

Solid Tumour Section

Mini Review

Testis: Germ cell tumors

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Classification

- Two main entities may be distinguished within testicular germ-cell tumours: seminomas and non seminomatous germ-cell tumours (NSGCT).
- Seminomas are composed of neoplastic germ cells.
- Non seminomatous germ-cell tumours present multiple histologic subtypes with neoplastic 1-embryonic tissues (embryonal carcinoma, immature and mature teratoma), or 2- extraembryonic tissue (yolk sac tumour and choriocarcinoma), which are usually associated and are therefore called mixed germ cell tumours (the most frequent being teratocarcinoma).
- There may be combined tumours of seminomatous and non seminomatous components.
- Intratubular germ cell neoplasia (ITGCN), also called carcinoma in-situ, appears as a precursor lesion of invasive tumours (common precursor for both seminomas and NSGCT), but it can also be observed in patients without development of a testicular germ-cell tumour (GCT).
- In adults, most testicular germ cell tumours are associated with ITGCN surrounding the invasive cancer.

Clinics and pathology

Disease

Testicular germ-cell tumours (GCT) and intratubular germ cell neoplasia (ITGCN).

Epidemiology

Testicular tumours represent 1 to 2% of all malignant tumours in men; 30% of patient are < 35 yrs; 3 groups can be distinguished according to the age: (1) tumours of the infant, (2) tumours of the adolescent and young adult, (3) tumours of the elderly man; most yolk sac tumours occur in children < 2yrs; in young adults, tumours are seminomas in 50% of the cases and

NSGCT in 40%; at presentation, patients with seminomas are generally older (med age 40 yrs) than those with NSGCT (med age 25 yrs). In the elderly persons, GCT are generally seminoma (spermatocytic seminoma) or teratoma with malignant transformation.

Clinics

Germ cell tumours represent 95% of testicular cancers; cryptorchism is a great predisposing factor, as well as the occurrence of a seminoma in the contralateral testis; a few cases have occurred in a familial setting; clinical presentation is generally a progressive and painless enlargement of the testis sometimes associated with gynecomastia.

Pathology

- Staging: the TNM (tumour/nodes/metastases) classification is the most used. The first parameter T ranges from pTis for ITGCN without associated GCT, to pT1 to pT4 for true GCT; a second classification commonly used by the urologists describes the tumour in 3 stages according to the limits of the tumour and the presence of lymph nodes invasion.

- Immunohistochemistry: yolk sac tumours are associated with a high level of a foeto-protein in the peripheral blood; in choriocarcinomas, syncytiotrophoblastic cells (but not the cytotrophoblastic cells) have a β HCG activity; β HCG can also be measured in seminomas with a syncytiotrophoblastic cells component, but placental alkaline phosphatase (PLAP) is more useful and specific (and also in ITGCN).

Treatment

The initial treatment in all cases is orchietomy with high ligation of the spermatic cord; patients with classical seminoma receive thorough irradiation of the retroperitoneum; chemotherapy is given only to patients presenting with advanced disease; the treatment of stages I and II of NSGCT is controversial; orchietomy may be followed by retroperitoneal

lymphadenectomy, radiation therapy, and chemotherapy.

Evolution

A 2 yrs event free survival after therapy is associated with cure in 90% of cases.

Prognosis

According to the clinical stage and to the tumour histopathological type; seminomas limited to the testis (stage I) or with subdiaphragmatic lymph nodes (stage II) are cured in over 95% of cases; in NSGCT (except choriocarcinomas) the overall cure rate is over 95% (40% to 95% in the case of metastases) but vary with the histologic predominant subtype; embryonal carcinomas are associated with a poorer prognosis; choriocarcinomas bear a grave prognosis.

Cytogenetics

Cytogenetics, morphological

i(12p) in 80% of cases.

Probes

According to some workers, D12Z3 gives a larger centromere signal in i(12p) than in normal chromosomes 12; for others who used the a-satellite sequence pa12H8 probe of the pericentriole zone of chromosome 12, no differences between normal chromosome 12 and i(12p) signals were found. In our experience, 12p anomalies can be highly variable and we would be cautious concerning FISH image interpretation without a karyotype.

Additional anomalies

Chromosome mode is most often hypertriploid or tetraploid in seminomas, and hypotetraploidy in nonseminomatous tumours.

- The most frequent numerical anomalies are trisomy X, 7, 8 and 12, monosomy 11, 13 and 18.
- Rearrangements in 1p23-36 and 7q11 regions are frequently associated with teratomas.
- Anomalies in 1p22 region are found in cases of yolk sac tumours.
- Duplications of the i(12p) occur during tumour evolution; it may be a prognosis factor: higher is the number of 12p copies higher appears to be the probability of therapy failure.
- Loss of chromosome 15 is noted in association with nonseminomatous tumours and also in the CIS adjacent to these tumours.
- The presence of hsr (homogeneously staining regions) and dmin (double minute) suggest amplifications of gene(s) during disease progression.

Variants

Other 12 chromosome anomalies leading to an increase in the number of 12p copies and a relative decrease in 12q copies.

Genes involved and Proteins

Note: The genes involved are unknown.

- Oncogene hypothesis: CGH (comparative genomic hybridization) and FISH using region specific probe delineated the amplified region in 12p11.2; the gene encoding the parathyroid hormone related peptide (mapped in 12p11) is a possible candidate.

- Antioncogene hypothesis: loss of heterozygosity (LOH) studies showed a high incidence of LOH in the 12q13 and 12q22 regions suggesting presence of candidate tumour suppressor genes.

To be noted

It has been suggested by some authors that the i(12p) are formed by non reciprocal centromeric interchanges, while others argue that the occurrence of partial trisomies 12p through i(12p) or others anomalies of 12p derive from uniparental origin.

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