Diagnosis and Treatment of Testicular Cancer

A Clinician's Perspective

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KEYWORDS

• Testicular cancer • Germ cell tumor • Seminoma • Nonseminoma • Active surveillance • Cancer of unknown primary

Key points

- Testicular germ cell tumors (GCTs) include seminoma and nonseminoma; both are highly curable even if metastatic.
- Different adjuvant therapy options exist for clinical stage I (CSI) disease although outcomes are similar to a strategy of surveillance and treatment only for those who relapse.
- LVI is associated with higher relapse rates in CSI nonseminoma but almost 100% can be salvaged with chemotherapy.
- Chance of teratoma in retroperitoneal postchemotherapy residual masses is higher if present in orchiectomy specimen and with increasing size of the mass.
- Histologic concordance rates between the retroperitoneum and lung masses are high; this can influence approach to further treatment.
- Isochromosome of the short arm of chromosome 12 (i12p) and OCT4 can be useful special tests to identify GCT in cancer of unknown primary (CUP).

ABSTRACT

Testicular germ cell tumors (GCTs) include seminoma and nonseminoma. Chance of cure is excellent for clinical stage I disease regardless of whether adjuvant treatment or a surveillance strategy with treatment only for those who relapse is used. Risk of recurrence is greater in nonseminoma with evidence of lymphovascular invasion, but most can be salvaged with chemotherapy and survival rates remain high. This article outlines key pathologic and clinical considerations in clinical stage I seminoma, nonseminoma, advanced disease, and assessment of cancer of unknown primary as a potential GCT.

OVERVIEW

A majority of testicular cancers are classified as GCTs (see also Howitt and Berney, Tumors of the Testis: Morphologic Features and Molecular Alterations, Surgical Pathology Clinics, 2015, Volume 8, Issue 4). Of these, 2 types exist: seminoma and nonseminoma. Risk factors for the development of GCT include gonadal dysgenesis, cryptorchidism, and positive family history.[1–4] In addition, HIV-positive men have an increased risk of developing seminoma.[5] Moreover, infertility has been linked to an increased risk of developing GCT.[6] Lastly, the finding of testicular microlithiasis on ultrasound is associated with a higher likelihood of diagnosis of GCT.[7]

Disclosures: B. Bernard has nothing to disclose. C.J. Sweeney has nothing to disclose related to subject matter of this article.

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Surgical Pathology 8 (2015) 717–723

http://dx.doi.org/10.1016/j.path.2015.07.006

1875-9181/15/$ – see front matter

Prognosis and treatment options vary with more advanced American Joint Committee on Cancer clinical TNM stage and International Germ Cell Cancer Collaborative Group classification. CSI is tumor confined to the testis with no radiographic evidence of retroperitoneal or distant metastases and normal tumor markers (β-subunit of human chorionic gonadotropin, alpha fetoprotein [AFP], and lactate dehydrogenase) postorchiectomy.

CLINICAL STAGE I SEMINOMA

OVERVIEW

Pure seminoma is a pathologic diagnosis with therapeutic implications.[8] Chance of cure is high even in advanced disease. Seminoma differs from nonseminoma in that men tend to present at an older age, with a median age at diagnosis of approximately 40 years.

Key Features
SEMINOMA

1. Pure seminoma accounts for approximately one-half of all GCTs.
2. The median age of diagnosis is approximately 40 years.
3. Light microscopy is often sufficient to distinguish between nonseminoma and seminoma.
4. Sharp cytoplasmic borders, prominent nucleoli, and clear cytoplasm make up the fried egg characteristic appearance.
5. Lymphocytes interspersed with tumor cells is a frequent finding.
6. After orchiectomy, active surveillance is the preferred treatment strategy for CSI given that most relapses are salvaged and survival is near 100%.
7. Most relapses occur within 3 years of orchiectomy.

GROSS FEATURES

Seminomas are bulky, soft, homogeneous masses. A Danish series of 1058 patients with GCT reported a diagnosis of seminoma in 52.4%.[9] It has been reported that risk of metastasis correlates with greater primary tumor size; however, 78% of cases in this series presented with CSI.

MICROSCOPIC FEATURES

Seminoma is defined by the absence of nonseminomatous components. Histologically, it shows clonal proliferation of cancerous germ cells with sharp cytoplasmic borders, prominent nucleoli, and clear cytoplasm (fried egg appearance) (see also Howitt and Berney, Tumors of the Testis: Morphologic Features and Molecular Alterations, Surgical Pathology Clinics, 2015, Volume 8, Issue 4). Furthermore, groups of lymphocytes are often observed interspersed with tumor cells. Light microscopy is the mainstay of distinguishing from nonseminoma and other testicular cancers.[8] The immunostains, OCT3/4, CKIT, and CD30, are useful, however, if ambiguity exists.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for a testicular mass includes torsion, epididymitis, hydrocele, varicocele, hernia, hematoma, spermatocele, and malignancy. Regarding seminoma, other possibilities include a nonseminomatous GCT (in particular, pure embryonal cell carcinoma [EC]) and lymphoma.

Differential Diagnosis
SEMINOMA

- Nonseminoma: distinguishing from EC can be problematic if cellular atypia exists; however, EC tends to have less defined cell borders and greater pleomorphism; EC stains positive for CD30 and SOX2 and this can help distinguish it from seminoma, which is in contrast positive for CKIT and D2-40.
- Testicular lymphoma tends to present in older men, invades into the interstitium, and stains positive for markers of lymphoid cell lineage (ie, leukocyte common antigen).
- Sex cord–stromal tumors tend to present in middle age and do not produce tumor markers but may be associated with hormonal abnormalities with consequent symptoms and signs, such as gynecomastia; specifically, antibodies can be used to distinguish from semionoma.
- Mesothelial cell proliferations, such as adenomatoid tumor or, rarely, mesothelioma—the latter can present as a recurrent hydrocele, can be diagnosed from cytology of the aspirate, and can be distinguished with imunostains.