

The Effects of Chemotherapy on Metastatic Testicular Germ Cell Tumors

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Abstract: Modern chemotherapy combined with surgery can achieve complete cure in over 90% of all patients with malignant testicular germ cell tumors. Even tumors that have already metastasized at the time of orchidectomy are curable by platinum-based multidrug treatment. Chemotherapy related changes can be seen in the residual tumor tissue in metastatic sites. In patients fully responding to chemotherapy these changes include complete necrosis of the tumor cells, and inflammatory-phagocytic response, fibrosis replacing the necrotic tumor tissue, and residual benign somatic tissue tissues in form of teratoma. Epithelial and stromal cells of these teratomas may display nuclear atypia, which is however not a reason for concern and should not be considered an indication for additional chemotherapy. Less commonly the lymph nodes contain cystic trophoblastic tumors. In contrast to metastatic classical biphasic or monophasic choriocarcinoma, cystic trophoblastic tumors portend a favorable clinical outcome. Patients with an incomplete response to chemotherapy and those with recurrences of the malignant tumor contain in metastatic sites foci composed of embryonal carcinoma cells, yolk sac carcinoma, or choriocarcinoma. The latter two subtypes of germ cell neoplasia may recur in several microscopic variant forms. Somatic forms of malignancy (also known as "non-germ cell malignancies") that develop occasionally in some treated patients include most often sarcomas and tumors resembling central primitive neuroectodermal neoplasms. These secondary malignancies are usually resistant to chemotherapy. The broad spectrum of morphologic findings in the lymph nodes of patients with treated metastatic testicular germ cell tumors clearly illustrates the importance of meticulous pathologic analysis of tissue changes related to chemotherapy.

Keywords: Testis, chemotherapy, teratoma, germ cell tumor, lymph node.

INTRODUCTION

Testicular germ cell tumors are relatively rare, accounting for less than 1% of all internal organ cancers in males. Nevertheless in the age group from 25 to 45 years they belong to the group of most common malignancies [1]. Not so long ago in the last century most of these tumors were lethal. With the advent of modern chemotherapy, the prognosis of malignant testicular germ cell tumors has improved dramatically and today more than 90% of all patients survive treatment for extended periods of time or are completely cured [1, 2].

Testicular germ cell tumors tend to metastasize preferentially to the periaortic abdominal lymph nodes and accordingly retroperitoneal lymph node dissection (RPLND) has become a routine treatment modality for patients with metastatic testicular neoplasia [3, 4]. The analysis of staging accuracy and long term outcome and survival data indicates that open surgical lymph node dissection gives results which are comparable with those obtained by a laparoscopic approach [5, 6]. Irrespective of the surgical approach it is important to remove as much of residual tumor as possible and to resect all enlarged lymph nodes. All the tissues removed by RPLND should be submitted for pathologic analysis and should be examined microscopically. Such

pathologic analysis of resected of RPLND material provides important data for planning of further treatment and for formulating the final prognosis.

PATHOLOGY OF TESTICULAR TUMORS

Primary testicular tumors may originate from germ cells, sex cord cells, or less commonly peritubular stromal and hematopoietic migratory cells [7, 8]. More than 90% of all tumors are of germ cell origin and malignant. For practical clinical purposes these germ cell tumors are classified into two major groups: seminomas and nonseminomatous germ cell tumors (NSGCT). The group of nonseminomatous germ cell tumors comprises several histologic subsets including pathologic entities such embryonal carcinoma, yolk sac carcinoma, choriocarcinoma, teratoma and mixed germ cell tumors.

Irrespective of their histology, all malignant testicular tumors metastasize preferentially to periaortic retroperitoneal lymph nodes. In advanced tumors there are also hematogenous metastases resulting in a spreading of tumor cells to lungs, liver, brain and less commonly to other internal organs of the body. Tumor deposits in distant metastatic sites usually resemble those in the primary site, but chemotherapy may produce significant changes in the morphology of neoplastic lesions [8, 9]. These changes are readily identifiable by routine light microscopy but sometimes additional immunohistochemical studies must be performed to properly characterize all the cellular components of metastatic tumors [10].

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PATHOLOGIC CHANGES SEEN IN TISSUES OBTAINED BY RETROPERITONEAL LYMPH NODE DISSECTION

Retroperitoneal lymph node dissection (RPLND) material, which usually includes lymphoid and connective tissue, must be catalogued and all the tissues submitted for pathologic examination should be identified. The number of lymph nodes identified on gross examination or microscopically should be recorded, although it has been shown that the number of the lymph nodes containing residual tumor does not correlate with the final outcome of the disease [11]. Special attention should be paid to enlarged lymph nodes, which should be bisected prior to embedding and their cut surface should be described. On gross examination it is thus possible to note the yellow areas of necrosis, fibrotic areas, cystic and often mucinous areas of residual tumor or obvious neoplastic solid tissue.

Microscopic changes in the RPLND material were described in the early days of modern chemotherapy of testicular germ cell tumors and were reviewed and extensively illustrated in the classical paper of Ulbright and Roth [9]. Additional observations and analyses have been reported subsequently contributing to our understanding of these chemotherapy related changes [10, 12-16]. Light microscopic data were supplemented with immunohistochemical, cytogenetic and even molecular biology data in some studies [10, 17-19].

Current pathology reports based on a detailed microscopic examination of the RPLND material will typically contain one of the following diagnoses:

- **No viable tumor identified.** The RPLND material usually contains in such cases only foci of tissue necrosis, fibrosis or the tissue may be infiltrated with numerous phagocytic cells.

- **Residual teratoma.** In such cases the tissue obtained RPLND contains tumor tissue composed of benign somatic tissues intermingled in a manner typically seen in teratomas.
- **Cystic trophoblastic tumor.** Such lesions are composed of cells resembling normal trophoblast often showing degenerative changes, but no signs of proliferative or invasive malignancy.
- **Viable malignant germ cell tumor.** These foci may contain embryonal carcinoma cells, yolk sac carcinoma or choriocarcinoma.
- **Secondary somatic malignancy.** These changes, also known as "non-germ cell malignancy" present in form of sarcoma, primitive neuroectodermal tumor or, less often, some other form of malignancy.

COMPLETE ERADICATION OF METASTATIC MALIGNANT CELLS

A complete response to chemotherapy can be predicted clinically on the basis of radiologic computerized tomographic findings [20, 21]. Complete pathologic response could be thus predicted in all patients who show greater than 90% reduction in the size of the abdominal masses. If clinically warranted a modified, partial RPLND can be recommended, since even with such a less inclusive approach only 2% of these selected patients will contain residual cancer in the lymph nodes [22].

Microscopic analysis of tissues removed by RPLND after chemotherapy shows that up to 2/3 of all patients will have complete response [21]. In such cases the retroperitoneal lymph nodes will contain only foci of necrosis consisting of amorphous eosinophilic material, usually circumscribed by fibrous tissue (Fig. 1A). Within the necrotic foci one may see occasional pyknotic nuclei or remnants of some cells, but typically there are no viable tumor cells to be found. Finding

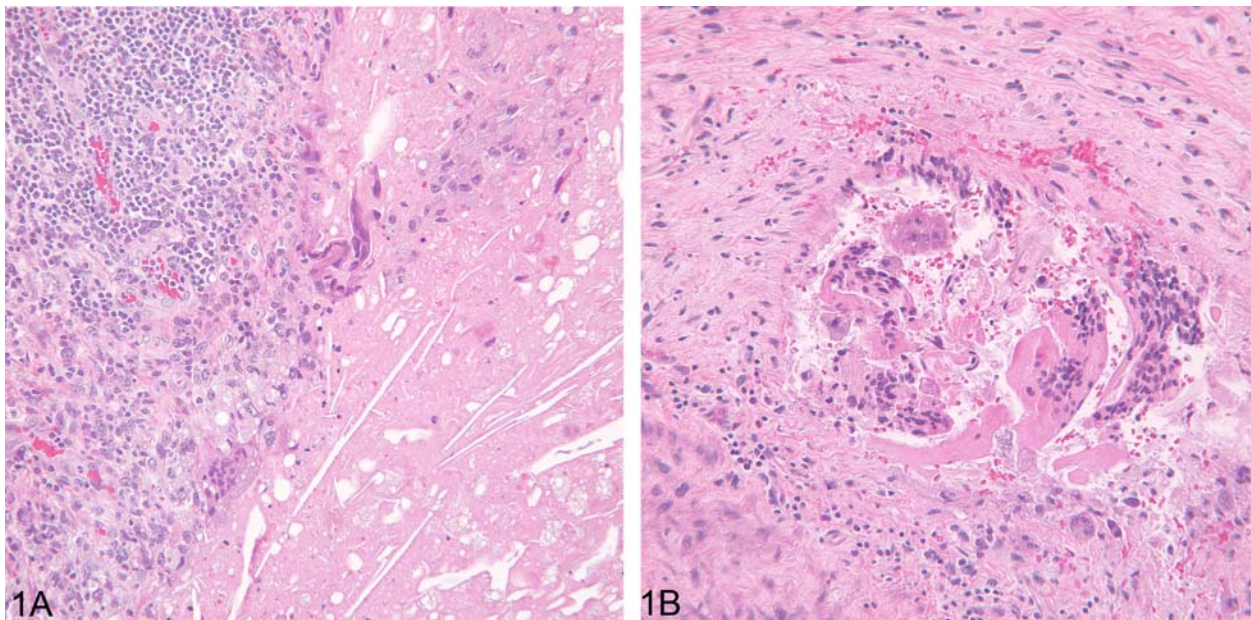


Fig. (1). Complete response to chemotherapy showing necrosis. (A) The lesion consists of a central necrotic zone, which appears eosinophilic, surrounded at the periphery with an inflammatory response. H&E, x 100. (B) Multinucleated giant cells, located centrally, are surrounded by fibroblasts and macrophages. H&E, x 100.

of smudged, vacuolated and or fragmented hyperchromatic cells need to be recorded [9] but the final pathology report should clearly state that no viable tumor cells were identified microscopically.

In case of any doubt one should perform additional immunohistochemical studies with antibodies to the nuclear transcription factor OCT3/4, and CD117 or cytokeratins. It has been shown that these antibodies react with embryonal carcinoma or seminoma cells that cannot be identified by routine light microscopy in completely necrotic tumors [23].

Foci of necrosis may be infiltrated or surrounded by phagocytic and other inflammatory cells (Fig. 1B). Most of these cells are macrophages and some of them multinucleated (Fig. 1C). Multinucleated cells should not be mistaken for syncytiotrophoblastic cells, but if there are any doubts immunohistochemistry with antibodies to hCG should be performed. Macrophages have clear or foamy cytoplasm (Fig. 2). These cells should not be mistaken for seminoma. Seminoma cells typically contain glycogen in their cytoplasm which may be demonstrated with the PAS staining. In more dubious instances immunohistochemistry for germ cell markers such as the antibody OCT3/4 could resolve the dilemma.

In addition to foci of necrosis RPNLD specimens removed from complete responders may contain areas of fibrosis, which may be hyalinized and relatively acellular or quite cellular (Fig. 3). The stromal cells are usually quite bland and show no nuclear atypia. On the other hand some spindle cells may be quite mitotically active and form microscopic fibrous nodules. Such nodules are usually well circumscribed, show no invasive margins and thus should not be mistaken for malignancy.

Nuclear atypia may be quite prominent in some stromal cells (Fig. 4). Obviously these changes must be interpreted contextually and should not be mistaken for malignancy [24,

25]. Ulbright *et al.* [24] believe that these stromal cells are derived from yolk sac elements. Such stromal cells may stain with antibodies to keratin supporting this interpretation. These cells may also be developmentally pluripotent and differentiate into other mesenchymal cells, most notably striated muscle cells [25]. Molecular biologic studies of allelic loss and chromosome p12 provide additional proof that the stromal cells are derived from the differentiation of malignant cells in the foci of the metastatic germ cell tumor [26]. In contrast to epithelial yolk sac carcinoma cells, stromal cells *per se* are not malignant.

TERATOMA

Teratomas, i.e. tumors composed of tissues derived from all three embryonal germ layers, are commonly found in post-chemotherapy RPLND material in patients with NSGCT. Reports published over many report that pure teratomas or teratomas admixed to foci or necrosis or fibrosis are found in 30-50% of all RPLND tissues removed from advanced NSGCTI tumors treated by chemotherapy [6, 9, 27].

Teratoma may be suspected during the dissection of the RPLND material, especially if it presents in form of large cystic masses. It may be also found in enlarged lymph nodes, which typically contain small cysts filled with mucous material. Occasionally such teratomas may continue to grow compressing adjacent structures and causing clinical problems [28, 29]. Such "growing teratomas" do not contain malignant germ cell tumor elements i.e., embryonal carcinoma, yolk sac carcinoma or choriocarcinoma and usually do not respond to the classical chemotherapy prescribed for malignant germ cell tumors.

Pathologic examination of post-chemotherapy teratomas from the RPLND material will usually reveal a variety of tissues intermixed one with another in a haphazard manner. The epithelial cells most often form intestinal or bronchial

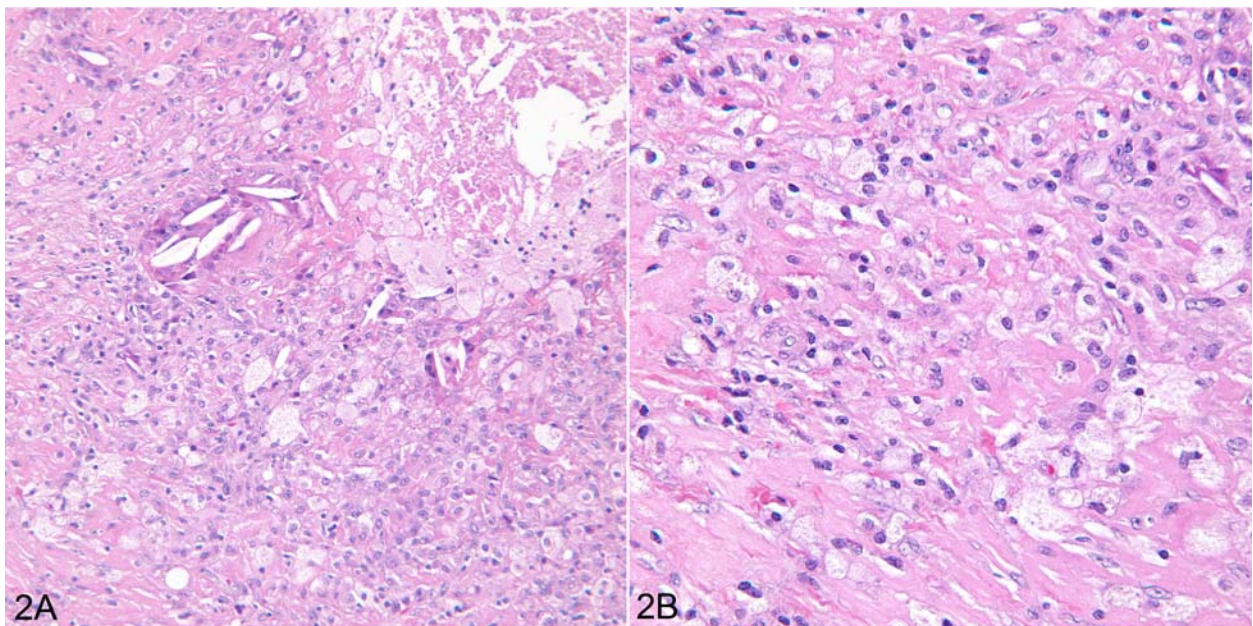


Fig. (2). Complete response to chemotherapy showing an inflammatory reaction. (A) The wall of this cavitory lesion is composed of macrophages, many of which are foamy, and multinucleated cells containing cholesterol clefts. H&E, x100. (B) Higher power view of foamy macrophages which could be mistaken for seminoma cells. H&E, x200.

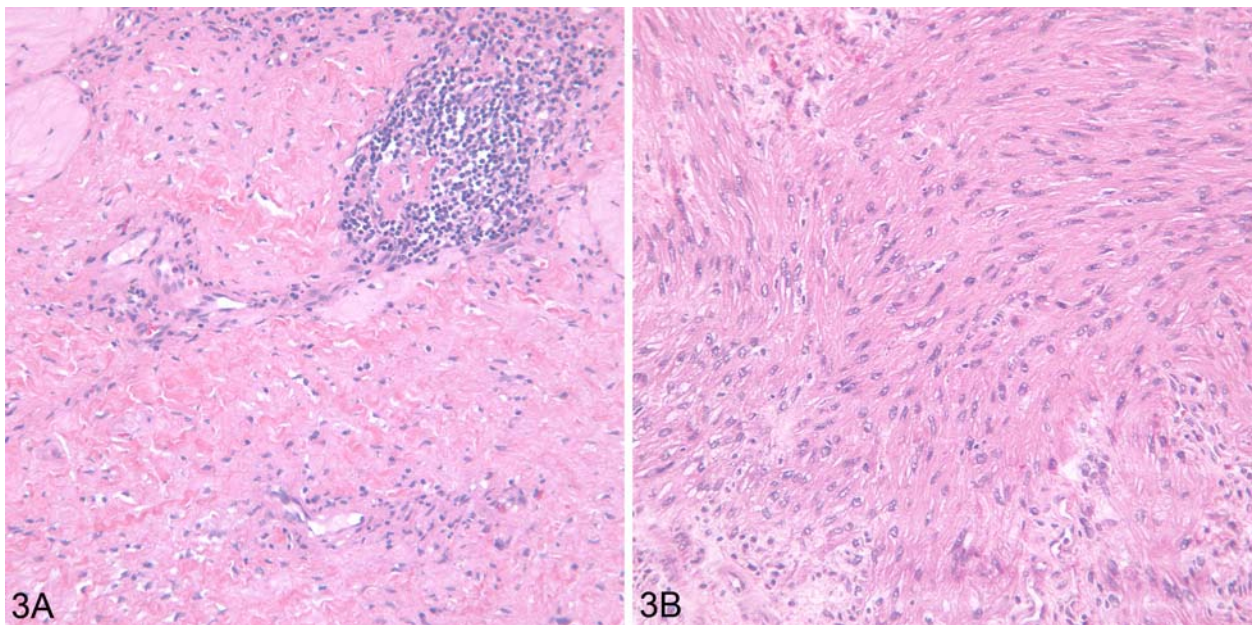


Fig. (3). Complete response to chemotherapy showing fibrosis. (A) Relatively acellular fibrous tissue is replacing most of the lymph node. H&E, x100. (B) Bundles of cells that have spindle shaped nuclei, have features of myofibroblasts and smooth muscle cells. H&E, x100.

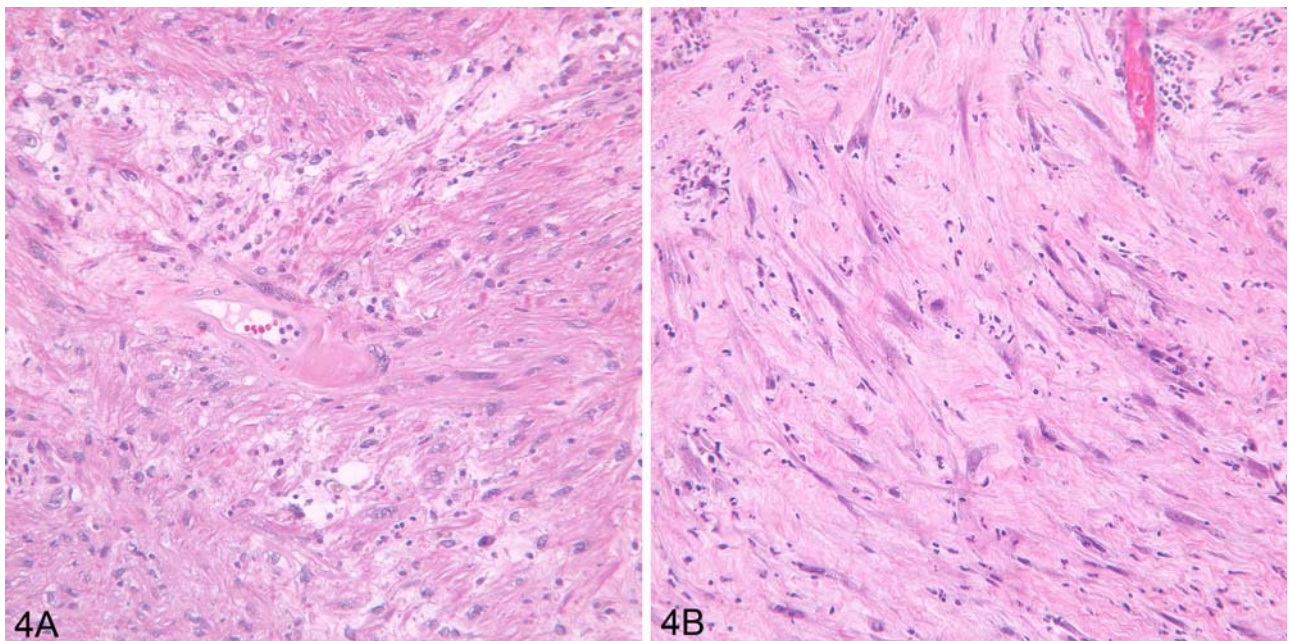


Fig. (4). Complete response to chemotherapy showing fibrosis. (A) Spindle cells appear focally enlarged and show pleomorphism. H&E, x100. (B) Pleomorphic spindle cells are surrounded by dense intercellular material. H&E, x100.

like lining of the cystic spaces. Such cysts may be surrounded by concentric layers of mesenchymal cells and even well differentiated smooth muscle cells reminiscent of early organogenesis (Fig. 5A). Parts of teratoma may be destroyed by the inflammatory reaction (Fig. 5B). Nests of keratin pearls are occasionally the only remnant of a teratoma that has been destroyed by macrophages (Fig. 5C).

Other glandular structures may be also found but organoid structures resembling thyroid or pancreas are less common (Fig. 6A). Occasionally such glandular cells form minor nodules resembling adenomas (Fig. 6B). Foci of immature fetal-like or keratinizing squamous epithelium are also found. Neuroepithelial nest varying in their maturity are

common in some lesions. Stromal cells may differentiate into smooth and skeletal muscle, cartilage and even bone.

The nuclei of various teratomatous elements are usually bland but not infrequently they may be enlarged, irregularly shaped, hyperchromatic, and pleomorphic (Fig. 7). Such cells also show significant nuclear atypia, such as irregular clumping of the chromatin and prominent nucleoli. In some portions of these teratoma mitoses are numerous and may even be atypical.

Nuclear atypia is most often seen in glandular epithelium, cartilaginous nodules or undifferentiated stromal cells. Atypia inside the glandular epithelium may be reminiscent of

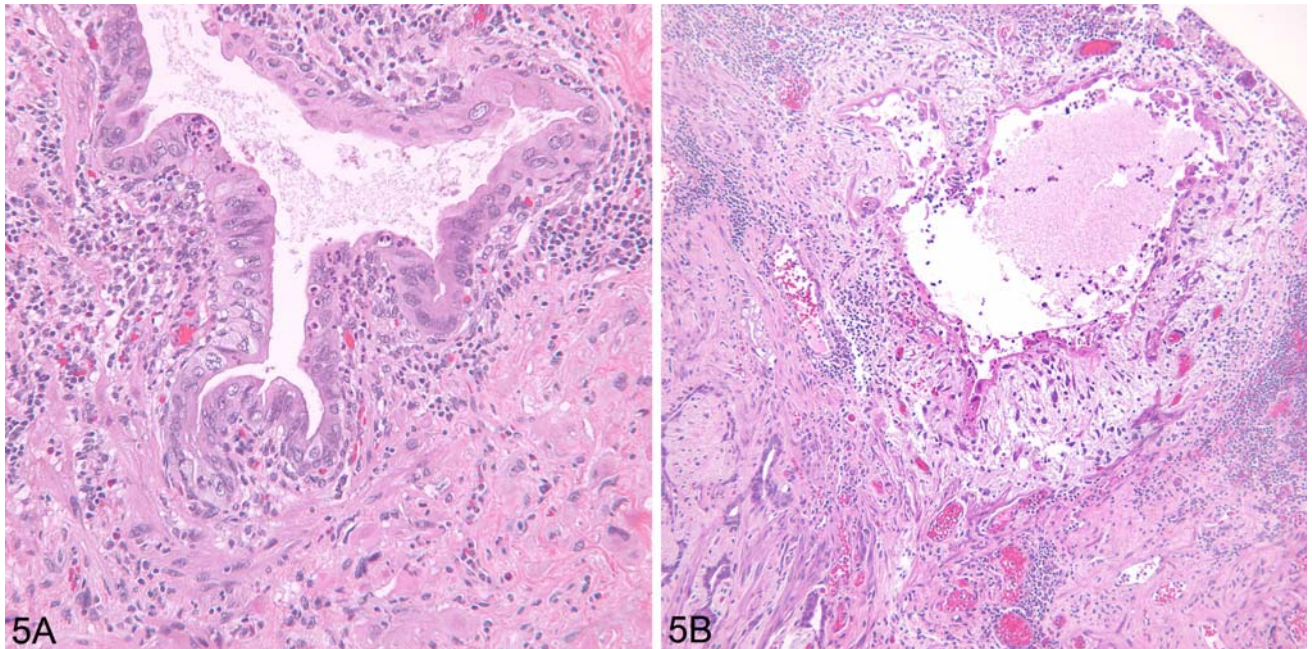


Fig. (5). Complete response to chemotherapy showing residual teratoma. (A) Cystic structure corresponds to a duct lined by cuboidal cells. The surrounding stroma contains focally inflammatory cells. H&E, 100. (B) Cystic structure mostly denuded of the epithelium is surrounded by stroma containing inflammatory cells. Smaller glands are seen in the adjacent stroma. H&E, x100.

adenocarcinoma in situ. Clinically this cytologic atypia is of no particular significance and patients in whom such lesions were found do not require additional treatment [9].

The size of teratomas found in the RPLND has prognostic significance. Accordingly 25% of all patients who have post-chemotherapy teratomas measuring more than 10 cm in diameter will have recurrence of the tumor following the resection of teratoma [29].

CYSTIC TROPHOBLASTIC TUMOR

Cystic trophoblastic tumor (CTT) is a rare benign lesion rarely encountered in the post-chemotherapy RPLND material that has been recently described in great detail by Ulbright *et al.* [30]. The lesion is typically cystic and may be adjacent to other teratomatous elements. The cysts of CTT is lined by mononuclear cytotrophoblastic cells, which have a pale eosinophilic cytoplasm with occasional vacuolization. Multinucleated syncytiotrophoblastic cells are not seen. The nuclei of these cells are often smudged and there is no

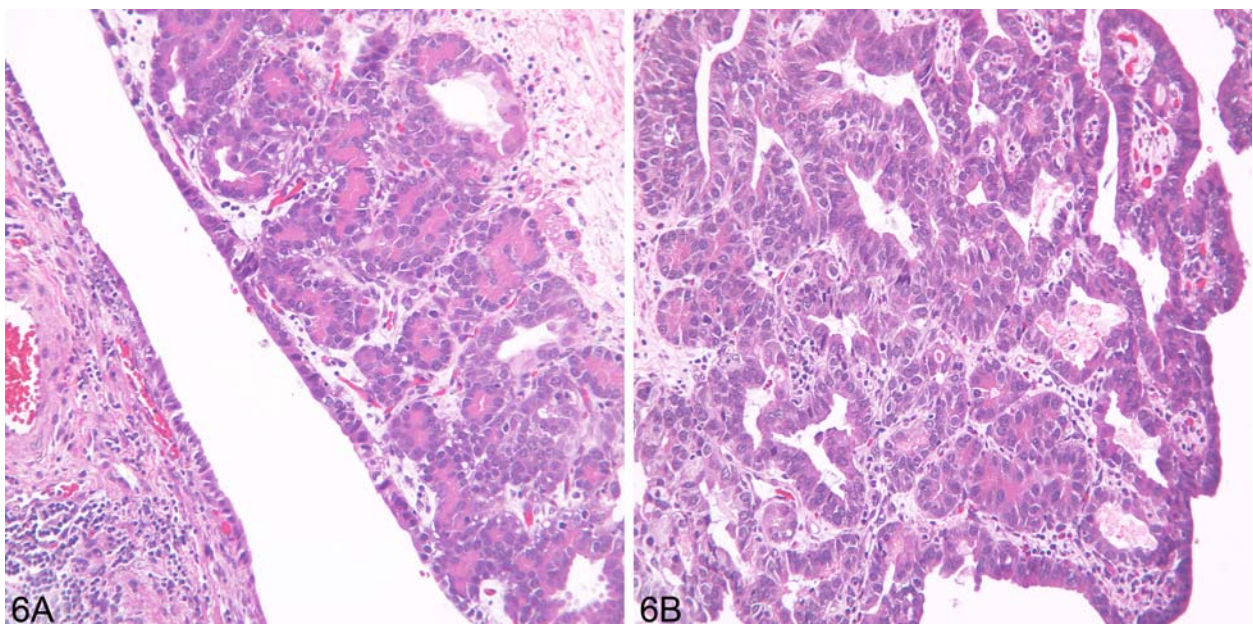


Fig. (6). Complete response to chemotherapy showing residual teratoma. (A) Pancreatic-like acini are found in the wall of this cystic lesion. H&E, 100. (B) Glandular structures are forming an adenoma-like nodule. H&E, x100.

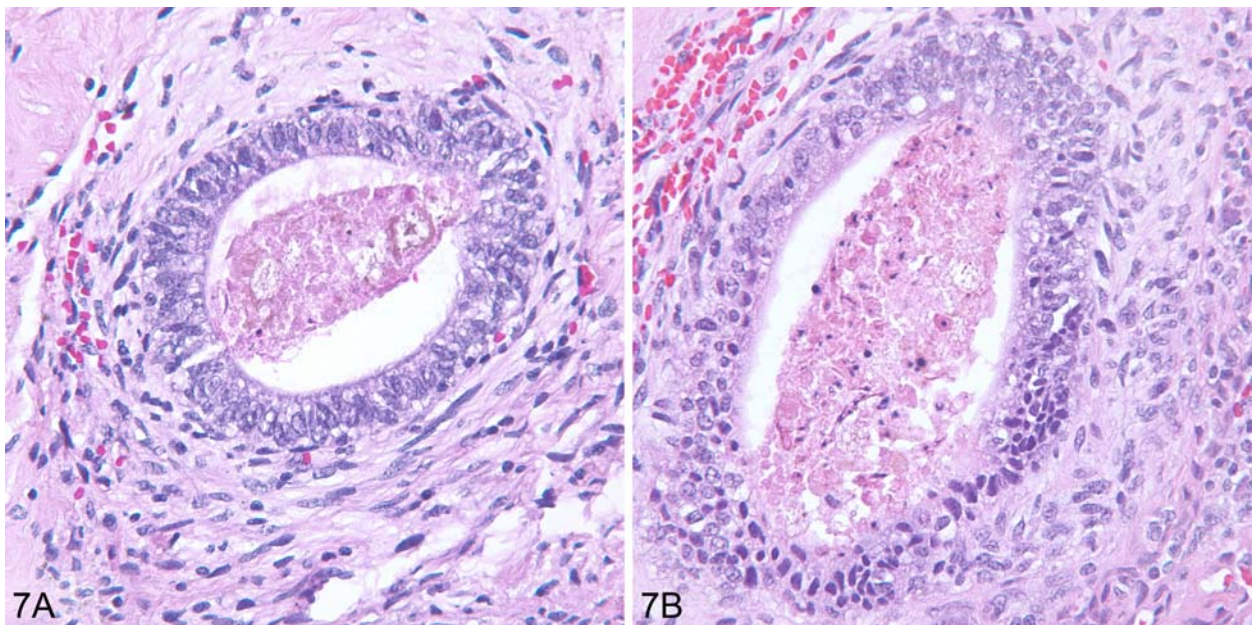


Fig. (7). Complete response to chemotherapy showing residual teratoma. (A) A nondescript duct-like structure is lined by densely packed cells and surrounded by fibroblastic cells. Both the epithelial and the stromal cells show some atypia. H&E, x100. (B) Higher power view of a similar gland illustrating the epithelial and stromal atypia. H&E, x200.

mitotic activity. The cysts of CTT are lined by a single cell layer, or stratified squamoid epithelium or epithelium projecting into papillary fronds. The cellular nests are sharply demarcated from the stroma and do not show any tendency for invasive growth or metastasis.

Most patients studied by Ulbright *et al.* [30] had normal serum human chorionic gonadotropin (hCG), or showed only mild elevation of hCG, with a mean of 8.0 mIU/ml. The authors conclude that post-chemotherapy CTT are benign lesions, which do not warrant additional chemotherapy and should not be confused with choriocarcinoma.

VIABLE RESIDUAL MALIGNANT GERM CELL TUMOR

Viable malignant germ cell tumor cells may be found not infrequently in the RPLND of patients with advanced stage NSGCT. Such patients typically have elevated serum tumor makers such as Alfa fetoprotein (AFP) or hCG [31], but in many cases the tumor markers may be not elevated [2-6]. Residual malignant germ cell elements are usually an indication for additional chemotherapy, and the pathologist's contribution in estimating the extent of viable malignancy is crucial. The proper counting of lymph nodes involved, the size or the malignant tumor in the lymph nodes and the size and composition of extranodal masses are important part of the pathologic examination and should be an obligatory part of each pathology report.

Residual malignant elements resemble usually those in the primary testicular tumor or recurrent germ cell neoplasia in other sites and can be classified as embryonal carcinoma, yolk sac carcinoma or choriocarcinoma [32]. In addition to these characteristic forms of germ cell malignancy there are atypical histologic variants. For example in some cases of choriocarcinoma one may see only mononuclear cytotrophoblastic cells [9]. This "monophasic choriocarcinoma" shows only focal immunohistochemical staining with antibodies to

hCG. Yolk sac carcinoma may present in several less common forms such as endometrioid, hepatoid or parietal yolk sac carcinoma. Endometrioid yolk sac carcinoma may be indistinguishable from endometrioid adenocarcinoma originating in a teratoma (Fig. 8). If in doubt one should perform immunohistochemistry since glandular structures of yolk sac carcinoma are usually AFP positive, which helps with the diagnosis. The hepatoid form of yolk sac carcinoma is also AFP positive. Parietal yolk sac carcinoma pattern can be recognized by the abundant hyaline extracellular material produced by this type of cancer (Fig. 9).

SECONDARY SOMATIC MALIGNANCY

Secondary somatic malignancies are malignant tumors developing from somatic tissues in teratomas. Such tumors do not contain embryonal carcinoma, yolk sac carcinoma or choriocarcinoma, the typical malignant components of NSGCT, and are therefore often colloquially known as "non-germ cell malignancies" [33]. Secondary malignancies originating in the post-chemotherapy RPLND specimens are similar to those evolving in primary metastatic sites of testicular and extragonadal germ cell tumors and are most often diagnosed as sarcomas [34]. Most commonly reported tumors are rhabdomyosarcomas [35]. Other forms of sarcoma, adenocarcinoma, peripheral neuroectodermal tumor and neuroblastomas [36]. Secondary somatic malignant tumors are usually resistant to chemotherapy [34, 35].

CONCLUSION

Metastatic malignant testicular germ cell tumors respond often very favorably to chemotherapy. Chemotherapy related changes recognized microscopically can be classified into several groups reflecting the response of the tumor to therapy. Proper classification and interpretation of pathologic changes in retroperitoneal lymph node dissection material is essential for planning of additional chemotherapy and for formulating the prognosis of these neoplasms.

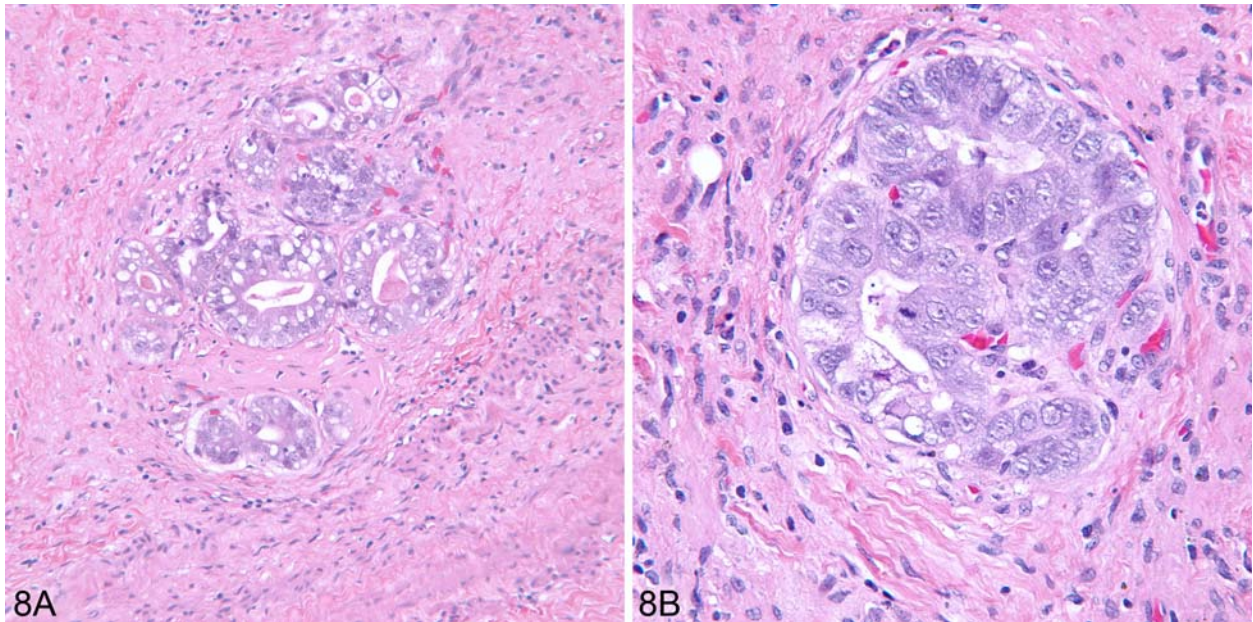


Fig. (8). Incomplete response to chemotherapy showing residual yolk sac carcinoma. (A) Endometrioid yolk sac carcinoma is composed of aggregates of atypical neoplastic glands. Tumor cells show vacuolization. H&E, x 100. (B) Endometrioid yolk sac carcinoma is composed of glands lined by cuboidal cells in a back to back arrangement. H&E, x200.

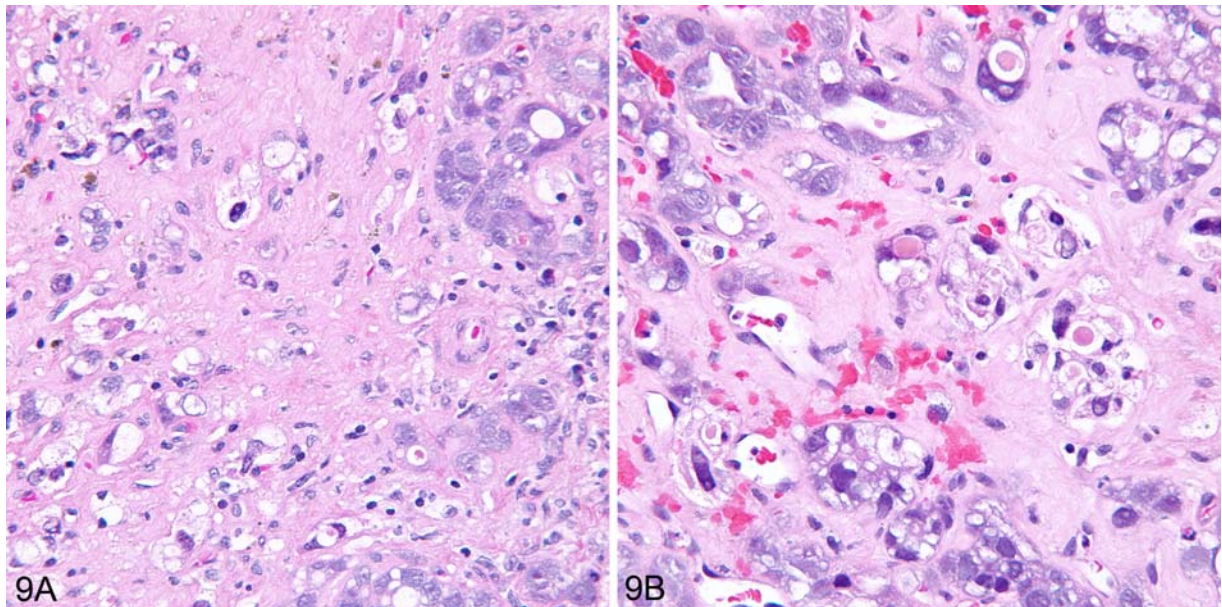


Fig. (9). Incomplete response to chemotherapy showing residual yolk sac carcinoma. (A) This tumor shows the yolk sac pattern in which solid groups or strands of tumor cells are surrounded by hyaline extracellular matrix. H&E, x100. (B) Higher power view of yolk sac carcinoma rich in extracellular hyaline matrix. It also contains round hyaline globules. H&E, x200.

ABBREVIATIONS

AFP	=	Alpha fetoprotein
CTT	=	Cystic trophoblastic tumor
hCG	=	Human chorionic gonadotropin
NSGCT	=	Nonseminomatous germ cell tumor
RPLND	=	Retroperitoneal lymph node dissection

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