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Therapy-related Acute Promyelocytic Leukaemia: A Paediatric Case Report and Literature Review

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Abstract ***Objective:*** To explore the clinical characteristics of therapy-related acute promyelocytic leukaemia (t-APL) after Langerhans cell histiocytosis (LCH) in a paediatric patient. ***Method:*** The clinical manifestations and laboratory findings of a rare paediatric case were analysed and relevant literatures were reviewed. ***Result:*** A paediatric patient with LCH who had completed the whole chemotherapy was admitted for proptosis and diagnosed as having relapsed LCH. However, the patient was finally diagnosed with t-APL after bone marrow immunophenotyping, fusion gene and a second bone marrow aspiration. Then, the patient was treated by the Chinese APL protocol. The patient responded well to the treatment and achieved complete remission after having completed induction chemotherapy. ***Conclusion:*** Paediatric doctors should take t-APL into consideration in their differential diagnosis when a LCH patients completed a whole session of chemotherapy. t-APL can be differentiated from relapsed LCH morphologically, immunologically, cytogenetically and molecular biologically.

Key words Acute promyelocytic leukaemia; Childhood; Therapy-related

Introduction

With more oncology patients successfully completing their chemotherapy and/or radiotherapy and surviving the primary malignancies, the incidence of secondary leukaemias has been on rise.[1-6] Over the past decades, cases of therapy-related acute promyelocytic leukaemia (t-APL) have been increasingly reported, accounting for 12% of all cases of APL. t-APL tends to develop following the treatment with topoisomerase II inhibitors.[1] So far, over 300 cases of t-APL have been reported, with 7% of them being paediatric patients.[1] t-APL remains rare in children. Presented in this report is a 3-year-old boy who developed APL after receiving treatment for LCH.

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Case Report

A 3-year-old boy was found to limp when walking and X-ray examination showed that his femoral neck, iliac and occipital bone had bone damage. Bone marrow aspiration (BMA) revealed a large number of granulocytes with accompanying toxic granulation. The diagnosis of LCH was established on the basis of pathological examination and immunohistochemical tests revealing such markers as CD1a, S-100, Lys and CD68. And the complete blood count (CBC) showed that white blood cell (WBC) count was 5.67×10^9/L, red blood cell (RBC) count 4.49×10^{12}/L, platelet (PLT) count 348×10^9/L, haemoglobin (Hb) 109 g/L. The total protein was 64.5 g/L, albumin 41.7 g/L

and total bilirubin 8.3 μmol/L. The erythrocyte sedimentation rate was 16 mm/h. Hypersensitive c-reactive protein was 2.05 mg/L. At that time, the patient had normal temperature, and physical checkup revealed no hepatosplenomegaly and lymphadenopathy. The patient had neither exanthema nor diabetes insipidus. Radiography did not reveal pulmonary infiltration of Langerhans cells. The patient was put on a chemotherapeutic protocol of DAL-HX 83/90[7] for 9 months, with the dosage of vincristine (VCR) being 19 mg/m^2. One single dose of etoposide (VP-16, 0.1 mg) was administrated. After the treatment, X-ray examination showed that the bone damage virtually disappeared. The patient was in complete remission (CR) after completing the induction chemotherapy.

In December 2012, 8 months after completion of the treatment, the patient complained of proptosis. Cranial chemotherapy showed destruction of orbital wall, parietal and sphenoid bones. And spine X-radiographs exhibited that the fourth lumbar vertebrae, the seventh and ninth ribs were damaged. BMA reported that "abnormal cells", suspected to be histiocytes, were over 15%. The patient was diagnosed with relapsed LCH and was given VCR (1.15 mg), VP-16 (225 mg), Vindesine (2.2 mg). Three days after discharging, the patient was hospitalised again for serious coughs. Physical examination revealed proptosis of the right eye as before, and did not find hepatosplenomegaly or lymphadenopathy. CBC showed that WBC count was 2.91×10^9/L, RBC count 5.81×10^{12}/L, PLT count 286×10^9/L, Hb 122 g/L. BMA showed hypercellularity, with infiltrated abnormal myeloid cells, characterised by presence of fine or coarse purple particles in cytoplasm and no presence of Auer rod, accounting for 35%. Phenotyping by flow cytometry showed the cells were positive for CD4, CD9, CD13, CD33, CD38, CD64, CD117, CD123 and MPO. Polymerase chain reaction (PCR) found the fusion gene of PML/RARα (bcr1) and cytogenetic analysis showed 46,XY karyotype. The patient was definitely diagnosed as having t-APL and was given chemotherapy (APL protocol involving all-trans-retinotic acid (ATRA) and arsenic trioxide (ATO), 2011 China).[8] At the time this paper was written, the proptosis was not conspicuous and the bone lesions shrank. He attained CR when the induction chemotherapy terminated and is still on chemotherapy.

Discussion

Cases of t-APL have been increasingly reported over the past decades, making up 12% of all APL cases (Table 1). Previous studies showed that development of t-APL was closely associated with chemotherapy, radiotherapy, and treatment involving immunosuppressive agents.[1] Moreover, the topoisomerase II (topo II) inhibitors, such as VP-16 and teniposide (VM-26), were believed to be major contributing

Table 1 Characteristics of patients with therapy related acute promyelocytic leukaemia: selected series in the literature

References	Number of cases	Sex ratio (M:F)	Age at first diagnosis (years)	Primary tumour	Treatment for primary tumour	Time to t-APL (months)	Treatment for t-APL	Outcome
[1]	326	1:1.7	49 (36-62)	Breast: 97 HM: 64 MS: 53 GM: 44 O: 23	Topo II: 44 Topo II+O: 132 O: 11 (n=187)	24 (16-41)	ATRA±O: 210 ATO: 25	Dead: 4 CR: 212
[4]	106	68:78	55 (12-82)	Breast: 60 NHL: 15 ST: 25 HM: 4 ND: 2	Topo II: 61 RT: 27 O: 8	25 (4-276)	CT: 16 ATRA±CT: 83 None: 6 NA: 1	Dead: 34 CR: 61 Relapse: 10
[9]	15	5:10	3 (0.5-12)	LCH: 11 ES: 1 N: 1 A: 1 NHL: 1	VP-16: 10 VP-16+O: 2 O: 2 RT: 1	37 (15-106)	CT: 7 SCT: 4 ATRA±CT: 3 NA: 1	Dead: 4 Alive: 11

HM, haematologic malignancies; MS: multiple sclerosis; GM, Genitourinary Malignancies; O, other; ATRA: all-trans-retinotic acid; ATO, arsenic trioxide; CR: complete remission; CT: chemotherapy; ST, solid tumour; ND, Nonneoplastic disorder; RT: radiotherapy; NA, not available; ES, Ewing sarcoma; N, neuroblastoma; A, astrocytoma; SCT, stem cell translation, Topo II, topoisomerase II

factors.[5] The median interval from the completion of treatment for primary disease to the development of APL lasts about 24 (16-41) months.[1] 90% of t-APL cases were found to have t (15; 17) translocation or PML/RARA fusion gene.[1,4] Most t-APL patients responded well to treatment.[1]

In the study of Armin Rashidi, 7% of t-APL cases occurred in the preadolescent population, and LCH is one of the most common primary haematological malignancies.[1] Ogami et al reviewed 15 childhood cases of t-APL, and found that 11 (73%) were secondary to LCH.[9] All of these patients had been treated with VP-16 for 15 to 106 months, and most of them were females from either Italy or Japan.

The case we presented in this report is different from previous patients in several respects:

The present case differed apparently from classic t-APL, despite the fact that it occurred after chemotherapy for LCH. The patient had been treated with VP-16 at a dosage of 0.1 g, which was substantially below previously reported dose limit.[4] In a French research of 348 LCH patients treated with VP-16, a cumulative dose of less than 2000 mg/m^2 would not be possible to develop t-APL. Whereas, in an Italian report of 241 LCH patients treated with a median cumulative VP-16 dose of 5000 mg/m^2, there were just 5 patients who suffered from t-APL.[4] Those findings demonstrated a close relation between the cumulative dose of VP-16 and t-APL in children.[4] The interval from the completion of treatment for primary disease to the development of APL was only 8 months, much shorter than the interval (2 years) reported by two previous large-sample studies.[1,4] Cytogenetically, the patient did not have t (15; 17), which was found in 90% of t-APL patients.[1,9] The discrepancies might be ascribed to impaired immunocompetence of the patient due to the prior 9-month chemotherapy, or abnormal proliferation of two cell lines induced by topo II inhibitors.[1,4]

The patient had been originally misdiagnosed with relapsed LCH since he had had primary LCH, and clinically LCH and AML shared some features. However, the patient was eventually diagnosed as having t-APL on the basis of BMA, immunophenotyping and fusion gene tests. Though juvenile t-APL is rare, paediatricians should take t-APL into account in their differential diagnosis.

In conclusion, t-APL might be related to the use of topo II-target agents. t-APL should be considered when a patient had LCH or relapsed LCH. They can be differentiated morphologically, immunologically, cytogenetically and molecular biologically. The t-APL responds well to such treatments as ATRA and ATO included. However, awareness of the features can help clinicians to avoid misdiagnosis.

Conflict of Interest

We declare that we have no conflict of interest.

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