

Clinical features of malignant lymphoma in children: a retrospective study of 45 cases

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Abstract: To investigate the clinical, pathological features and prognosis of lymphoma in children. The data of 45 children with malignant lymphoma who were hospitalized during the period from January 2013 to March 2018. The clinical data of 45 children were analyzed. 32 were male and 13 were female. The median age of onset was 10 years. The 27 cases (60%) was in the lymph nodes and 18 cases (40%) was outside the lymph nodes. The extranodal side was common in the abdominal cavity. There was a statistically significant difference between the onset of Hodgkin's lymphoma (HL) and Non-hodgkin's lymphoma (NHL) ($p<0.05$). Pathological type HL was mainly classical Hodgkin's lymphoma (CHL), and 11 cases of Burkitt lymphoma (BL) in NHL Next, 8 cases of ALK negative large B-cell lymphoma and 6 cases of T-lymphoblastic lymphoma (T-LBL). 41 cases (91.1%) were stage III and IV. Hodgkin's lymphoma was positive for Epstein-Barr virus expression, and had different degrees of infection during or after chemotherapy. 5 cases were negative for EB virus expression. Only 1 of the children had infection during chemotherapy. Non-Hodgkin's lymphoma was negative for Epstein-Barr virus expression. Children with malignant lymphoma are mainly NHL, which is more common in male children. The most common pathological types are Burkitt's lymphoma, ALK-internal large B-cell lymphoma and T-lymphoblastic lymphoma. The main site of onset of malignant lymphoma in children is lymph nodes. Hodgkin's lymphoma is associated with EB virus infection.

Keywords: Childhood lymphoma; Epstein-Barr virus; Clinical features; Pathological type

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1. Introduction

Lymphoid neoplasia are the most common neoplasms in children and adolescents worldwide and represent a major reason of tumor death[1,2]. Generally, malignant lymphomas have been grouped into two categories: Hodgkin's lymphoma (HL) and Non-Hodgkin's lymphoma (NHL). They are many different histological subtypes[3]. HL is one of the most curable forms of cancer with 5-year survival rate exceeding 98%[4].

Most reports of NHLs in children and adolescents are high grade lymphomas, including Burkitt's lymphoma (BL), diffuse large B-cell lymphoma (DLBCL), lymphoblastic lymphoma (LBL) and anaplastic large cell lymphoma (ALCL). Epstein-Barr virus has been shown to be closely related to the development of various tumors[5-7], such as BL, HL, NHL, nasopharyngeal carcinoma. Epstein-Barr virus play an important role in lymphoma subtypes. However, the pathogenesis of EBV infection in a variety of tumors is unclear, and there is no optimal treatment for EBV-related tumors. This study retrospectively analyzed the clinical data of 45 children with malignant lymphoma to understand its clinical, pathological features and prognosis.

2. Materials and Methods

2.1. Research object

45 patients with lymphoma who were hospitalized

for blood pediatrics at the Affiliated Hospital of Qingdao University from January 2013 to 2018. Inclusion criteria: 0-15 years; according to the WHO 2008 classification criteria, confirmed by pathological biopsy.

2.2. Clinical data collection

The data included age, gender, starting position, clinical stage, pathological results, EB virus expression, course of disease, imaging examination, bone marrow cytology, etc.

2.3. Staging and typing

Hodgkin's lymphoma was staged using the Ann Arbor system. Non-Hodgkin's lymphoma was staged according to the Stjude Children's Institute NHL staging system. The academic classification was based on the WHO2008 classification criteria.

2.4. Statistical analysis

Retrospective analysis was performed using SPSS 21.0 software. Measurement data and count data were expressed as mean \pm standard deviation, percentage or rate. Single-factor analysis of clinical and pathological parameters of stage I, II and III and IV were used Pearson test. Age, sex, and start of analysis were analyzed by Cox proportional hazard model location, clinical stage and other factors.

3. Results

3.1. Epidemiological characteristics

45 children with malignant lymphoma, 32 were male and 13 were female, the ratio of male to female 2.46:1. There were 9 males and 2 females in Hodgkin's lymphoma with the ratio of male to female 4.5:1, 22 males and 12 females with non-Hodgkin's lymphoma, male to female ratio of 1.83:1. Most lymphomas showed a male predominance including classical Hodgkin's lymphoma (CHL) (M/F=4.5), BL

(M/F=2.67), ALCL ((M/F=1.33), DLBCL (M/F=2)). The lowest age of 45 children with malignant lymphoma was 2 years old, the maximum age was 15 years, and the median age was 10 years (2-15 years). The median age of HL was 10 years (3-13 years), and the median age of NHL was 11 years (2-15 years). According to the following age distribution, the incidence of malignant lymphoma in children was more common in school-age children, with the highest number of children aged 6 years and older, accounting for 79.2% (Table 1).

Table 1. Distribution of age in 45 children with malignant lymphoma

| Age (year old) | Number of cases (n) | Percentage (%) |
|----------------|---------------------|----------------|
| 0~ | 1 | 2.2 |
| 3~ | 7 | 15.6 |
| 6~ | 11 | 24.4 |
| 10~ | 26 | 57.8 |

Table 2. The primary site of 45 cases of malignant lymphoma

| primary site | Number of cases (n) | Percentage (%) |
|------------------|---------------------|----------------|
| lymph nodes | 27 | 60 |
| neck | 23 | 51.1 |
| armpit | 4 | 8.9 |
| Extranodal site | 18 | 40 |
| abdominal cavity | 5 | 11.1 |
| nasal cavity | 4 | 8.9 |
| Gut | 2 | 4.4 |
| Parotid gland | 2 | 4.4 |
| Maxilla | 1 | 2.2 |
| Tonsil | 1 | 2.2 |
| Gum | 1 | 2.2 |
| Soft palate | 1 | 2.2 |
| airway | 1 | 2.2 |

3.2. Primary and affected parts

In this study, 27 cases (60%) occurred in lymph nodes and 18 cases (40%) extranodal site involvement. All HL occurred in lymph nodes, 47.1% of NHL presentde an exteanodal site involvement at the time of diagnosis. The most common extranodal site of NHL involved the abdominal cavity (11.1%), nasal cavity (8.9%). The most common site of the lymph nodes was cervical lymph nodes. In this study, 25 cases of malignant lymphoma occurred in other organs, including NHL in 19 cases, were more common in Burkitt's lymphoma (7 cases) and ALK negative large B-cell lymphoma (4 cases) (Table 2).

common NHLs observed in children were BL (32.35%), ALK negative ALCL (23.5%), TLBL (17.6%), (Table 3).

3.4. Clinical staging

Of the 45 children with malignant lymphoma, 41 (91.1%) cases were stage III and IV. 32 (71.1%) cases were stage III and IV in NHL. Most cases were Burkitt's lymphoma. Of the HL, stage III and IV were 9 cases (20%). Stage III and stage IV of children with malignant lymphoma were more common in school-age children, a total of 25 cases (55.5%), who were mainly male children. Only 4 patients (8.9%) were stage II disease, no stage I cases, (Table 4).

3.3. Pathological type

The majority (34/45, 75%) of lymphoma were NHL. 11 cases (25%) were HL. Of the NHL, the proportion of mature B-cell lymphomas and T-cell lymphomas was 55.6% and 20%, respectively. The most common pathological type in Hodgkin's lymphoma was classical Hodgkin's lymphoma (24.4%). The three

3.5. Epstein-Barr virus expression

In this group, 6 cases of children with malignant lymphoma were positive for Epstein-Barr virus, accounting for 13.3%, all of which were Hodgkin's lymphoma, including 4 males and 2 females. The ratio of male to female was 2:1, and the median age was 8.5

years. The pathological type was mainly mixed cell type (MC). The expression of Epstein-Barr virus in non-Hodgkin's lymphoma was negative. Five of the six patients with positive EB virus expression in HL (5/6,

83.3%) had different degrees of infection during and/or after chemotherapy. The other 5 EBER-negative children were treated with chemotherapy or only 1 case of infection after chemotherapy, (Table 5).

Table 3. Pathological types, age, and gender composition of 45 children with malignant lymphoma

| Pathological types | Cases (n) | Percentage(%) | Median age (years) | gender(M: F) |
|----------------------------|-----------|---------------|--------------------|--------------|
| HL | 11 | 25 | 10 | 4.5: 1 |
| CHL | 11 | 24.4 | 10 | 4.5: 1 |
| CHL,NS | 6 | 13.3 | 12 | 5: 1 |
| CHL,MC | 5 | 11.1 | 5.5 | 4: 1 |
| NHL | 34 | 75 | 11 | 1.83: 1 |
| B-cell Lymphoma | 25 | 55.6 | 10 | 2.57: 1 |
| BL | 11 | 24.4 | 10 | 2.67: 1 |
| ALBL | 7 | 15.6 | 9 | 1.33: 1 |
| BLBL | 3 | 6.7 | 13 | 3(M) |
| FL | 2 | 4.4 | 8.5 | 1: 1 |
| DLBCL | 2 | 4.4 | 10.5 | 2: 1 |
| T-cell Lymphoma | 9 | 20 | 10.5 | 2: 1 |
| TLBL | 6 | 13.3 | 12 | 1(M) |
| Peripheral T cell lymphoma | 1 | 2.2 | 11 | 1(F) |
| ENKTCL | 1 | 2.2 | 10 | 1(M) |
| ALK positive ALCL | 1 | 2.2 | 9 | 1(M) |

Table 4. Clinical staging of 45 cases of malignant lymphoma

| Clinical staging | HL | NHL |
|------------------|----|-----|
| I | 0 | 0 |
| II | 2 | 2 |
| III | 2 | 7 |
| IV | 9 | 23 |

Table 5. Expression of Epstein-Barr virus in 45 children with malignant lymphoma

| Pathological type | EBER1mRNA (+) | EBER1mRNA (-) |
|-------------------|---------------|---------------|
| HL | 6 | 5 |
| NS | 1 | 4 |
| MC | 5 | 1 |
| NHL | 0 | 34 |

3.6. Prognosis

Of the 45 patients, 3 patients gave up treatment during the post-diagnosis chemotherapy and 2 patients died. After 2 courses of chemotherapy in 40 patients, 35 (87.5%) achieved complete remission (CR) by cytology and imaging evaluation, and 1 case (2.5%) was partial remission (PR). 2 patients (5%) relapsed after 1 course of treatment. 2 patients (5%) developed central nervous system infiltration during chemotherapy.

4. Discussion

Lymphoma is a malignant tumor that is highly heterogeneous in lymph nodes and/or extranodal lymphoid tissues. Generally, malignant lymphomas have been grouped into two categories: HL and

NHL[8]. Malignant lymphoma is one of the most common malignant tumors in children[9], and children of all ages can develop disease. The incidence of malignant lymphoma in children is second only to acute leukemia and intracranial tumors[10]. According to reports[11], the incidence of malignant lymphoma in children in China accounted for 16.6%-23.2% of all malignant tumors, and showed an upward trend. As mentioned above, children with malignant lymphoma are more common in male school-age children. The ratio of male to female in this group is 2.46:1, and the median age is 10 years.

There is no obvious specificity in the clinical manifestations of malignant lymphoma in children. The most common is painless, progressive lymphadenopathy, and may be accompanied by systemic symptoms such as respiratory system and

digestive system. Children with lymphoma extranodal lymphoma are more than adults. In this data, of the distribution of onset sites, 60% (27/45 cases) of children with malignant lymphoma originated as lymph nodes. 40% (18/45 cases) originated from extranodal lymph nodes, of which 11.1% of the abdominal cavity and 8.9% of the nasal cavity were more common, and the incidence of other parts was lower. Malignant lymphoma has occur in lymph nodes than extranodal site, which is slightly different from other reports[12,13]. Hodgkin's lymphoma was mainly caused by lymph node, non-Hodgkin's lymphoma onset is not limited. The internal position of the lymph nodes was most common in cervical lymph node. This was consistent with domestic reports[14]. In this study, the extranodal lymph nodes could be found in various parts and organs of the body, including the uncommon parotid glands, gums, tonsils, and airways. Children with non-Hodgkin's lymphoma had diverse clinical manifestations and easily misdiagnosed[15]. The pathological type of malignant lymphoma in children was different from that in adults. The proportion of LBL and BLL and ALCL was higher than that of adults. Indolent lymphomas such as follicular cell lymphoma, which are more common in adults, were rare in children[16]. Children with lymphoma were more common in pathological types with high malignancy and high invasiveness. Therefore, children with malignant lymphoma had a late stage. The most important prognostic factors for lymphoma were disease stage and pathological type[17]. Phase I of NHL was a low risk factor with a remission rate of 87%. Phase III-IV was a high risk factor with a response rate of only 26% to 44%[18]. In this data, children with malignant lymphoma in the advanced stage (stage III, IV) reached 91.1%. Although children with malignant lymphoma had a late stage, the overall prognosis was better than that of adults[19,20]. Childhood lymphoma was sensitive to chemotherapy, and combined chemotherapy was better. Children with lymphoma were generally not treated with surgery. Surgery was only used for clinical biopsy, and residual lesions could be completely resected. Therefore, early detection, early recognition and early treatment of childhood malignant lymphoma were particularly important.

EBV was a double-stranded DNA virus that induces tumors in the γ subfamily of herpesviridae[21]. Most people could be infected for a lifetime after infection with EBV in childhood. A variety of benign and malignant clinical diseases were closely related to EBV infection[22,23]. Possible tumorigenic mechanism of EBV: in latent infection, EBV-DNA was not expressed or underexpressed in cells. Under certain conditions, a large number of EBV-DNA fragments were integrated into the host DNA, so that the host cells could continue to grow, proliferateand[15]. In patients with Hodgkin's lymphoma, EBV infection

might rapidly progress the disease and reduce overall survival[16]. In situ hybridization was a gold indicator for detecting positive expression of Epstein-Barr virus[25]. In this study, in situ hybridization was used to detect the expression of EBER1 mRNA in 45 children with malignant lymphoma tissue samples. A total of 6 cases of EB virus were found, and the positive expression rate of EB virus was 54.5%. In this group of patients with positive EBV expression, the incidence of infection during chemotherapy was higher than that of children with negative EBV expression. The degree of infection was severe. Two children with positive EBV expression relapsed after chemotherapy. Stem cell transplantation, EBV-associated lymphoma treatment, in addition to selecting sensitive chemotherapy regimens according to different types, was necessary to effectively eliminate EBV infection and activity against EBV infection itself.

5. Conclusion

Childhood malignant lymphoma is one of the most common malignant tumors in childhood and adolescence. Epstein-Barr virus infection is closely related to the occurrence, development and prognosis of malignant lymphoma in children. Further study of the relationship between EBV and lymphoma, early treatment, effective clearance of EBV infection and activity is of great significance for lymphoma.

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