Unusual Presentation of Ewing Sarcoma in the Adrenal Gland: A Secondary Malignancy from a Survivor of Burkitt Lymphoma

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The occurrence of Ewing sarcoma as a secondary malignancy is an extremely rare event in long-term cancer survivors. In addition, the occurrence of Ewing sarcoma in the adrenal gland is highly unusual. In this case report, we treated a 20-year-old male patient with cyclophosphamide, doxorubicin, vincristine, dexamethasone, and methotrexate and cytarabine chemotherapy following a diagnosis of Stage IV Burkitt lymphoma. Following complete remission, he had been maintained for 2 years without evidence of disease. However, a regular follow-up computed tomography scan found a left adrenal gland mass and a biopsy revealed positive membrane-localized mic-2 expression (CD99) and the presence of the translocation of the EWSR1 gene. To our knowledge, this is the first case report of Ewing sarcoma occurring in the adrenal gland of a patient who was treated with cyclophosphamide, doxorubicin, vincristine, dexamethasone/methotrexate and cytarabine chemotherapy for Burkitt lymphoma.

Key words: Burkitt lymphoma – Ewing sarcoma – secondary malignancy

INTRODUCTION

Burkitt lymphoma is a subtype of B-cell non-Hodgkin lymphoma (NHL) usually displaying a highly aggressive clinical course owing to the high proliferation rate of Burkitt lymphoma cells as indicated by extremely high Ki-67 expression (1,2). Thus, the remaining viable lymphoma cells can grow rapidly between chemotherapy cycles eventually resulting in drug resistance. These characteristics of Burkitt lymphoma lead to poor outcomes when Burkitt lymphoma patients are treated with CHOP or CHOP-like chemotherapy regimens (3,4). However, the introduction of short duration, high-intensity chemotherapy, a technique used to treat acute lymphoblastic leukemia (ALL), has markedly improved outcomes (1,5–7). As a result, Burkitt lymphoma is now considered as one of the NHLs that has a high probability of cure with an overall cure rate of 75–90% (8,9). However, considering its common incidence in children and adolescents, closer follow-up for long-term survivors of Burkitt lymphoma is necessary in order to prevent and manage chemotherapy-related late complications including secondary malignancy (10).

The occurrence of secondary malignancy has been an emerging issue in medical oncology as the number of long-term cancer survivors increases due to the advancement of treatment modalities (11,12). Furthermore, the risk of secondary malignancy is increased in patients receiving high-dose chemotherapy followed by autologous stem cell transplantation compared with patients receiving conventional chemotherapy (13). Therefore, surveillance of secondary malignancy may be important in patients with Burkitt
lymphoma considering its high curability rate and the intensity of treatment. Recently, we diagnosed a case of secondary Ewing sarcoma (EWS) that was incidentally found during regular follow-up in a patient whose Burkitt lymphoma had been cured with intensive chemotherapy. EWS is a rare disease in which cancer cells are mainly found in the bone or soft tissue and occurs most often as a primary rather than secondary tumor. Thus, only a few reports have been published regarding the occurrence of EWS as a secondary malignancy (14–16). Owing to the histopathology of EWS with small, round cells, it is often difficult to discriminate it from lymphoma cells. Since the possibility of EWS as a secondary malignancy may have clinical value in the follow-up of long-term survivors of Burkitt lymphoma, we report this case with a literature review.

CASE REPORT

A 20-year-old male patient was diagnosed with Burkitt lymphoma after he underwent an urgent right hemicolectomy due to intussusception. The pathologic finding of the specimen showed a 4.5 × 1.5 cm-sized mass in the terminal ileum with involvement of the mesoappendix (Fig. 1), and microscopic findings were compatible with Burkitt lymphoma including positivity for c-Myc translocation. The staging work-up revealed liver invasion as well as mesenteric and retroperitoneal lymph node enlargements without evidence of bone marrow invasion. The patient received intensive chemotherapy with HyperCVAD (cyclophosphamide, vincristine, doxorubicin and dexamethasone) alternating with MA (methotrexate and cytarabine) for up to eight cycles. Following the completion of the planned cycles of chemotherapy, he had been followed without evidence of disease relapse for 2 years. However, a follow-up computed tomography (CT) scan revealed a 3.2 cm sized mass in the left adrenal gland (Fig. 2). The patient did not have any constitutional symptoms and there were no manifestations associated with the adrenal mass. In order to confirm a relapse of Burkitt lymphoma, a CT-guided biopsy was performed but there was no evidence of lymphoma cells apart from some cells exhibiting atypical morphology. Considering the absence of systemic symptoms and pathology findings, this incidental adrenal mass was followed. Three months later, a follow-up CT scan showed an increase in the mass up to 11 cm (Fig. 2B). Although the patient still had no symptoms such as fever, weight loss or abdominal pain, his blood tests showed an elevation of serum lactate dehydrogenase, 1004 IU/l (normal range: 240–480 IU/l). The positron emission tomography–CT scan revealed a hypermetabolic mass in the left adrenal gland, with the suspicion of lymphomatous involvement (Fig. 2C). The re-biopsy of the mass showed tumor cells positive for CD99 (Fig. 3) and fluorescence in situ hybridization analysis demonstrated the presence of the translocation of the EWSR1 gene. The patient was diagnosed with EWS and the staging work-up showed no evidence of metastatic disease. Thus, he underwent curative resection of the left adrenal mass and received systemic chemotherapy consisting of vincristine, doxorubicin and cyclophosphamide alternating with ifosfamide and etoposide. The patient responded to treatment. Thus, he has been without the evidence of disease for 8 months since April 2012.

DISCUSSION

The occurrence of EWS in cancer survivors has been reported sporadically and the latent period between the diagnosis of primary cancer and secondary malignancy is variable from 1 to 16 years. The majority of primary cancers are hematologic malignancies such as ALL (Table 1). As a result, most patients undergo intensive multi-agent combination chemotherapy comprising antitumor antibiotics, alkylating agents, vinca alkaloids and anti-metabolites. In this case, the patient received intensive chemotherapy consisting of HyperCVAD alternating with MA, a regimen utilized to treat patients with ALL. Thus, the effect of intensive chemotherapy may contribute to the development of EWS. Considering the relatively short latent period of this patient (~2 years), the previous exposure to doxorubicin might be associated with secondary EWS because topoisomerase II inhibitor-associated secondary malignancy is known to have relatively shorter latent period than alkylating agents. The diagnosis of EWS in our case was based on the positivity of membrane-localized mic-2 expression (CD99) and the presence of the translocation of the EWSR1 gene. Primary EWS is characterized by a distinct non-random chromosomal translocation which involves the EWS gene on chromosome 22. These translocations result in the fusion of distinct genes on different chromosomes with the most frequent translocation being t(11;22)(q24;q12), which leads to the formation of the EWS–FLI1 fusion gene. This translocation is present in more than 85% of EWS cases (17). The second most common translocation is the t(21;22)(q11;q12), which leads to the formation of the EWS–ERG fusion gene and has been identified in ~5–10% of cases (18). Consistent with these findings, the first case of secondary EWS following treatment for ALL showed the EWS–FLI1 translocation, and the other case series reporting six cases of secondary EWS also showed the EWS gene rearrangement (18,19). However, the occurrence of EWS in the adrenal gland as in our case is extremely unusual. Over 70% of EWSs involve bones, especially the diaphysis of long bones such as the femur with the remaining cases involving soft tissues. Previous case reports have described adrenal EWSs and the uncommon adrenal involvement may be explained by tumor cells that originate from neural crest cells (20–22).

Since the treatment outcome of adult Burkitt lymphoma has improved following the introduction of intensive chemotherapy, the development of relapse of the disease or refractoriness to chemotherapy has been lowered. Thus, our previous retrospective analysis with 38 adult Burkitt
lymphoma patients who received the LMB protocol showed 73.7% with a complete response and 75% with a 5-year progression-free survival (7). However, the risk of relapse still exists after the completion of chemotherapy and the majority of relapses are reported to occur within 6 months to 1 year at the end of treatment (1). In this case, the patient maintained his complete response status for 2 years following the completion of his planned chemotherapy. In addition, his adrenal mass was incidentally found during a regular follow-up. Although there were no constitutional symptoms such as B symptoms, our first impression was relapse of Burkitt lymphoma rather than another adrenal gland tumor including pheochromocytoma because the radiologic imaging findings strongly suggested the relapse of lymphoma. Indeed, the invasion of the adrenal gland by a lymphoma appears in up to 25% of NHLs and shows a poor prognosis (23,24). However, the first biopsy failed to show evidence of lymphoma with only a few cells exhibiting atypical morphology. If we had initiated chemotherapy under the impression of relapsed Burkitt lymphoma following the first biopsy result, the patient might not have received proper treatment. Thus, our case underscores the importance of pathological diagnosis by repeating biopsies prior to treatment in lymphoma patients who have the likelihood of disease relapse.

Secondary malignancy in Burkitt lymphoma patients is an extremely rare event and so there are few reports of such cases. Indeed, the estimated cumulative probability of developing secondary malignancy among those who had survived from NHL was higher in patients with lymphoblastic lymphoma or large-cell lymphoma than in patients with small, non-cleaved cell lymphoma including Burkitt lymphoma (25). However, considering that secondary EWS occurred predominantly in hematologic malignancy patients who received intensive chemotherapy comprising topoisomerase II inhibitor or alkylating agents, the occurrence of EWS might be possible in patients with Burkitt lymphoma as our case. Owing to its rarity, the treatment outcome has never been prospectively compared between primary and secondary EWSs. However, a recent retrospective analysis including 58 cases of secondary EWS showed inferior survival outcomes compared with patients with primary EWSs. Furthermore, secondary EWSs were more likely to have axial tumors and smaller tumors than primary EWSs in the retrospective analysis (26). However, there are no data...
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<th>Publication year (ref.)</th>
<th>Primary cancer</th>
<th>Chemotherapy for primary cancer</th>
<th>Additional treatment for primary cancer</th>
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DNR, daunorubicin; VP-16, etoposide; ADR, doxorubicin; ACT, actinomycin-D; MTZ, mitoxantrone; BLE, bleomycin; VCR, vincristine; VBL, vinblastine; DTIC, dacarbazine; CPA, cyclophosphamide; MEL, melphalan; IFO, ifosfamide; MTX, methotrexate; Ara-C, cytarabine; 6-MP, 6-mercaptopurine; 6-TG, thioguanine; HU, hydroxyurea; PD, prednisone; i-aspl, i-asparagine; RT, radiotherapy; TBI, total body irradiation; SCT, stem cell transplantation.
regarding histological or genetic difference between primary and secondary EWSs. In fact, we found the same gene rearrangement diagnostic of primary EWS in our case.

In conclusion, we experienced a rare case of secondary EWS occurring in the adrenal gland in a patient who had been treated with HyperCVAD/MA chemotherapy for Burkitt lymphoma. To our knowledge, this is the first case reporting EWS as a secondary malignancy in a patient with Burkitt lymphoma.

**Conflict of interest statement**

None declared.

**References**