Case Report

The First Case of Primary Testicular Germ Cell Tumor Containing Nephroblastoma as the Only One Non-germ Cell Component

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Adult extrarenal nephroblastomas (Wilms’ tumor) are extremely rare tumors. They show a higher incidence of non-seminomatous elements and these so-called ‘teratoid’ Wilms’ tumors are suggested to be of germ cell origin. To date, however, the number of reported cases with gonadal teratoma containing nephroblastoma is very low, and due to this reason, there are no standardized criteria for the categorization and treatment of these lesions. To our knowledge, the first case of nephroblastoma arising in a non-atrophic testis has been reported and it is associated with a teratoma as morphologically identifiable germ cell tumor and rhabdomyosarcoma as a second non-germ cell element. We report the second case of an adult nephroblastoma that arose within the primary testicular teratoma in a non-atrophic testis. Teratoma and nephroblastoma within the same testis may have an important point to clarify the developmental mechanism in nephroblastic differentiation of germ cell tumors.

Key words: nephroblastoma – teratoma – germ cell tumors – adult extrarenal nephroblastoma – Wilms’ tumor

INTRODUCTION

Nephroblastoma (Wilms’ tumor) is a malignant embryonal neoplasm of the kidney and derived from nephrogenic blastemal cells (1). Despite its rarity, it is the most common childhood renal malignancy (2). Ninety-eight percent of the cases occur in individuals under 10 years of age, although presentation in adulthood has been reported (1). Despite Wilms’ tumor being one of the original paradigms of Knudson’s two-hit model of cancer formation (3), it has become apparent that several genetic events contribute to Wilms’ tumorigenesis (4).

Very rarely, nephroblastoma occurs in extrarenal sites without primary renal involvement and the diagnosis is almost always made after surgical intervention. The tumor can be located in the retroperitoneum, uterus, cervix, gonads, skin and even in the thorax (1,2). In contrast to renal Wilms’ tumors, little is known about the origin and molecular mechanism(s) involved in the development of extrarenal Wilms’ tumors and there are no standardized criteria for the categorization and treatment of these lesions because of its rarity (5,6). They show a higher incidence of non-seminomatous elements and these so-called ‘teratoid’ Wilms’ tumors are suggested to be of germ cell origin (5).

Non-germ cell malignant tumors, like nephroblastoma, may arise in primary or metastatic germ cell tumors (GCTs) and nephroblastomas are most likely derived from extragonadal teratomas (1,5). To date, the number of reported cases with gonadal teratoma containing nephroblastoma is extremely rare. To our knowledge, Emerson et al. (2) have reported the first case of the tumor composed primarily of nephroblastoma, teratoma and rhabdomyosarcoma in a non-atrophic testis, and we report the second case of a nephroblastoma arose within the primary testicular teratoma in a non-atrophic testis. However, the development of teratoma...
containing nephroblastoma as the only one non-germ cell element in a non-atrophic testis has not been reported previously.

**CASE REPORT**

A 19-year-old man presented to the urology clinic with a complaint of right testicular swelling, which had been present for ≈2 months. He had no history of cryptorchidism and chemotherapy. The physical examination revealed a normal left testis and a hard and painless mass in the lower pole of the right testis. Scrotal ultrasonography showed a 4 cm mass in the lower pole of the right testis. Serum human chorionic gonadotropin (hCG) was 549 mIU/ml and α-fetoprotein (AFP) was 350 ng/ml. Radical inguinal orchietomy was performed.

Gross examination of the surgical specimen showed an encapsulated solid mass with 4 cm in size, largely replacing the lower pole of the testis. The cut surfaces were heterogeneous with cystic and hemorrhagic areas.

Microscopically, the tumor involved the lower pole of the right testis and tunica albuginea was invaded. Three types of tumors were observed in the entire testis; mainly testicular teratoma and nephroblastoma within the teratoma and intra-tubular germ cell neoplasia in the adjacent testicular parenchyma. The teratomatous component consists of islands of cartilage and cystic structures lined by the squamous epithelium and enteric-type epithelium. A focus of tubular and glomeruloid structures were determined within the teratomatous component of the tumor. They had an organoid arrangement resembling renal tissue. Figure 1 showed that hematoxylin–eosin staining of tumor. The nephroblastic focus was composed of mixtures of tubular structures of atypical epithelium and islands of primitive blastemal cells (Fig. 2).

In the immunohistochemical analysis of the nephroblastomal structure, the tissue showed strong immunoreactivity for pancytokeratin and focally immunoreactivity for WT-1, but no immunoreactivity for chromogranin, synaptophysin and glial fibrillary acidic protein (Fig. 3).

Post-orchiectomy controls of the testicular tumor markers showed an hCG of 939 mIU/ml and an AFP of 2904 ng/ml. A computed tomography (CT) scan of the thorax and abdomen revealed multiple lymphadenopathies with 3 cm in greatest dimension, a lymphadenopathy with 7 × 6 cm in size in distal paraaortic area just anterior to the vena cava and bilateral retrocrural lymphadenopathy, but no evidence of thoracic disease.

The patient received adjuvant chemotherapy with four courses of bleomycin, etoposide and cisplatin (BEP) upon the diagnosis of intermediate risk (7), stage IIIC non-seminomatous GCT (NSGCT) according to the 2002 TNM staging system of the International Union Against Cancer (UICC) (8). However, the patient could not reached the expected marker half-life and normal serum AFP and hCG level after BEP chemotherapy, and a second-line chemotherapy with TIP schedule (paclitaxel, ifosfamide, cisplatin) was performed. Cystic liver metastasis was determined by CT after second cycles of TIP chemotherapy. Because of the progression on TIP chemotherapy and poor performance
status, the treatment had been terminated. The patient died in the 18th month after diagnosis.

DISCUSSION

Nephroblastoma is a neoplasm derived from nephrogenic blastemal cells that is almost always seen in the kidneys of young children; it is rare in adults. Moreover, adult extrarenal nephroblastoma is extremely rare and seen most frequently in the post-chemotherapy setting of patients with metastatic testicular GCTs (1,5,9,10).

On the other hand, the testicular GCTs are the most frequent malignancies in men between 15 and 35 years of age. Typically, more than 90% of cases are cured including 70–80% patients with metastatic disease (11). Teratomas are composed of several types of tissue representing different germinal layers. They may be composed exclusively of well-differentiated, mature tissues or have immature, fetal-like tissues (1). Most teratomatous elements in the testis occur as a component of mixed GCTs, which represent about one-third of all testicular GCTs and contain teratoma in ~50% of the cases (9).

Teratoma may be associated with somatic-type malignancies, and this entity is defined as a teratoma containing a malignant component of a type typically encountered in other organs and tissues, e.g. sarcomas and carcinomas (1). Non-germ cell malignant tumors may arise in primary or metastatic GCTs and this entity, designated ‘teratoma with malignant transformation’, arises in 3–6% of patients with metastatic GCTs (1,12).

It was postulated that they develop from either malignant transformation of preexisting teratomatous elements or by differentiation of totipotential germ cells with concomitant malign transformation. Examples of transformed cell types include rhabdomyosarcoma, angiosarcoma, primitive neuroectodermal tumor (PNET), adenocarcinoma, nephroblastoma and leukemia (1,13). However, Emerson et al. have reported the first case report of nephroblastoma within a primary testicular teratoma, to date, and stated their observation of loss of heterozygosity at 11p13, the locus of WT1 inactivation in patients genetically predisposed to nephroblastoma (2). This loss may be an important genetic mechanism in nephroblastomatous differentiation of GCTs and the authors have concluded that these data support a common clonal origin for nephroblastoma and the other GCT components (2). After malign transformation, overgrowth of immature tubules, blastemal and stroma may result in nephroblastoma-like tumors (9).

Care must be taken not to confuse chemotherapy-induced atypia with the development of a secondary malignancy and the somatic components should be recognized because somatic type malignancies generally appear to indicate a worse prognosis when present in a metastasis, but not necessary when present in the primary tumor and they generally do not respond to platinum-based chemotherapy as do germ cell malignancies of the usual type, although testicular cancer patients who have developed nephroblastoma in metastatic sites have often had a favorable clinical outcome (1,2,13). The differentiation from PNET is important, as they have a better prognosis. Morphologically, they show a typical triphasic pattern of the epithelium, blastema and stroma. Immunohistochemically, they do not stain with neuroendocrine markers and are negative for CD99 (14).

The association of Wilms’ tumor with teratoma has been described to varying extents in multiple reports (2,6,9,12,14,15). Because of its rarity, there are no standardized criteria for the categorization and treatment of these lesions (6). Some authors preferred the use of the term ‘teratoid Wilms’ tumor’ to describe a rare variant of nephroblastoma (6,16), whereas the others have reported occurrences of GCTs with a focus of Wilms’ tumor (2,5,6,15).

The association of teratoma and Wilms’ tumors, although rare, is well documented, particularly in nephroblastoma metastases of malignant teratomas; however, the delineation between primary testicular nephroblastoma-associated teratoma and extrarenal nephroblastomas developed within metastatic lesions of teratoma has not been precisely defined (1,6,12). To date, data have been reported on ~200 patients with teratoma with malignant transformation, often in case reports and almost all in metastatic teratomas (12).

Orlowski et al. (17) have reported an intrascrotal nephroblastoma without germ cell elements and not involving the testis. Vanasupa et al. (18) have reported the development of a nephroblastoma, and NSGCT in an atrophic testis. Gillis et al. (5) have published the first report on the chromosomal and molecular characterization of an extrarenal Wilms’ tumor. Rebischung et al. (12) have reported the second case of an adult nephroblastoma arose within the primary testicular teratoma in association with a primary testicular GCT in their case series. To our knowledge, Emerson et al. (2) have reported the first case of nephroblastoma arising in a non-atrophic testis in association with a teratoma as morphologically identifiable GCT and rhabdomyosarcoma as a second non-germ cell element. We report the second case of an adult nephroblastoma arose within the primary testicular teratoma in a non-atrophic testis. However, the development of teratoma containing nephroblastoma as the only one non-germ cell element in a non-atrophic testis has not previously been reported. Therefore, the apparent co-incidence of these two distinct tumors teratoma and nephroblastoma within the same testis may have an important point to clarify the developmental mechanism in nephroblastomatous differentiation of GCTs, even though no chromosomal analysis was performed on our specimen. This analysis could have affirmed or contradicted the chromosomal findings of previous studies performed by Emerson et al. (2) and Gillis et al. (5).

Moreover, AFP and β-HCG levels are elevated in 80–90% of patients with NSGCT at the time of diagnosis (19). However, mature teratomas had no high AFP and hCG levels. There are reports showing AFP-producing nephroblastoma (20–22). Distant metastatic foci that may contain

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non-seminomatous component other than teratoma and nephroblastoma components may be responsible for the raised AFP and hCG levels in our case.

In conclusion, we report the second case of an adult nephroblastoma within the primary testicular teratoma in a non-atrophic testis. However, the tumor contained nephroblastoma as the only one non-germ cell element in a non-atrophic testis and such a case has not been reported yet. Therefore, the co-incidence of these two distinct tumors within the same testis may be a model to elucidate the developmental mechanism in nephroblastomatous differentiation of GCTs.

Conflict of interest statement

None declared.

References