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Testis-Preserving Tumor Enucleation Is Applicable in Children with Immature Testicular Teratoma

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Keywords
Testicular teratoma · Immature · tumor · Enucleation · Testis-preserving surgery · Treatment

Abstract
Introduction: This study investigated the biological characteristics of immature testicular teratoma in children and explored the feasibility of testis-preserving tumor enucleation. ***Methods:*** We retrospectively reviewed the cases of 23 children who received a pathologic diagnosis of immature testicular teratoma between January 2005 and December 2018. Ages ranged from 16 days to 13 months (mean: 6 months and 5 days). Painless testicular enlargement was the main clinical manifestation, and the course of disease ranged from 20 days to 4 months (mean: 1.4 months). The tumor volume ranged from 1.5 × 1.2 × 0.5 to 6 × 5 × 4.5 cm. Elevated levels of alpha-fetoprotein were measured in 21 patients. Preoperative ultrasound examination showed a cystic/solid mass with calcification. ***Results:*** Excision of the affected testis was done in 10 patients and testis-preserving tumor excision in 13 patients. Postoperative chemotherapy was not employed. Nineteen patients were followed up for 1–10 years, and all showed disease-free survival without recurrence or metastasis. ***Conclusion:*** Immature testicular teratoma is found predominantly in children aged <1 year, and its biological characteristics are different from those in adults. Immature testicular teratoma is largely benign in children and can be managed by testis-preserving tumor enucleation, as for other benign tumors (such as mature teratoma). Postoperative monitoring and follow-up are necessary.

Introduction

In children, the incidence of testicular tumor is about 0.5–2.0 per 100,000, and testicular tumor accounts for 1–2% of solid tumors in children and 3% of all testicular tumors [1]. Testicular tumor in children is mainly germ cell tumor, and teratoma accounts for 31–65% of instances, of which immature teratoma accounts for 5–10% [1, 2]. Immature testicular teratoma is rare in children, and its treatments and biological characteristics are still poorly understood and controversial. In this study, we retrospectively reviewed 23 children who received a pathologic diagnosis of immature testicular teratoma between January 2005 and December 2018. Here, we summarize the biological characteristics of immature testicular teratoma and report the results of our studies of the feasibility of testis-preserving excision in these children.

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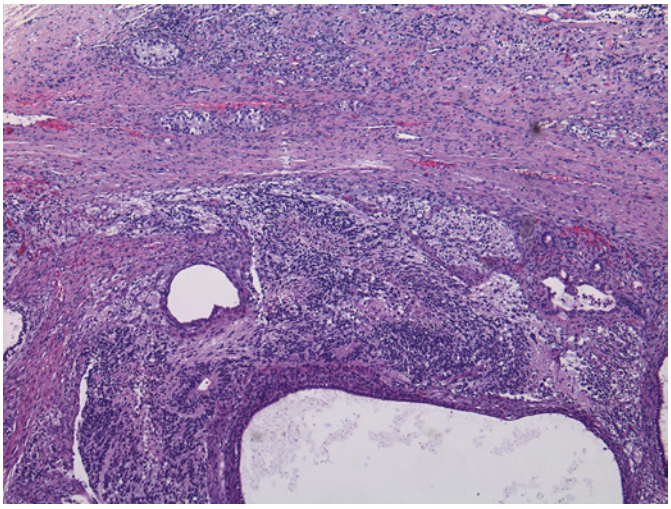

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Fig. 1. Immature embryonic tissues (mainly nerve tissues such as primitive neural tubes). HE ×50.

Materials and Methods

General Characteristics

Twenty-three patients initially were included in this study. Their ages ranged from 16 days to 13 months (mean: 6 months and 5 days). Fifteen patients were aged less than 6 months; only one is older than 1 year. Tumor was found in the left testis of 13 patients and in the right testis of 10 patients. Of note, 1 patient had both left immature testicular teratoma and right mature testicular teratoma. Painless enlargement of the testis was noted in 22 patients. The course of disease ranged from 20 days to 4 months (mean: 1.4 months). Prenatal ultrasound examination showed a pelvic mass in 1 patient, and postnatal examination showed cryptorchidism with a tumor.

Preoperative Examination

All the children received preoperative ultrasound examination. Mixed echoes (cystic/solid) were noted in all these children. Cysts of different sizes were present in the tumor, and calcification was noted in 15 cases. The tumor volume ranged from 1.5 × 1.2 × 0.5 to 6 × 5 × 4.5 cm. Alpha-fetoprotein (AFP) examination was done in 21 patients. AFP was 26,687 ng/mL in patients aged 16 days, 49–723 ng/mL in patients aged 1–6 months (median: 173 ng/mL), and 14–97 ng/mL in patients aged 6–13 months (median: 57 ng/mL). Testicular teratoma was suspected in 20 patients, and testicular tumor of undefined type was diagnosed in 4 patients by preoperative ultrasound examination.

Methods

Of 23 patients, an inguinal incision for resection of the affected testis was made in 1 patient with cryptorchidism. In 4 patients who were undefined type by ultrasound before operation, frozen section examination during operation was made, which showed immature testicular teratoma, and then resection of the affected testis was made in 3 patients with tumor diameter >3 cm (grade 3 immature testicular tumor) or testis-preserving resection in 1 patient with tumor diameter <3 cm (grade 2 immature testicular tumor). In the remaining 19 patients, resection of the affected testis was made in 7 patients when the tumor diameter was >3 cm, and testis-preserving tumor enucleation was performed in 12 patients in whom the tumor diameter was <3 cm.

Results

In 23 patients, postoperative pathologic examination showed immature testicular teratoma (Fig. 1). Nineteen patients received follow-up (resection of affected testis: $n = 9$; testis-preserving tumor enucleation: $n = 10$), and the duration of follow-up ranged from 1 year to 10 years (mean: 4 years and 1 month). All these patients showed disease-free survival, and recurrence and metastasis were not observed. In 10 patients (resection of affected testis: $n = 3$; testis-preserving tumor enucleation: $n = 7$), AFP examination was performed routinely after surgery until the patient was aged 8–12 months and AFP returned to normal.

Discussion

Teratoma is an embryonic tumor caused by abnormal development of embryonic cells in the primordial germ. Malignant testicular teratoma accounts for 60% of testicular teratomas in adults, but testicular teratoma is mainly benign in children [3]. Mature testicular teratoma is the major type of testicular teratoma in children and often is benign, which has been widely accepted, and recurrence has never been reported after surgical resection [1–3]. However, little is known about immature testicular teratoma. There are immature embryonic tissues (mainly nerve tissues such as primitive neural tubes and immature daisy-like masses) in the mature tissues, the biological characteristics of immature testicular teratoma are still poorly understood, and recurrence is occasionally reported in immature testicular teratoma [4, 5]. The use of testis-preserving tumor enucleation and postoperative chemotherapy is still controversial in patients with immature testicular teratoma.

As we reported [6], the median age at presentation and maximum tumor diameter between mature teratoma and immature teratoma were 20.5 (IQR 11.25–52.75) months versus 5 (IQR 3.25–6.75) months and 1.95 (IQR 1.30–2.78) cm versus 3.8 (IQR 3.12–5.00) cm, respectively. Immature teratomas were more likely to present at a young-

er age and have a lager tumor size than mature teratomas ($p < 0.001$). Akiyama et al. [2] reported that the age of patients with immature testicular teratoma ranged from 3 to 10 months (mean: 7 months) at surgery, which was significantly younger than the age of patients with mature testicular teratoma in the same period (mean: 19 months). Serum AFP is secreted by the yolk sac cells in the early fetal period and also by the proximal small intestine and the liver. Increased AFP is present in more than 90% of children with testicular endodermal sinus tumor, but almost all patients with mature teratoma show normal serum AFP levels [1]. Thus, AFP measurement is helpful for the differential diagnosis of benign and malignant teratomas and may guide the timing of surgery and postoperative chemotherapy. In addition, dynamic measurement of AFP is also important for monitoring postoperative recurrence and metastasis. Serum AFP may physiologically increase after birth, but the level returns to normal at 8–12 months of age [1]. Immature testicular teratoma is found mainly in children aged <12 months, and thus, measurement of serum AFP has limited value in the preoperative differential diagnosis of immature testicular teratoma. The American Puberty Testicular Tumor Study Group found the AFP was often lower than 100 ng/mL, although it physiologically increases in children with testicular teratoma and aged 6–12 months [7]. In the present study, 8 patients with immature testicular teratoma were aged 6–12 months, and their AFP was 14–97 ng/mL, which is consistent with previous reports. In our study, 10 patients were followed up at 8–12 months of age, and their serum AFP returned to normal.

Ultrasound examination is preferred for testicular tumor. Evidence shows that the sensitivity of ultrasound examination is as high as 96.6% in the diagnosis of testicular tumor [8]. The European Urology Annual Conference in 2005 recommended ultrasound as the preferred examination in the diagnosis of testicular tumor. In our hospital, the accuracy of ultrasound examination is as high as 93.1% in the preoperative diagnosis of testicular tumor in children. Testicular teratoma is usually composed of tissues from different germinal layers, which suggests that the features of testicular teratoma are diverse: mixed echoes are usually observed; the mass has cystic, solid, and/or calcified echoes; calcified and/or adipose tissues may be present; and the calcified tissues have different shapes (star-like, patchy, plaque-like, or nodular) and poor blood flow. Our experience shows calcification, presence of a cystic cavity, and blood flow are the main features in the differential diagnosis of teratoma versus endodermal sinus tumor.

Immature testicular teratoma in children is significantly different from that in adults. Some clinicians propose that immature testicular teratoma in children is a benign tumor [1, 2, 9–13], and they suggest that adjunctive therapy is not needed after surgery for these children. Weissbach et al. [14] first reported testis-preserving tumor enucleation in 1984. Thereafter, this surgery has been widely applied in the treatment of benign testicular tumors in children (such as mature teratoma and dermoid cysts), and some clinicians propose that this surgery may not increase the possibility of postoperative recurrence in cases of benign tumor and is safe and feasible [15]. In addition, the testis is a major sexual organ in males, and thus, testis-preserving surgery is functionally, physiologically, and psychologically important for patients with testicular tumor. Ahmed et al. [1] showed that sufficient testicular tissues in ultrasound examination and that normal serum AFP before surgery or AFP <100 ng/mL for patients aged 6–12 months are indications for testis-preserving tumor enucleation in children with testicular tumor. Steiner et al. [16] speculated that the tumor diameter should be <2.5 cm for testis-preserving surgery. Some clinicians postulate that immature testicular teratoma is benign in children, and testis-preserving tumor enucleation is recommended [1, 2, 9–13]. However, postoperative recurrence and metastasis are occasionally reported [4, 5]. Thus, several clinicians propose that testis-preserving tumor enucleation should be used cautiously in children with immature testicular teratoma [17].

In this study of 23 children, testis-preserving tumor enucleation was performed in 13 patients: 19 patients received postoperative follow-up (resection of affected testis: $n = 9$; testis-preserving tumor enucleation: $n = 10$); follow-up was conducted for 1–10 years (mean: 3.5 years), and all the patients showed disease-free survival. Recurrence and metastasis were not observed; atrophy and necrosis of the testis were also not noted in 10 patients who received testis-preserving tumor enucleation. Thus, we speculate that (1) the biological characteristics of immature testicular teratoma in children are different from those in adults; immature testicular teratoma is largely benign in children; and thus, its prognosis is better than that of teratoma at other sites. (2) The presence of normal testicular tissues in ultrasound examination, a clear boundary between tumor and normal tissues, and a tumor diameter of <3 cm are indications for testis-preserving tumor enucleation. The testis of children is important for endocrine function, psychological development, and fertility in adulthood. (3) Although the accuracy of ultrasound examination is as high as 93.1% in the preoperative diagnosis of testicular tumor

in children at our hospital, intraoperative pathologic examination is not routinely performed. Thus, the clinicians responsible for ultrasound examination should be experienced in the diagnosis of testicular tumors. If preoperative ultrasound examination cannot confirm that the teratoma is benign, intraoperative pathology examination is recommended before testis-preserving tumor enucleation. (4) Recurrence and metastasis are occasionally reported in patients with immature teratoma, and thus, close monitoring and follow-up are recommended after surgery regardless of testis-preserving surgery.

Conclusions

Immature testicular teratoma is rare in children, and its biological characteristics are different from those in adults. Immature testicular teratoma is largely benign in children and can be managed by testis-preserving tumor enucleation, as for other benign tumors (such as mature teratoma).

Statement of Ethics

This research was approved by the Medical Ethics Committee of Beijing Children's Hospital, Capital Medical University.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

In the process of manuscript creation, Dr. WeiPing Zhang, Ning Sun, and Hongcheng Song contributed to the design and revision of the article.

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