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Histiocytic necrotizing lymphadenitis in children: A clinical and immunohistochemical comparative study with adult patients

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ABSTRACT

Objectives: Limited information is available regarding the characteristics of histiocytic necrotizing lymphadenitis (HNL) in children. This study compares the clinical and laboratory features as well as the immunohistochemical findings of HNL in children with those of adults.
Study design: Retrospective analysis.
Methods: Thirty patients who underwent a biopsy of a cervical lymph node and were histologically proven to have HNL were enrolled in this study. There were 13 children and 17 adults. CD68, CD163 and myeloperoxidase expression were analyzed by immunohistochemical staining.
Results: Children had more bilateral lymphadenopathy ($P = 0.045$) and a higher expression of CD68 ($P = 0.043$) than did the adult patients. However, there was no significant difference between the groups in the following variables: patient gender, presence of fever, size and necrosis of enlarged lymph node, multiplicity of lymphadenopathy, WBC count, ESR, CRP, recurrence, and expression of myeloperoxidase and CD163.
Conclusions: The clinical and immunohistological characteristics of HNL in pediatric patients are similar to those of adults. Bilateral involvement of lymph nodes and a high expression of CD68 were the only features significantly associated with children with HNL.
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1. Introduction

Histiocytic necrotizing lymphadenitis (HNL), also known as Kikuchi–Fujimoto disease, was first described independently by both Kikuchi and Fujimoto et al. in 1972 [1,2]. This rare and unusual form of lymphadenitis preferentially affects young females, with a majority of patients under the age of 30 years old, in a 3–4:1 ratio [3,4]. A variable percentage of patients (30–50%) may develop a low grade fever associated with upper respiratory symptoms in addition to the lymphadenopathy [5]. Extranodal involvement is uncommon, but skin rash, hepatitis, arthritis, oral ulcers, and eye involvement have been reported [5,6]. Laboratory tests may reveal high C-reactive protein level (CRP) or erythrocyte sedimentation rate (ESR), leukopenia, and atypical lymphocytes. Definitive diagnosis depends on lymph node biopsy. Three histopathological variants have been reported: proliferative, necrotizing, and xanthomatous. The etiopathogenesis of HNL is still unknown. Infectious agents (Epstein–Barr virus, herpes virus 6 and 8, toxoplasma, yersinia, brucella, human immunodeficiency virus, and human T-cell lymphotropic virus type 1) and genetic associations (human leukocyte antigen class-2) have been implicated [7]. HNL affects individuals of all ages, particularly young women, but there are few descriptions of this disease in the pediatric literature [8–12]. Therefore, the aims of the present study include evaluation of the clinical, laboratory, and immunohistochemical features of HNL in Korean children and comparison of these findings with those of Korean adults diagnosed with HNL.

2. Methods

2.1. Patients and tumor samples

The clinical and pathological data of 13 children who underwent excisional biopsy and were diagnosed with HNL at the Department of Otolaryngology, HNS, The Catholic University of Korea, Bucheon, Korea, from April 2008 to December 2011, were reviewed. The criteria for enrolment included HNL may vary but often meet the following criteria. Microscopically, the

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affected nodes showed focal, well-circumscribed, paracortical necrotizing lesions. There were abundant karyorrhectic debris, scattered fibrin deposits, and collections of mononuclear cells. Plasma cells and meutrophils were very scanty. The exclusion criteria were the following: (1) history of excisional or incisional biopsy of HNL for diagnosis; (2) history of prior HNL; (3) coexistent cervical tuberculosis or other granulomatous lesions; (4) other coexistent systemic diseases such as systemic lupus erythematosus. The mean age of the children was 12.3 years (range 5–17 years). All of the patients received antibiotic treatment for sustained fever or enlarged lymph nodes. We also studied, as a comparative group, 17 adult patients, between the ages of 18 and 63 (mean 28.8 years). Biopsy of a lymph node was usually performed in the outpatient department after several weeks of follow-up. The interval between onset of symptoms and cervical lymph node excision biopsy ranged from 6 days to 8 weeks. The Institutional Review Board of Bucheon St. Mary's Hospital approved the retrospective review of medical records and use of archived tumor specimens.

2.2. Immunohistochemistry

All archival tissue samples were routinely fixed in formalin and embedded in paraffin. Immunohistochemistry was performed on 3-μm paraffin sections using an automated immunohistochemical stainer (Ventana Medical Systems, Inc., Tucson, AZ, USA). Sections were deparaffinized using EZ Prep™ (Ventana) solution. Deparaffinized tissue sections were pretreated with cell conditioning solution (Ventana) at 95 °C for 60 min. To block the endogenous hydroperoxidase activity, UV INHIBITOR was performed at 37 °C for 4 min before the detect primary antibody.

The primary antibodies for CD168, CD163, and myeloperoxidase were diluted in Dako Antibody Diluent (Dako Cytomation, Glostrup, Denmark) with background-reducing components to the following dilutions: CD68 – 1:100 dilution (Dako), CD163 – 1:100 dilution (Abcam Ltd., Cambridge, UK), and myeloperoxidase – 1:100 dilution (Abcam Ltd.). Then, the primary antibodies were incubated for 32 min at 37 °C, while HRP-labeled secondary antibody was incubated for 8 min at 37 °C. To visualize the signal for protein, the HRP-labeled secondary antibody was exposed to UV DAB with UV DAB H_2O_2 for 8 min and UV COPPER for 4 min (UV COPPER changes the DAB color to a reddish brown). Lastly, the slides were counterstained with Hematoxylin II (Ventana) for 4 min and Bluing Reagent (Ventana) for 4 min.

2.3. Semiquantitative analyses of immunohistochemical staining

The immunohistochemical staining was interpreted by two independent pathologists who were blind to the lymph node status of the patients corresponding to the sections. The expression of each antibody was quantified based on the extent of staining. Inflammatory cells which showed distinct cytoplasmic staining were considered positive. The percentage of positive cells was graded on the following scale: grade 0 (negative), grade 1 (1–30% positive cells), grade 2 (31–70% positive cells), or grade 3 (71–100% positive cells).

Table 1
Demographic profiles of histiocytic necrotizing lymphadenitis patients.

Case	Age (years)	Gender	Fever (>37.5 °C)	WBC (/mm^3)	ESR (mm/h)	CRP (mg/dL)	Bilate-rality	Multi-plicity	CD68	CD163	Myelope-roxidase
Children											
1	5	M	+	3800	20	7.23	+	+	3+	0	1+
2	6	F	+	3810	14	16.90	+	+	2+	0	1+
3	9	M	+	3130	10	1.40	–	+	3+	0	1+
4	11	M	+	3730	35	7.30	+	+	2+	0	2+
5	13	F	–	7210	23	2.11	–	+	2+	0	0
6	13	F	–	4230	28	10.29	–	+	2+	0	1+
7	13	M	+	5600	24	40.00	+	+	3+	0	1+
8	13	M	–	3460	3	0.10	–	+	2+	1+	1+
9	14	F	–	4520	17	0.52	–	+	2+	0	1+
10	14	M	+	4730	22	0.46	+	+	3+	0	0
11	15	F	+	2210	33	27.60	+	+	3+	0	1+
12	17	M	–	4300	18	10.20	+	+	3+	0	1+
13	17	F	–	5850	6	3.74	–	+	3+	0	1+
Adults											
14	18	F	–	4460	31	0.80	+	+	0	0	0
15	18	F	–	3200	21	16.41	–	–	2+	0	2+
16	19	F	+	3080	23	9.80	+	+	2+	0	0
17	22	F	+	6430	17	8.70	–	+	2+	0	1+
18	22	M	+	4050	17	37.72	–	+	3+	0	1+
19	23	F	–	5910	8	0.34	–	–	3+	1+	1+
20	23	F	–	4200	37	71.00	–	+	1+	0	1+
21	25	F	+	2880	20	10.10	–	+	2+	0	0
22	26	M	–	4490	2	2.06	–	–	1+	1+	1+
23	29	M	–	2830	7	1.25	+	+	2+	0	0
24	31	F	–	6200	34	1.62	–	+	2+	0	1+
25	32	F	+	6230	28	13.60	–	+	3+	0	2+
26	32	F	–	6120	2	0.45	–	+	1+	0	1+
27	32	M	–	7340	46	21.70	–	+	1+	0	1+
28	26	F	+	3340	29	0.50	–	+	2+	0	1+
29	29	F	–	5450	37	15.20	–	+	3+	0	1+
30	63	F	–	7030	33	2.61	–	+	3+	0	1+

WBC, white blood cell count; ESR, erythrocyte segmentation rate; CRP, C-reactive protein; level 0, no expression; 1+, weak expression; 2+, moderate expression; 3+, marked expression.

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