Intratubular Trophoblasts in the Contralateral Testis Caused Elevation of Serum Human Chorionic Gonadotropin Following Complete Remission of Stage II Testicular Tumor: A Case Report

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We report the case of a 22-year-old male who had a history of metastatic right testicular tumor successfully treated with chemotherapy and surgery. Twenty-one months after the initial treatment, the serum human chorionic gonadotropin started to increase gradually, but whole body imaging including the left testis revealed no abnormal finding except testicular microlithiasis. A biopsy of the left testis revealed intratubular germ cell neoplasia, unclassified type. After the human chorionic gonadotropin level reached 6.6 mIU/ml, he underwent left high orchiectomy. Histology demonstrated a small malignant germ cell tumor as well as intratubular germ cell neoplasia, unclassified type, both of which were negative for human chorionic gonadotropin staining. Besides these lesions, there were tiny foci of human chorionic gonadotropin-immunoreactive intratubular trophoblasts. Serum human chorionic gonadotropin normalized immediately after the orchiectomy, and he had no sign of recurrence at 6 months. The present case will provide new insight into the diagnosis of testicular tumor recurrence with isolated elevation of a serum tumor marker.

Key words: cell transformation – neoplastic – human chorionic gonadotropin – seminiferous tubules – testicular neoplasms – trophoblasts

INTRODUCTION

When the serum tumor maker (STM) is elevated during the follow-up for testicular germ cell tumors (GCTs), we should bear in mind the possibility of metachronous development of contralateral testicular GCT as well as the development of metastasis. However, some patients have presented elevated STM without any radiologically abnormal findings at the diagnosis of relapse, a condition which is called ‘isolated elevation of STM’ (1,2). These patients are generally treated with systemic chemotherapy against possible metastatic disease. Here, we report a case with isolated elevation in human chorionic gonadotropin (hCG) who was treated by contralateral orchiectomy. The pathological findings revealed radiologically undetectable hCG-negative metachronous testicular GCT with the hCG-positive intratubular trophoblasts (ITTs) (3). To our knowledge, this is the first case of ITT related to serum hCG elevation.

CASE REPORT

A 19-year-old unmarried male underwent right orchiectomy for a testicular tumor. The serum lactic dehydrogenase,
α-fetoprotein and hCG values were all elevated. The hCG was measured by the kit using a β-subunit specific antibody. The pathology was pT1 non-seminoma consisting of embryonal carcinoma, immature teratoma and yolk sac tumor. At orchietomy, an open biopsy of the left testis was done because testicular ultrasonography (US) revealed microlithiasis. Scattered foci of intratubular germ cell neoplasia, unclassified (IGCNU) were shown in the biopsy specimens. The computed tomography (CT) showed retroperitoneal lymph node (RPLN) metastasis (16 × 8 mm). The patient achieved complete remission with three courses of BEP (bleomycin, etoposide plus cisplatin) and subsequent RPLN dissection. The pathology of RPLN revealed residual mature teratoma. The patient continued remission until 21 months after the initial treatment; thereafter, isolated elevation in the serum hCG was observed. As shown in Fig. 1, the time course of serum hCG levels was marked by a slow but continuous elevation. Testosterone tests to rule out a false-positive hCG (4,5) were repeatedly negative. Whole body imaging including chest and abdominal CT and brain MRI did not show any findings to suggest relapse. A left testicular US and MRI revealed no abnormalities except microlithiasis.

When the serum hCG reached 3.1 mIU/ml (cut-off level: 0.5 mIU/ml), we performed an open biopsy of the left testis again (Fig. 1). Scattered IGCNU foci were shown, but no invasive GCT was found. Because the hCG levels further increased to 6.6 mIU/ml (Fig. 1), we elected to perform an orchietomy under a suspicion of a radiologically undetectable invasive GCT. According to the wish of the patient, testicular sperm extraction (TESE) at the orchietomy was planned for the chance of fatherhood in the future. The examination by stereomicroscopy of the removed testis revealed a 3 mm tumor at the center of the testis, and TESE was done using apparently normal tissues in a distant area. Serum hCG normalized immediately after the left orchietomy (Fig. 1). The patient is doing well without relapse at 6 months after the orchietomy. Androgen replacement has not yet initiated because he does not suffer from symptoms associated with androgen deprivation.

Figure 2 showed the hematoxylin–eosin staining of the left testis revealed a small nodule of GCT, which corresponded to the tumor detected at TESE. The GCT cells grew without any specific structural pattern and were faintly stained for both c-kit and CD30 but not for D2-40. A detailed histological subclassification was impossible for the tiny tumor. Unexpectedly, the tumor was negative for hCG staining, but scattered small foci with strongly positive staining for hCG were found within seminiferous tubules separate from the tumor. The diagnosis of ITTs was made because the foci consisted of multinucleated syncytiotrophoblastic cells. Although there was diffuse distribution of IGCNU that were positive for both c-kit and placental alkaline phosphatase (PLAP) staining around the ITTs, the ITTs were negative for both c-kit and PLAP staining.

**DISCUSSION**

In general, patients with isolated elevation of STM are treated by systemic chemotherapy for radiologically undetectable metastasis when the contralateral testis appears normal. In the present case, we performed left orchietomy due to previously detected IGCNU and a relatively slow increase in the serum hCG. The serum hCG normalized soon after the left orchietomy. The pathology revealed three abnormal findings in the left testis: IGCNU, ITTs,
testicular tumors. Interestingly, immunohistochemical analysis of hCG presented as positive staining only in ITTs, but not in IGCNU nor testicular tumors. These findings suggested that the source of the serum hCG elevation was ITTs in the left testis. In the present case, orchiectomy obviated aggressive salvage chemotherapy under MIS staging. The clinical situation of isolated elevation in STM at relapse is thought to be similar to stage IS disease. In the literature,

Figure 2. Histopathological findings of the left testicular specimen. (A) HE, ×40 (inset: ×200, upper left; ×400, lower right), (B) hCG, ×40 (inset, ×200), (C) c-kit, ×100, (D) CD30, ×200, and (E) D2–40, ×200. Three components were observed: GCT (star), IGCNU (arrowhead), and ITT (arrow). The GCT component (star) consisted of undifferentiated cells (A), which were negative for hCG staining (B). These cells grew without any specific structural pattern and were faintly stained for both c-kit (C) and CD30 (D) but not for D2-40 (E). A detailed histological subclassification was impossible for the tiny tumor. The ICGNU component (arrowhead) consisted of morphologically atypical cells within seminiferous tubules distributed in areas apart from GCT (A). They stained positively for c-kit (C) and D2-40 (E), but negatively for hCG (B). Small hCG-positive foci (arrow) were present within seminiferous tubules (B). They consisted of atypical cells with abundant and eosinophilic cytoplasm (A), and they negatively stained for c-kit (C). These foci were diagnosed as ITT. GCT, germ cell tumor; HE, hematoxylin–eosin; hCG, human chorionic gonadotropin; IGCNU, intratubular germ cell neoplasia, unclassified type; ITT, intratubular trophoblast.
there is a suggestion that the measurement of the hCG level in the spermatic vein blood might be a clue to the diagnosis (6). Thus, in the clinical setting with isolated elevation in STM, the possibility of bilateral testicular tumor should be kept in mind, even if radiological examinations fail to detect abnormal findings in the contralateral testis.

The presence of IGCNU is a well-known risk factor for development of bilateral metachronous testicular GCT. Bilateral testicular GCT is reported to occur in 0.5–5% of testicular cancer patients (7). About 40% of cases present synchronously, and 60% present metachronously (7). About half of cases with IGCNU progress to invasive GCT within 5 years (8). On the other hand, ITT, as well as intratubular seminoma (9) and intratubular embryonal carcinoma (9,10), is considered to be an intermediate stage between IGCNU and invasive GCT. Berney et al. (3) reported that ITTs were found in adjacent parenchyma in 18% of seminoma cases and 11% of mixed tumor cases. The authors suggested that ITT might be a precursor of invasive seminoma with syncytiotrophoblastic giant cells. ITT is characterized by positive staining of hCG, which is in contrast to the hCG-negative features of other differentiated intratubular neoplasms and IGCNU. In fact, IGCNU presented negative staining of hCG in our case. The pathological and clinical importance of ITT is not well known. However, the present case indicated that the lesion can be an invisible source of serum hCG. Another interesting finding is that serum hCG started to rise 21 months after treatment of right GCT, at which time IGCNU had already been detected in the left testis. This clinical course might indicate that ITTs developed at the time of serum hCG elevation.

CONCLUSION

ITT is one of the differentiated forms of intratubular neoplasias. Although the pathophysiology of the ITT remains unclear, the present case will provide a new insight into the diagnosis of recurrence with isolated elevation in STM.

Conflict of interest statement

None declared.

References