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## Pseudo-"solid pseudopapillary neoplasms" of the testis: in reality Sertoli cell tumors

Dear Editor,

We read with interest and concern 2 reports published in Human Pathology [1,2] concerning testicular neoplasms that were felt to be "testicular analogues" of the well-known "solid pseudopapillary neoplasm" (SPN) of the pancreas; albeit in 1 of the 2 articles; the authors preferred to designate the tumors as *primary signet ring stromal tumors* of the testis [1]. Although we acknowledge that the pseudopapillae in the SPNs may be limited in amount, their apparent absence, according to the descriptions of the microscopic findings in all of the 14 tumors in these 2 reports, struck us as unusual for a tumor the authors were placing in the SPN category.

The 14 tumors had foci of signet ring–type cells as well as solid, nested, and trabecular patterns of growth. They shared many immunohistochemical reactivities with SPNs, including nuclear β-catenin, CD10, CD56, and α-1-antitrypsin in the subset of cases studied by this method. The authors reported that they were negative for inhibin (0/12) and calretinin (0/12). Eleven analyzable tumors had exon 3 mutations in the *CTTNB1* gene that encodes β-catenin. In our estimation, these tumors fall within the Sertoli cell tumor, not otherwise specified (NOS) category of testicular tumors, and should not be regarded as SPNs.

Signet ring–type cells are a well-recognized feature of Sertoli cell tumor, NOS. They have previously been illustrated in Sertoli cell tumors by authorities in testicular pathology [3-7] (see p. 119, Fig. 5.18 [3]; p. 367, Fig. 5.39D [4]; p. 248, Fig. 6-20 [5]; p. 790, Fig. 12-79, and p. 791, Fig. 12-83 [6]; p. 716, Fig. 14 [7]), and they are almost certainly due to large fat vacuoles in the cytoplasm. One of us coauthored a large study indicating so, and in that series, they were seen in 26 (43%) of 60 cases [7]. The reactivity of Sertoli cell tumor, NOS, for a variety of antigens including nuclear β-catenin [8-10] and CD56 [11] is well established, as is their variable positivity for inhibin and calretinin. In 5 series, the rate of inhibin reactivity in Sertoli cell tumors varied from 25% to 90% [12-16], and a recent study showed calretinin reactivity in 43% [16]. Negative staining for inhibin and calretinin, therefore, does not exclude Sertoli cell tumor. We are not aware of studies that have looked for CD10 or

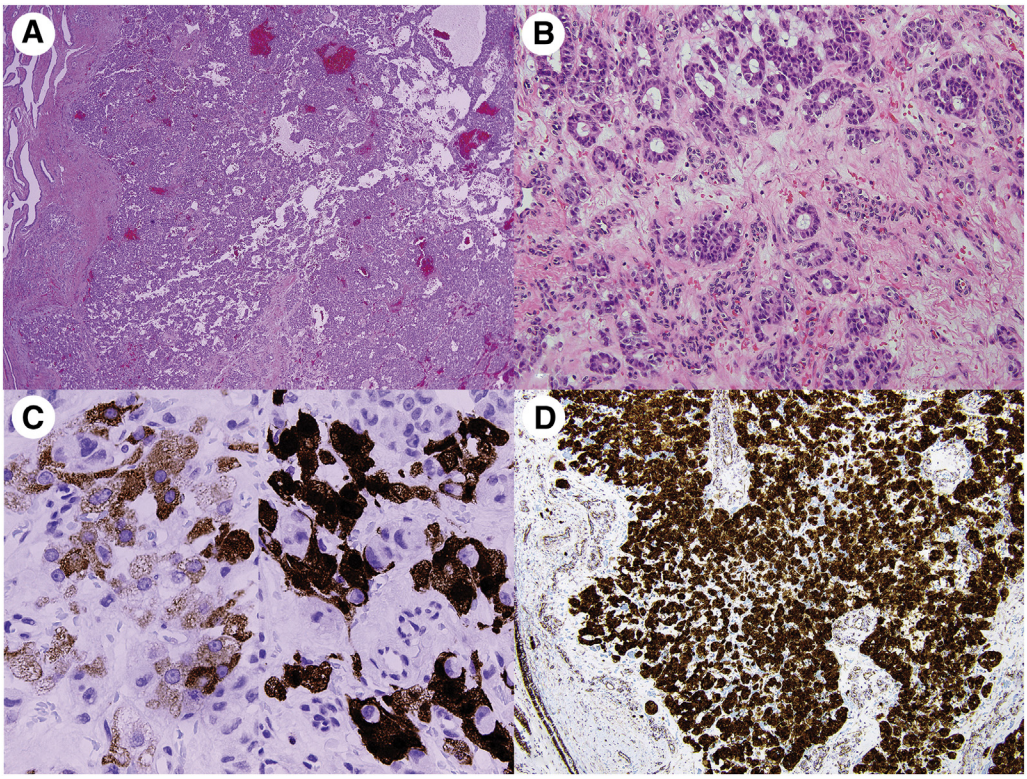


**Fig. 1** Sertoli cell tumor from a 43-year-old man shows solid and trabecular growth with irregular spaces (A), prominent hollow tubules (B), patchy inhibin (left) and calretinin (right) positivity (C), and strong, diffuse nuclear and cytoplasmic reactivity for β-catenin (D).

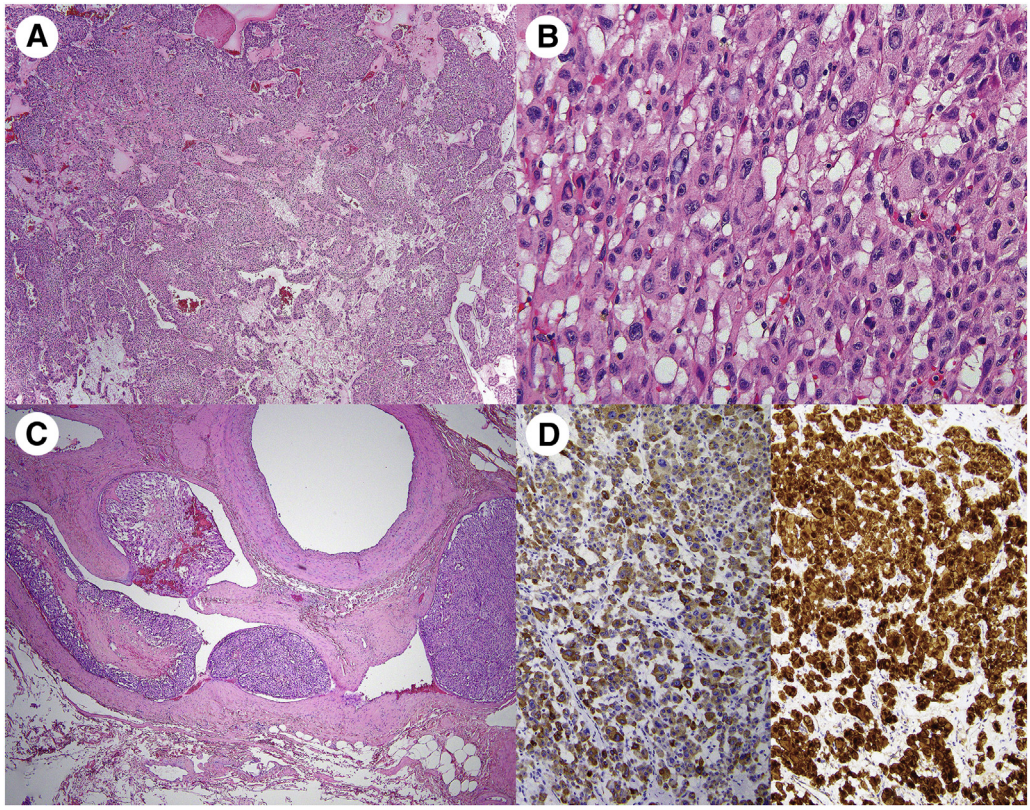


**Fig. 2** Sertoli cell tumor from a 23-year-old man shows anastomosing solid nests (A), prominent nuclear pleomorphism with intranuclear cytoplasmic inclusions and vacuolated cytoplasm (B), conspicuous large vessel invasion in the paratestis (C), and strong, diffuse cytoplasmic reactivity for inhibin (left) and nuclear and cytoplasmic reactivity for β-catenin (right; D).

α-1-antitrypsin reactivity in testicular Sertoli cell tumors, but ovarian ones are frequently CD10 positive [17]. In addition, Sertoli cell tumors, NOS, harbor the same exon 3 mutations in the *CTTNB1* gene [9,18] as described in the testicular tumors considered SPN analogs [1,2]. Our conclusion from these data is that there is a long-established overlap in many of the immunohistochemical reactivities and molecular genetic features of testicular Sertoli cell tumors and pancreatic SPNs.

We wish to illustrate 2 recent cases of Sertoli cell tumor that we readily found in our files that showed similar morphologic features to those the authors illustrated and that exhibited strong nuclear reactivity for β-catenin (known to correlate with the *CTNNB1* mutation [9]) as well as significant reactivity for both inhibin and calretinin (Figs. 1 and 2). They presented as testicular masses in 43- and 23-year-old men who had negative serum marker studies. In the first case, there was significant hollow tubular/glandular differentiation, a feature that is not seen in SPNs, although this case also showed the nested, trabecular, and solid foci the authors emphasized in their descriptions of "SPN analogs." This tumor showed patchy inhibin and calretinin reactivity and diffuse nuclear and cytoplasmic positivity for β-catenin. The second case had solid, nested, and trabecular patterns with foci of vacuolated tumors cells (?signet ring cells) and displayed significant nuclear pleomorphism; it prominently invaded paratesticular blood vessels. It had diffuse inhibin and β-catenin reactivity (calretinin was not performed). It was classified as a malignant Sertoli cell tumor, NOS.

In our opinion, these cases illustrate that Sertoli cell tumors of the testis have overlapping features with those of SPN. They additionally share a mutation of a gene that is altered in a variety of tumors other than Sertoli cell tumor and SPN, illustrating what is becoming increasingly evident concerning the nonspecificity of many molecular genetic changes in tumors. We think that it is a mistake to equate such tumors with the solid pseudopapillary tumor of the pancreas, which has a mostly indolent behavior, because it may well lead to undertreatment when, in fact, early aggressive surgical management with retroperitoneal lymph node dissection may be lifesaving. Our second case is a prime example of an aggressive Sertoli cell tumor that should not be regarded as a SPN.

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## Pseudo–"solid pseudopapillary neoplasms" of the testis: in reality Sertoli cell tumors—reply

Dear Editor,

We would like to thank Drs Ulbright and Young for their comments on our articles about pancreatic analog of solid pseudopapillary neoplasm of the testis [1], in which we have described a total of 7 testicular tumors that have the morphologic features, immunohistochemical profile (positivity for β-catenin, cyclin D1, CD10, CD56, NSE, [often] synaptophysin; uniform negativity for inhibin, calretinin, SF-1, and chromogranin), and oncogenic somatic mutation in exon 3 of the *CTNNB1* (β-catenin) gene identical to those seen in solid pseudopapillary neoplasms (SPNs) of the pancreas [2,3].

In addition, in a separate article, we have described 13 signet ring cell testicular tumors that have immunohistochemical profile and β-catenin mutations identical to those encountered in SPN of the pancreas [4]. These 13 testicular tumors were hypothetically likened to pancreatic SPN based on the fact that most pancreatic SPNs (20/22) in our files have a signet ring cell component. We acknowledged that it would need some time to recognize that these 13 signet ring cell tumors of the testis and SPN of the pancreas likely represent the same entity in different anatomic sites.

Drs Ulbright and Young, on the contrary, point out that all these testicular tumors should be classified as Sertoli cell tumors, not otherwise specified (NOS) [1]. They consider the latter a well-established tumor based on the fact that 5 other groups of pathologists thought that this entity exists (their references [3–7]). We have, however, never found a single article that would prove that Sertoli cell tumor, NOS, represents a homogeneous entity, and the mere fact that "5 groups of pathologists thinks so" is not solid proof for such a statement.

The World Health Organization classification blue book [5] describes the immunoprofile of Sertoli cell tumors, NOS, as follows: "Inhibin is positive in 50% of these tumors and nuclear β-catenin in 60-70%. Calretinin, SF-1, CD99, Melan A and WT1 are also typically positive." In our opinion, testicular tumors that are inhibin, calretinin, and SF-1 negative and that contain no adenomatous-tubular structures have nothing in common with any known entities bearing the name *sertoli* and should be better called *unclassified testicular tumors*.

But if one poses the question "What do the seven tumors published in our two papers [2,3] and the two testicular tumors reported by Mengoli et al. [6] have in common with pancreatic SPN?" our answer is "everything": morphology, presence of hyaline globules, immunoprofile, and mutation in the exon 3 of the *CTNNB1* gene. What do these 9 tumors [2,3,6,7] have