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Editorial

News in the classification of WHO 2022 testicular tumours

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Summary
The novelties in WHO 5th edition classification of genitourinary tumours are: a) nomenclature changes, including the replacement of the term "primitive neuroectodermal tumour" with "embryonic-type neuroectodermal tumour" and of "carcinoid" with "neuroendocrine tumour". Also, seminoma is now placed in a "germinoma" family of tumours, while sertoliform cystoadenoma was moved from adnexal tumours to Sertoli cell tumours; b) new entities, specifically signet ring stromal tumour, myoid gonadal stromal tumour and well-differentiated papillary mesothelial tumour.

Key words: WHO, testis, classification

Introduction

Testicular neoplasms are rare tumours, accounting for less than 6 cases for 100,000 males for year in Italy [1]. Some rare histotypes will not be encountered even once a decade! The 5th edition of the World Health Organization (WHO) [2] was published in June 2022. This new blue book was built upon the work of the 4th edition [3], especially concerning germ cell tumours (GCTs). Indeed, GCTs are still subdivided into germ cell neoplasia in situ (GCNIS)-derived and GCNIS-unrelated groups, as introduced in the 4th edition.

GCNIS-derived germ cell tumours

Among GCNIS-derived GCTs, the most common type is testicular seminoma, that have been reported in a "germinoma" family of tumours in the new classification. The reason is the unification of terminology (i.e.: dysgerminoma, seminoma and germinoma) used for neoplasms with similar morphology, immunochemistry and molecular features throughout the body [4]. Seminoma with syncytiotrophoblastic cells is recognised as the only subtype of seminoma and it gives the possibility of an accurate follow-up by measuring serum beta-human chorionic gonadotrophin. Among non-seminomatous GCTs, the latest blue book introduced some important and substantial changes for teratoma with somatic transformation (TST). In the WHO 4th ed. [3], the diagnosis of TST was established with a pure population of atypical mesenchymal or epithelial cells occupying at least one low-power field (i.e. a x4 objective, 5 mm in diameter). As there is a need of standardisation of microscopical low power

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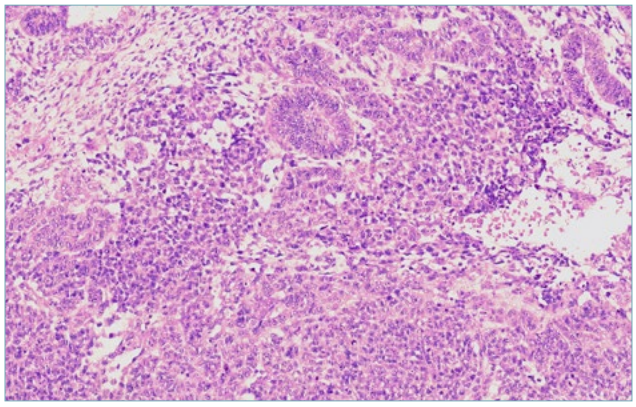

Figure 1. Embryonic neuroectodermal tumour in teratoma with somatic transformation. A typical appearance (HE).

fields and a growing shift towards digital pathology, in the 5th ed. [2] only the size cutoff (≥ 5 mm) is present among essential diagnostic criteria. Another change is related to teratomas featuring areas of small round blue cells with neural differentiation (Fig. 1), often referred to as 'transformed teratoma' among urologists. These were previously defined as "primitive neuroectodermal tumours" (PNETs), one of the most common forms of TST [5,6]. Nevertheless, PNET has now been replaced with "embryonic-type neuroectodermal tumour" (ENET) both in testicular and ovarian tumours [7]. This change has been introduced to avoid the confusion with a true Ewing sarcoma which has been rarely identified in the testis [8]. The absence of the Ewing sarcoma translocation of EWS1:FLI1 and the similarity with their CNS counterparts were already highlighted in the previous WHO 4th edition, but in the 5th edition the terminology has finally been modified.

GCNIS-unrelated germ cell tumours

Spermatocytic tumour (ST) maintains the same nomenclature considering its indolent nature in the great majority of cases. However, there are few reports of metastatic ST in the literature with associated GCNIS-related tumours that are worthy of further investigations [9,10]. An important change has been made in the classification of neuroendocrine tumours, as the term "carcinoid" has been discarded throughout the current WHO classifications. The new denomination "testicular neuroendocrine tumour, prepubertal-type" (prepubertal NET) underlines the GCNIS-unrelated origin of a neoplasm that arises in the setting of a prepubertal teratoma in about 25% of cases. The assessment of testis NET prognosis is difficult, but mitotic index and Ki-67 may be of importance. GCNIS-derived NET is instead reported in rare cases to arise in post-pubertal type teratoma [11].

Sex cord stromal tumours of the testis

Sex-cord stromal tumours (SCSTs) represent about 5% of all testicular tumours. They are usually purely composed of sex cord elements, but they can also combine variably with cells of the testicular gonadal stroma. Leydig cell tumours (LCTs) are the most common subtype (75% of cases), followed by Sertoli cell tumours (SCTs). A large percentage of the latter molecularly shows a mutation in the CTNNB1 gene, leading to nuclear staining of β-catenin in neoplastic cells. This feature can also be used diagnostically [12,13].

In the 5th ed. of the WHO classification, two new entities were added. Firstly, the signet ring stromal tumour [14-16] (Fig. 2 A-B), although there is a debate about whether it belongs to the morphological spectrum of SCTs as they both show an identical marker profile, including the aforementioned positive nuclear staining reaction of b-catenin. Secondly, the myoid gonadal stromal tumour which is listed as a separate entity because it differs from other sex cord tumours both morphologically and immunohistochemically (Fig. 2 C-D) [17].

The sertoliform cystadenoma is located in the rete testis and it was previously classified among the testicular adnexal tumours. It is now listed with the SCTs due to strong histological and immunohistochemical overlaps [18].

The intratubular large cell hyalinising SCT was allocated to "genetic tumour syndromes" in the new WHO classification because it is only described in patients with Peutz-Jeghers syndrome [19]. In contrast, the large cell calcifying SCT continues to be included both among sporadic tumours and genetic tumour syndromes, as it can also occur as part of the Carney complex (Fig. 3) [20].

Mixed and undifferentiated SCSTs are now divided into two separate categories. Mixed SCSTs consist of a variable combination of germ line tumour elements and stromal elements. SCST NOS is instead reserved for SCSTs made up of undifferentiated/immature sex cord stromal cells which cannot be subtyped precisely.

SCSTs are usually indolent tumours with a good prognosis. Nevertheless, metastases can occur, even in morphologically typical tumours. These cases show a progressive course, due to the poor response to chemotherapy. Since only metastases

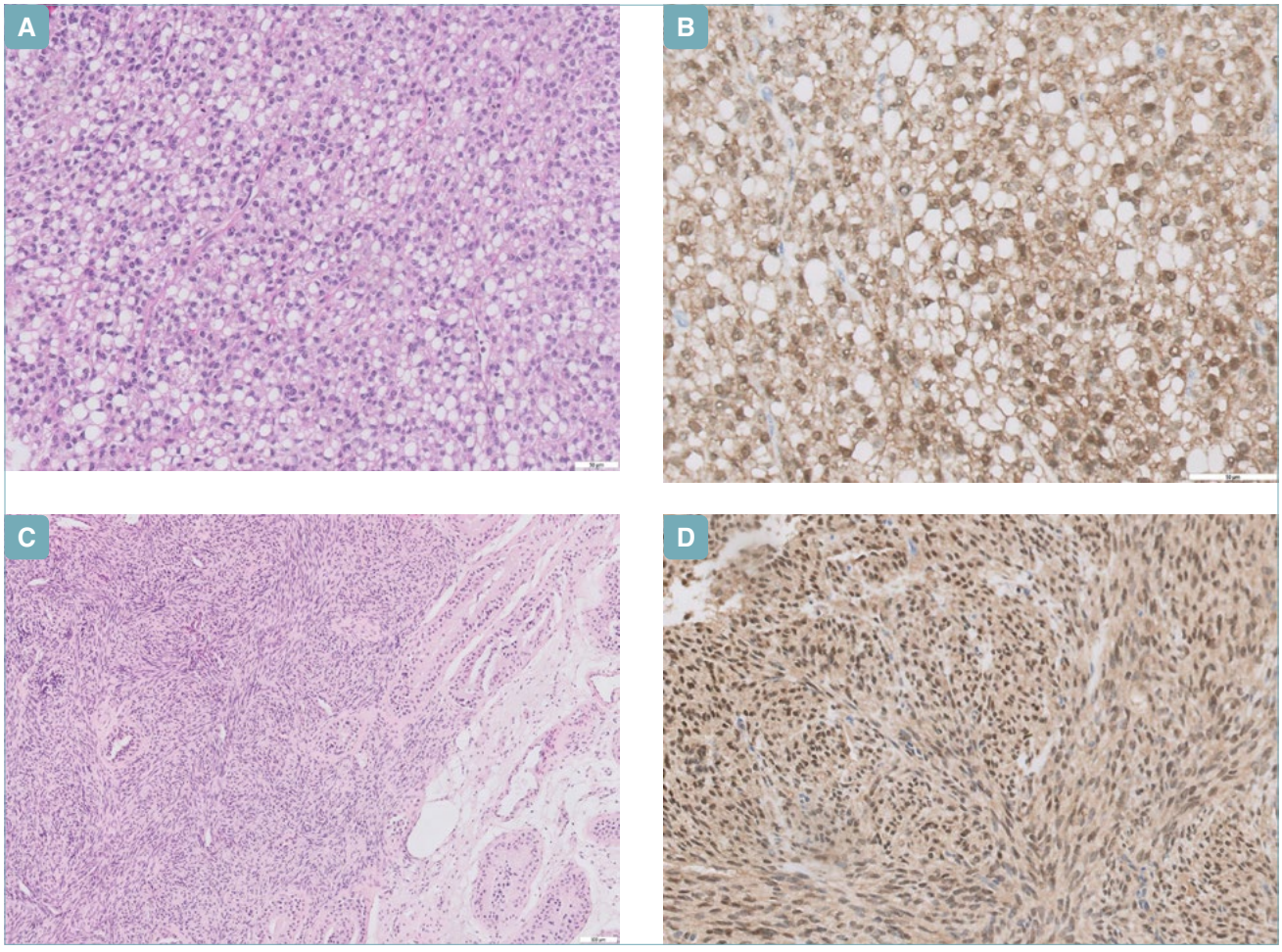

Figure 2. (A) Signet ring cell stromal tumour (HE). (B) Signet ring cell stromal tumour (β-catenin stain). (C) Myoid stromal tumour (HE) (D) Myoid stromal tumour (S100 stain).

represent a clear (but late) criterion for malignancy [21], it is important to collect histopathological parameters to predict malignant biological behaviour. These include size (> 5 cm), presence of necrosis, infiltrative growth, lymphatic or blood vessel invasion, moderate to severe nuclear atypia and an increased mitotic rate (> 5 mitoses/2 mm^2) [22]. The Leydig cell tumour Scaled Score (LeSS) was introduced for LCTs, but it still needs to be further established [23]. At the same time, it remains unclear how patients with SCSTs should be treated because so far only studies with small cohorts have addressed this topic. Orchiectomy is sufficient for tumours without risk factors [24,26]. If only one risk factor is present, an orchiectomy and regular check-ups should be performed [27]. An additional retroperitoneal lymph node dissection is favoured in patients with 2 or more risk factors or UICC stage IIa [28].

Tumours of the testicular adnexa

The rare adnexal tumours of the testis are described in a separate, systematically structured chapter. The category includes tumours of the rete testis, the epididymis, the spermatic cord, the testicular appendices and the mesothelium of the tunica vaginalis [28]. Adenomatoid tumour is the most common entity and it habitually shows indolent behaviour. Only about 23% of adnexal tumours are malignant, including malignant mesothelioma and some types of carcinoma [27,28]. Well-differentiated papillary mesothelial tumour is an entity that has been introduced in the latest WHO blue book. It features bland papillary neoplasms without evidence of invasive foci or with minimal stromal invasion [29], retained BAP1 expression and no CDKN2a deletion. So far, there is evidence that it carries a favourable prognosis.

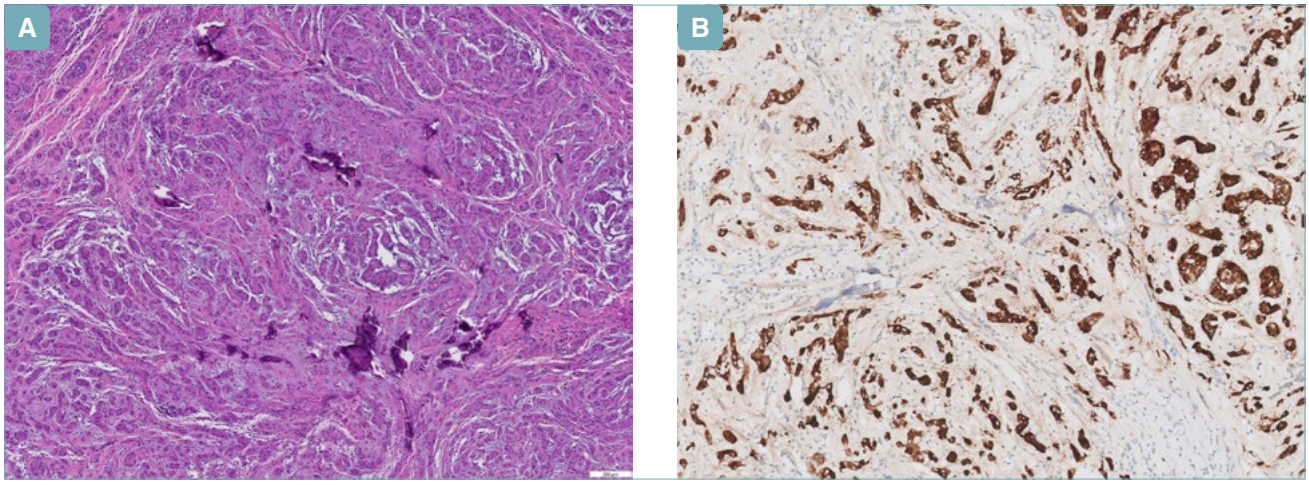

Figure 3. (A) Large cell calcifying Sertoli cell tumour (HE). (B) Large cell calcifying Sertoli cell tumour (Inhibin stain).

Conclusions

For testicular tumours, only minor changes introduced in the 2022 WHO 5th edition of genitourinary tumours are worthy of mention. Nomenclature changes and the introduction of new entities (i.e. Signet ring stromal tumour, myoid gonadal stromal tumour, and Well-differentiated papillary mesothelial tumour) are the true novelties and pathologists must be aware of them for a correct reporting.

Conflicts of interest

The authors declare no conflicts of interest.

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Ethical consideration

The authors declare no ethical conflicts.

Authors' contributions

MC conceptualization, writing, review; FB writing, review; GMP review.

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