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Clinical and Experimental Study of Castleman Disease in Children

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Background. Castleman disease (CD) is a rare lymphoproliferative disease that is often underdiagnosed or misdiagnosed, especially in children. For this reason, we describe the clinical manifestations, diagnosis and treatment of CD in 11 children. ***Procedure.*** A retrospective study was performed to analyze the clinical features of 11 children with CD in a single institution from January 2001 to December 2012. All had computed tomography (CT) and lymph node resection for pathology diagnosis. ***Results.*** The average age of patients was 9.67 ± 4.26 years (range 1.3–15.5 years) including eight males (72.73%) and three females (27.27%). All but two (18.18%) had multicentric Castleman disease (MCD). Human immunodeficiency virus (HIV) or human herpes virus 8 (HHV8) infected cells were not detected in all patients. All patients were misdiagnosed in outside hospitals without tissue examination. Only in one case, the preoperative CT scan suggested CD. After treatment, 10 out of 11 children with CD in our study were disease free in the follow-up period ranging from 12 to 136 months (average 65.1 ± 10.21 months). ***Conclusion.*** CD in children is rare, and is frequently misdiagnosed clinically. Our study shows that surgical resection is very effective in the treatment of unicentric Castleman disease (UCD). The rare UCD patient and all MCD patients treated with the modified NHLBFM-90 protocol had good prognosis. Pediatr Blood Cancer 2015;62:109–114.

Key words: castleman disease; children; HHV8; POEMS syndrome

INTRODUCTION

Castleman disease (CD) is a non-clonal lymphoid disease characterized by angiofollicular lymphoid hyperplasia, and/or benign plasma cell infiltration of unknown etiology. Castleman first described this rare primary lymph node disease in 1954 [1], which was followed by a more detailed report publised in 1956 [2]. According to recent reports in the literature [3–5], CD can be classified as unicentric Castleman disease (UCD) and multicentric Castleman disease (MCD) based on clinical and radiological findings; or classified as hyaline vascular type (HV), plasma cell type (PC), and mixed type (Mix) based on pathological features. CD in children is rare; therefore only few clinical and experimental studies are available in the literature. As a result, misdiagnosis of CD is common. The objective of this paper is to describe the clinical manifestations, diagnosis and treatment options of CD in children.

METHODS

After approval from our Institutional Review Board, patients were screened from January 2001 to December 2012. Eleven children with CD were identified and treated in our hospital. A retrospective analysis was performed on these patients by using the medical history and imaging data (including ultrasound and CT). The blood antibodies of HIV and HIV-RNA were tested by Western blotting and real-time PCR, respectively. The κ, λ, and HHV8 expression were detected by immunohistochemistry stains on the affected lymph node tissue of these children.

RESULTS

Medical History

The group was comprised of eight males (73%) and three females (27%), with an average age of 9.67 ± 4.26 years (range 1.3–15.5 years). They were further classified as two children with MCD, nine children with UCD. Ten children had the diagnosis of HV and one child had PC, without mix type (Table I). All patients were misdiagnosed in outside hospitals without tissue examination. The most common clinical diagnosis given at the outside hospitals was infectious mononucleosis (IM) or lymphoma. Patients received various forms of treatments accordingly with the average duration of 16.27 ± 10.21 months.

Among 11 CD patients, two (No. six and No. nine) had comorbidity including polyneuropathy, organomegaly (hepatosplenomegaly), endocrinopathy, monoclonal protein (M-protein) and skin changes (POEMS) syndrome. One patient (No. eight) had a comorbidity of intermenstrual bleeding. HIV or hepatitis B virus infection was not detected in any of these cases. Among nine children with UCD patients, eight children were cured after complete resection of the involved lymph nodes. One UCD patient with unresolved clinical symptom post-surgery, and two children with MCD were treated with chemotherapy based on the modified B-NHL-BFM-90 protocol [6].

After treatment, we were able to determine that 10 patients were alive and disease free on follow-up visits ranging from 12 to 136 months (65.1 ± 10.21 months). Unfortunately, one patient was lost to follow-up.

Imaging Features

Ultrasound results of 11 children with CD were as follows: isolated lesions were more common, which showed a round homogeneous hypoechoic area, with complete and smooth edges.

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TABLE I. Clinical and Pathological Characteristics of Pediatric CD Patients

No	Age (yr.)	Gender	Clinical classification	Histology	Clinical feature	Pathogenetic location	Hb (g/L)	PLT ($\times 10^9$/L)	GLB	ALB	ESR	CRP	HIV	HBSAg	Treatment	Follow-up (months)	Status
1	1.3	M	UCD	HV	Mass	Neck	97	310	↑		Normal	Normal	-	-	Resection	136	A-NED
2	6	M	UCD	HV	Mass	Neck	112	227	↑	Normal	Normal	Normal	-	-	Resection	100	A-NED
3	13.5	M	UCD	HV	Mass	Neck	118	128	↑		Normal	Normal	-	-	Resection	75	A-NED
4	6.1	M	UCD	HV	Mass	Neck	110	156	↑	Normal	Normal	Normal	-	-	Resection	62	A-NED
5	11.2	F	UCD	HV	pain in her epigastrium and left knee	Retroperitoneal	81	385	↑		↑	↑	-	-	Surgical excision Chemotherapy	42	A-NED
6	11.4	F	UCD	HV	Cough and rash	Retroperitoneal	134	288	↑	Normal	Normal	Normal	-	-	Resection	56	A-NED
7	12.6	M	UCD	HV	Mass	Neck	118	190	Normal	Normal	Normal	Normal	-	-	Resection	66	A-NED
8	15.5	F	MCD	HV	Intermenstrual bleeding	Neck and mediastinum	82	56	↑	Normal	↑	↑	-	-	Surgical excision Chemotherapy	66	A-NED
9	12.8	M	MCD	PC	Cough and rash	Neck, armpit and hilus pulmonis	69	455	↑		↑	↑	-	-	Surgical excision Chemotherapy	36	A-NED
10	13	M	UCD	HV	Pallor	mesenterium	50	128	↑	Normal	Normal	Normal	-	-	Resection	Lost	
11	10.9	M	UCD	HV	Mass	under the collarbone	127	207	Normal	Normal	Normal	Normal	-	-	Resection	12	A-NED

ALB, albumin; A-NED, alive and no evidence of disease; CRP, C Reactive Protein; ESR, erythrocyte sedimentation rate; GLB, globulin; Hb, hemoglobin; HV, Hyaline vascular type; MCD, multicentric Castleman disease; PC, plasma cell type; UCD, unicentric Castleman disease.

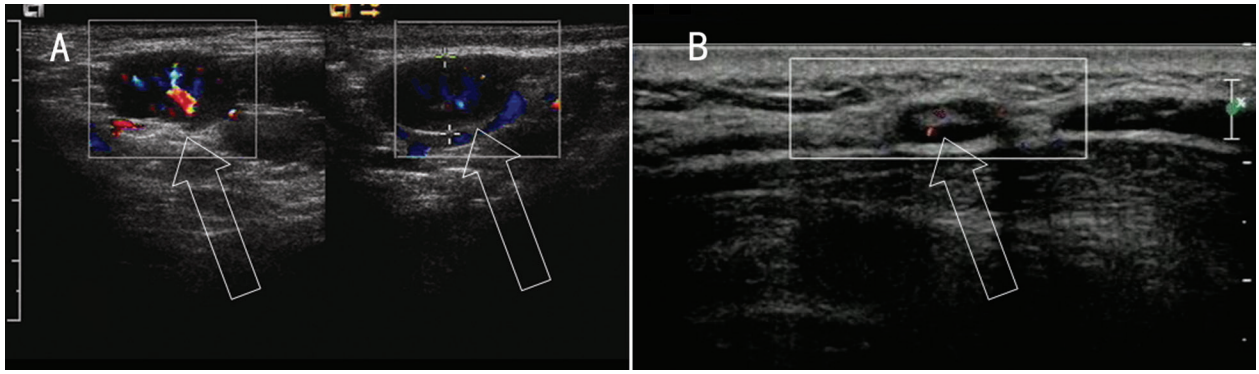

Fig. 1. Color Doppler flow imaging of HV type of CD in the right neck revealed increased blood flow with signal abnormality resembling many branches of thick wall vessels in and around the lesional lymph node (A) compared to the Color Doppler flow imaging of normal lymph node (B).

A mild enhanced echo was often seen behind the mass. The diameter ranged from 2 to 9 cm, with an average of 3.6 ± 2.1 cm. Color Doppler Flow Imaging (CDFI) showed increased blood flow with signal abnormality resembling many branches of thick wall vessels in and around the lesional lymph node (Fig. 1).

Unenhanced CT scans of 10 patients in HV showed isolated demarcated round or lobulated mass lesions with equal density compared with adjacent normal muscle in eight children. Two children had lessons with heterogeneous density, in which small calcifications were seen scattered throughout. Lesions were markedly and homogeneously enhanced in arterial phase, and its CT density was similar to the adjacent large vessels. The lesions of patients with PC compressed the surrounding structure with shifting of the latter but no vascular invasion was found (Fig. 2).

After transfer to our hospital, CT scan was performed on all patients, but only one patient was suggested as CD, all other patients had nonspecific imaging diagnosis.

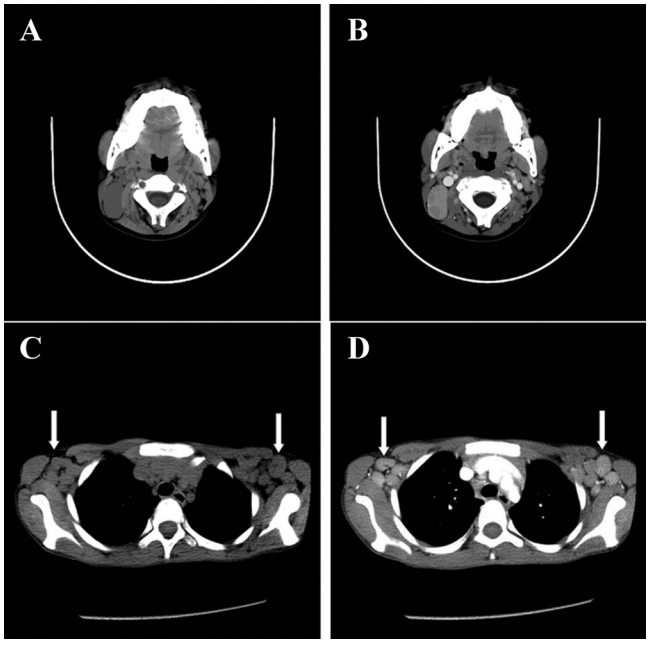

Fig. 2. Unenhanced CT scans of HV type of CD in the right neck showed isolated demarcated round or lobulated mass lesions with equal density compared with adjacent normal muscle (A). Lesions were markedly and homogeneously enhanced in arterial phase, and their CT density was similar to the adjacent large vessels (B). CT scan of PC type of CD in bilateral axillae showed that the lesions compressed the surrounding structure with shifting of the latter but no vascular invasion was found (C), which was better seen on enhanced CT scan (D).

Pathological Features and Laboratory Testing

The pathological features of 10 children with HV type CD were characterized by preserved lymph node follicular architecture. Germinal centers range from atrophic to hypertrophic, with lamination of the mantle cell layer around the germinal center forming an onion skin pattern (Fig. 3A). Angiogenesis, with blood vessels containing thickened and hyalinized wall arise in subcortical areas (Fig. 3B) and follicles (lollipop, Fig. 3C).

The characteristic pathological finding of PC type was sheets and clusters of mature plasma cells infiltrated into interfollicular zone and medulla, but not into lymphatic sinus structure (Fig. 3D).

Both κ and λ light chains were expressed in 11 specimens by immunohistochemical stains with a normal κ/λ ratio (Fig. 4A and B). No positive expression for the human herpes virus 8 (HHV8) was found in all lymph nodes examined (Fig. 4C).

DISCUSSION

Castelman Disease is more common in adults than in children and is often misdiagnosed in children [7,8]. Castleman originally reported that the incidence of the disease was not gender specific [2], but since then, various reports have shown the differences between genders. Parez et al. [9] showed that women had a higher incidence of CD than men. They found that the male-to-female ratio was 1.00:1.24. However, men had a significantly higher incidence than women in the group of Chinese patients reported by Cui et al. [10]. Our study and Cui's study support that Chinese males have a higher incidence of CD, but further study is needed because of the limited number of cases allotted. Only a small number of older children suffering from the PC type of CD from our study of limited number of patients (one PC in 11 children with CD). Based on our extensive literature search, the 1.3 years old child diagnosed with CD in our study is the youngest affected patient.

The exact cause of CD is unclear. At present, it is generally believed that interleukin-6 (IL-6) produced by the lymph nodes plays a very important role in the occurrence and development of CD [4].

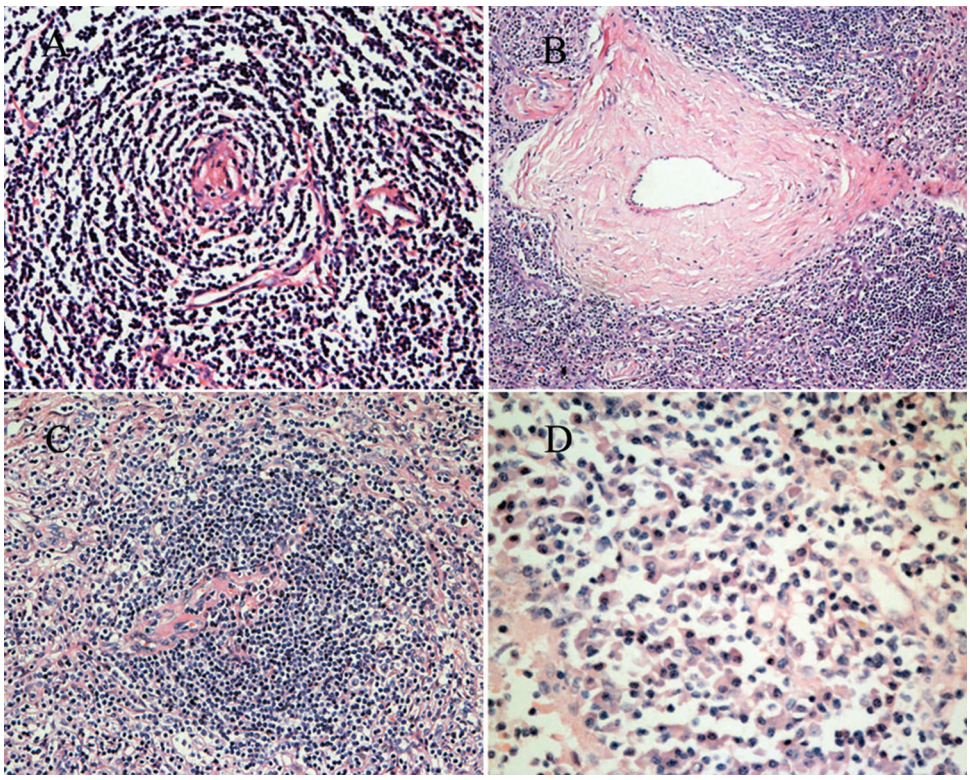

Fig. 3. Histology of CD with HV variant showed germinal centers range from atrophic to hypertrophic, with lamination of the mantle cell layer around the germinal center forming an onion skin pattern (A, HE × 100). Angiogenesis, with blood vessels containing thickened and hyalinizd wall arise in sub-cortical areas (B, HE × 200) and follicles (lollipop, C, HE × 200). Histology of lymph node of CD with PC variant showed sheets and clusters of mature plasma cells infiltrated into the interfollicular zone and medulla (D, HE × 400).

Several studies reported that the occurrence of MCD in adults was closely related to HHV8 infection in AIDS patients [11,12], but controversy exists between MCD and HHV8 in patients without HIV infection [13]. Recently, Sandrine Leroy et al. [14] found that MCD was closely related to HHV8 infection in a meta-analysis of 32 children with a history of MCD. However, in our study no HHV8 infected cells were found in the pathological specimens of all children, which is consistent with Chinese adults with CD [15]. These studies do not support the evidence of relationship between HHV8 infection and CD incidence in Chinese patients.

POEMS syndrome was present in two of our cases with CD. The POEMS syndrome is a rare multisystem disease, characterized by polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes (POEMS). M-protein and polyneuropathy are the major diagnostic criteria in these lesions, and the remainders, including CD, are the minor criteria. The diagnosis of POEMS syndrome must have two main diagnostic criteria, and at least one minor criterion [16]. There were 2 CD children with POEMS syndrome in our group, including one who was 11.4 years old. To our knowledge, this patient is the youngest reported case of POEMS syndrome [17].

Other nonmalignant lymphoproliferative disorders in children should be distinguished from CD. The common differential diagnosis includes IM, Kawasaki disease (KD), Rosai–Dorfman disease (RDD), IgG4-related disease, and Autoimmune Lymphoproliferative Syndrome (ALPS). IM is caused by Epstein Barr (EB) virus. Patients suffer from fever, with swollen lymph nodes and hepatosplenomegaly [18]. Diagnosis of IM can be made by clinical characteristics and lab tests for antibodies against EB virus and high percentages of atypical lymphocytes in peripheral blood [19]. KD is the most common cause of childhood-acquired heart disease in western countries. In addition to swollen lymph nodes, there are skin and mucosal characteristic lesions. Ultrasound characteristics of IM and KD are similar but different compared to CD. For example in IM and KD, ultrasound shows round-shaped nodes melted in packets resembling clusters of grapes [20], and no hypervascular signals that are usually seen in CD patients. Coronary artery dilatation usually can be seen through imaging examination in KD patients with daily fever lasting for at least 5 days. The diagnosis of KD is based on clinical symptoms and examinations [21]. RDD is a non-neoplastic proliferation of S-100 (+), CD68 (+), and CD1a (−) histiocytes with emperipolesis. Clinically it is characterized by painless bilateral cervical lymphadenopathy with or without cutaneous involvement. The cutaneous rash ranges from unifocal to diffuse. Isolated skin manifestation without lymph node involvement is rare [22]. IgG4-related disease is a recently recognized autoimmune systemic disorder that has been described in various organs [23], which includes autoimmune pancreatitis as part of the disease spectrum that cannot be seen in CD patients. Dense infiltration of lymph nodes by IgG4-positive plasma cells in patients with IgG4-related disease produces lymphadenopathy of varying sizes [24]. However, the clinical characteristics of RDD,

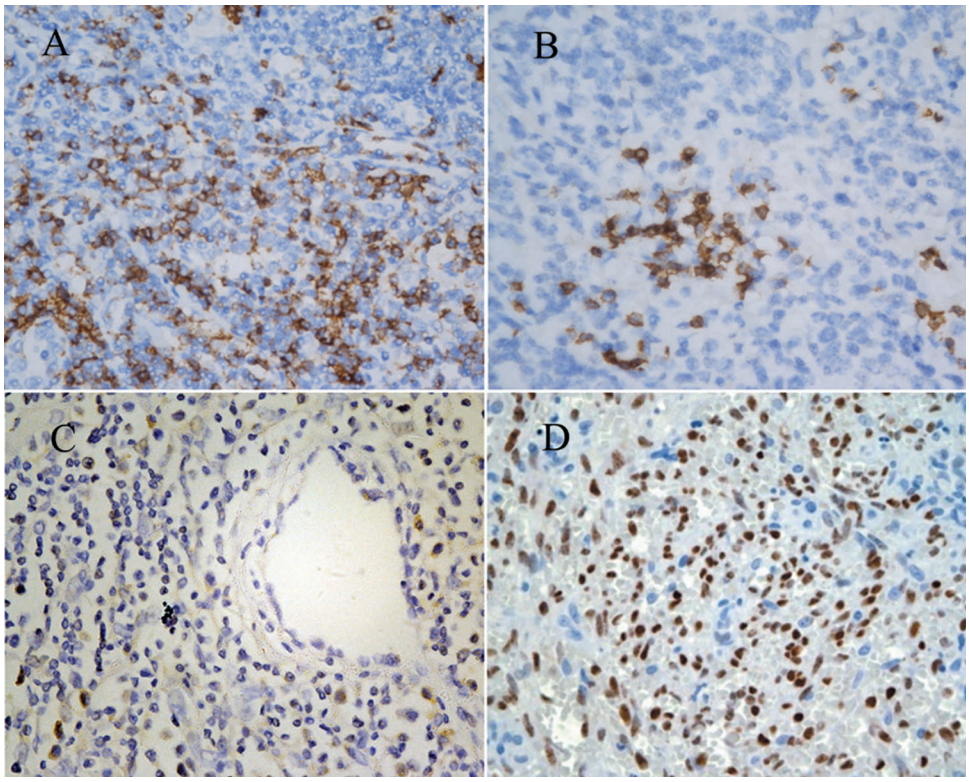

Fig. 4. Immunohistochemical stains for κ (A, original magnification × 400) and λ (B, original magnification × 400), showed both cytoplasmic and membranous immunoreactivity. By immunohistochemistry stain, no HHV8 positive cell was detected in our patient's tissue (C, original magnification × 400) compared to positive control for HHV8 (D, original magnification × 400).

CD and IgG4-related disease are very similar in some children; therefore a definitive diagnosis requires tissue pathology confirmation. ALPS is a rare inherited disorder of apoptosis, most commonly due to mutations in the FAS (TNFRSF6) gene, presenting with lymphadenopathy, splenomegaly, and cytopenia. ALPS and CD with POEMS have some overlapping clinical and laboratory features. Obtaining discriminating screening laboratory biomarkers (such as serum vitamin B-12 and ferritin levels) is needed; and, in the setting of a highly suspicious clinical scenario for ALPS, pursuing testing for somatic FAS mutations must be done when germ-line mutation testing is negative [25].

Swollen lymph nodes are common in children, and no treatment is needed in most cases. CD is a rare lymphoproliferative disease that is often underdiagnosed or misdiagnosed, especially in

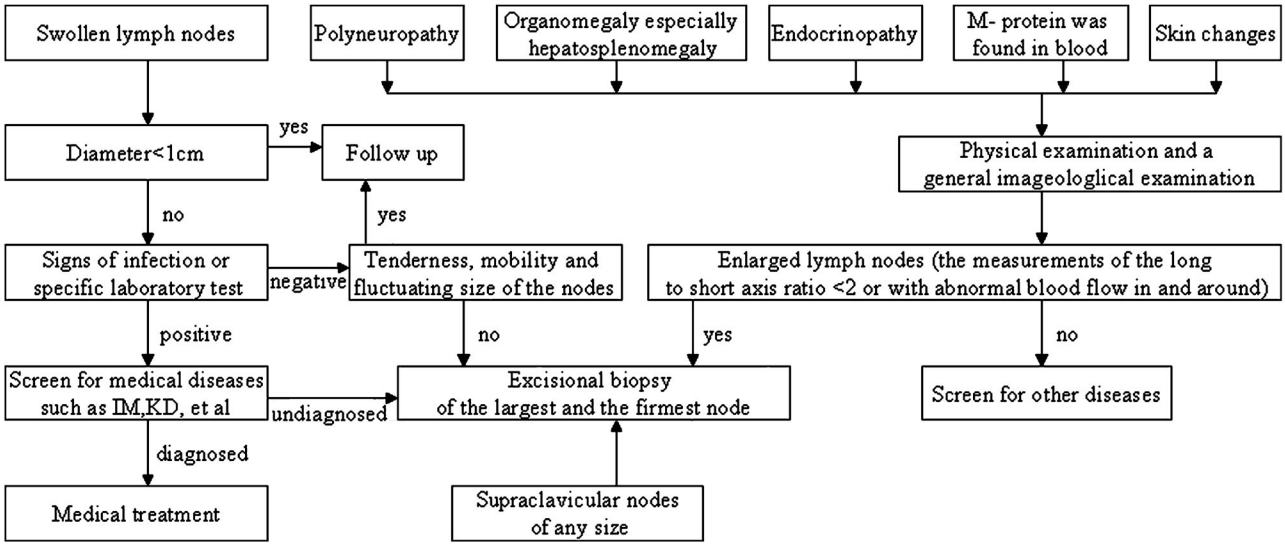

Fig. 5. The diagnostic decision tree flow chart for CD.

children. A diagnostic decision tree flow chart summarized by our group may be helpful in the diagnosis of CD [20,26–28] (Fig. 5).

There is no recognized guideline for the treatment of CD, but in most cases, surgical resection is considered as the first choice for the treatment of UCD [29]. Baek HJ et al. [30] reported an adolescent with relapsed unicentric-plasma cell variant CD, who had no response to combination chemotherapy with rituximab after incomplete resection or to radiation after relapse. She was eventually cured with complete surgical resection. If tissue examination is needed in the diagnosis of lymphadenopathy, biopsy of the lymph node may be sufficient for a diagnosis of lymphoma, but will not provide cure in case of CD. Since intraoperative diagnosis has little value in a definitive diagnosis of lymphadenopathy, a complete lesional lymph node resection may be optimal, especially in patients with a strong clinical suspicion for CD to avoid a second surgery. If complete resection is difficult to achieve or may cause serious complications, the preoperative imaging diagnosis (such as ultrasound, CT or PET-CT) will be very important in making the best surgical decision [31,32].

Since MCD was described as: the rarity of the condition, its heterogeneous presentation and the lack of guidelines on clinical assessment, the treatment regimens are variable among different institutions [33]. Drug therapies for MCD include anti-IL-6 monoclonal antibodies, chemotherapy, corticosteroids, and rituximab, given in monotherapy or in combination [33–35]. The common chemotherapy regimens used in adults with MCD were often CHOP (cyclophosphamide, vincristine, doxorubicin and prednisone) or CVAD (rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone) [33,35], which are derived from the treatment protocol of B-Non-Hodgkin's Lymphoma. However, research has shown that the modified B-NHL-BFM-90 protocol [6] is very effective in Chinese children and adolescents with B-Non-Hodgkin Lymphoma, resulting in a significant increase in the survival rates [6]. Based on this finding, we used this protocol instead of CHOP or CVAD in children with CD.

In our study, 10 out of 11children with CD treated in our hospital, were disease free at the last follow-up. Unfortunately, we were unable to obtain one child's follow-up data. This demonstrates that the prognosis of CD in children is good. The cure rate is significantly higher in our study than those reported in adults [36]. The key to achieve excellent prognosis in CD is to obtain preoperative diagnosis accompanied by complete surgical resection of lesional tissue. If necessary, especially in MCD, optimal chemotherapy regiments will further assure the cure of CD in children.

CONCLUSION

CD in children is rare and more commonly misdiagnosed compared with adults. Our study demonstrates the important clinical characteristics in Chinese pediatric CD patients. One characteristic is male predominance; the other is no relationship between HIV or HHV8 infection and CD incidence. The prognosis for pediatric CD maybe is better than adults. The key for the cure of CD in children is preoperative diagnosis based on clinical presentation and imaging findings, complete surgical resection, and using optimal chemotherapy regimens if necessary, especially in MCD. With this approach, the prognosis of CD in children can be excellent.

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