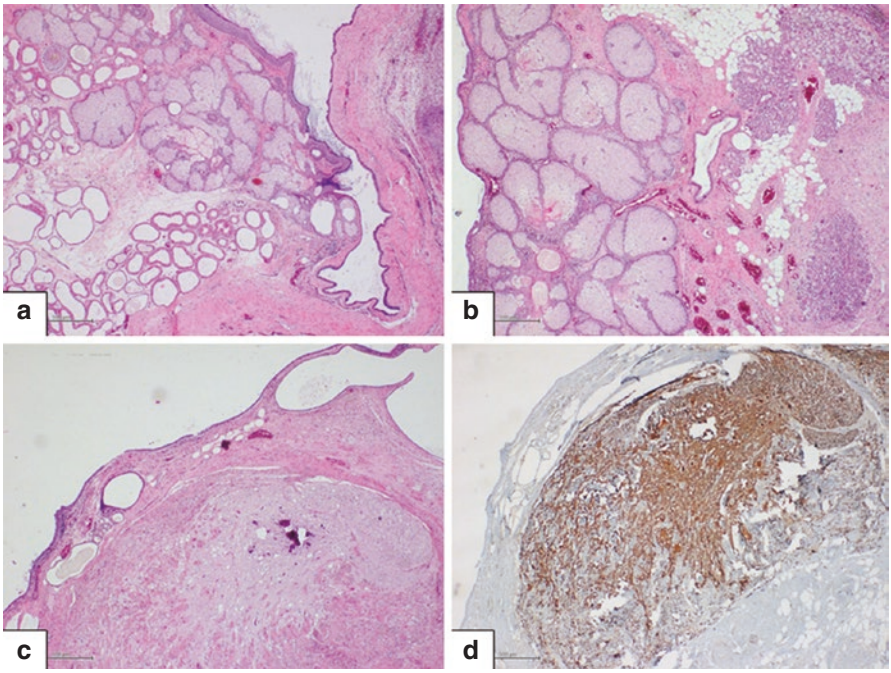

Fig. 10.7 Mature teratoma. (**a**, **b**) The tumor is composed by several mature tissues including squamous and columnar epithelium, hair, sebaceous, and sweat glands. (**c**) Mature nervous tissue. (**d**) S100 immunostain

both prepuberal and postpubertal patients regardless of the sex, accounting for 15% of all mediastinal masses in adults and 25% in children [2]. Mediastinal pure teratoma is a localized neoplasm without neoplastic spread. Macroscopically, the mass appears well-demarcated and encapsulated. The cut surface is variegated depending on the histological components and often comprises soft or fleshy areas, corresponding to fibrous and cartilaginous components, and cystic areas filled with serous, mucoid, or keratinaceous debris. Hair, fat, teeth, or bone is sometimes present. Histological appearance of teratoma is quite variable and characterized by the presence of different somatic tissue in a haphazard distribution. *Mature* teratoma is composed by adult-appearing tissues, which may include skin and adnexa, respiratory mucosa, pancreatic glands, nervous tissue, muscle, fat, cartilage, bone, and teeth. Other tissues are rarely present (see Fig. 10.7). *Immature* teratoma is composed by fetal-appearing tissues, which usually consist of neuroectodermal tissue forming tubules and rosettes. Other fetal tissues are rarely present and include primitive mesenchymal tissue, cartilage, bone, rhabdomyoblasts, and others. Although immunohistochemistry is generally unnecessary for diagnosis of teratoma, it may play a role in the characterization of the immature components. The most useful markers in this setting include S100 and synaptophysin (for neural components), desmin and myogenin (for muscle components), and S100 and glial fibrillary acidic

protein (for cartilaginous components) [1]. Pure mediastinal teratoma has generally a good prognosis in all age groups after the complete resection of the neoplasm. The presence of fetal-type tissues does not seem to affect the prognosis [26].

Choriocarcinoma

Choriocarcinoma is a germ cell neoplasm constituted by trophoblastic tissues. Mediastinal pure choriocarcinoma is an exceedingly rare neoplasm occurring in anterior or posterior mediastinum of adult male patients [2]. Some patients present paraneoplastic symptoms like gynecomastia and thyrotoxicosis [31]. Macroscopically, choriocarcinoma is a poorly demarcated mass with extensive hemorrhagic and necrotic areas. The neoplasm usually infiltrates the mediastinal structures at the time of the diagnosis [26]. Histologically, choriocarcinoma is constituted by syncytiotrophoblastic and cytotrophoblastic cells in variable proportion. Syncytiotrophoblasts are large multinucleated cells with abundant cytoplasm and numerous pleomorphic nuclei. Cytotrophoblasts are mononuclear cells with clear or eosinophilic cytoplasm, roundish nuclei, and prominent nucleoli. Because of the natural tendency of trophoblastic cells to reach to the vessels, choriocarcinoma is a largely vascularized neoplasm with dilated vascular sinusoids and abundant hemorrhagic lacunae. Immunohistochemically, choriocarcinoma cells express cytokeratins, hCG, glypican 3, and inhibin [28]. SALL4 is usually positive only in the mononucleated cells [1]. OCT4, PLAP, αFP, CEA, CD30, and vimentin are negative [1]. Mediastinal choriocarcinoma is a highly aggressive neoplasm with a poor prognosis [2].

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