CASE REPORT

Primitive Neuroectodermal Tumor as the Second Malignant Neoplasm in a Long-Term Survivor Child of Acute Lymphoblastic Leukemia: A Case Report

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Abstract Acute lymphoblastic leukemia (ALL) is a common pediatric cancer. The second malignant neoplasms (SMNs) in long-term survivors of pediatric ALL are relatively rare. Herein we report a 10-year-old girl who was diagnosed as primitive neuroectodermal tumor (PNET) 5 years after the initial diagnosis of ALL with radiotherapy-free treatment. PNET is an exceedingly rare neoplasm in SMNs of survivors of childhood ALL. It is predisposed to be misdiagnosed and the pathogenesis is unclear. The outcome is poor. Long-term follow-up is necessary for the survival children of ALL.

ACUTE lymphoblastic leukemia (ALL) is the most common malignancy affecting children, accounting for approximately 20% of all pediatric cancers.^[1] Owing to the substantial improvement of multi-agent systemic chemotherapy without radiation, the cure rate is now about 90%.^[2] With the increase in survival rate of childhood

cancer, a relatively rare but serious and potentially fatal complication may serve as the risk of developing the second malignant neoplasms (SMNs). SMNs are more unusual in pediatric ALL,^[3] especially after elimination of prophylactic cranial irradiation.^[4] Primitive neuroectodermal tumor (PNET), an aggressive tumor of central nervous system (CNS), is a kind of exceedingly rare SMNs in survivors of childhood ALL.^[5-8]

CASE DESCRIPTION

In July 2013, a 5-year-old girl who suffered from bone pain and skin ecchymosis with a white blood

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cell count of $15 \times 10^9/L$ came to see a doctor in our hospital. Scattered petechia was the remarkable positive finding of physical examination. There was no splenomegaly, hepatomegaly and sternal tenderness. Bone marrow aspiration showed a 96% replacement of B-precursor lymphoblasts which immune-phenotype expressed CD34, CD19, CD10, CD13, CD123, CD9, CD58, CD38, cCD79a, TdT, HLA-DR and cIgM partly. Common fusion genes, such as TEL/AML1, BCR/ABL, P190, P210, E2A/PBX1, MLL/AF4, SIL-TAL1, were found to be negative. Cytogenetic analyses revealed normal karyotypes. Her medical history was otherwise uneventful. Family history was negative for malignant diseases. She was diagnosed as standard-risk ALL and treated with the protocol of Chinese Childhood Leukemia Group-2008 (CCLG-2008).^[9] The patient received prophylactic treatment for CNS through intrathecal multi-drug chemotherapy and high-dose systemic methotrexate. No craniocerebral irradiation was administered. The total treatment duration was three years. The total doses of anthracyclines and alkylators were as follows: daunorubicin 150 mg/m^2 , cyclophosphamide 2000 mg/m^2 . In maintenance therapy, dose of methotrexate was at least 20 mg/m^2 per week and that of 6-mercaptopurine was at least 50 mg/m^2 per day. The patient remained complete remission continuously throughout therapy until October 2018, when she came back to the hospital with complaint of pain in her right chest wall and osseous pain of her knee and ankle.

Laboratory examination showed the peripheral blood cells counts were normal. Chest CT showed a large mass in her right hemithorax. Contrast enhanced CT (**Figure 1A, 1B**) confirmed remarkable hypervascularity of the mass. Transthoracic puncture biopsy and pathology revealed diffuse small blue round cells,

which was consistent with lymphoblastic leukemia. Bone marrow biopsy was carried out, and the similar microscopic pathology findings were found (**Figure 2A, 2B**). Next-generation sequencing demonstrated point mutations (SH2B3, EP300, FAT1, WHSC1). Tumor cells were immuno-negative for hematopoietic system common antigen (PAX5-, CD5-, TdT-, CD34-, MPO-, CD10-) and positive for CD99 and CD117 with a clear membrane pattern (**Figure 2C, 2D**), which indicated possibility of neurogenic tumor. Molecular analysis of tumor tissue by fluorescence *in situ* hybridization showed EWSR1 gene segregation. The mass in her chest was diagnosed as primitive neuroectodermal tumor (PNET). Because the patient was too weak to bear any intensive treatment, she received palliative treatment, and passed away a few months later.

DISCUSSION

ALL accounts for about 20% of all malignancies in children.^[1] Owing to the advances in chemotherapy, the outcomes of ALL after treatment has improved substantially, with the cure rate of approximately 90% now.^[2] Although the second malignant tumors in long survivors of pediatric ALL are rare, it is most commonly identified as acute myeloid leukemia, myelodysplastic syndrome and non-meningioma brain tumors.^[3] From January 2008 to April 2015 in the CCLG-ALL 2008 cohort, only 4 cases of SMNs among ALL 940 childhood happened in our institute.^[10]

PNETs are a group of extremely rare aggressive tumor of CNS that originate from neuroectoderm and comprise primitive undifferentiated small round cells characteristically. The Ewing family tumors, including Ewing's sarcoma and PNET, is the second most common malignant bone tumor in children and adoles-

Figure 1. Contrast-enhanced chest CT images of the patient showing a large mass in the right hemithorax. The mass was $4\text{cm} \times 6\text{cm}$ in size, with remarkable hypervascularity in peripheral part (arrow) and necrosis in central part. A. Transverse section CT image; B. coronal section CT image.

Figure 2. Microscopic histopathology findings of the thoracic tumor.

A. Pathology of the transthoracic needle core biopsy showing diffuse small blue round cells in tumor tissue (HE staining, 40×); B. pathology of bone marrow biopsy showing diffuse small blue round cells (HE staining, 40×); C. transthoracic needle core biopsy showing positive immunohistochemical staining for CD99 (10×); D. transthoracic needle core biopsy showing positive immunohistochemical staining for CD117 (10×). Diffuse positive cells are tan.

cents.^[11] PNET is an exceedingly rare SMN in survivors of childhood ALL (**Table 1**).^[5-8] Chemotherapy, radiation therapy and surgical resection are main treatment for PNETs, but the outcomes are poor.^[12]

The risk of SMNs as the first post-treatment event of childhood ALL is lower and depends on whether radiation is carried out in the therapy. The overall cumulative risk of an SMN 15 years after diagnosis of ALL is three times higher when cranial irradiation is administered (3.5% vs. 1.2%).^[4] PNET may occur many years after cerebral radiation therapy and methotrexate treatment for leukemia. Children with ALL who were heterozygous for thiopurine methyltransferase or thiopurine S-methyltransferase low-activity polymorphisms had an excessive risk of SMNs if exposed to cranial irradiation.^[13] In the current case we report, CNS preventive therapy was composed of intrathecal multi-drug chemotherapy and high-dose systemic methotrexate. No craniocerebral irradiation was administered.

Apart from cerebral irradiation, several chemotherapy drugs also play an important role in devel-

oping SMNs. The duration and intensity of methotrexate/6-mercaptopurine maintenance therapy of childhood ALL impact on the risk of SMNs.^[13] Irradiation, alkylating agents, and topoisomerase II inhibitors, such as anthracyclines and epipodophyllotoxins, can induce DNA damage.^[14] In the current case, the doses of anthracyclines, alkylators, methotrexate and 6-mercaptopurine do not appear to exceed the standard doses.

At present, multi-agent systemic chemotherapy and radiotherapy-free for most childhood ALL has replaced conventional cerebral irradiation combined with chemotherapy in worldwide. For many pediatric malignancies, excess treatment should be avoided in children patients. Although the cure rates for some SMNs were as favorable as those obtained for their primary cancer counterparts, future strategies should continue to focus on prevention of SMNs, especially radiation-induced tumors.^[15] The survivors need to be diligent in the follow-up of their whole life.

P53 mutation in chromosome 17 is a common mutation in PNET as a SMN.^[5,6] In this patient, P53

Table 1. Reported cases of childhood ALL with PNET as the second malignant neoplasm in literature

Studies*	Age (years)	Sex	Family history	Radiation therapy	PNET diagnosis# (years)	Gene mutation	Outcome
Antillon <i>et al.</i> 1997 ^[5]	7	Female	Breast cancer in a maternal great-aunt	No	10	P53 (exon 5-9)	Relapse
Suarez <i>et al.</i> 2004 ^[6]	3	Male	Negative	Not mentioned	5	P53 (exon 7)	Off therapy and disease-free for 2 years
Yoshida <i>et al.</i> 2005 ^[7]	7	Male	Mother died of breast cancer; maternal grandfather died of gastric cancer; kindred marriages	Cranial radiotherapy, 22Gy	8	Not mentioned	No evidence of recurrent tumor for 4 months
Sobowale <i>et al.</i> 2011 ^[8]	0.7	Female	Not mentioned	Cranial radiotherapy, 24 Gy	16	Not mentioned	Death

*only studies reporting childhood ALL are included. #refers to years after diagnosis of ALL. ALL, acute lymphoblastic leukemia; PNET, primitive neuroectodermal tumor.

mutation is negative and rates of point mutation were about 50% respectively, embryonic mutation was considered. The pathogenesis of mutation related to protein synthesis remains unclear. Single-cell sequencing technology should be applied to predict abnormal genes of first primary cancers to improve the insight into cancer cell populations responsible for SMNs, which will lead to better outcome of patient. This important issue deserves further studies in future.

In conclusion, we herein report a case of PNET after diagnosis of ALL and radiotherapy-free treatment, which is often predisposed to be misdiagnosed. Because the patient was too sick to bear the subsequent chemotherapy, she received palliative treatment, and passed away a few months later. Considering SMNs in long-term survival children of ALL, long-term close follow-up is necessary.

Conflict of interests

None.

Consent

Written informed consent was obtained from the patient's guardian.

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