

REVIEW

The World Health Organization 2016 classification of testicular non-germ cell tumours: a review and update from the International Society of Urological Pathology Testis Consultation Panel

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The World Health Organization (WHO) released a new tumour classification for the genitourinary system in early 2016 after consensus by pathologists with expertise in these organs. It utilized the framework of the 2004 classification, and incorporated the most up-to-date information concerning these tumours. In testicular tumours, the majority of the changes occurred in the nomenclature and classification of germ cell tumours; however, several modifications were also made for non-germ cell tumours. Among sex cord–stromal tumours, sclerosing Sertoli cell tumour (SCT) is no longer recognized as a separate entity but as a morphological variant of SCT not otherwise specified (NOS), as *CTNNB1* gene mutations have been noted in both neoplasms but not in

the other forms of SCT. Similarly, the lipid cell variant is not separately classified, but is considered to be a morphological variant of SCT NOS. Large-cell calcifying SCT is recognized as a distinct entity that occurs either sporadically or in association with Carney complex, with the latter patients having a distinct germline *PRKARIA* gene mutation. Intratubular large-cell hyalinizing Sertoli cell neoplasia is also accepted as a separate entity linked with Peutz–Jeghers syndrome. The subcategories of ‘mixed’ and ‘incompletely differentiated’ forms of sex cord/gonadal stromal tumours have been replaced by ‘mixed and unclassified sex cord–stromal tumours’. New entities introduced in the latest WHO revision include: myoid gonadal stromal tumour and ‘undifferentiated

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gonadal tissue', a putative precursor lesion of gonadoblastoma, whereas juvenile xanthogranuloma

and haemangioma are included in the miscellaneous category of tumours.

Keywords: ISUP, non-germ cell tumours, testicular tumours, World Health Organization 2016 Classification

Introduction

The World Health Organization (WHO) held a consensus meeting in Zurich Switzerland in March 2015 to finalize the WHO 'Classification of Tumours of the Urinary System and Male Genital Organs'. Prior to this meeting, a large group of pathologists from across the globe with expertise in the field communicated over several months to propose revisions to the 2004 WHO classification.¹ The proposed revisions were collected as a baseline for the new classification and reference text. An expert subgroup of pathologists organized into four organ-based committees met in Zurich to discuss the proposed revisions, develop a consensus, and approve and finalize the new classification and text, which was published in the form of the familiar 'Blue Book' in January 2016.² Several important changes were adopted for tumours of the testis and paratesticular tissues, mostly related to germ cell tumours, and less so for the other groups. This review will provide an overview of the non-germ cell tumours, and highlight the most important changes in the current classification as compared with the prior classification. During the last decade, relatively few changes were made in the nomenclature of non-germ cell tumours; however, new information has emerged that has led to a better understanding of their pathogenesis.

As in other organ systems, preliminary steps have been made towards a molecular-based classification, although much more additional work is required before a clinically useful one is in place for testicular tumours. Nonetheless, the WHO 2016 classification incorporated up-to-date molecular data, and the current WHO 2016 classification of non-germ cell tumours, presented in Table 1, is in part based on this information.

Sex cord–stromal tumours

Sex cord–stromal tumours are relatively uncommon, but represent the second largest group of primary testicular tumours (after germ cell tumours).³ Overall, they account for 4% of testicular tumours; however, the frequency increases to 8% in the paediatric

population.^{4,5} Leydig cell tumour is the most common pure tumour in this category, followed by Sertoli cell tumour (SCT), granulosa cell tumour, and pure stromal tumour. However, in our experience, SCTs are more often seen in consultation practice, because of their relative unfamiliarity, more diverse morphological spectrum, and frequent lack of specific immunohistochemical markers.³

Leydig cell tumour, historically also termed 'interstitial cell tumour', may present with hormonal manifestations, including gynaecomastia and, rarely, Cushing's syndrome or isosexual pseudoprecocity puberty in children.^{4–6} These tumours occur over all age ranges, but have a lower frequency in children. Little is known about their pathogenesis, except a rare association with germline fumarate hydratase mutations in patients with hereditary leiomyomatosis and renal cell carcinoma syndrome,⁷ or activating mutations of the luteinizing hormone receptor in children.⁸ Another rare association is with Klinefelter syndrome; however, many of the reported cases in this context may represent 'nodular' Leydig cell hyperplasia, a common finding in Klinefelter patients.^{9,10} Most cases of Leydig cell tumour have diagnostic morphological findings, and do not require additional studies (Figure 1A–C).

If the morphology of Leydig cell tumour is unusual, especially when spindle or clear cell features are noted, immunohistochemistry may be helpful. Lack of nuclear β -catenin expression and strong inhibin staining support the diagnosis of Leydig cell tumour over SCT. A clinically important differential diagnostic consideration is testicular 'tumour' of the adrenogenital syndrome (TTAGS)/testicular adrenal rest tumour, which is considered to be an extreme form of nodular hyperplasia of testicular steroid cells that is induced by high circulating levels of adrenocorticotrophic hormone, and that typically does not require orchiectomy and regresses following dexamethasone treatment.^{11–13} Helpful features that differentiate TTAGS from Leydig cell tumour include, in the former, bilaterality, prominent bands of collagen between nests of cells, abundant cytoplasmic lipofuscin pigment, spotty cytological atypia, a hormonal profile with high 17-hydroxyprogesterone and adrenal androgen levels, and frequent regression after

Table 1. World Health Organization (WHO) 2016 classification of non-germ cell tumours of the testis*

Sex cord–stromal tumours
Pure tumours
Leydig cell tumours
Malignant Leydig cell tumour
Sertoli cell tumour
Malignant Sertoli cell tumour
Large-cell calcifying Sertoli cell tumour
Intratubular large-cell hyalinizing Sertoli cell tumour
Granulosa cell tumour
Adult granulosa cell tumour
Juvenile granulosa cell tumour
Tumours in the fibroma-thecoma group
Mixed and unclassified sex cord–stromal tumours
Mixed sex cord–stromal tumour
Unclassified sex cord–stromal tumour
Tumour containing both germ cell and sex cord–stromal elements
Gonadoblastoma
Miscellaneous tumours of the testis
Ovarian epithelial–type tumours
Serous cystadenoma
Serous tumour of borderline malignancy
Serous cystadenocarcinoma
Mucinous cystadenoma
Mucinous borderline tumour
Mucinous cystadenocarcinoma
Endometrioid adenocarcinoma
Clear cell adenocarcinoma
Brenner tumour
Juvenile xanthogranuloma
Haemangioma
Haematolymphoid tumours
Diffuse large B-cell lymphoma
Follicular lymphoma, NOS
Extranodal NK/T-cell lymphoma, nasal-type

Table 1. (Continued)

Plasmacytoma
Myeloid sarcoma
Rosai–Dorfman disease

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NK, Natural killer; NOS, Not otherwise specified.

*Reproduced from the WHO classification of tumours of the testis and paratesticular tissue.

medical therapy.^{12–15} Immunohistochemical findings are also useful in that patients with TTAGS do not express androgen receptor, unlike those with Leydig cell tumour, and are more frequently positive for neuroendocrine markers (synaptophysin and CD56).

As a small minority of Leydig cell tumours are clinically malignant, a thorough evaluation of morphological features associated with malignancy should be performed to ensure proper management of these tumours¹⁶ (Figure 1D). Kim *et al.* proposed that two or more of the following features correlated with malignant potential: size >50 mm, infiltrative borders, cytological atypia, three or more mitotic figures per 10 high-power fields, vascular invasion, and necrosis. Malignant Leydig cell tumours are resistant to currently available chemotherapy and radiotherapy, and have a poor prognosis if metastatic. No changes were made in the WHO 2016 classification related to Leydig cell tumours.

Sertoli cell tumours account for ~1% of all testicular neoplasms.¹⁷ Historically, approximately one-third of SCTs have been reported in children, although there is some controversy regarding the neoplasms in the paediatric age group, as many, in fact, may represent juvenile granulosa cell tumours.^{18,19} On rare occasions, SCTs develop in patients with androgen insensitivity syndrome.²⁰ Although tubular architecture with nodular growth is the most distinctive feature of SCT, cords, nests, sheets and, rarely, single cells in a fibromatous/fibroblastic stroma may also be focally present or may represent the predominant pattern in some tumours. *CTNNB1* gene mutations and immunohistochemical nuclear localization of β -catenin have recently been described as characteristic molecular alterations in approximately 60–70% of those SCTs in the ‘not otherwise specified’ (NOS) group. In the WHO 2004 classification, tumours considered as distinct forms of SCT included lipid-rich, sclerosing and large-cell calcifying types. In the current classification, lipid-rich SCT has been removed as

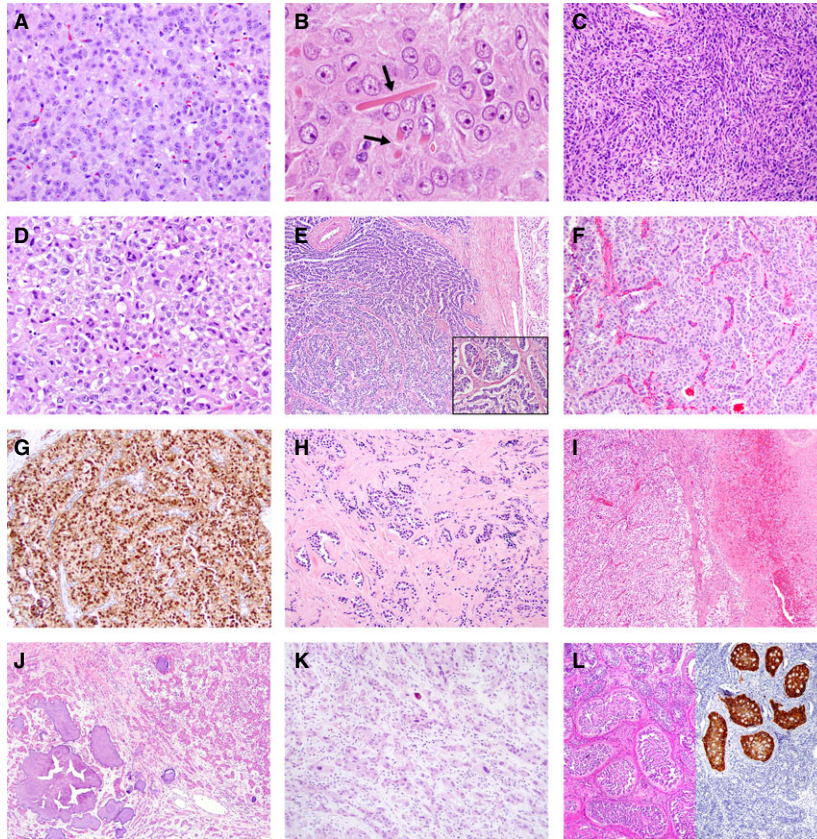


Figure 1. A–D, Leydig cell tumour. A, Uniform nuclei with prominent nucleoli and abundant eosinophilic cytoplasm. B, Reinke crystals marked by arrows. C, Spindled cell morphology. D, Malignant Leydig cell tumour showing marked nuclear pleomorphism and prominent mitotic activity. E–K, Sertoli cell tumour. E, Low magnification of Sertoli cell not otherwise specified (NOS) shows a circumscribed margin and trabecular arrangement; the inset shows a trabecular and nested pattern. F, Characteristic appearance with solid architecture and nuclear palisades. G, Nuclear β -catenin. H, An example of a tumour that was previously termed 'sclerosing Sertoli cell tumour' but is now classified as 'Sertoli cell tumour NOS' with the notation of abundant stroma shows bland Sertoli cells forming tubules in a dense collagenous background. I, Malignant Sertoli cell tumour showing an invasive growth pattern, cellular pleomorphism, and areas of necrosis. J–K, Large-cell calcifying Sertoli cell tumour showing large eosinophilic cells in a fibromyxoid stroma and prominent calcifications. L, Intratubular large-cell hyalinizing Sertoli cell neoplasia showing intratubular neoplastic proliferation of large Sertoli cells with prominent deposits of extracellular basement membrane; strong inhibin expression can be seen on the right side.

a separate entity, as it is now established that many SCTs contain variable proportions of lipid-rich cells. Although it is rare to find an SCT consisting entirely of lipid-rich Sertoli cells, the presence of any amount of lipid-rich cells is considered to be within the morphological spectrum of SCT NOS.³ A specific study investigating β -catenin expression or *CTNNB1* gene mutations in lipid-rich SCT is not available; however, it is now known that many SCTs NOS (showing β -catenin expression) contain variable amounts of lipid.

Similarly, sclerosing SCT is not separately classified in the 2016 classification.^{21,22} It has been recently reported that SCT NOS and the sclerosing variant harbour the same molecular alterations, including *CTNNB1* gene mutations, and show nuclear β -catenin expression in similar proportions.^{23–25} However,

those tumours with abundant sclerosing stroma appear to metastasize less frequently than the more cellular forms of SCT NOS. It is therefore recommended to indicate a sclerosing pattern for those SCTs NOS that have a hypocellular collagenous stroma constituting >50% of the tumour (Figure 1E–H). Malignant SCTs, in general, are uncommon, and morphological criteria similar to those used for malignant Leydig cell tumours are used to predict unfavourable behaviour²⁶ (Figure 1I).

Large-cell calcifying SCT (LCCSCT) was described by Proppe and Scully in 1980 as a rare subtype of SCT. These tumours show characteristic morphological features, and are frequently bilateral and multifocal when they occur on an inherited basis.^{3,27–29} They were subsequently linked to Carney complex,

which is characterized by familial occurrence, cardiac myxomas, and other features, although they more commonly occur sporadically. LCCSCT has a unique morphology, containing Sertoli cells with abundant eosinophilic cytoplasm and variable amounts of calcifications present in a myxoid, often neutrophil-rich background (Figure 1J,K). An intratubular component may be seen. Germline *PRKARIA* gene mutations on chromosome 17q22–24 are seen in up to 70% of Carney complex-associated tumours, but have also been reported in sporadic cases.^{30,31}

Intratubular large-cell hyalinizing Sertoli cell neoplasia is an intratubular neoplastic proliferation of large Sertoli cells with lightly eosinophilic cytoplasm and prominent extracellular basement membrane deposits. It has been recognized as a distinct entity associated with Peutz–Jeghers syndrome, with a characteristic mutation in the *STK11* gene.^{32,33} Historically, these neoplasms have been considered within the morphological continuum of LCCSCT; however, they differ from LCCSCT in many respects, including: clinical presentation (often associated with gynaecomastia), almost exclusive intratubular growth, and specific germline mutations. They are multifocal, bilateral, and clinically benign.³ In the WHO 2016 classification, intratubular large-cell hyalinizing Sertoli cell neoplasia has been described as a separate entity under SCTs (Figure 1L).

The granulosa cell tumour category includes adult and juvenile variants, both of which have a morphological spectrum similar to that seen in their ovarian counterparts. Adult granulosa cell tumours are composed of small cells with pale nuclei, often showing grooves, that typically grow in sheets, microfollicles, nests, cords and trabeculae in a fibrocollagenous or oedematous background, whereas juvenile granulosa cell tumours usually show solid and follicular patterns with immature nuclei³ (Figure 2A,B). The former occurs in a broader age range, from teenagers to elderly individuals, whereas the latter is the most common tumour of the testis in the first 6 months of life, and is rare outside of childhood.^{3,34–36} No known epidemiological associations exist for adult granulosa cell tumours, but juvenile granulosa cell tumours may occur in cryptorchid testes or dysgenetic gonads.^{36–38}

The tumours in the fibroma/thecoma group are derived from the testicular parenchymal stroma or that of the tunica albuginea. They are invariably benign, and no modifications were made in the WHO 2016 classification³⁹ (Figure 2C).

The subgroups of ‘mixed forms’ and ‘incompletely differentiated’ under sex cord/gonadal stromal

tumours of 2004 have been replaced by ‘mixed and unclassified sex cord–stromal tumours’, respectively, in the new WHO classification.³ The former is defined as showing two or more distinct forms of sex cord–stromal elements, whereas the latter shows indeterminate differentiation of the tumour cells (Figure 2D,E). These tumours may, on occasion, behave in a malignant fashion, with the morphological criteria employed for the assessment of malignancy in Sertoli and Leydig cell tumours being useful for judging malignant risk.^{26,40,41} Because malignant behaviour is not uniformly predictable with currently available methods, there are no separate benign and malignant categories, unlike in the WHO 2004 classification.

The myoid gonadal stromal tumour is considered to be an emerging entity in the WHO 2016 classification. It is composed of spindle-shaped/fusiform cells with features of both smooth muscle and gonadal stroma. To date, <10 examples have been reported in the English-language literature. They occur predominantly in middle-aged men, but show an age range of 4–49 years (median 41 years).^{42–44} They are usually circumscribed but unencapsulated and small (12–35 mm), and are often centred adjacent to the rete testis. The fusiform tumour cells are arranged in tightly packed, short fascicles. The nuclei are tapered and euchromatic, with inconspicuous to small nucleoli, and are surrounded by scant to moderate amounts of eosinophilic cytoplasm (Figure 2F). The background is collagenous, with variability in different fields and among different tumours. Interspersed small thin-walled vessels may be seen. Often, normal tubules are incorporated within the tumour, especially at the periphery. The tumours coexpress S100 and smooth muscle actin, and can be distinguished from fibroma and leiomyoma on the basis of morphology and S100 expression (Figure 2G). FOXL2, SF1 and weak expression of inhibin are noted in the majority of tumours.⁴³ Reticulin staining may be helpful in distinguishing myoid gonadal stromal tumours from unclassified sex cord–stromal tumours, as the stain envelops groups of sex cord cells (which may be morphologically inconspicuous) in the latter.⁴⁰

Tumour containing both germ cell and sex cord–stromal elements

Gonadoblastoma is the only entity in this category in the new classification. The entity of ‘germ cell–sex cord/gonadal stromal tumour, unclassified’ has been removed from the classification, as its existence is

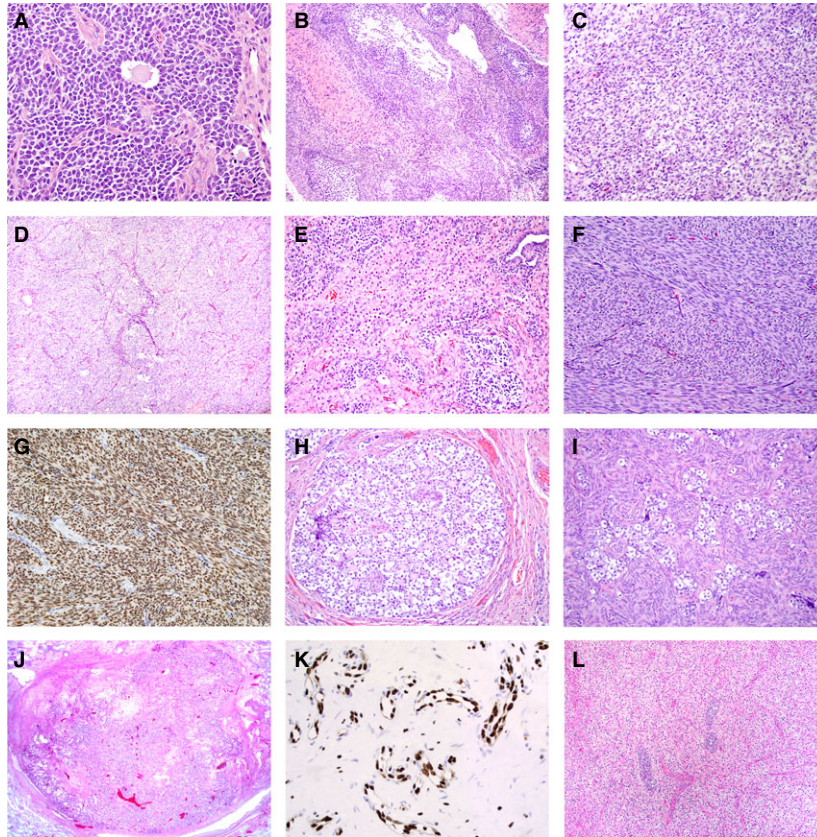


Figure 2. A, Adult granulosa cell tumour showing features similar to those of the more common ovarian neoplasm, including Call-Exner-like bodies and uniform pale nuclei with grooves. B, Juvenile granulosa cell tumour showing lobules of follicles with myxoid material. C, Fibroma with bland spindle cells in a collagenous background. D, Sex cord-stromal tumour unclassified, showing non-distinctive spindle cells in short fascicles. E, Sex cord-stromal tumour of mixed type showing intermingled Sertoli cells and Leydig cells. F,G, Myoid gonadal stromal tumour containing myoid spindled cells that strongly express S100. H, Gonadoblastoma with a large nest of intermingled neoplastic and non-neoplastic germ cells, sex cord cells, and prominent hyaline basement membrane material. I, Undifferentiated gonadal tissue ('dissecting gonadoblastoma') showing neoplastic germ cells in cords, small groups and single cells admixed with sex cord cells. At this power, the sex cord cells are not readily visible, and it appears that the germ cells are infiltrating in the stroma. J,K, Haemangioma showing a nodular well-circumscribed tumour composed of thin-walled capillary channels in a collagenous stroma; cells lining the vascular channels strongly express ERG, an endothelial marker. L, Juvenile xanthogranuloma with sheets of confluent mononuclear round to oval cells with abundant pale to eosinophilic cytoplasm; note the normal tubules entrapped within these mononuclear cells.

debatable. Most, or perhaps all, of the cases reported in the literature lacked evidence of neoplastic germ cells, and they probably represented sex cord-stromal tumours with entrapped, non-neoplastic germ cells.⁴⁵

In 1953, Scully introduced the term 'gonadoblastoma' to designate a steroid hormone-secreting gonadal tumour composed of germ cells and sex cord cells resembling immature granulosa or Sertoli cells (Figure 2H). In 1970, he published a series of 74 cases detailing its clinicopathological features.⁴⁶ The characteristic feature of gonadoblastoma comprises discrete, round nests composed of germ cells, small sex cord cells resembling immature Sertoli or granulosa cells, and round deposits of basement membrane with occasional calcifications. There are variable

arrangements of these elements in the cell nests. External to the nests there are cells similar to Leydig cells (but lacking Reinke crystals) or luteinized cells of ovarian stromal origin. Many of the germ cells resemble the cells of germinoma (dysgerminoma/seminoma), whereas others morphologically resemble spermatogonia. Left alone, gonadoblastoma will progress to dysgerminoma/seminoma in at least 50% of the cases, and into a non-seminoma tumour-type in another 8%.⁴⁶

A putative precursor lesion to gonadoblastoma, 'undifferentiated gonadal tissue', has been reported adjacent to gonadoblastomas and in dysgenetic gonads.⁴⁷ This lesion consists of compressed cords of germ cells and sex cord cells in a stroma-rich

background rather than the classic nested arrangement of gonadoblastoma⁴⁶ (Figure 2I). The germ cells show the same immunophenotypic properties as those in the classic form of gonadoblastoma.⁴⁷ Undifferentiated gonadal tissue is considered within the gonadoblastoma spectrum rather than as a distinct entity. It was recognized by Scully as a 'dissecting' or 'infiltrating' form of gonadoblastoma, emphasizing its mimicry of invasive dysgerminoma/seminoma, from which it must be distinguished.⁴⁸

Miscellaneous tumours of the testis

Ovarian epithelial-type tumours have been retained in the WHO 2016 classification under the above heading. This group includes tumours arising either from the testis or the paratestis, or resembling ovarian surface epithelial tumours. They include serous cystadenoma, serous tumour of borderline malignancy, serous cystadenocarcinoma, mucinous cystadenoma, mucinous borderline tumour, mucinous cystadenocarcinoma, endometrioid adenocarcinoma, clear cell adenocarcinoma, and Brenner tumour.^{49–56} Serous borderline tumours are most frequent, followed by mucinous tumours. Unlike what is seen with carcinomas, no metastases or recurrences have been observed with the borderline tumours. In the current edition, carcinoid is not included in the miscellaneous category, but is classified with the germ cell tumours as a form of 'monodermal teratoma' of the prepubertal type.

Two other entities, juvenile xanthogranuloma (a histiocytic disorder of infants and young children) and haemangioma (a benign vascular tumour) are included under the miscellaneous tumours in the WHO 2016 classification^{57–59} (Figure 2J–L). Few examples of juvenile xanthogranuloma of the testis exist in the English-language literature. It is debatable whether juvenile xanthogranuloma is a neoplastic disorder or not, but its potential to progress at other sites in some cases provides a rationale for placing it in the miscellaneous tumour category.^{60,61} It occurs in children aged <13 months, is composed of mononuclear histiocyte-like cells, and grows in a diffuse infiltrative pattern. Touton giant cells can be identified in some cases. The immunoprofile includes diffuse CD68 positivity and S100 and CD1a negativity.^{57,58,62} In testicular cases, surgical resection is curative. Testicular haemangiomas are rare, and occur in a wide age range, from infants to adults. The tumours are usually small (10–40 mm) and circumscribed. Cavernous, epithelioid, capillary and

anastomosing types have been described. Immunostains, including those for CD31, FL1, and CD4, are helpful.⁵⁹ The haemangiomas are invariably benign. The last category, haematolymphoid tumours, contains various tumour types that may arise primarily in the testis/paratestis.^{63–74} The scope of this article does not allow their discussion here.

In summary, the largest group of tumours in the non-germ cell tumour category is represented by the sex cord–stromal tumours, which represent 5% of all testicular tumours. Among the sex cord–stromal tumours, Leydig cell tumours predominate, followed by SCTs. Although the WHO 2016 classification retains the main framework of non-germ cell tumours of the testis from the 2004 classification, significant additions/alterations are seen in the classification of these tumours, primarily based on additional information and knowledge gained since the publication of the previous edition.

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