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Pure Choriocarcinoma of Testis with Tumor-Infiltrating Lymphocytes and Granulomas

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Pure choriocarcinoma is very rare in the testes, and host immune responses including tumor infiltrating lymphocytes are unusual in choriocarcinoma. This study reports a case of pure testicular choriocarcinoma with extensive lymphocytic infiltrate and granulomatous inflammation. Scrotal ultrasonography revealed a heterogeneous, hyperechoic intratesticular mass. β-human chorionic gonadotropin levels were elevated in a radioimmunoassay. The hemorrhagic and necrotic solid mass was composed of two cell populations - mononuclear pleomorphic cells and intimately admixed multinucleated smudged cells. The tumor cells were positive for cytokeratin 7, epidermal growth factor receptors, human placental lactogen and p57. Many inflammatory cells were present within the tumor. The majority of infiltrating cells were CD8-positive cytotoxic cells, which also expressed granzyme-B and TIA-1. The tumor cells were positive for FasL, but negative for Fas. Therefore, this case seemed to escape the host defense response to the tumor due to the loss of Fas, although the cellular host immune response was still active.

Key Words: Testis, choriocarcinoma, tumor-infiltrating lymphocyte, granuloma

INTRODUCTION

Pure choriocarcinoma in the testes is very rare, representing less than 1% (0.19%) of testicular germ cell tumors; however, it is admixed with other germ cell tumor elements in 8% of testicular germ cell tumors.[1] Seminoma is typically associated with prominent lymphocytic infiltrate and an excellent prognosis.[2,3] However, such host immune responses are unusual and have not been well defined in choriocarcinoma. Here, we describe a case of pure testicular choriocarcinoma with extensive lymphocytic infiltrate and granulomatous inflammation.

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CASE REPORT

A 28-year-old man was admitted with complaints of right scrotal discomfort for a period of 3 weeks. A physical examination revealed a nontender, movable hard mass on the right testis. Scrotal ultrasonography revealed a heterogeneous, hyperechoic intratesticular mass, suggesting a malignant germ cell tumor. The β-human chorionic gonadotropin level was elevated (4.743, normal range: 0-0.01 IU/mL), and α-fetoprotein levels were normal (2.03, normal range: 0-15 ng/mL) in the radioimmunoassay. A right orchiectomy was done.

Upon gross examination, the testis was 5.5 × 4 cm in size and was nearly replaced by a hemorrhagic and necrotic solid mass (Fig. 1A). Histologically, the tumor showed extensive hemorrhage and necrosis. Viable tumor cells were generally present in the periphery of the hemorrhagic and necrotic areas. The tumor was composed of two cell populations - mononuclear pleomorphic cells and intimately admixed multinucleated smudged cells (Fig. 1B). The tumor cells were diffusely positive for pan-cytokeratin, cytokeratin 7, and epidermal growth factor receptors and focally positive for human placental lactogen, p57 (Fig. 1C), placental alkaline phosphatase, epithelial membrane antigens, carcinoembryonic antigens and negative for vimentin, α-fetoprotein, c-kit and CD30. Peculiarly, many inflammatory cells were present in

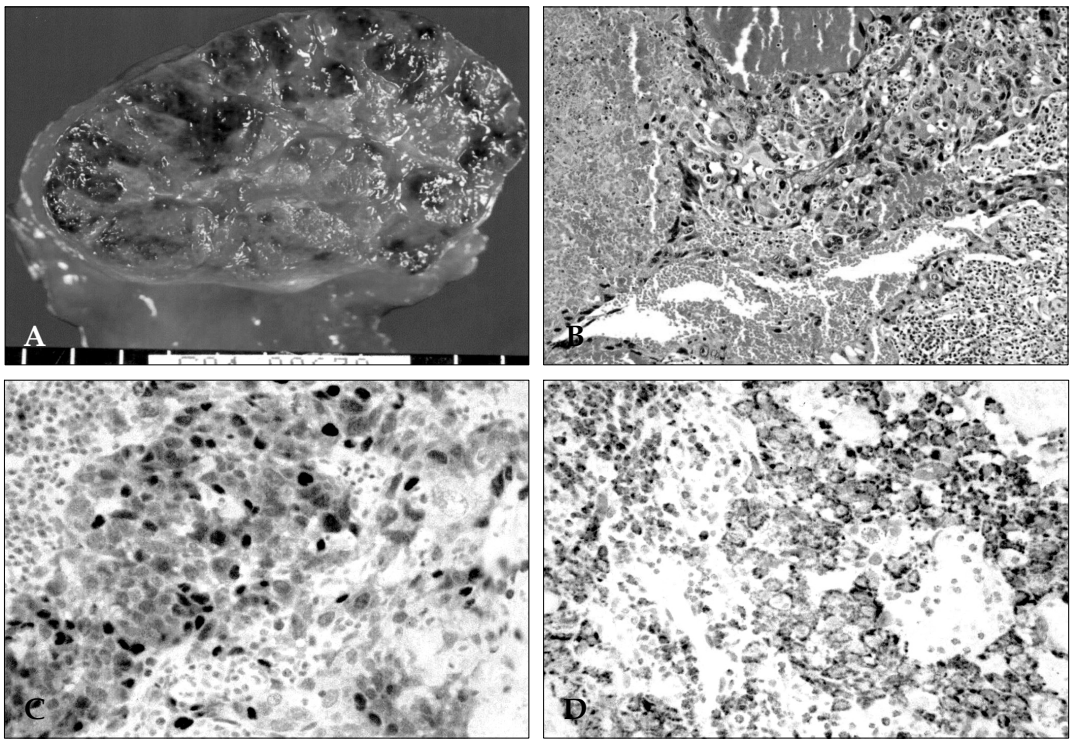

Fig. 1. Upon gross examination, the testis was 5.5 × 4 cm in size and was nearly replaced by a hemorrhagic and necrotic solid mass (A). Histologically, the tumor was composed of two cell populations-mononuclear pleomorphic cells and intimately admixed multinucleated smudged cells (B). The tumor cells were positive for p57 (C) and FasL (D).

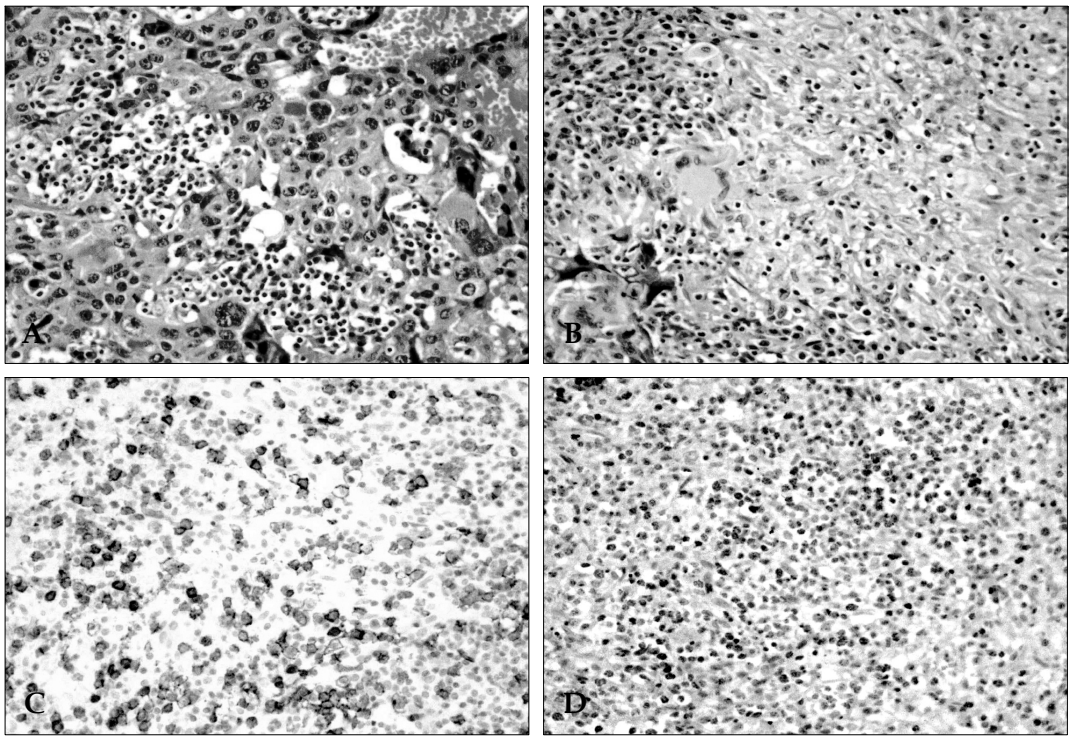

Fig. 2. Several inflammatory cells were present within the tumor nests (A). Loose aggregates of epithelioid histiocytes forming granulomas were also noted (B). The infiltrating cells were mostly CD8-positive cytotoxic T-cells (C), which also expressed TIA-1 (D).

the connective tissue between tumor nodules and within tumor nests (Fig. 2A). These cells were mostly CD3-positive T-lymphocytes and CD68-positive histiocytes. Many plasma cells were also admixed. Most of the T-cells were CD8-positive cytotoxic cells (Fig. 2C), which also expressed granzyme-B and TIA-1 (Fig. 2D). Occasionally, loose aggregates of epithelioid histiocytes forming granulomas were noted (Fig. 2B). The immunostainings of Fas and FasL showed that the tumor cells were diffusely positive for FasL (Fig. 1D), but negative for Fas. In contrast, infiltrating lymphocytes were strongly positive for both Fas and FasL.

Postoperative abdominopelvic computed tomography showed multiple lymph node enlargements in both the inguinal and common iliac areas and in the left paraaortic area. The patient received three cycles of chemotherapy with BEP (Bleomycin, Etoposide, Cisplatin) and is well at present, 6 months after surgery. Lymph nodes enlargements were not changed.

DISCUSSION

There is a wide range of patterns of cellular immune response to different histological tumor types. The immunocompetent cells that infiltrate tumors are mostly T-lymphocytes and macrophages, with a few B-lymphocytes and very few NK-cells.[4] The number and type of tumor-infiltrating lymphocytes (TIL) have been reported to be significant determinants of outcome in a variety of malignancies, including non-Hodgkin's lymphoma, esophageal carcinoma, malignant melanoma, colorectal carcinoma, and breast cancer.[2] An active host immune response is considered to inhibit tumor growth and metastasis.[2]

In testicular germ cell tumors, seminoma is typically associated with prominent lymphocytic infiltrate and an excellent prognosis.[2,3] Intense infiltrates of immunocompetent cells are present within the connective tissue surrounding the tumor lobules, with frequent individual lymphocytes within the tumor itself.[2] TIL in seminoma are predominantly T-cells with primarily a CD8+ phenotype.[5] B-cells tend to accumulate and occasionally form lymphoid follicles with a phenotypic pattern of B-cell antigens that is comparable to secondary lymphoid follicles.[5] This suggests both the functional maturation of B-cells and a cytotoxic T response. Most cytotoxic T-lymphocytes (CTL) infiltrating seminoma tumor nests express immunohistochemical markers of cytotoxic potential and activity, i.e. TIA-1 and granzyme B.[3] A significant proportion of apoptotic seminomatous tumor cells are in direct contact with CD3+ and granzyme B+ cells, and a number of activated CTLs show a strong linear correlation with the apoptotic index in seminoma,[3] suggesting that apoptotic tumor cell death may be triggered by cytotoxic granule effectors.[3] In a study of testicular seminomas, a lower TIL count was associated with a significantly increased risk of relapse according to univariate analysis.[2] These results suggest that the activity of the antitumor host immune response is a determinant of outcome, which may result from apoptotic tumor cell death by CTL[2,3] and lead to speculation about a potential role for immunotherapeutic strategies in this tumor type.[2] Similar lymphoid infiltrate is only rarely observed in non-seminomatous germ cell tumors, including choriocarcinoma.[3]

Choriocarcinoma is a malignant tumor of the trophoblast. In normal placentation, trophoblasts show "controlled invasion" at the placental site as part of the normal process of implantation,[6] without being rejected and without destroying the tissue.[7] It is noteworthy that the trophoblast normally behaves in a manner that is interpreted as indicative of malignancy. Therefore, choriocarcinoma is unique in that it represents a malignant transformation of a tissue that inherently has invasive and metastatic properties.[6]

Immunocompetent cells, which are known to be involved in the rejection pathways of malignant cells, can also be identified in early pregnancy decidua. In choriocarcinoma, a significantly increased number of lymphocytes that are positive for CD8, CD3 and mast cell tryptase positive granulocytes have been observed in comparison with the samples from normal pregnancy, but lymphocytes positive for natural killer cell marker CD56 are significantly decreased in choriocarcinoma, which suggests the necessity of a balance between T and NK cells in controlling trophoblast invasion.[7] The expression of MHC class I mole-

cules is required by professional antigen-presenting cells or neoplastic cells for specific CTL activation,[3] and human trophoblast and choriocarcinoma cell lines express a truncated HLA class I molecule[8] which can initiate a cell-mediated immune response. Cell-mediated immunity to trophoblast antigens was also noted in women with recurrent spontaneous abortion *in vitro*.[9]

In contrast, choriocarcinoma cells can induce immunosuppression by down-regulation of interleukin-2, the interleukin-2 receptor alpha chain, and its Jak/Stat signaling pathway, which might play a key role in the expression of choriocarcinoma, as well as in the survival of the fetal allograft.[10] Choriocarcinoma cell culture supernatant suppresses lymphocyte activity, which is demonstrated by decreased surface activation of classical activation markers such as CD25, CD69, CD71, CD134, and CD3/HLA-DR.[11]

In the present case, many TIA-positive, granzyme B-positive cytotoxic T-cells infiltrated the tumor nodules of choriocarcinoma, which suggests that the immunosuppressive activity of choriocarcinoma cells is limited and that the cell-mediated immune reaction to trophoblast antigens is still active in this tumor. Many histiocytes which occasionally formed granulomas were also found within the tumor. During malignancies, the immune escape of tumor cells and successful tumor outgrowth may be attributed to the inability of the immune system to react to the tumor.[6]

In addition to cytotoxic granule release, CTL-triggered apoptosis may be mediated by the Fas/Fas ligand (FasL) pathway.[3] There is now adequate evidence indicating that the susceptibility of tumor cells to Fas-mediated apoptosis is largely reduced through the aberrant loss of Fas.[6] FasL expression under physiological conditions is frequently limited, and FasL is expressed more frequently in malignant cells when compared with their non-malignant counterparts.[6] Aberrant FasL expression by tumors has been implicated in the abrogation of the host antitumor response by killing of Fas-positive effector lymphocytes,[6] and this ligand could have a significant role in local tissue destruction, metastatic spread, and immune escape of tumor cells.[6]

Although the expression of Fas or FasL in testicular seminoma is controversial,[3] human choriocarcinoma cells are known to co-express Fas and FasL.[6] Fas receptors are down-regulated when compared to a Fas-sensitive cell line. Therefore, it is possible that choriocarcinoma evades immune attack by down-regulation of Fas receptors and by killing lymphocytes through the expression of FasL.[6] The Fas/FasL system may represent a mechanism by which malignant trophoblasts become resistant to apoptosis, escape immune surveillance, and metastasize,[6,12] resulting in the clinical sequelae characteristic of choriocarcinoma.[6] In the present case, the tumor cells were diffusely positive for FasL, but negative for Fas, in contrast to infiltrating lymphocytes which were strongly positive for both Fas and FasL. Therefore, we speculate that the present case would be biologically aggressive in spite of the active cell-mediated immune reaction. Because restoring the apoptotic potential of cancer cells in modulating the expression and activity of certain key components of the cell death machinery could be an attractive strategy for therapeutic intervention in the management of choriocarcinoma,[6] such therapy might be useful for this particular case.

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