Human Pathology (2016) **51**, 51–56

ELSEVIER

Human PATHOLOGY

www.elsevier.com/locate/humpath

Original contribution

Mixed germ cell–sex cord stromal tumor of the testis with an intratubular component: a problem in differential diagnosis☆

Lawrence M. Roth MD*, Liang Cheng MD

Department of Pathology, Indiana University School of Medicine, Indianapolis, IN 462012-5120

Received 22 October 2015; revised 9 December 2015; accepted 16 December 2015

Keywords:
Testis;
Mixed germ cell–sex cord stromal tumor;
Intratubular germ cell neoplasia;
Germ cell tumor;
Sex cord stromal tumor

Summary The origin of mixed germ cell–sex cord stromal tumor (MGC-SCST) of the testis is uncertain, and a controversy exists as to whether the germ cells in these tumors are neoplastic. Although intratubular components of the common and several uncommon forms of testicular germ cell tumors have been described, to our knowledge, intratubular MGC-SCST has not previously been reported in detail. In a study of 13 cases of testicular MGC-SCST, we observed entrapped seminiferous tubules in 7 cases and an intratubular component in 2, both of which were associated with extensive entrapped tubules. Intratubular MGC-SCST is distinguished from entrapped tubules by the occurrence of germ cells resembling spermatogonia in the adluminal compartment and the absence of tubular lumens. By way of contrast, the adluminal compartment of entrapped tubules is composed entirely of immature Sertoli cells, and lumen formation is observed in favorably oriented tubules. Although the germ cells in our cases of MGC-SCST do not show histologic features of malignancy, the observation of spermatogonia-like cells in the adluminal compartment of the tubule, sometimes with concomitant germ cell proliferation, and the infiltrative pattern of the germ cells in the extratubular component support their neoplastic nature. The intratubular component tends to be more centrally located than the adjacent entrapped seminiferous tubules suggesting that it originates from the latter. The tubules of intratubular MGC-SCST are not expanded except in the advanced stage and are approximately the same size as entrapped seminiferous tubules but are considerably smaller than those of the uninvolved testis that shows active spermatogenesis.

1. Introduction

Intratubular components of most testicular germ cell and some Sertoli cell tumors have been described. Among the germ cell tumors, intratubular components of classical seminoma, embryonal carcinoma, yolk sac tumor, teratoma, and spermatocytic tumor have been described [1]. Although intratubular choriocarcinoma is unknown, intratubular syncytiotrophoblastic cells occur.

In 1972, Talerman [2,3] reported the first cases of mixed germ cell–sex cord stromal tumor (MGC-SCST), both involving the ovary. To our knowledge, intratubular MGC-SCST has been previously mentioned in the literature and illustrated only on a single occasion but was not described in detail [4]. In this study, we report 2 instances of an intratubular component in 13 cases of testicular MGC-SCST, compare it with entrapped seminiferous tubules and other nonneoplastic as

☆ Disclosures: The authors declare no competing interests. All procedures were performed in compliance with relevant laws and institutional guidelines. No outside financial support was provided to the authors for the research presented in this manuscript.

* Corresponding author.
E-mail address: lroth@iupui.edu (L. M. Roth).

http://dx.doi.org/10.1016/j.humpath.2015.12.016
0046-8177/

well as neoplastic conditions, and discuss the criteria for and the differential diagnosis of this unusual condition.

2. Materials and methods

Thirteen cases of MGC-SCST of the testis were obtained from the personal consultation files of the late Professor Aleksander Talerman or from the files of the Indiana University Health Pathology Laboratory (IUHPL), Indianapolis, IN. The 2 cases of intratubular MGC-SCST were from Dr Talerman's material, and 1 was described in a previous investigation [5]. The tissue specimens from the IUHPL were fixed in formalin, routinely processed, and embedded in paraffin. Sections were stained with hematoxylin and eosin. In the material from the IUHPL, paraffin blocks were available, and in the material from Dr Talerman, a limited number of unstained sections were available for immunohistochemical study. Paraffin blocks or unstained sections of the cases having intratubular MGC-SCST were not available for study in this investigation.

For a description of the methodology used for immunohistochemical studies, see Roth and Cheng 2015 [6].

3. Results

Of the 13 patients with testicular MGC-SCST in our study, 12 were adults; the only prepubertal patient was 8 years old. All 7 tumors that contained entrapped tubules occurred in mature adults, and the seminiferous tubules of the testis away from the neoplasm showed active spermatogenesis. The ages were known in 5 of these patients and varied from 25 to 41 years with a mean and median age of 33 years.

Entrapped seminiferous tubules were prominent in the 2 tumors that had elements of intratubular MGC-SCST and in 1 of 5 cases without intratubular MGC-SCST. They were scarce in the remaining cases. The 2 tumors containing elements of intratubular MGC-SCST had a predominant invasive component that resembled unclassified sex cord stromal tumor but unlike the latter contained foci of infiltrating germ cells reminiscent of spermatogonia. The intratubular component was variably located within the invasive component and consisted of tubules that contained neoplastic germ cells resembling spermatogonia without further maturation admixed with nonneoplastic Sertoli cells. Nearby entrapped seminiferous tubules were located peripheral to the intratubular component. The involved tubules were not expanded except in the advanced stage and were approximately the same size as entrapped but nonneoplastic seminiferous tubules in the corresponding tumor but were considerably smaller than seminiferous tubules with active spermatogenesis.

Like the seminiferous tubules of the normal adult testis, both the intratubular component and entrapped seminiferous tubules can be divided into basal and adluminal compartments. The distinction between intratubular MGC-SCST and entrapped tubules is made by the appearance of the adluminal compartment; the basal compartments are similar.

The identification of spermatogonia-like cells in the adluminal compartment served to distinguish intratubular MGC-SCST from entrapped seminiferous tubules (Fig. A). In the intratubular component, we were unable to identify cells and nuclei with the dimensions of preleptotene (early) primary spermatocytes or cells with the nuclear features of primary spermatocytes in the leptotene stage or beyond. In some tubules involved by intratubular MGC-SCST in both of our cases, the neoplastic spermatogonia-like cells underwent proliferation and became the major cellular component; only a few residual Sertoli cells were identified (Fig. B).

The Sertoli cells were immature in the adluminal compartment and mature in the basal compartment of both intratubular MGC-SCST and entrapped tubules. The adluminal compartment of entrapped tubules is composed entirely of nonneoplastic Sertoli cells with a small round or oval nucleus, some with a small but distinct nucleolus, and abundant pale eosinophilic cytoplasm. The entrapped tubules sometimes had lumens lined by immature Sertoli cells, but the majority appeared solid probably due to tangential or oblique sectioning (Fig. C). The basal compartments of intratubular MGC-SCST and entrapped seminiferous tubules consisted of nonneoplastic spermatogonia cradled by mature Sertoli cells. The nuclei of the spermatogonia had finely granular or stippled chromatin; no preleptotene primary spermatocytes were identified. The Sertoli cells were irregular in shape, and the cytoplasm was abundant but indistinct. Lipofuscin pigment served as a marker for the cytoplasm of some mature Sertoli cells of an entrapped tubule in our first case of intratubular MGC-SCST (Fig. C, inset). The Sertoli cell nuclei sometimes contained an identifiable distinct nucleolus.

In our first case of intratubular MGC-SCST, a rare multinucleated spermatogonium (atypical germ cell) was located in the basal compartment of an entrapped tubule (Fig. D). In 1 case of MGC-SCST with entrapped seminiferous tubules but no neoplastic intratubular component, spermatogonia located in the basal compartment of the tubules expressed SALL4, but not OCT4.

In our investigation, we encountered a case of Sertoli cell nodule that contained numerous spermatogonia. The involved tubules contrasted sharply with the surrounding seminiferous tubules that had lumens and showed active spermatogenesis. The lesion consisted of clusters of normal-sized to slightly expanded seminiferous tubules without tubular lumens (Fig. E). The immature Sertoli cells and spermatogonia sometimes surrounded rounded aggregates of hyaline basement membrane material (Fig. E, inset).

The seminiferous tubules in a newborn testis superficially resembled the intratubular component of MGC-SCST; however, it differed in that the tubules were small and contained spermatogonia and immature Sertoli cells; the interstitium consisted of loose connective tissue containing Leydig cells, and no background sex cord stromal tumor was present (Fig. F).