Pathol. Oncol. Res. (2017) 23:513–517
DOI 10.1007/s12253-016-0120-3

ORIGINAL ARTICLE

# More Cases of Benign Testicular Teratomas are Detected in Adults than in Children. A Clinicopathological Study of 543 Testicular Germ Cell Tumor Cases

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Received: 21 March 2016 / Accepted: 28 September 2016 / Published online: 28 October 2016


**Abstract** Benign testicular teratomas are always thought to be pediatric neoplasms and previously all the teratoid tumors in the adult testis regarded as malignant. Recently, three publications reported benign testicular teratomas in adulthood and the latest WHO classification refers them as "prepubertal type of teratomas" which rarely appear in adulthood. These neoplasms behave benign and seemingly analogous independently whether they appear in pre- or postpubertal patients. The aim of our study was to investigate the frequency of benign testicular teratomas both in children and adults. 593 cases of testicular neoplasms were found in a period of 17 years ranging from 1998 to 2014 in the archive of our department (Department of Pathology, Medical Center, Pécs University). 543 cases diagnosed as germ cell tumor which have all been further evaluated in conjunction with the clinical data available. Of all germ cell tumor cases 14 (2.5 %) were pure teratomas. Ten out of 14 were the WHO-defined "conventional" teratoma, 4 of the 14 were the "benign or the so called prepubertal type" from which three occurred in adult patients. Only one of the 14 occurred in childhood, indicating that benign prepubertal type teratomas –which are regarded generally as childhood tumors- are more frequently detected in adults than in children. Benign adult testicular teratomas comprised 21 % of all pure teratoma cases in our series. Practicioners in the field have to be aware of its existence also in adulthood to avoid overtreatment and not to expose their patients to unnecessary chemotherapy, retroperitoneal lymphadenectomy (RLA) and the potential complications of these interventions.

**Keywords** Benign teratoma · Mature teratoma · Germ cell tumor · Testis · Postpubertal · Testicular neoplasms

The presented scientific contribution is dedicated to the 650th anniversary of the foundation of the University of Pécs, Hungary

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## Introduction

According to the current WHO classification of testicular tumors, there are two major groups: the first is the group of the germ cell tumors, accounting for approximately 95 % of the cases, including several entities of partly different histogenesis, and the second is the non-germ cell tumors' group accounting for 5 % of the cases including the sex-cord stromal tumors, the mixed germ cell - sex-cord stromal tumors, the mesenchymal and hematopoietic tumors. This classification is primarily based on histogenesis, which is well demonstrated by the multiply modified tetrahedron model of germ cell tumors. [1, 2].

Until recently testicular teratomas have been divided into 2 groups: those occurring in childhood (prepubertal teratoma) and those diagnosed in adulthood (postpubertal teratoma). The prepubertal type is a benign, usually childhood tumor. The teratomas occure in adulthood are defined by the WHO as predominantly part of mixed germ cell tumors and just rarely pure neoplasms, which is almost always malignant and tends to metastasize. Recent publications in the past few years have described and confirmed the existence of benign teratomas even in the postpubertal period. [3–5] In spite of this, the clinical and pathological thinking changes slowly and the postpubertal testicular teratomas, even today, frequently considered to be always malignant regardless of their histologically mature or immature phenotype. Treatment protocols recommend chemotherapy and/or radiotherapy based on tumor stage, supplemented by RLA if necessary [6–8]. This outdated approach can put an enormous burden on a patient, in addition to not being indicated the case as a benign tumor.

In 2014, our previous study analyzing two cases [4] was the second publication in the literature suggesting that benign teratomas can develop in postpubertal testis as well. Moreover, two years earlier, in 2012 we also proposed in routine histological reports the existence of benign postpubertal teratoma after assessing the molecular and histopathological analysis of two adult cases. Since that time we have had two more (so far unpublished) cases, one of them in the examined time period indicated above.

The most significant molecular pathological feature of benign postpubertal teratomas is the lack of isochromosome 12p (i12p), which is otherwise present in most germ cell testicular tumors. According to our observations, benign teratomas are characterized by younger age (as compared to malignant cases), presence of organoid, mature, squamous cyst and non-dermal (intestinal, respiratory, tubal, etc.) elements, lack of intratubular germ cell neoplasia (ITGCN) in the surrounding testicular tissue and a relatively smaller size. Apart from this, contrary to malignant cases in adults, serum tumor markers are also consistently negative.

The main objective of the present study was to analyze the cases documented in our department to determine the relative frequency of benign testicular teratomas in adults as compared to other testicular tumors, as such a data are not available in the literature. Another aim was to point out the possibility of overtreatment and its potential risks as well as to draw the attention to the misleading denominations of prepubertal or postpubertal type of testicular teratomas of the current WHO classification.

## Materials and Methods

We performed a retrospective analysis of testicular tumors archived in our department in the past 17 years. All the cases of pure teratomas including benign adult teratomas, the mixed germ cell tumors with or without teratoid elements, pure seminomas, sex-cord stroma and the pure yolk sac tumors, pure embryonal carcinomas and all the cases belonging to the "other tumors" group have been collected (Table 1).

All original 4 μm H & E stained slides were available, as well as all immunohistochemical reactions performed at the time of diagnosis. All the benign type teratomas were

**Table 1** Testicular tumors diagnosed from 1998 to 2014

| Tumor histology | | | Average age |
|---|---|---|---|
| Testicular tumor | 593 | 100% | |
| Germ cell tumor | 543 | 92% | 34 |
| Seminoma | 264 | 49% | 38 |
| Mixed germ cell tumor | 205 | 38% | 30 |
| Pure teratoma | 14 | 3% | 23 |
| *Benign teratoma* | *4* | *1%* | 14 |
| "*conventional*" *WHO defined teratoma* | *10* | *2%* | 26 |
| Pure embryonal carcinoma | 55 | 10% | 30 |
| Pure yolk sac | 5 | 1% | 24 |
| Sex cord stromal | 11 | 1,5% | 49 |
| Other | 39 | 6,5% | 58 |

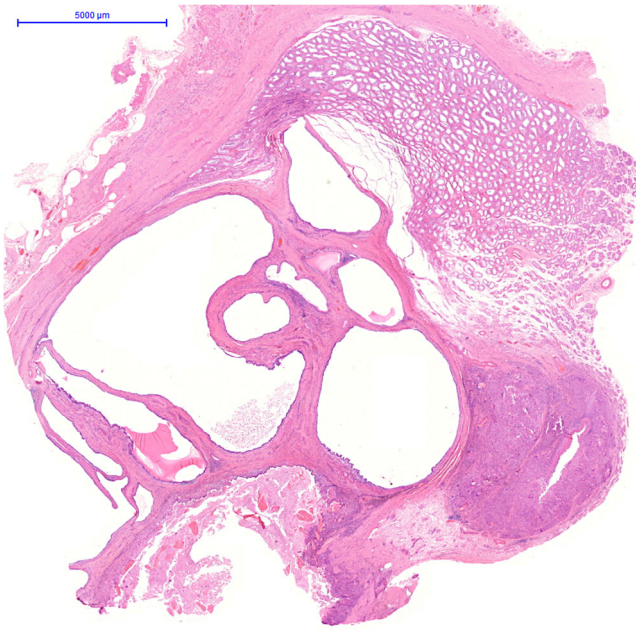



**Fig. 1** Benign postpubertal teratoma, haematoxylin eosin staining, lupe magnification. Note the preserved part of the testis right above, the fibrous capsule of the organ and the cystic appearance of the tumor in the center and lower left

examined by additional immunohistochemistry (PLAP, CD30, CK, AFP, βHCG) and the FISH reactions were performed in the Leiden University Medical Center as previously described by Zhang et al. [3] H&E and immunohistochemical slides were independently re-evaluated by three pathologists (TT, EK, DS) based on the WHO classification.

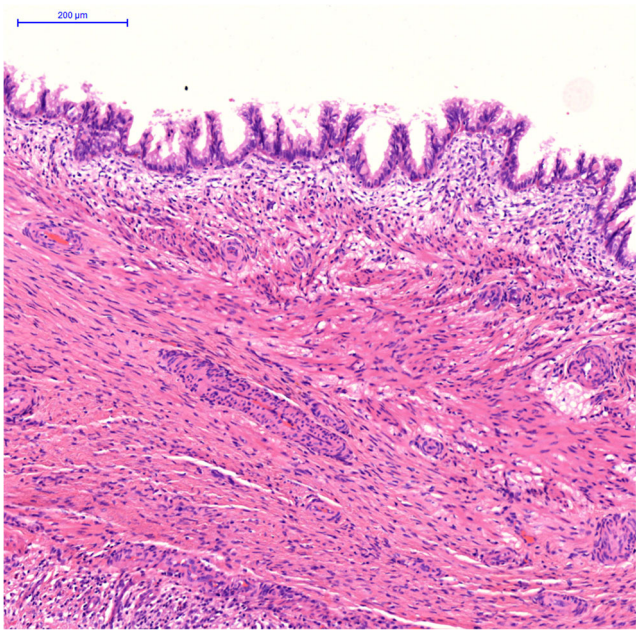



**Fig. 2** Benign postpubertal teratoma, haematoxylin eosin staining. The cyst is lined by columnar epithelium of tubal type. Note the preformed muscle layer in the wall

## Results

593 cases of testicular tumors were collected from our archives from which 11 cases were sex-cord stromal and 39 cases were of other – mostly hematopoietic –origin. Of all the 543 germ cell tumors, 264 cases (49 %) was seminoma and slightly more than 10 % (55 cases) was pure embryonal carcinoma. 205 cases (38 %) were mixed germ cell tumor.

Further examination of our samples revealed that of all germ cell tumor cases, 14 (3 %) were pure teratomas (Table 1). Only one of the cases occurred in childhood. Detailed histological analysis of the group focusing on the type and maturity of the tissue elements revealed 10 "conventional" pure teratomas and 4 other cases which later showed mature squamous cyst; pure mature intestinal tissue with a completely organoid appearance without mitotic or apoptotic activity (bilayered tunica muscularis, mature neural elements, enterochromaffin cells), as well as cysts with mature organoid tubal-type and respiratory epithelium. (Figs. 1 and 2). Intratubular germ cell neoplasia

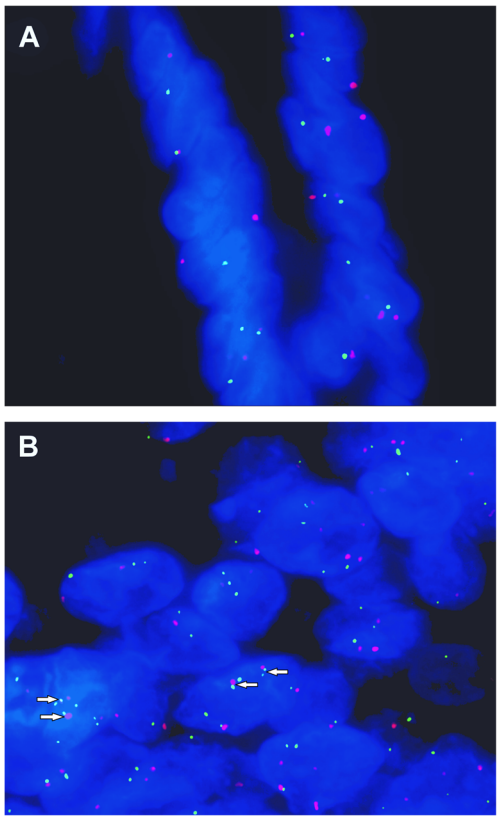
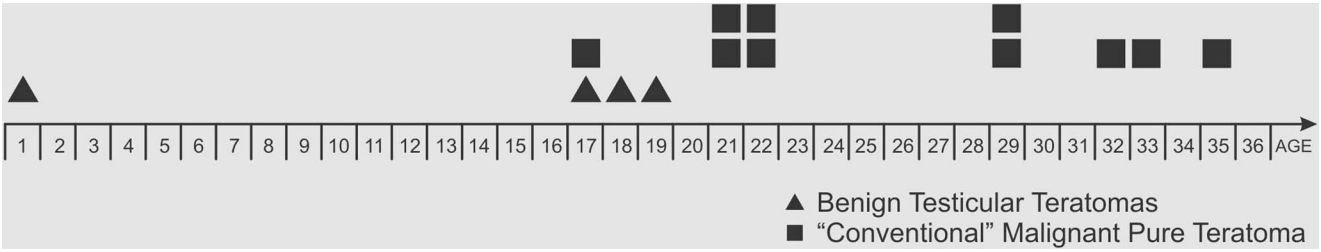



**Fig. 3** a and b FISH images of cases with and without 12p abnormalities. Red and green signals represent the centromeres of chr. 12 and the 12p13 locus (ETV6 gene) respectively. In the benign a "prepubertal type" of teratoma (3**a**) the signal pattern indicates disomy of chromosome 12 without 12p abnormalities (same number of green and red signals). In the postpubertal immature teratoma (3**b**) polysomy of chromosome 12 with signal patterns indicating i(12p) at least in a proportion of cell nuclei is seen (excess of green signals to red, with two green adjacent to a single red signal, see the arrows)

**Table 2** Age distribution of pure teratomas




was absent in all the cases ( negative PLAP immunreaction). These 4 cases (19, 18, 17 and 1-year-old patients respectively) were identified as "benign", the so called *prepubertal type* teratoma (Table 1).

The mean age of the patients with testicular neoplasms of different histology were 30, 23, 38, 49 and 30 years in the group of mixed germ cell tumor, pure teratomas, seminoma, sex cord stroma tumors and pure embryonal carcinoma respectively. In the group of "benign teratoma" –including all the cases - the mean age was 14 years, without the pediatric one it turned up to 18 years. (Tables 1 and 3) Suprisingly, those "benign testicular teratomas" occurred in adult patients comprised 21 % (3/14) of the pure teratoma group. These three adult patients are completely asymptomatic and radiologically free of tumors (follow-up: 62, 54 and 24 months) (Table 3).

In our FISH analysis all the four benign teratoma cases showed the characteristic lack of isochromosome 12p (i12p) (Fig. 3a and b).

## Discussion

Our results -which correspond with the large clinical studies in view of the proportions of different histological types of germ cell tumors- suggest that even though benign testicular teratomas account for a relatively small proportion of all germ-cell testicular tumors, they are nevertheless more frequently detected in adults than in children in our series. [9–11] It is conspicuous, that the benign postpubertal testicular teratoma cases occurred at the margin of the adult- and childhood (around 18 years of age), the mean age of the group is much below than that of all the other testicular tumor groups. It may suggest, that these cases are the late manifestation of those tumors began at pediatric age. (Table 2) Comparing our data to those published earlier, the mean age of the group in this series was lower (18 vs. 24 years) [3] (Table 3).

The younger age of the patients, the lack of tumor markers and also the relatively smaller size (not exceeding 3–4 cm) at presentation all suggest the presence of a benign-type testicular teratoma in a given adult. The most significant molecular pathological feature of benign postpubertal teratomas –as we found in our cases- is the lack of isochromosome 12p (i12p), which is otherwise present in most malignant germ cell testicular tumors. According to our observations, benign teratomas are characterized by younger age as compared to malignant cases (18 v 26 years of age), presence of organoid, mature, squamous cyst and non-dermal (intestinal, respiratory, tubal, etc.) elements, lack of intratubular germ cell neoplasia (ITGCN) in the surrounding testicular tissue and a small size. Apart from this, contrary to malignant cases in adults, serum tumor markers are also consistently negative.

The facts above and the 21 % frequency of the benign type of teratoma in our adult series makes it really important to consider this entity even in adulthood. Both pathologists, oncologists and urologists have to be aware of its existence to avoid overtreatment and not to expose their patients to unnecessary chemotherapy, RLA and their potential complications. The relatively high frequency of the tumor should urge us to perform the i12p molecular studies on tissue samples of pure adult testicular teratomas -especially when supported by the

**Table 3** Clinical and pathological features of benign teratomas

| Size | | | | Abnormal | | |
|---|---|---|---|---|---|---|
| Case | Age | (cm) | Histologic findings | 12p | Treatment | Follow-up |
| 1 | 19 | 0.8 | squamous cyst, intestinal epithelium, organoid | Neg | PO, RLA | A&W; 62mo |
| 2 | 18 | 1.3 | squamous cyst, serous epithelium | Neg | RO | A&W; 54mo |
| 3 | 17 | 3.8 | squamous cyst, respiratory epithelium, organoid | Neg | RO | A&W; 24mo |
| 4 | 1 | 3.3 | variety of somatic-type, mature elements | Neg. | RO | A&W; 47mo |

*A&W* alive and well; *PO* partial orchiectomy, *RO* radical orchiectomy; *RLA* retroperitoneal lymphadenectomy

phenotype- to exclude or confirm the benign dignity/behavior of the neoplasm thereby sparing the patient from further stressful unnecessary operations or even chemotherapy.

It is still not clear how benign teratomas can develop in postpubertal testicles. We share the opinion of *Oosterhuis* et al. [5] that these cases could be the late manifestation of the benign childhood teratomas. According to this theory, the small size of the benign teratoma prevents it from being detected in childhood, but as it grows together with the patient, finally it will reach a detectable size after puberty. Following the reasoning of *Oosterhuis* et al. [5] we also suggest that this is not a separate entity, but an unusual clinical manifestation of the same prepubertal tumor. This theory, however, still needs to be proven by further histological and molecular studies.

Exact name of this tumor-variant or entity "benign postpubertal teratoma" [3, 4] or "Type I mature teratoma" [5, 12] could be the subject of debate being the first is misleading. Clinicopathological data from the past few years seem to suggest that the prepubertal and postpubertal cases of benign teratomas (histologically the *prepubertal type of teratomas*) are the same. However it needs to be confirmed by different studies on further cases, we recommend to call the entity simply as "benign testicular teratoma" which name expresses all the important features of this entity and it is not misleading.

It is of utmost importance that clinical protocols also consider the possibility of the above mentioned entity in order to spare young and otherwise healthy patients' unnecessary and stressful treatments and their complications.

**Acknowledgments** Authors are much obliged and grateful to Dr. Béla Kajtár for preparation of the FISH images.

**Compliance with Ethical Standards** This study was performed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975 and 1983.

**Conflict of Interest** No interest.

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