A Case of Somatic-Type Malignant Tumor with Isochromosome 12p Arising from a Mature Cystic Teratoma without Genetic Alteration

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Introduction

Germ cell tumors (GCTs) are a heterogeneous group of neoplasms that occur in the ovary, testes, and different extragonadal sites along the midline of the body, such as the mediastinal regions and the midline of the brain. They develop in both sexes at any age and present a variety of clinical and histological features. It is known that somatic-type malignant tumors, i.e. cancer and sarcoma, may occur from GCTs of any organ, but the World Health Organization (WHO) classification has assigned slightly different names for SMTs of each organ. SMTs are thought to be derived from one of the three germ layers which constitute the teratoma. Based on this concept, the WHO classification of SMT of the testes has been given the name “teratoma with somatic-type malignancy”. The WHO classification system of the ovary distinguishes between GCTs and monodermal teratomas and SMTs are considered to originate from dermoid cysts and are categorized as monodermal teratomas².

Recently, knowledge about the pathogenesis of GCTs has accumulated a molecular biology perspective³. There is general agreement that chromosomal alteration separate pathogeneses for prepubertal and postpubertal teratoma, most ovarian teratomas are derived from benign germ cells in a parthenogenetic-like process. Furthermore, it is known that somatic-type malignant tumors, such as cancer and sarcoma, rarely arise from dermoid cysts. Herein, we present the case of a patient diagnosed with a malignant neuroepithelial component arising from a mature teratoma. Fluorescence in situ hybridization (FISH) revealed that i(12p) was detected in the malignant component but was absent from the teratomatous portion.

**Key words:** Mature cystic teratoma, Somatic-type malignant tumor, Germ cell tumor, Isochromosome 12p, Postpubertal testicular teratoma

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lymph nodes were suspected. Serum tumor markers (CA19-9, CA125, and NSE) were elevated. The patient underwent ovarian cystectomy after a clinical diagnosis of suspected immature teratoma.

Gross examination of the resected ovarian cystic tumor revealed components containing sebaceous material, hair, and bone, with a surrounding solid component (Fig. 1A). Histological examination of the ovarian cyst revealed a mature cystic teratoma comprising skin, adipose tissue, respiratory tract, cartilage, lamellar bone, and neural tissue (Fig. 1B, D). Malignant small round tumor cells were observed around the necrotic tissue. Small round cell tumors were present adjacent to the area of the mature central nervous system and was composed of sheets of poorly differentiated cells with high nuclear-cytoplasmic ratio, frequent mitoses, and fibrillary background (Fig. 2A, B). Several foci of lymphovascular invasion were also seen (Fig. 1C). Immunohistochemical studies revealed that tumor cells expressed the neural markers, synaptophysin, CD56, GFAP, S-100, and Olig-2, but lacked the expression of keratin and SALL-4 (Fig. 2C, D). Fluorescence in situ hybridization (FISH) for i(12p) was performed by using the mixture of a Spectrum red-labeled centromeric alpha-satellite DNA probe (CEP12) and a Spectrum green-labeled subtelomeric (Tel12) DNA probe for chromosome 12p. Both probes were purchased from CytoCell (CytoCell, UK). FISH revealed that i(12p) was present in the malignant component, but absent in the teratomatous portion (Fig. 3). Comprehensive agreement of the present patient was obtained before surgery.

**Discussion**

Considering the pathogenesis of the present case, we first distinguished between immature and mature teratomas. In the area of the mature teratoma, three germ layers (endoderm, mesoderm, and ectoderm) were detected and features suggesting immaturity of the teratoma were not observed. In addition, the small round tumor cells did not resemble the immature neural tube. Immunohistochemically, SALL-4 was negative and there was no finding that suggested immaturity of the teratoma.

Next, the small round tumor cells observed in this case were considered. The histological and immunostaining features of this tumor were similar to those of a central primary primitive neuroectodermal tumor (cPNET). Malignant neural tumors arising from mature cystic teratomas are rare, but similar cases have been reported in the past. Small round cell tumors are treated as a cPNET, which is a secondary malignant transformation (SMT)\(^7\). According to the WHO classification, the Japanese Society of Obstetrics and Gynecology, and The Japanese Society of Pathology for ovarian tumors, SMTs are categorized into monodermal teratomas and expected to arise from dermoid cysts\(^7\). Based on molecular biological findings, it is also well established that most ovarian teratomas are derived from benign germ cells in a parthenogenetic-like process\(^8\).
Then, we considered the results of the FISH analysis of the teratomatous component. J.B. Kum et al. reported that in testicular teratomas, the somatic-type malignancies that developed in germ cell tumors have the same genetic alterations, detectable by FISH and loss of heterozygosity studies, as in the corresponding teratomas\(^5\). With regard to testicular lesions, SMTs usually demonstrate i(12p), which is characteristically derived from germ cell neoplasia in situ (GCNIS)-derived embryo cells. It was interpreted that the SMT component was genetically of the same origin as a GCT\(^5\). The molecular genetic relationship between the teratoma and the somatic-type malignancy is unestablished. The origin of ovarian mature cystic teratoma is similar to that of prepubertal-type testicular teratoma and dermoid cyst at any age in that it arises from a nontransformed germ cell\(^9\). Unlike testicular teratomas, this is not yet well demonstrated in ovarian tumors, but it was speculated that SMTs arising from dermoid cysts had no 12p abnormality. In this case, FISH revealed that i(12p) was detected in the malignant component, but it was absent in the teratomatous portion. Chromosome 12p abnormalities, including i(12p) are fundamental abnormalities that account for many types of malignant GCTs of the testes, whereas the major pathway of ovarian teratoma was similar to that of prepubertal teratoma of the testes, which usually lacks the 12p abnormality\(^10\). However, Christopher reported that teratomas in mixed ovarian GCTs had a different pathogenesis, similar to that of postpubertal testicular teratomas. Christopher analyzed 14 cases of ovarian GCTs by using FISH. In case of mixed yolk sac tumor and teratoma, five out of six (83%) cases had detectable i(12p) in their nonteratomatous components; in the teratomatous component, this was four out of six (66%)\(^11\). Thus, one third of the tumors of mixed GCTs did have i(12p). Despite the negative results for i(12p), it is a possible that the teratomatous area was associated with a postpubertal teratoma. For this reason, it is possible that the cPNET component is an SMT arising from postpubertal testicular teratoma.

At present, it is hard to ascertain whether the mature teratoma observed in the present case was a prepubertal or postpubertal teratoma. However, it is difficult to categorize this case in accordance with ovarian tumor classification, because the teratomatous area in our case did not represent a dermoid cyst. Collectively, the present case of an SMT harboring i(12p), which arose from a mature teratoma without i(12p), provides an example that ovarian SMTs can be derived not only from dermoid cysts, but also from mature teratomas. It is also an example that was not consistent with tumors in the categories of current classification systems.

In conclusion, we presented a case of an SMT harboring a 12p gain, which occurred from the mature teratoma without a 12p gain; therefore, we should reconsider the preexisting knowledge of the pathogenesis of ovarian GCTs.

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**Conflicts of Interest**

The authors declare that they have no conflicts of interest.

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