

Pseudoneoplastic lesions of the testis and paratesticular structures

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Abstract Pseudotumors or tumor-like proliferations (non-neoplastic masses) and benign mimickers (non-neoplastic cellular proliferations) are rare in the testis and paratesticular structures. Clinically, these lesions (cysts, ectopic tissues, and vascular, inflammatory, or hyperplastic lesions) are of great interest for the reason that, because of the topography, they may be relevant as differential diagnoses. The purpose of this paper is to present an overview of the pseudoneoplastic entities arising in the testis and paratesticular structures; emphasis is placed on how the practicing pathologist may distinguish benign mimickers and pseudotumors from true neoplasia. These lesions can be classified as macroscopic or microscopic mimickers of neoplasia.

Keywords Testis · Paratesticular structures · Pseudotumor · Tumor-like · Benign mimics

Introduction

There are many lesions that can simulate a neoplasm in the testis or paratesticular structures. Their incidence among tumors arising within the scrotal sac varies according to different series from 6 to 30% [16, 32]. These pseudoneoplastic lesions can be divided into those that only macroscopically imitate neoplasia (Table 1) and those that microscopically imitate neoplasia, regardless of whether they form a macroscopic mass (Table 2). The latter group causes more problems to the practicing pathologist in terms of the correct classification of a giving lesion. Hereby, we summarize main tumor-like lesions and benign mimickers that may be seen in the testis and paratesticular coverages, with emphasis on morphologic criteria for the differential diagnosis from true neoplasia.

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Table 1 Macroscopic mimickers (pseudotumors) of testicular and paratesticular neoplasia

Vascular lesions
Intratesticular hemorrhage
Segmental testicular infarction
Organized testicular hematocoele
Cholesterol granuloma of the tunica vaginalis
Inflammatory lesions
Nonspecific infectious inflammatory lesions
Specific infectious inflammatory lesions
Non-infectious inflammatory lesions
Idiopathic inflammatory lesions
Idiopathic granulomatous orchitis
Testicular malakoplakia
Testicular sarcoidosis
Meconium periorchitis
Sperm granuloma
Cysts
Testicular cysts
Albuginea cysts
Parenchymal cysts (Epidermoid cysts)
Rete-testis cysts- Cystic dysplasia of the rete testis
Epididymal cysts and Spermatoceles
Spermatic cord cysts
Ectopic tissues
Adrenal cortical rests
Spleno-gonadal fusion
Testicular appendages
Miscellaneous other lesions
Fibrous pseudotumors; (Fibromatous periorchitis- Nodular periorchitis)
Amyloidosis
Polyorchidism
Sclerosing lipogranuloma

Macroscopic mimickers (pseudotumors) of testicular and paratesticular neoplasia

This group of lesions refers to those that macroscopically imitate a neoplasia. Frequently, these lesions affect both compartments and are therefore difficult to establish if one or both are affected. For this reason, we classify the tumor-like lesions according to their etiology.

Vascular lesions

The majority of the vascular disorders of the male gonad are not confused with a tumor because, in addition to causing acute symptoms, they usually affect the entire gonad. However, in the rare situation in which the vascular lesion is segmental, it can simulate neoplasia, as follows:

1. Intratesticular hemorrhage, which occurs spontaneously [24] or in the context of anticoagulation treatment [15], may simulate a tumor at ultrasound examination.

2. Segmental testicular infarction, a lesion clinically characterized by slight local pain unrelated to any acute episode [20], may be related to isolated or systemic vasculitis [43, 103] with morphology of polyarteritis nodosa [21], giant cell vasculitis [94], or Wegener granulomatosis [45]. Up to year 2000, 81 cases of systemic vasculitis with testicular tumor-like lesion have been recorded [45]. Other cases are seen in the context of a hematological disease (sickle cell anemia) [53] or associated with nonspecific perivascular fibrosis. Any of the phases of an infarction can be observed from acute (with hemorrhage) to healing stage (Fig. 1). Currently, the clinical diagnosis can be suspected with Doppler sonography [81], avoiding orchiectomy.
3. Organized testicular hematocoele and other hemorrhages in the tunica vaginalis are rarely confused with a neoplasia [89], but this can happen occasionally in long-standing cases because of fibrous thickening with cholesterol granuloma formation in the tunica vaginalis (Fig. 2) [61]. Exceptionally, a true testicular neoplasia presents clinically with a hematocoele [86].

Inflammatory lesions

Similar to what was stated for vascular tumor-like lesions, inflammation that simulates a neoplasia usually has atypical clinical features; these entities can be grouped as follows:

1. Nonspecific infectious inflammatory lesions with a tumor-like presentation are frequently chronic processes causing

Table 2 Microscopic mimickers of testicular and paratesticular neoplasia

Testicular
Inflammatory-reactive lesions
Lymphocitic orchitis (Testicular pseudolymphoma)
Rosai-Dorfman disease
Sertoli cell hyperplasia
Pick adenoma
Hamartomatous proliferation testicular feminization syndrome
Interstitial cell hyperplasia
Leydig cell hyperplasia
Testicular “tumor” of the adrenogenital syndrome
Hyperplasia of the rete testis
Epididymis
Adenomatoid hyperplasia
Tunicas albuginea-vaginalis
Mesothelial hyperplasia
Spermatic cord
Vasitis nodosa
Inflammatory pseudotumor (Funiculitis proliferans)
Miscellaneous other lesions

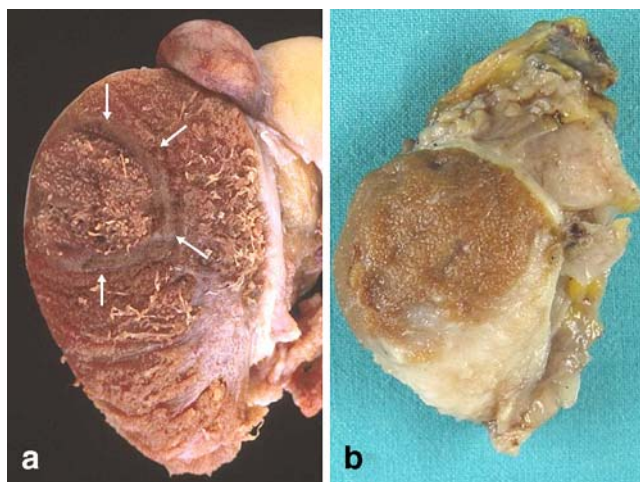


Fig. 1 Segmental testicular infarction. **a** Acute hemorrhagic with reinforcement of the peripheral area (*arrows*). **b** Healing fibrosis

progressive fibrosis, which may clinically [38] or sonographically [23] simulate neoplasia. Rarely a testicular, epididymal, or vas deferens abscess can look like a neoplasia [84]. Very occasionally, testicular neoplasia can clinically imitate an acute inflammatory process [44].

2. Specific infectious inflammatory lesions. The entities of this group that most often have been confused with neoplasias are granulomatous inflammation in tuberculosis [87], brucellosis [49], syphilis [5], fungal infections [42], and parasite diseases [9]. These lesions are usually not problematic for the pathologist.
3. Noninfectious inflammatory lesions. This group of tumor-like lesions include different entities among which can be highlighted:
 - (a) Idiopathic granulomatous orchitis, probably of autoimmune aetiology, of which around 230 cases have been published [4], is characterized by tubular granulomas (tubular orchitis; Fig. 3) or interstitial granulo-

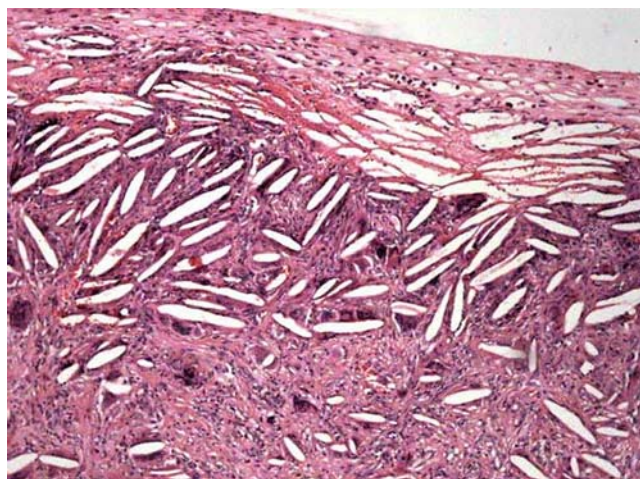


Fig. 2 Cholesterol granuloma in the tunica vaginalis (H&E)

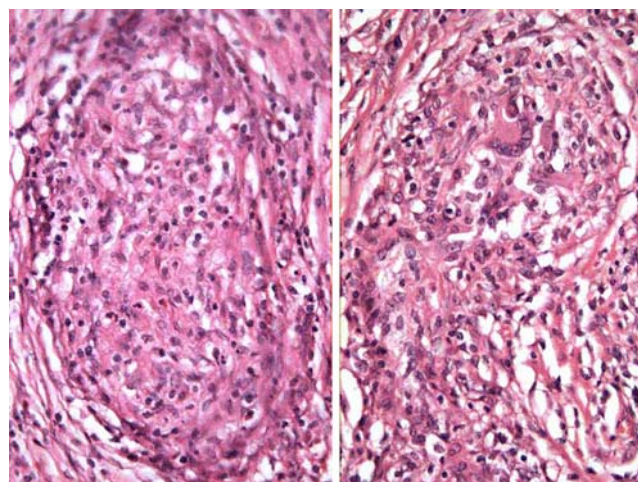


Fig. 3 Idiopathic granulomatous orchitis characterized by tubular granulomas (tubular orchitis)

mas (interstitial orchitis). The presence of intratubular giant cells differentiates this entity from infectious granulomatous orchitis [70]. Diffuse testicular hypoechoic involvement with only peripheral low-resistance flow on color Doppler sonography is a typical but not pathognomonic pattern [72].

- (b) Malakoplakia. This lesion is secondary to a mononuclear decrease in cyclin–guanine monophosphate that impairs the killing of bacteria. Fusion of the phagolysosomes with bacterial rests produces the characteristic Michaelis–Gutman bodies in the cytoplasm of the macrophages (von Hansemann cells) [1] (Fig. 4). Giant cells are occasional or absent. Testicular involvement represents only 12% of genital malakoplakia with around 388 cases in the literature [19, 56]; exceptionally, it may affect the epididymis only [31]. It has been related to idiopathic granulomatous orchitis [56, 57] and chronic xantogranulomatous inflamma-

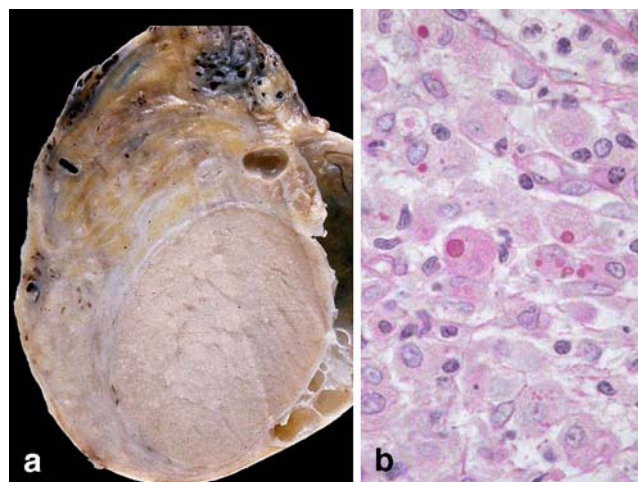


Fig. 4 Malakoplakia. **a** Macroscopic appearance with a homogeneous aspect. **b** The characteristic Michaelis–Gutman bodies in the cytoplasm of the macrophages (von Hansemann cells) (PAS)

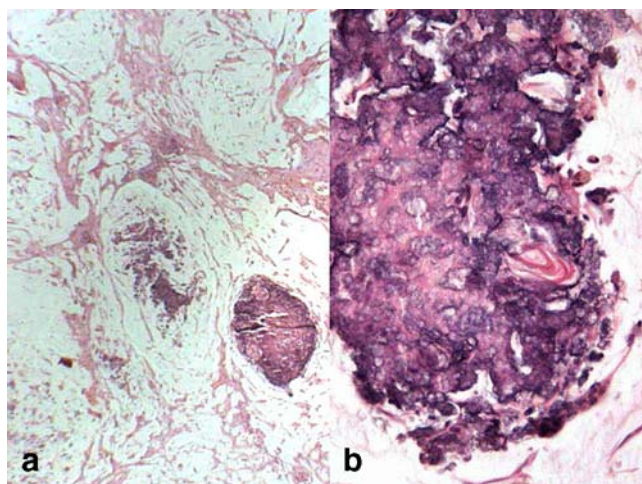


Fig. 5 Meconium periorchitis. **a** calcified pearls resulting from the calcification of the remains of squamous cells or lanugo hairs. **b** Keratin rest in one of the calcifications (H&E)

tion of testis [85, 109, 110]; this last also reported in the spermatic cord [64, 100].

- (c) Sarcoidosis. Testicular involvement in a systemic sarcoidosis [39] is exceedingly rare, and its presentation as the primary form is even rarer; in these cases, the epididymis is affected more with the testicle being involved by contiguity [83].
4. Meconium periorchitis. This is an infrequent lesion (around 30 cases being reported) that typically presents in the first months of life; most times there is a clinical history with obstetric problem that has caused the passing of meconium toward the testicular surrounding structures [29]. The macroscopic appearance is a myxoid material with calcified pearls resulting from the calcification of the remains of squamous cells or lanugo hairs [107] (Fig. 5). Suspicion of neoplasia, although very uncommon in this period of life, may be caused by a scrotal mass or sonographically detectable calcifications [6]. Clinically, the peritesticular and spermatic cord enlargement can simulate a paratesticular rhabdomyosarcoma.
5. Sperm granuloma. As its name indicates, this granulomatous lesion with few giant cells is the consequence of extravasation of spermatozoa generally postvasectomy (40% of vasectomized men and 2.5% of general population) [108]. When it produces a tumor-like lesion, it is usually located in the deferent duct or the epididymis [22] with firm nodules of 0.7 to 4 cm with occasional cysts formation.

Cysts

The majority of the cysts with a tumor-like appearance are paratesticular structures, but the testicle may occasionally

have some cystic lesions that can be confused with a neoplasia.

1. Testicular cysts occur in approximately 8–10% of patients with a lump in the testis, including those of the tunica albuginea or the parenchyma [33].
 - (a) Tunica albuginea cysts do not usually cause any diagnostic problem, unless if they are complex cysts [74].
 - (b) Parenchyma testicular cysts can be more difficult to distinguish from a neoplasia and if there is the slightest suspicion of an intracystic content, one must suspect a malignant neoplasia [107]. Special consideration deserves the testicular Epidermoid cyst, which must only be lined with squamous epithelium (Fig. 6). It is recommended that the specimen is examined “in toto” to avoid underdiagnosis of any area of teratoma (especially among postpubertal patients) or intratubular germ cell neoplasia, as sonographically it is not possible to distinguish between these lesions [54, 106]. Epidermoid cysts represent 1% of the masses of the testes. Recent genetic studies have shown that there is no chromosome 12p abnormality [14], thus supporting its distinction from teratoma.
 - (c) Tubular ectasia of the rete testis secondary to obstruction and generally located in the mediastinum area of the testes (Fig. 7) [69], is usually bilateral and very different from cystic dysplasia of the rete testis, a congenital lesion with complete testicular parenchyma substitution [68].
2. Epididymal cysts and spermatoceles are relatively frequent and the majority are in relation to the inflammatory processes. The differential diagnosis with other entities are related to its size, and similar to the other cystic formations a true neoplasia must be considered in case of observing any content in its interior [108].

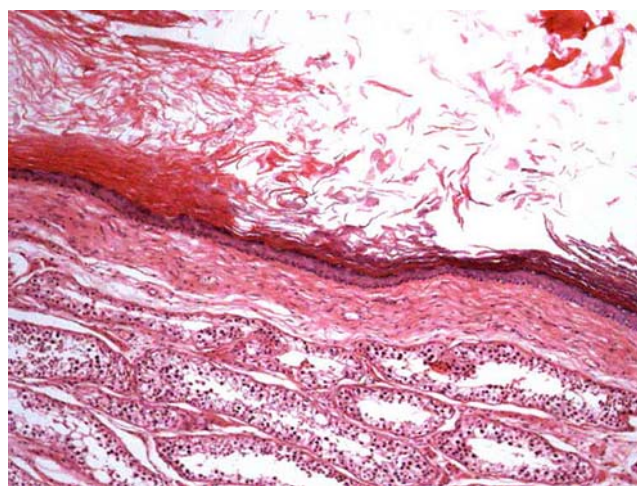


Fig. 6 Epidermoid cyst, which must only be lined with squamous cell epithelium (H&E)

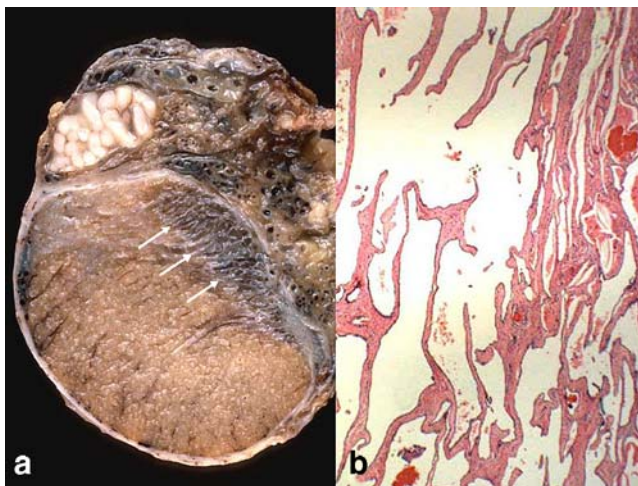


Fig. 7 **a** Tubular ectasia of the rete testis located in the mediastinum area of the testes (*arrows*). **b** Microscopic aspect (H&E)

3. Spermatic cord cysts. The majority of these cysts do not cause any diagnostic doubts, only the occasional Epidermoid cysts [46, 105] can simulate a neoplasia. These cysts can be unilocular or multilocular depending on their origin [65], and the multilocular must be distinguished from the exceptional cystadenomas of probably Müllerian origin [55].

Ectopic tissues

1. Ectopic adrenocortical tissue is relatively frequent in the tunica albuginea, rete testis, epididymis, and spermatic cord and occasionally reaches the size to be symptomatic. Its incidence ranges from 2.5 to 15% [17, 102]. It is made up of adrenal cortical nodes surrounded by a connective tissue band and of about 5 mm in diameter

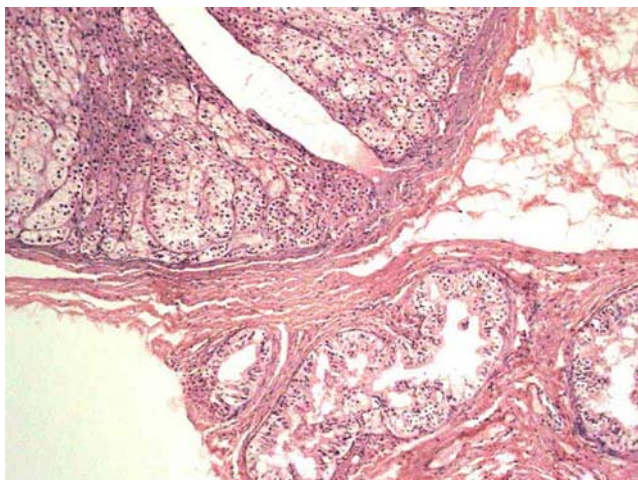


Fig. 8 Ectopic adrenocortical tissue. Adrenal cortical nodes surrounded by a connective tissue band in continuity with epididymis. (H&E)

on average (Fig. 8); for which reason, they are not clinically palpable. Only in cases of congenital adrenal hyperplasia or Cushing syndrome, ectopic adrenocortical tissue can be prominent and appear as a tumor-like lesion [90].

2. Splenic–gonadal fusion, as its name indicates, is the fusion of spleen and gonad. It is more frequent on the left side, with about 148 published cases [41]. Morphologically, the ectopic splenic tissue can be in close relation to the head of the epididymis or the upper pole of the testis (Fig. 9) or being separated from it; likewise, there may or may not be a structural continuity between the normal spleen and the ectopic tissue [30]. The same alteration has been described in women, but it is much less frequent than in men, probably because it is much easier to find it clinically in men. In about 30% of the cases, it is associated with complex malformations such as micrognathia, peromelia, or phocomelia (absence of upper portion of a limb) [30, 60, 95]. In three of the reported cases, the fusion was associated with a germ cell tumor of the testis [41].
3. An exceptional hepato-gonadal fusion is reported [26].

Testicular appendages

There are five testicular appendages, but for the surgical pathologist, only three can be of interest (appendix testis or hydatid of Morgagni, appendix epididymis, paradidymis or organ of Giraldes; Fig. 10). These structures are not usually the origin of a tumor-like lesion, but in rare cases of large-sized cysts, it may present as a paratesticular mass [93]. A case of ectopic epididymal tissue in an appendix testis [101] has recently been reported.

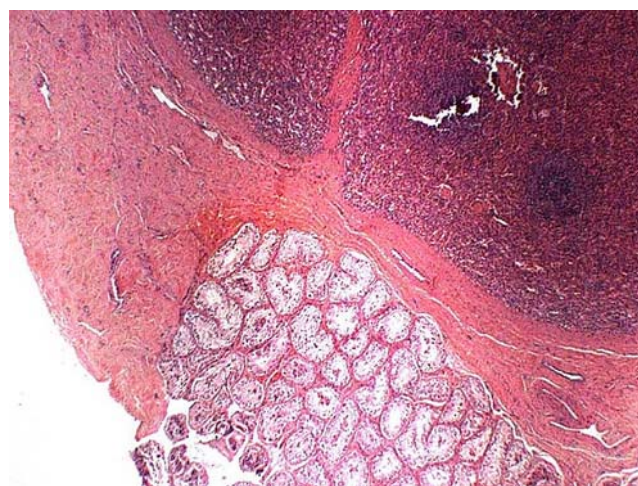


Fig. 9 Splenic–gonadal fusion. The ectopic splenic tissue in close relation with the upper pole of the testis (H&E)

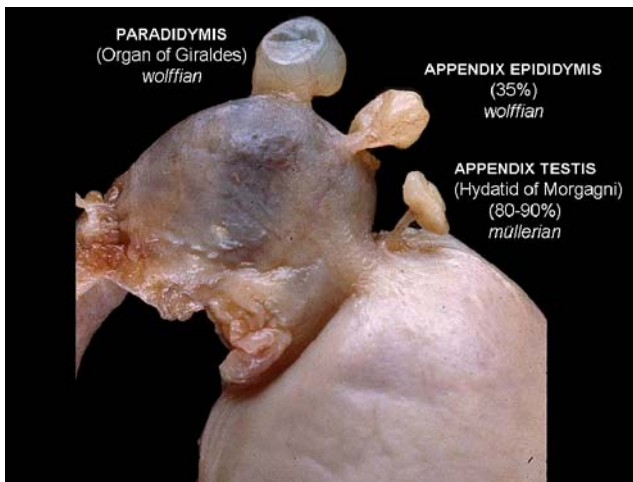


Fig. 10 Normal testicular appendages

Miscellaneous other lesions

1. Fibrous pseudotumors. This name refers to a fibrosis phenomenon with paucicellular hyalinized collagen (Fig. 11) presenting as nodular (single or multiple) or diffuse lesion of the testicular tunics [96, 71]. Sometimes, a node can be free (scrotal mouse) [108]. This broadly considered spectrum of lesions has received diverse names: chronic periorchitis, fibromatous periorchitis, nodular periorchitis, fibrous proliferation of the tunica, nonspecific paratesticular fibrosis, granulomatous periorchitis, nodular fibrous pseudotumor, fibrous pseudotumor, inflammatory pseudotumor, fibroma, reactive periorchitis [108], indicating its controversial pathogenesis. Some cases have been reported preceded by trauma or infection, and on occasion, an inflammatory component can be observed and granulation tissue suggesting the possibility that there might

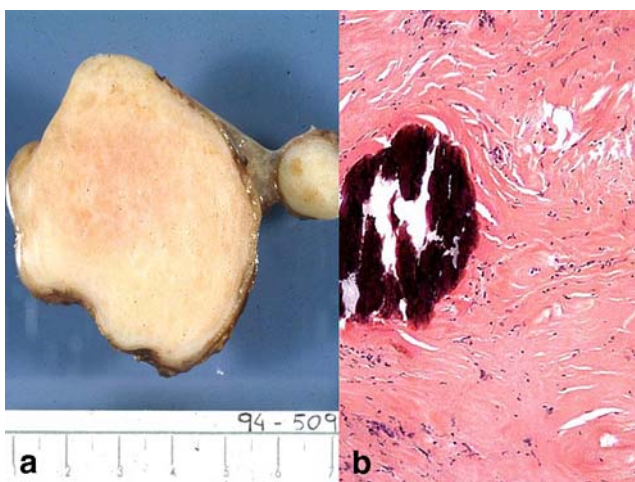


Fig. 11 Fibrous pseudotumor. **a** Well outlined fibrous-like nodule. **b** Paucicellular hyalinized collagen with calcification

be the healing of an inflammatory pseudotumor, (which will be described later on) [10]. Although radiologically, it is not difficult to recognize, upon occasion, an intraoperative frozen section becomes necessary.

2. Amyloidosis. It is usually bilateral and present in a patient with a prior history of amyloidosis [34]; more rarely, it is a primary form that by being a cryptorquidic patient simulates a testicular tumor [13].
3. Polyorchidism or supernumerary testes is a rare condition, which is easy to recognize. However, the sonography can occasionally be different from that of the normal testis, and the condition may then be tumor suspicious [79].

Microscopic mimickers of testicular and paratesticular neoplasia

Lesions or cellular changes that microscopically imitate a neoplasia are included under this category, whether or not they make a clinical mass. These changes are closely related to the structure of the organ in which they arises, as follows.

Testicular

Inflammatory-reactive lesions Some lesion, already described above such as xantogranulomatous orchitis, idiopathic granulomatous orchitis and malakoplakia could be considered under this category; their microscopic confusion with a neoplasia (seminoma for example) is not currently a usual event; therefore, we preferred to include them in the macroscopic mimickers (pseudotumors).

The situation is different with lymphocytic orchitis or testicular pseudolymphoma [2, 3], which is characterized by a lymphocytic and plasmocellular reaction that may be

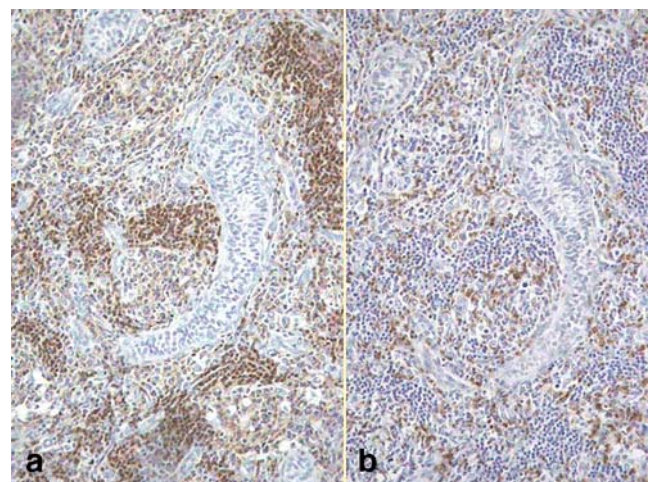


Fig. 12 Lymphocitic orchitis. Lymphocitic cellular infiltration of polyclonal type. **a** CD45RA (lymphocytes B). **b** UCHL-1 (lymphocytes T)

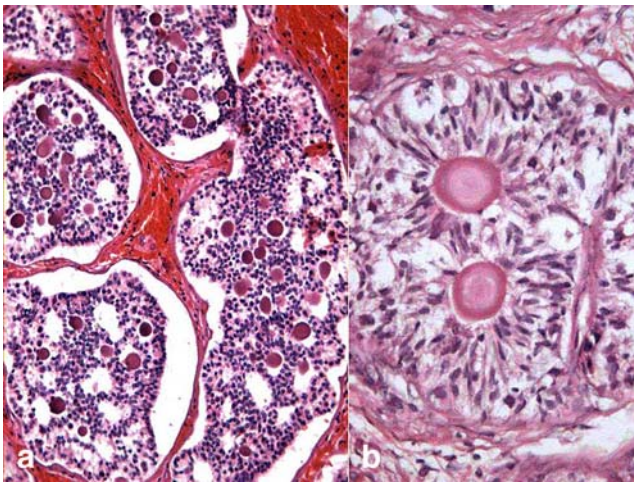


Fig. 13 Sertoli cell hyperplasia. **a** Nonencapsulated nodules of Sertoli cells (Pick's adenoma). **b** Sometimes there are areas that mimic Call-Exner bodies

confused with a lymphoma, but immunohistochemistry will show that the cellular infiltrate is polyclonal (Fig. 12). Among these idiopathic lesions, we can include Rosai–Dorfman disease; histological examination of the testicular mass reveals an inflammatory lesion comprising lymphocytes, plasma cells, and sheets of pale staining histiocytes, some containing lymphocytes within their ample cytoplasm, suggestive of emperipolesis. The histiocytes stained positive for CD68, S100 by immunohistochemistry and negative for CD1a, while ultrastructural examination confirmed emperipolesis [25].

Sertoli cell hyperplasia In a series of situations, nonencapsulated nodules of Sertoli cells can be found, especially known in cryptorchid testes as Pick's adenomas (Fig. 13a) [77]. Because of their appearance, these should be distinguished from the actual Sertoli cell tumors that generally are larger and sometimes there are areas that mimic Call-Exner bodies (Fig. 13b) A differential diagnosis with a yolk-sac tumor is not usually in the scope, but the immunohistochemistry study with AFP, calretinin, α -inhibin, and CD 99 can help [40].

A special consideration merit the androgen insensitivity syndrome or testicular feminization (male pseudohermaphroditism, caused by a failure of androgen receptor binding) that in 63% of cases can have tubular hamartomas (tubules lined by immature Sertoli cells) [82] that must be differentiated from the Sertoli cell adenomas and sex cord tumor with annular tubules [76].

Interstitial cell hyperplasia In testicles with marked tubular atrophy, such as in the Klinefelter's syndrome, it is possible to see Leydig cell nodules that must be distinguished from Leydig cell tumors. An interstitial growth without expansive pattern favors hyperplasia (Fig. 14) [62].

Nodules of eosinophilic cells appearing to be Leydig cells are found in the patients with adrenogenital syndrome [18, 48] and Nelson's syndrome (adrenocorticotropic hormone-secreting pituitary adenoma after bilateral adrenalectomy), some of this last syndrome with excessive testosterone production [91]; proof that these interstitial cells are not only morphologically similar to Leydig cells but also have the functional property of these cells. These nodules are usually bilateral and of a large size with cellular pleomorphism and pigmentation. The clinical history and a complete endocrinological profile avoid an unnecessary orchiectomy [78] because only one case of aggressive behavior is published [18].

Hyperplasia of the rete testis The normal rete testis epithelium is flat, but in some hyperestrogenic situations (treatment or hepatic dysfunction), the epithelium may become columnar and rarely a micropapillary growth of bland cells can be observed. The diagnosis of rete testis hyperplasia is subjective, and adenomatous lesions are rarely seen [35, 63]. In some cases, there are intracytoplasmic hyaline eosinophilic globules resembling a yolk sac tumor, but the negative stains of α -fetoprotein or placental alkaline phosphatase help to rule this differential diagnosis [99].

Pseudohyperplasia of the rete testis and epithelial reaction in case of germ cell invasion and cryptorchidism must be differentiated from real hyperplasia of the rete testis [62].

Epididymis

Benign microscopic mimickers of cancer in the epididymis are very rare. Cysts may occur but do not resemble tumors microscopically. However, some cases of adenomatoid hyperplasia of the rete testis can involve the epididymis, and occasionally, they may become macroscopically apparent [93].

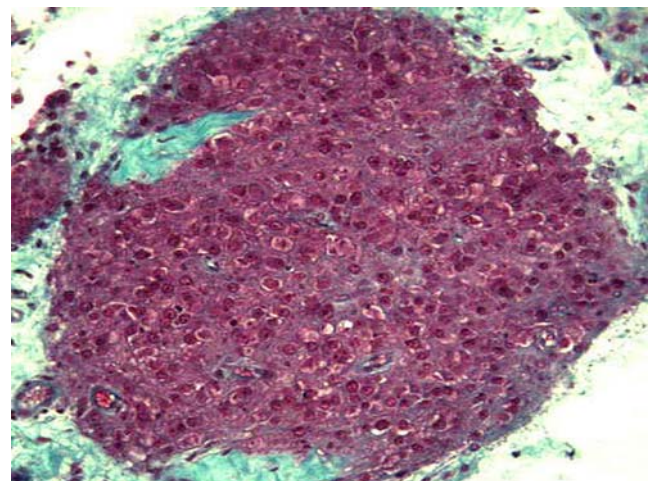


Fig. 14 Leydig cell hyperplasia

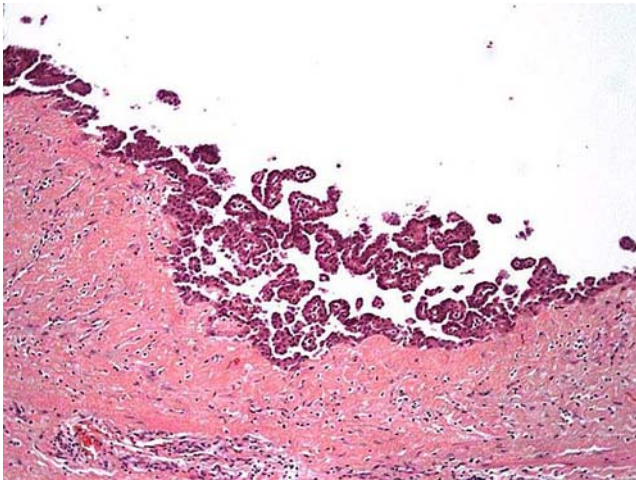


Fig. 15 Mesothelial hyperplasia. The bland nucleus, no true invasion and associated inflammatory elements, can be useful to distinguish from malignant mesothelioma

Tunica albuginea and vaginalis

Non-neoplastic mesothelial lesions involving the paratesticular region include mesothelial cysts and reactive mesothelial hyperplasia [73].

Mesothelial hyperplasia is the most important benign mimicker of the testicular tunics. It is present as a reactive lesion in hydrocele or hernia but may also be found microscopically in older men [80]. The mesothelial proliferation has an epithelial appearance, and rarely, a spindle cell proliferation can be present. In the differential diagnosis with mesothelioma, the bland nucleus, no true invasion, and associated inflammatory elements can be useful (Fig. 15) [11, 98]. Recently, a case was published with “atypical” mesothelial hyperplasia on one side and “well differentiated” mesothelioma on the contralateral [97]. This case is an example of the subjective interpretation of some mesothelial proliferative lesions because some malignant mesotheliomas lack cellular atypia. In these cases, an extensive confluence or prominent infiltration favors a malignant diagnosis. Unfortunately, the immunohistochemical expression of benign and malignant mesothelial proliferations are similar (low- and high-molecular-weight cytokeratins and vimentin) [11, 28], and only the metastatic neoplasias can be differentiated by the CEA, Ber-EP4, and B72.3 expression [27]. Only deoxyribonucleic acid ploidy can distinguish some borderline lesions [28].

Spermatic cord

The vas deferens and the soft tissues of spermatic cord can have benign mimickers.

1. Vasitis nodosa is a ductular proliferation, generally after vasectomy [36], although it can be seen following other

trauma on that area, [75]. It has a microglandular morphology (Fig. 16) with mild nuclear atypia and perineural growth [7] or benign vascular invasion [8] that may be mistaken for malignancy [104]. The frequent hyperplasia of nerve fibers in the adventitia can explain the painful symptoms in some patients [36]. The coincidence with microscopic sperm granulomas and inflammatory reaction can help in the correct diagnosis. An analogous epididymal lesion also occur [88].

2. Proliferative funiculitis is the inflammation of the spermatic cord usually the result of an extension of vasitis. The soft tissues of the spermatic cord are also the most common site of an inflammatory pseudotumor in the male genital tract [37, 50, 58]. The lesion is ill defined, myxoid with white-gray color, and a moderate cellular proliferation with loose collagen fibers and irregular infiltration of inflammatory cells. An exceptional case has been reported that was largely infiltrated by mast cells [92]. In some cases, a prominent spindle cell proliferation mimics a sarcoma (pseudosarcomatous myofibroblastic proliferation), but low mitotic index, a capillary pattern, inflammatory cells, and absence of atypical mitoses speak against a diagnosis of sarcoma. Unfortunately, immunohistochemistry is only partly helpful because the cells express actin and vimentin, less strongly desmin and exceptionally cytokeratin. Two cases of this lesion in epididymis [12, 51] and one in the rete testis [47] have been reported.

Embryonic remnants

Although ectopic tissue usually is more problematic for constituting a mass, some of them can cause microscopic diagnostic doubts for which reason they can be included in

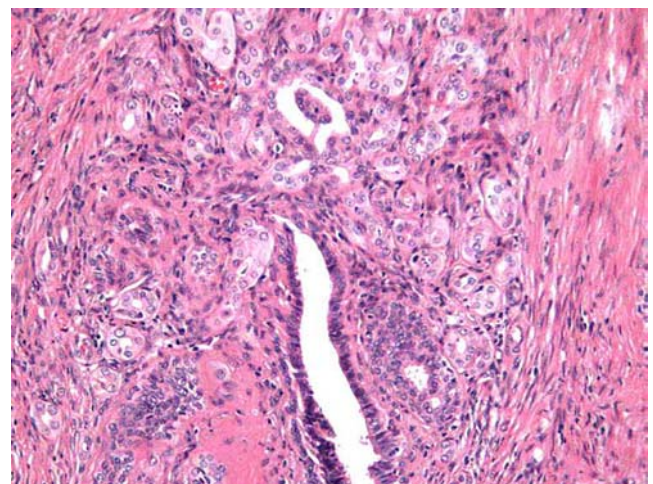


Fig. 16 Vasitis nodosa. Ductular proliferation with a microglandular morphology

this group of benign mimics. The presence of seminiferous tubules within the tunica albuginea [67], Leydig cells in rete testis, albuginea, spermatic cord, or within sclerotic tubules [59, 66], prostate gland in the epididymis [52], and special circumstances with muscular rete testis hypertrophy [27] can mimic a neoplasia.

The lesions described constitute a large heterogeneous group, without etiological or pathogenic relations among them or with true neoplasias. However, in spite of that, the patient with one or more of these tumor-like and/or benign mimickers can have a concomitant or ulterior true neoplasm.

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