Pathology (■ 2017) ■(■), pp. 1–12

REVIEW: 50TH ANNIVERSARY ISSUE

Pitfalls in the interpretation of specimens from patients with testicular tumours, with an emphasis on variant morphologies

THOMAS M. ULBRIGHT

Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indiana University Health Pathology Laboratory, Indianapolis, IN, United States

Summary

Accurate diagnosis of primary and metastatic tumours is essential in testicular cancer. While many cases are straightforward, some pose difficulties, especially when variant morphologies occur. Seminoma with 'atypical' features, including increased nuclear pleomorphism and crowding and greater cytoplasmic density with loss of membrane definition, mimics embryonal carcinoma, although ancillary features (fibrous septa, lymphocytes) and immunohistochemistry are of great help. Other deceptive seminoma features include prominent to exclusive intertubular growth, microcystic/tubular patterns, and signet-ring tumour cells. Conversely, embryonal carcinomas may have 'seminoma-like' foci, as may Sertoli cell tumours with diffuse growth and pale cytoplasm. Solid pattern yolk sac tumour mimics seminoma and, conversely, microcystic seminoma resembles yolk sac tumour. Other architectural patterns, ancillary yolk sac tumour features (intercellular basement membrane deposits, hyaline cytoplasmic globules) and immunohistochemistry aid in distinction from seminoma. Embryonal carcinomas may show, in addition to 'seminoma-like' foci, pseudoendodermal sinus-like structures, sieve-like patterns, endometrioid-like morphology and prominent zones of stratified columnar tumour cells. These may cause confusion with yolk sac tumour and teratoma, although careful attention to cytological features usually suffices for accurate diagnosis. Recent work has defined 'new' primary trophoblastic tumours, i.e., cystic trophoblastic tumour and epithelioid trophoblastic tumour. The newly termed 'spermatocytic tumour' occasionally consists mostly of a monotonous proliferation of intermediate-sized tumour cells with prominent nucleoli, thereby simulating either seminoma or embryonal carcinoma. Prostatic adenocarcinoma remains the most common tumour to metastasise to the testis and can cause confusion with rete carcinomas and primary germ cell tumours. Post-chemotherapy resections pose their own challenges. Effete tumour cells in areas of necrosis and prominent fibroxanthomatous reactions should not be interpreted as persistent, viable germ cell tumour. 'Fibrosis' often has atypical widely scattered spindle tumour cells in a densely collagenous background but does not merit additional treatment apart from excision. The marked cytological atypia that may occur in metastatic teratoma may be disconcerting but, again, the proper treatment is complete surgical excision rather than more chemotherapy. Glandular and sarcomatoid yolk sac tumours, which are almost exclusively seen after chemotherapy, resemble adenocarcinomas and sarcomas, respectively. Unlike *de novo* malignancies, they are mostly seen in sites expected for metastases.

Key words: Testicular neoplasm; germ cell tumour; seminoma; embryonal carcinoma; yolk sac tumour; trophoblastic tumour; teratoma; Sertoli cell tumour; post-chemotherapy resection; sarcomatoid yolk sac tumour; immunohistochemistry.

Received 30 June, accepted 20 July 2017
Available online: xxx

INTRODUCTION

Testicular germ cell tumours, the most common solid malignancies of young men, represent a stunning success of modern oncology. The landmark paper of Einhorn and Donohue[1] defines a turning point in the treatment and prognosis of these tumours, to the degree that a very high proportion of these cases are now considered 'curable'. The truth of this statement is reflected in a simple comparison of the 10-year net cancer-specific survival of patients with these neoplasms in the pre-modern chemotherapy era (69%) versus the post-modern chemotherapy era (98%).[2] The current emphasis is on tailoring individual therapy to minimise toxicity and potential complications. Pathologists play an important role in this process, which depends on accurate diagnosis and pathologic staging. This role extends not only to the initial specimen obtained from these patients (usually an orchiectomy) but also to all that are resected following cisplatin-based treatment. One could make a strong argument that what the pathologist contributes to the care of testicular germ cell tumour patients is even more critical in the latter situation.

In this article, we will discuss some of the pitfalls associated with the assessment of specimens from patients with testicular germ cell tumours that may lead to misdiagnosis. This necessarily involves a consideration of a number of morphological variants, both common and uncommon. After primary testicular tumours are considered, we will discuss post-chemotherapy resections and how the findings in those specimens impact subsequent therapy.

PRIMARY TESTICULAR TUMOURS

Seminoma, the most common testicular tumour (representing about 50% of the germ cell tumours and 45% of primary

Print ISSN 0031-3025/Online ISSN 1465-3931
DOI: https://doi.org/10.1016/j.pathol.2017.07.013

Please cite this article in press as: Ulbright TM, Pitfalls in the interpretation of specimens from patients with testicular tumours, with an emphasis on variant morphologies, Pathology (2017), https://doi.org/10.1016/j.pathol.2017.07.013

testicular neoplasms[3]) may show some deceptive features that result in diagnostic confusion. A lesser proportion of seminomas are now managed with radiation treatment (either adjuvant or therapeutic) than in the past, with surveillance and chemotherapy having supplanted this modality for many patients. Nonetheless, radiation continues to be used for some and is an extremely effective modality for both the prevention of clinical retroperitoneal disease (for clinical stage I patients) and the treatment of small volume retroperitoneal metastases. Because non-seminomatous tumours (i.e., any testicular germ cell tumour that contains a component other than seminoma, regardless of the presence or absence of seminoma in the same neoplasm) are resistant to radiation, an accurate diagnosis of a pure seminoma is crucial for those patients who will receive radiation. Incorrect diagnosis of seminoma may not only lead to ineffective treatment but also limit subsequent chemotherapy because of the cumulative effect of radiation and chemotherapy with respect to bone marrow toxicity.

Adequate tumour blocking is important to optimise an accurate diagnosis of pure seminoma. Although no study has addressed the question of what constitutes sufficient blocking, a general guideline of at least 10 tumour blocks of larger, grossly homogeneous-appearing neoplasms, and complete blocking of smaller specimens, if the entire tumour can be submitted in 10 blocks or less, appears reasonable.[3] However, additional tumour blocks are indicated if a large neoplasm has a more variegated appearance or if pre-orchiectomy tumour marker studies [especially alpha-fetoprotein (AFP)] are elevated and these decline to normal levels after the testis is excised. Some may make the argument that persistent elevation of AFP after an orchiectomy showing an apparently pure seminoma should also prompt additional tumour sampling, but regardless of what is found in such additional material, these patients will be managed as having non-seminomas. It is important to keep in mind that seminoma, far from being a terminally differentiated form of germ cell tumour, as it was once considered,[4] is now regarded as a potential precursor from which other germ cell tumour types originate. Srigley *et al.*[5] provided ultrastructural evidence that occasional (4/47) light microscopically typical seminomas may exhibit distinct epithelial differentiation when they identified small groups of seminoma cells with projecting microvilli arranged around early lumens and joined by tight junctional complexes and desmosomes. This was considered an early phase in the transformation of seminoma to embryonal carcinoma. Oosterhuis *et al.*,[6] using ploidy data of seminomas and non-seminomas, supported a similar histogenetic model as developed by Srigley *et al.* wherein the non-seminomas develop from seminomas secondary to loss of chromosomal material. This histogenetic concept is now widely accepted by those with special interest in testicular germ cell tumours, but it is remarkable how few treating physicians are familiar with it or understand its implications. Once a seminoma, therefore, is not always a seminoma. AFP elevation following an orchiectomy showing a pure seminoma may well correspond to yolk sac tumour differentiation in a metastatic site and not an error of initial tumour sampling or because of pathologist oversight. We should also mention that there is a report of minimal AFP elevation associated with some morphologically pure testicular seminomas.[7] This phenomenon likely corresponds to minuscule foci of very subtle yolk sac tumour differentiation in otherwise pure seminomas; however, it is noteworthy that such cases behaved as pure seminomas.[7]

It can be difficult to distinguish seminomas from embryonal carcinoma. Although most seminomas have clear or pale cytoplasm and crisp cell membranes, some do not. Instead, the cytoplasm is denser and the membranes are ill-defined (Fig. 1A). Often in such cases the nuclei are more atypical in appearance, with greater crowding and pleomorphism as compared to the classical, relatively uniform polygonal nuclei of seminoma. In the absence of overt epithelial differentiation at the light microscopic level, it is our experience that most such cases are a part of the seminoma spectrum. On the other hand, a comprehensive morphological review of 180 embryonal carcinomas showed 11% with 'seminoma-like' foci (Fig. 1C).[8] These areas consisted of solid aggregates of embryonal carcinoma cells with clear cytoplasm, distinct cytoplasmic membranes and rather evenly spaced nuclei. However, careful microscopic examination showed a greater degree of nuclear pleomorphism and irregularity in such cases than in seminoma, but admittedly this distinction is somewhat subjective. Fortunately, such areas occurred in the context of more usual-appearing embryonal carcinomas, which greatly facilitated the correct interpretation, although they may theoretically exist in isolation. When doubt persists whether a neoplasm is seminoma or embryonal carcinoma, immunohistochemistry may prove extremely valuable. Several markers exhibit differential reactivities in these two tumours.[9] For seminoma (but not embryonal carcinoma) these include podoplanin, CD117 (Fig. 1B), and SOX17; and for embryonal carcinoma (but not seminoma) they include CD30 (Fig. 1D), AE1/AE3 cytokeratin and SOX2. Several markers should be employed in light microscopically equivocal cases, with the diagnosis indicated by a careful assessment of the preponderance of light microscopic evidence and immunoreactivities. It should be borne in mind that occasional immunohistochemical infidelities do occur. For those seminomas having a degree of embryonal carcinoma-like appearance (referred to as 'seminoma with atypia' by Tickoo *et al.*[10]), one study noted presentation at more advanced American Joint Committee on Cancer (AJCC) stage than classic seminoma,[10] but there is no evidence that such 'atypical seminomas' require different treatment other than for classic seminoma. Therefore, we do not use any different terminology for such tumours.

Seminomas, although mostly considered in terms of prototypical appearance, may show a number of variant features that could contribute to diagnostic confusion or even tumour oversight if the pathologist is not aware of them. Intertubular growth (Fig. 2A), a common focal feature in seminoma, may rarely be an exclusive pattern.[11] Often these are cases where a distinct testicular mass is not found either on clinical or gross examination. In the study of Henley *et al.*,[11] none of 12 patients with an exclusively intertubular seminoma had a known presentation as a testicular mass. Instead, they presented with pain, infertility, small testicular size, cryptorchidism or secondary to metastases. Only one of 10 cases with available gross descriptions showed a distinct mass on macroscopic examination. At low power microscopic examination, the seminiferous tubules are typically more widely separated than normal and there is often an associated but variably intense lymphocytic infiltrate (Fig. 2A). In very subtle cases only small clusters of seminoma cells are found in the interstitium, not uncommonly admixed with non-

Please cite this article in press as: Ulbright TM, Pitfalls in the interpretation of specimens from patients with testicular tumours, with an emphasis on variant morphologies, Pathology (2017), https://doi.org/10.1016/j.pathol.2017.07.013