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Case Study

Peripheral T-Cell Lymphoma, Not Otherwise Specified and Concurrent Seminoma in Testis

Junichi Kitagawa,[1] Naoe Goto,[3] Yuhei Shibata,[1] Nobuhiko Nakamura,[1] Hiroshi Nakamura,[1] Nobuhiro Kanemura,[1] Takeshi Hara,[1] Katsuyoshi Takata,[2] Yasuharu Sato,[2] Tadashi Yoshino,[2] and Hisashi Tsurumi[1]

Concurrent seminoma and malignant lymphoma of the testis is rare. We present a case of concurrent seminoma and peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) in a 54-year-old man who complained of painless left testicular enlargement. Radical left orchiectomy was performed. Macroscopically, the tumor (4.0 × 3.0 cm) was creamy, soft, and homogeneous, and microscopic evaluation revealed an alveolar structure of large cells that formed sheets, as well as colonization by other abnormal cells in a 1.0 × 1.0 cm area. The portion of the tumor comprising large abnormal cells was diagnosed as a seminoma, which was positive for c-kit by immunohistochemistry; the other portion was diagnosed as CD3/CD8, TIA, and granzyme B-positive PTCL-NOS. These two portions were clearly differentiated from one another. The patient received CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) therapy and achieved complete response for 50 months. To our knowledge, this is the first reported case of synchronous advanced seminoma and PTCL. 〔*J Clin Exp Hematop 55(3) : 169-174, 2015*〕

Keywords: PTCL-NOS, seminoma, cytotoxic molecule, testicular tumor

INTRODUCTION

Testicular tumors are generally rare, representing only 1-2% of tumors in men. They are found more frequently in individuals between the ages of 20 and 35 years,[1,2] with a clear predominance of tumors of germinal origin. Tumors of this lineage are the most common globally, accounting for between 85% and 90.4% of primary testicular neoplasms.[1] Non-Hodgkin's lymphoma accounts for approximately 70% of all lymphomas. Unlike Hodgkin's lymphoma, non-Hodgkin's lymphoma often occurs in extranodal sites, and 85% of non-Hodgkin's lymphoma is B cell lymphoma.[3]

Peripheral T-cell lymphoma (PTCL) is a heterogeneous group of malignant lymphocytic neoplasms of post-thymic T-cell origin. Primary testicular lymphoma is defined as testicular involvement at the time of diagnosis. This is a rare disease that accounts for 1-8% of all testicular cancers.[4] Almost all cases are B cell lymphomas. In contrast to seminoma, this cancer is more frequent in men older than 50 years of age.[5]

Here, we report a case of seminoma and cytotoxic molecule-positive PTCL originating concurrently in the testis.

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[1]Department of Hematology, Gifu University Graduate School of Medicine, Gifu, Japan
[2]Department of Pathology, Okayama University Graduate School of Medicine, Okayama, Japan
[3]Department of Hematology Gihoku Kosei Hospital, Gifu, Japan
Corresponding author: Hisashi Tsurumi, M.D., Ph.D., First Department of Internal Medicine, Gifu University Graduate School of Medicine, 1-1 Yanagido, Gifu 501-1194, Japan
E-mail: htsuru@gifu-u.ac.jp

CASE REPORT

A 54-year-old man was admitted to our hospital due to a painless left testicular mass that had rapidly enlarged during the past month. There were no comorbid conditions. On physical examination, a non-tender lump measuring 4.0 × 3.0 cm, firm-to-hard in consistency, was present as a painless left testicular enlargement, and hydrocele was present. There was no generalized lymphadenopathy. Serological data were as follows: prostate-specific antigen, 1.489 ng/mL (a tumor marker for prostate carcinoma; normal range is under 4 ng/mL); human chorionic gonadotropin (HCG), 2.9 mIU/mL; β-HCG, 0.2 ng/mL; and α-fetoprotein, 8.1 ng/mL (tumor markers for germ cell tumors; normal range of HCG < 1.5 mIU/mL, of β-HCG < 0.1 ng/mL, and of α-fetoprotein < 20 ng/mL); lactate dehydrogenase, 196 U/L; and soluble

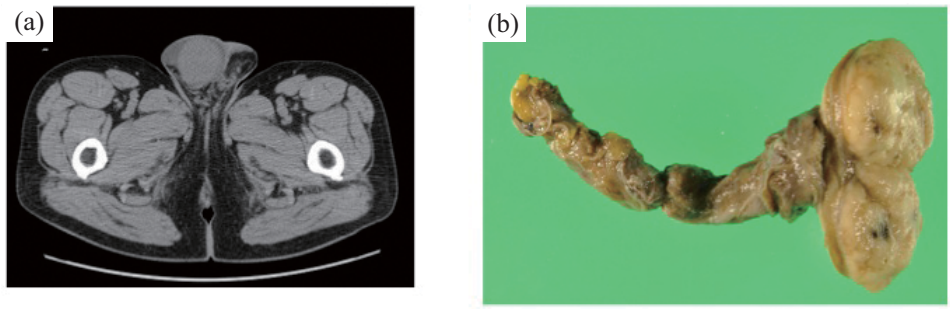

Fig. 1. Testicular findings. (***1a***) Pelvis plain computed tomography showed right testicular enlargement. (***1b***) Macroscopically, the testicular tumor was a creamy, soft, homogeneous mass.

interleukin-2 receptor, 209 U/mL (< 519 U/mL). A complete blood count with differential, serum electrolytes, and renal and liver function tests were within normal limits. Computed tomography showed right testicular swelling (Fig. 1a). Radical right orchiectomy was performed under general anesthesia. Macroscopically, the testicular tumor consisted of a creamy, soft, homogeneous mass (Fig. 1b). Microscopic evaluation (discussed in detail below) revealed an alveolar structure of large cells that formed sheets; in addition, partial colonization by other abnormal cells was noted in a 1.0 × 1.0 cm area. The pathological diagnosis was seminoma and peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS). Positron emission tomography/computed tomography scans after orchiectomy showed neither local involvement nor metastasis (data not shown). According to the staging system for seminomas and the Ann Arbor staging system for lymphomas, the clinical stages were I and IE, respectively. The patient received 4 courses of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) and 4 courses of intrathecal infusion of methotrexate as prophylaxis for central nervous system (CNS) relapse. Radiation therapy was performed to prevent relapse in the contralateral testis after completion of chemotherapy. After 50 months of follow-up, the patient has been relapse free.

PATHOLOGICAL FINDINGS

Histopathological and immunohistochemical analyses

Histopathological features were assessed on hematoxylin and eosin-stained sections of formalin-fixed, paraffin-embedded tissues. Immunohistochemical studies were performed on paraffin-embedded or unfixed frozen sections using a three-step ABC method. Primary antibodies used targeted the following molecules: CD3 (rabbit polyclonal), CD8 (C8/144B), CD30 (Ki-1), CD79a (JCB117), CD246 (ALK1), Ki-67 (MIB-1), c-kit (rabbit polyclonal), LCA (2B11 + PD7/26), and placental alkaline phosphatase (PLAP) purchased from Dako Japan Inc. (Tokyo, Japan); CD20 (L26), CD4 (1F6), and CD56 (1B6) purchased from Novocastra (Newcastle, UK); CD5 (4C7) purchased from MBL (Nagoya, Japan); TIA-1 (TIA-1) purchased from Abcam (Cambridge, UK); and granzyme B (GrB-7) purchased from KAMIYA Biomedical Company (Seattle WA, USA). Epstein-Barr virus was detected by an EBV DNA probe and an RNA *in situ* Hybridization Detection Kit (Dako).

Histopathological findings

One part of the tumor consisted of uniform large cells arranged in sheets with lymphocytic infiltration, which was diagnosed as classic seminoma. The seminoma cells were round or polygonal with a distinct membrane, clear cytoplasm, and nuclei containing prominent nucleoli (Fig. 2a upper left, & 2b). In the testicular tumor, almost all areas contained seminoma cells, but colonization by abnormal lymphocytes was found in only one portion (Fig. 2a lower right). These abnormal cells were of medium to large size, with pleomorphic, hyperchromatic, and vesicular nuclei and prominent nucleoli, and were thus diagnosed as PTCL-NOS (Fig. 2c).

Immunohistochemical findings

Immunohistochemical studies revealed that the seminoma cells were positive for c-kit (Fig. 2d), PLAP (data not shown), and Ki-67 (labeling index 30%). In general, c-kit (CD117) is observed diffusely in 85-100% of classical seminoma cases. In the present case, the classical seminoma cells were mostly negative for CD30. On the other hand, the lymphoma cells were negative for c-kit and PLAP, and positive for Ki-67 (labeling index 50-60%). The lymphoma cells had an alveolar structure of large cells with a diffuse pattern of atypical lymphoid cell growth. These were weakly positive for CD3 (Fig. 2e, 2f) and CD8 (Fig. 2g), positive for CD5, TIA-1 (Fig. 2h), granzyme B (Fig. 2i), and CD30, and negative for CD10, CD20, CD79a, CD56, ALK1, and EBER.

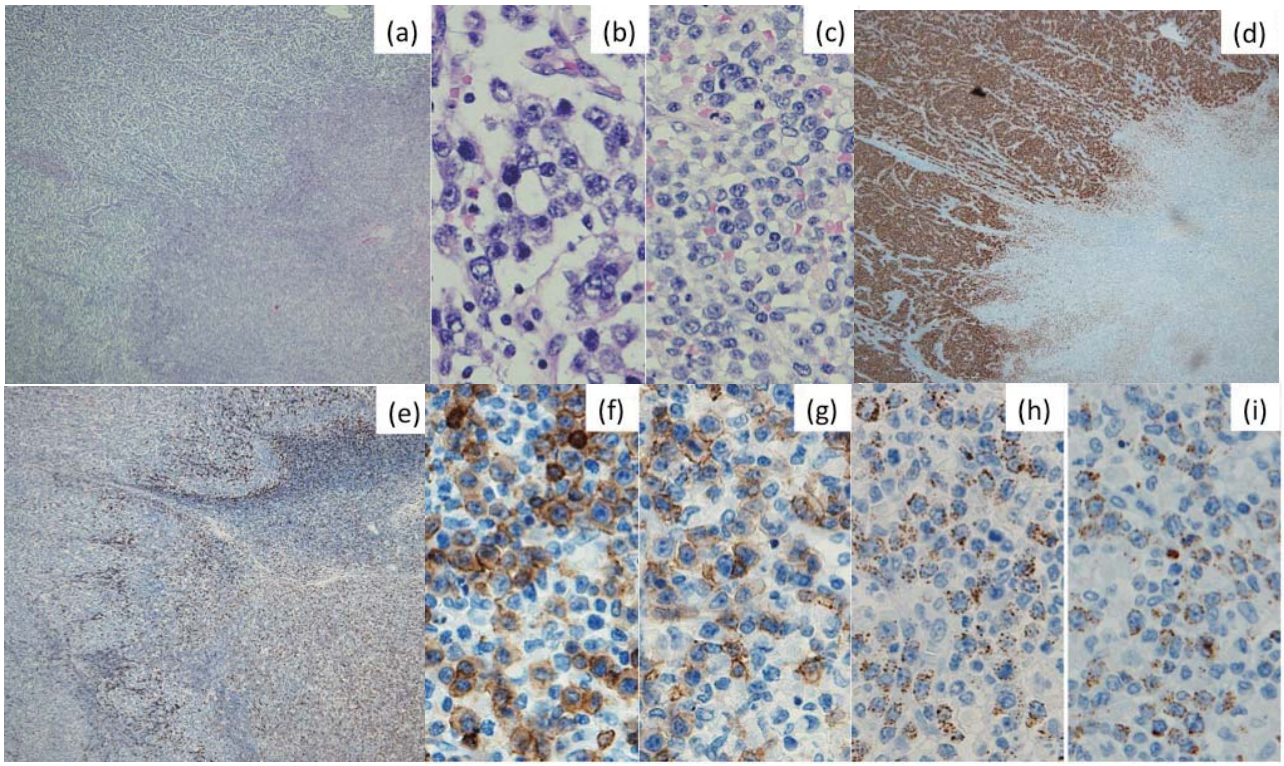

Fig. 2. Histopathological features. (***2a***) Low magnification view of the testis tumor reveals two distinct areas: peripheral T cell lymphoma, not otherwise specified (PTCL-NOS) (*lower right*) and seminoma (*upper left*). (***2b***) Under high magnification, the seminoma cells are arranged in sheets with normal lymphocytic infiltration; their shape is round or polygonal with a distinct membrane, clear cytoplasm, and nuclei containing prominent nucleoli. (***2c***) PTCL cells are medium to large in size with pleomorphic, hyperchromatic, and vesicular nuclei and prominent nucleoli. (*2a-2c*) H&E stain. By immunohistochemical analyses, seminoma cells are positive for (***2d***) c-kit, and PTCL cells are weakly positive for (***2e***: low power view; ***2f***: high power view) CD3 and (***2g***) CD8. Additionally, PTCL cells are positive for (***2h***) TIA-1 and (***2i***) granzyme B.

Molecular analyses

Polymerase chain reaction was used to analyze the immunoglobulin heavy chain gene and the T-cell receptor γ-chain gene rearrangement, and was performed according to standard procedures described previously.[6] Genotypic analyses demonstrated clonal rearrangement of the T-cell receptor γ-chain gene (Fig. 3).

DISCUSSION

The present tumor was a $CD30^{+}$ lymphoma, and was thus differentiated from anaplastic large cell lymphoma; however, this tumor was also positive for CD3 and CD5, which are mature T cell markers, leading to a final diagnosis of PTCL-NOS.

PTCLs usually present as advanced disease, and are a heterogeneous group of neoplasms characterized by widespread dissemination, aggressive behavior, and poor survival. Primary testicular lymphoma accounts for 1-2% of all non-Hodgkin's lymphomas, while the most common subtype of testicular lymphoma is diffuse high-grade B-cell lymphoma.[4] Rarely, anaplastic lymphoma, Burkitt's lymphoma, or Hodgkin's lymphoma may arise in the testis as a primary tumor.[5,7,8] T-cell lymphoma of the testis is rare, either as primary or secondary involvement. Testicular lymphomas have a tendency to manifest extranodally, for example in the skin, Waldeyer's ring, CNS, or bone marrow, as well as in the contralateral testis at the time of presentation or relapse.[9] A considerable relapse rate to extranodal sites, such as in the CNS or contralateral testicle, has been reported despite use of doxorubicin-based chemotherapy.[4] Whereas a seminoma of limited stage has a high cure rate, testicular T-cell lymphoma has an aggressive course and poor prognosis. Aggressive behaviors of primary testicular T-cell lymphoma have been reported by other authors,[5,8,10-14] and the best treatment options are orchiectomy and chemotherapy, along with radiation.[15]

No obvious pathophysiologic link exists between seminoma and PTCL, and we know of no common risk factors.

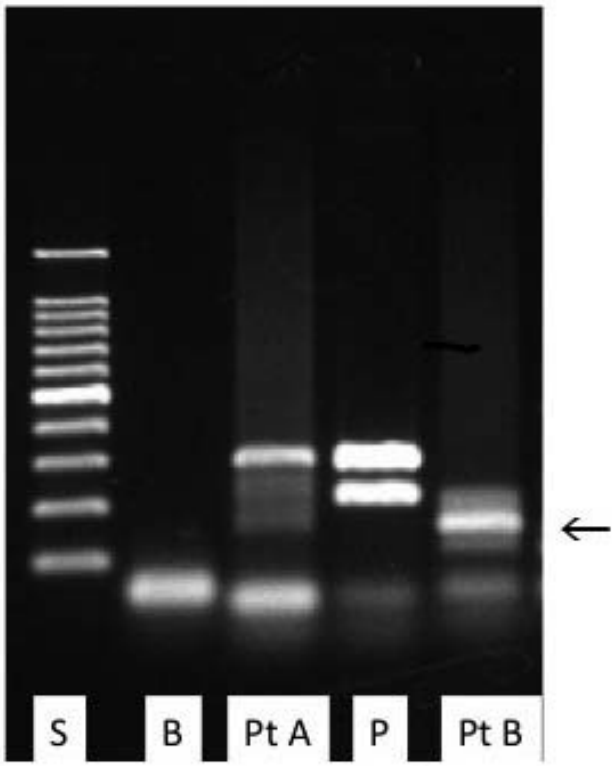

Fig. 3. Polymerase chain reaction analysis of *T-cell receptor-γ* gene rearrangements. Lane S: size markers. Lane B: blank. Polymerase chain reaction amplification without primer. Lane Pt A and Pt B: tissue samples of the present case using different primers, showing presence of a clonal *T-cell receptor-γ*-positive cell population. P: positive control (T-cell lymphoma)

Malignancies occur sometimes after treatment of germ cell tumors, but concurrent observation is infrequent. There have been some cases of synchronous occurrence of lymphoma and testicular germ cell tumors reported in the literature,[16-19] but these were not PTCL. The concurrent management of two different malignant tumors is difficult. Orchiectomy is performed for radial therapy of seminoma with stage I, and the best therapy for testis lymphoma stage IE is orchiectomy, chemotherapy, and radiation therapy in the contralateral testis.

Generally, PTCL-NOS is mostly positive for CD4, but $CD8^+$ PTCL like our case is occasionally observed.[3] Recent studies have identified a number of early and indolent lymphoproliferative disorders that lie at the interface between benign and malignant classification. In this category, indolent $CD8^+$ T-cell lymphoproliferative disorder of the skin, and indolent T-cell lymphoproliferative disorder of the GI tract are newly categorized. Both disorders contain $CD\ 8^+$ clonal cells (which have clonal T-cell receptor rearrangement) in the mucosa and have chronic clinical courses, but are non-progressive.[20] Thus, the present case may be differentiated from these entities due to the presence of the seminoma in the testis, not epithelium, granzyme B positivity, and a high Ki-67 positivity rate.

If observing only polymerase chain reaction (PCR) results, our case may be suspected of possible reactive proliferation of cytotoxic lymphocytes due to false positive PCR results. False-positive results may occur due to the sensitivity of PCR and nonuniform (skewed) amplification of target T-cell gene rearrangements. The latter problem may occur when the total T-cell number in a sample is limited, or with physiological skewing of the T-cell repertoire, as seen with aging, post transplantation, or T-cell reactions in autoimmune or (nonlymphoid) malignancies. However, histopathologically, the lymphoma cells of our case were clearly distinguished from reactive lymphocytosis. In the paraffin sections, the cytotoxic lymphocytes, which were invasive in the seminoma, had a small, round shape and were strongly positive for CD3 and CD8. Conversely, the lymphoma cells had a medium to large, pleomorphic shape and proliferated continuously, with high expression of CD3 and CD8. These results led to a diagnosis of PTCL-NOS.

PTCL-NOS cases positive for cytotoxic molecules, such as TIA-1 and granzyme B, as in the present case, reportedly have poorer prognoses than those without cytotoxic molecules (median survival 8 months vs. 40 months).[21] Our case first presented with a tumor of very small size, and treatment was successful despite diagnosis of cytotoxic molecule-positive PTCL.

To our knowledge, this is the first report of an advanced seminoma with concurrent $CD8^+$ and cytotoxic molecule-positive PTCL.

CONFLICT OF INTEREST: The authors declare no conflicts of interest.

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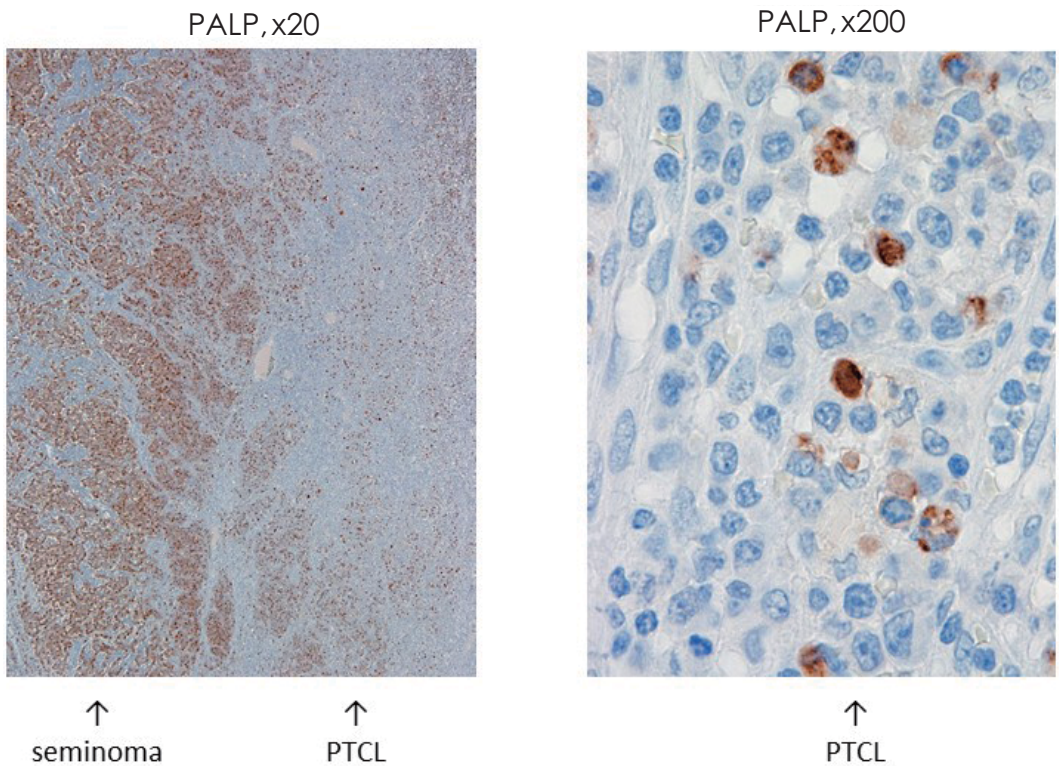

Supplementary file. PLAP findings. Seminoma cells were positive for PLAP and lymphoma cells were negative for PLAP.