Ultrasonographic Evaluation of Cervical Lymph Nodes in Kawasaki Disease

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ABSTRACT. *Objective.* **Kawasaki disease (KD) is one of the common causes of cervical lymphadenopathy during early childhood. The purpose of this study was to compare the ultrasonographic feature of cervical lymph nodes in patients with KD, bacterial lymphadenitis, and infectious mononucleosis.**

Design. **We studied 22 patients with KD, 8 with presumed bacterial lymphadenitis, and 5 with Epstein-Barr virus infectious mononucleosis. We examined the cervical nodes by ultrasonography using a 7.5-MHz or 10-MHz transducer of a B-mode sector scanner in all patients with a chief complaint of fever and a visible cervical mass during a fixed time interval (July 1995-March 2000).**

Results. **In KD patients, transverse ultrasonograms demonstrated multiple hypoechoic-enlarged nodes forming one palpable mass, which resembled a cluster of grapes. The ultrasonographic appearance of these nodes was similar in patients with acute Epstein-Barr virus infection, but differed from the pattern in presumed bacterial lymphadenitis. Five KD patients had had fever and cervical lymphadenopathy for several days before other manifestations of KD were noted. In these patients, it was possible to differentiate by ultrasonography between KD and presumed bacterial lymphadenitis at an early stage.**

Conclusion. **Ultrasonographic features of cervical lymph nodes were different for KD than for presumed bacterial lymphadenitis. Ultrasonographic evaluation might be of value for diagnosis of KD patients with cervical lymphadenopathy at an early stage of the disease.** *Pediatrics* **2002;109(5). URL: http://www.pediatrics.org/cgi/content/full/109/5/e77;** ***Kawasaki disease, cervical lymphadenopathy, ultrasonography, bacterial lymphadenitis, EB virus infection.***

ABBREVIATIONS. KD, Kawasaki disease; CAL, coronary artery lesions; IVGG, intravenous gammaglobulin; EBV, Epstein-Barr virus; IM, infectious mononucleosis; WBC, white blood cell; CRP, C-reactive protein.

Kawasaki disease (KD) is an acute febrile illness of unknown cause that occurs primarily in infants and young children.[1] Between 20% and 25% of untreated patients develop coronary artery lesions (CAL), which can lead to myocardial infarction or even death.[2] Early diagnosis and treatment with intravenous gammaglobulin (IVGG) can reduce the risk of cardiac complications of KD.[3] Because there are no specific diagnostic tests for KD, the diagnosis is established by the presence of 5 of 6 criteria in the absence of some other explanation for the illness.[1] The Japanese diagnostic criteria include the following: 1) fever persisting for 5 days or longer; 2) nonexudative conjunctival injections; 3) oral mucosal changes; 4) changes of the peripheral extremities; 5) rash, primarily truncal; and 6) cervical lymphadenopathy (at least 15 mm in diameter). Cervical lymphadenopathy is the least common diagnostic criterion and is present in approximately 50% to 75% of KD patients. In contrast, the other 5 criteria are present in greater than 90% of patients with KD.[4] Nevertheless, we have experienced patients who had only fever and cervical lymphadenopathy at the initial examination.[5] The clinical presentation in KD patients may initially resemble that of other infectious diseases, including bacterial and viral infections. It is important to recognize KD at an early stage so that appropriate therapy can be initiated. For this reason, we investigated cervical lymphadenopathy by ultrasonography as a means of differentiating between KD and other infectious diseases, such as presumed bacterial lymphadenitis and acute Epstein-Barr virus (EBV) infection presenting as infectious mononucleosis (IM).

MATERIALS AND METHODS

Patients

Eligible patients were those who presented to our hospital with fever and lymphadenopathy that was visible as an anterior or posterior cervical mass. Illness day 1 was determined as the first day of fever for all patients. All of the patients were Japanese. Informed consent for participation in the study was obtained from the participants' parents.

KD

KD patients were diagnosed by the standard diagnostic criteria.[1] Only KD patients who had a cervical mass at presentation were included. All patients were examined by ultrasound before receiving standard Japanese treatment with IVGG (Venilon, Teijin Co, Ltd, Tokyo, Japan), 400 mg/kg/d for 5 days and oral aspirin (30 mg/kg/d). This treatment was initiated on diagnosis. Two-dimensional echocardiography was used to detect the presence of CAL. Coronary arteries with diameters of 4 mm or more were classified as abnormal, in accordance with the KD Cardiovascular Lesion Diagnostic Criteria of the Research Committee on KD.[6]

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Presumed Bacterial Cervical Lymphadenitis

The diagnosis was based on clinical symptoms of acute bacterial lymphadenitis that included a tender cervical neck mass with overlying erythema and red color, and supportive laboratory data including an elevated white blood cell count (WBC) and C-reactive protein (CRP) level. Aspirates for bacterial culture were performed when clinically indicated. Diagnosis of bacterial lymphadenitis was further confirmed by a clinical improvement on appropriate intravenous antibiotic therapy. Ultrasound examination was performed before initiation of intravenous antibiotics.

EBV-IM

The diagnosis was based on a clinical presentation of sore throat, fever, and bilateral cervical lymphadnopathy accompanied by atypical lymphocytes in the peripheral blood. All patients were positive for IgM and IgG antibodies to EBV capsid antigen and were negative for antibody to EBV nuclear antigen during the acute stage. No patients required steroid therapy.

Ultrasonography

The measurement of the cervical neck mass was performed by one investigator (N.T.). When bilateral lymphadenopathy was present, the larger of the neck masses was examined by ultrasonography. At the time of admission, ultrasonograms of cervical lymph nodes were obtained using a 7.5-MHz or 10-MHz transducer of a B-mode sector scanner (Aloka SSD-2200, Aloka Co, Ltd, Tokyo, Japan). Ultrasonography required 3 to 5 minutes per patient and adequate studies were obtained from all patients without sedation. Photographs of ultrasound images were recorded by one investigator (N.T.).

RESULTS

Over the 4-year study period, 35 patients who presented with fever and a cervical neck mass were enrolled. Twenty-two patients ultimately met the diagnostic criteria for KD, 8 patients were diagnosed with presumed bacterial lymphadenitis, and 5 patients were diagnosed with EBV-IM.

KD

Of the 22 patients who ultimately met the diagnostic criteria for KD, 15 were boys and 7 were girls (mean age: 2.6 years; range: 0.2–7.0 years; Table 1). Ultrasonographic evaluation of cervical lymph nodes was performed on the patients on illness day 2 to 7 (mean: 4.0) on admission. In these patients, the diagnosis for KD was made on illness day 4 to 7 (mean: 5.0). The mean peripheral WBC and neutrophil counts were 16 150/mm^3 (range: 9200–30 500/mm^3) and 11 612/mm^3 (range: 4554–23 790/mm^3), and the mean CRP level was 9.0 mg/dL (range: 2.7–20.9 mg/dL) at the time of the cervical lymph nodes evalu-

TABLE 1. Patients With KD, Presumed Bacterial Lymphadenitis, and EBV-IM

Variable	Case	Age	Gender	Neck Mass		Illness Day‡		Culture
				Numbers*	Size (mm)†	US Evaluation	Diagnosis§	
KD	1	6	F	1 u	30 × 20	4	5	ND
	2	2	M	1 u	50 × 40	5	5	ND
	3	3	M	1 u	45 × 40	2	5	ND
	4	3	M	1 u	25 × 25	3	5	ND
	5	3	F	1 u	55 × 50	3	5	ND
	6	3	M	1 u	25 × 25	7	6	ND
	7	0.2	M	1 u	30 × 20	3	4	ND
	8	2	M	1 u	30 × 30	3	5	ND
	9	3	M	1 u	50 × 30	3	5	ND
	10	2	M	1 u	40 × 35	2	4	ND
	11	2	M	1 u	20 × 20	3	4	ND
	12	2	M	1 u	40 × 30	5	5	ND
	13	2	F	1 u	50 × 30	6	6	ND
	14	0.6	F	1 u	30 × 30	5	5	ND
	15	2	M	1 u	40 × 20	7	7	ND
	16	1.1	M	1 u	50 × 30	3	5	ND
	17	4	F	1 u	40 × 40	4	7	ND
	18	7	M	1 u	30 × 20	2	5	ND
	19	1.5	F	1 u	30 × 20	4	4	ND
	20	5	M	1 u	50 × 50	5	5	ND
	21	1.3	M	1 u	30 × 20	4	4	ND
	22	4	F	1 u	30 × 20	5	5	ND
Presumed bacterial cervical lymphadenitis	1	7	F	1 u	30 × 30	4		ND
	2	1	M	1 u	60 × 20	5		ND
	3	0.7	F	1 u	60 × 50	8		*Staphylococcus aureus*
	4	0.7	M	1 u	60 × 60	12		ND
	5	3	M	3 b	15 × 15	2		ND
	6	4	F	2 b	50 × 50	6		*Staphylococcus aureus*
	7	0.4	M	1 u	60 × 40	4		ND
	8	4	F	1 u	30 × 30	3		ND
EBV-IM	1	1	M	3 b	50 × 30	5		ND
	2	2	M	3 b	40 × 30	10		ND
	3	5	F	4 b	50 × 40	23		ND
	4	1.7	M	2 b	40 × 30	2		ND
	5	4	F	2 b	65 × 45	13		ND

US indicates ultrasonography; u, unilateral; b, bilateral; ND, not done.
* Total numbers of nodes that could be visualized.
† Size of the largest cervical mass.
‡ Illness day 1 was determined as the first day of fever.
§ Illness day on which patients met KD criteria.

ated. Twelve (54.5%) of the KD patients did not fulfill the Japanese diagnostic criteria when their cervical lymph node evaluation was performed by ultrasonography (Table 2). Moreover, on admission 5 (41.7%) of these 12 KD patients had only cervical lymphadenopathy, in addition to fever for <5 days, when the ultrasonographic evaluation of cervical lymph nodes was performed. These 12 KD patients did not fulfill the diagnostic criteria for KD until 1 to 3 (mean, 2) days after evaluation of the cervical lymph nodes. Two patients developed CAL. The echocardiograms of a 2-year-old boy on illness day 15 revealed a coronary aneurysm of the right coronary artery with a maximum diameter of 12 mm and a left coronary artery aneurysm with a maximum diameter of 15 mm. The echocardiograms of another 1-year-old boy showed one right coronary aneurysm with a maximum diameter of 5.4 mm on illness day 17.

All the KD patients in our study had a single unilateral cervical mass. Transverse ultrasonograms (Fig 1) demonstrated multiple enlarged nodes, each 5 to 10 mm in diameter, which formed 1 palpable mass. The nodes were hypoechoic relative to surrounding tissue. Together, they resembled a cluster of grapes. All 22 KD patients had a similar pattern on their ultrasonograms.

Presumed Bacterial Cervical Lymphadenitis

Eight patients were diagnosed with presumed bacterial cervical lymphadenitis. Four were boys and 4 were girls (mean age: 2.6 years; range: 0.4–7 years; Table 1). Two of the 8 patients with presumed bacterial lymphadenitis developed fluctuant nodes while receiving intravenous antibiotics. Needle aspiration was performed and the purulent aspirate grew *Staphylococcus aureus* in both cases. The remaining patients had resolution of fever and lymph node swelling on intravenous antibiotics and did not require additional intervention. Ultrasonographic evaluation of cervical lymph nodes was performed on illness day 2 to 12 (mean: 5.5). The mean counts of WBC and neutrophils were 18 088/mm^3 (range: 11 300–25 000/mm^3) and 11 910/mm^3 (range: 6425–19 824/mm^3), and the mean CRP level was 8.8 mg/dL (range: 4.1–24.3 mg/dL). Patients with presumed bacterial lymphadenitis had both unilateral and bilateral lymphadenopathy. All patients with presumed bacterial lymphadenitis demonstrated a well-defined mass that had a large central hypoechoic component with a satellite of normal-sized lymph node (Fig 2).

EBV-IM

Five patients were diagnosed with EBV-IM. Three were boys and 2 were girls (mean age: 2.8 years; range: 1–5 years; Table 1). Ultrasonographic evaluation of cervical lymph nodes was performed in the patients on illness day 2 to 23 (mean: 10.6). The mean peripheral WBC and neutrophil counts were 20 760/mm^3 (range: 7800–35 400/mm^3) and 6038/mm^3 (range: 2496–9735/mm^3), and the mean atypical lymphocyte counts were 7440/mm^3 (range: 195–17 700/mm^3). The mean CRP level was 1.6 mg/dL (range: 0.5–2.4 mg/dL).

Transverse ultrasonograms of the largest neck mass in all patients with EBV-IM demonstrated multiple enlarged nodes each measuring 5 to 15 mm in diameter in a single neck mass (Fig 3). The ultrasonogram of the largest neck mass in all IM patients showed a pattern similar to that in KD. There were no differences in the ultrasonograms obtained on different illness days in these patients.

Laboratory Data Statistics Among the 3 Patient Groups

The neutrophil counts in the patients with KD and in those with presumed bacterial cervical lymphadenitis were more increased than those of patients with EBV-IM ($P < .05$, respectively, by the Mann-Whitney test). The levels of CRP were higher in the patients with KD and in those with presumed bacterial cervical lymphadenitis than in patients with

TABLE 2. KD Patients Who Did Not Fulfill the Diagnostic Criteria at US Evaluation

Case*	Illness Day		Presence of Manifestations at US Evaluation					
	US Evaluation	Diagnosis†	Fever‡	Cervical Lymphadenopathy	Conjunctival Injection	Oral Mucosal Changes	Peripheral Changes	Rash
1	4	5	+	+	+	−	+	+
16	3	5	+	+	−	+	+	+
8	3	5	+	+	−	+	+	−
11	3	4	+	+	+	+	−	−
4	3	5	+	+	−	+	−	−
18	2	5	+	+	−	+	−	−
7	3	4	+	+	−	−	−	+
3	2	5	+	+	−	−	−	−
5	3	5	+	+	−	−	−	−
9	3	5	+	+	−	−	−	−
10	2	4	+	+	−	−	−	−
17	4	7	+	+	−	−	−	−

US indicates ultrasonography.
Five cases at the bottom had 2 symptoms, such as fever and cervical lymphadenopathy, at the early stage. Illness day 1 was determined as the first day of fever.
* Same case number in Table 1.
† Illness day on which patients met KD criteria.
‡ Duration of fever was shorter than the 5 days defined by Japanese diagnostic criteria.
+ indicates present; −, lacking.

Fig 1. Cervical lymphadenitis in KD. Transverse ultrasonograms of a 4-year-old girl (case 17; A), a 1.5-year-old girl (case 19; B), and a 5-year-old boy (case 20; C)—a unilateral palpable mass—shows multiple enlarged lymph nodes measuring 5 to 10 mm in diameter. The nodes are slightly hypoechoic relative to surrounding tissues. Each mass resembled a cluster of grapes.

Fig 2. Cervical lymphadenopathy in presumed bacterial lymphadenitis. Transverse scans of a 7-year-old girl (case 1; A), a 1-year-old boy (case 2; B), and a 4-year-old girl (case 8; C) demonstrate a well-defined mass with a large central hypoechoic component with small nodes.

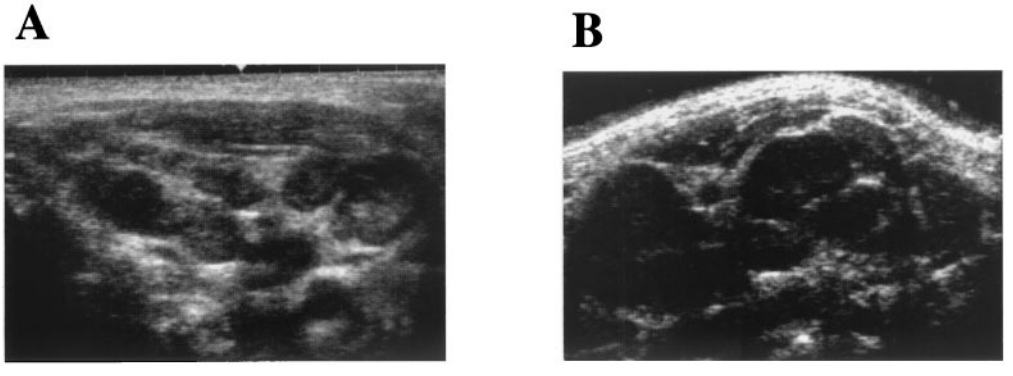

Fig 3. Cervical lymphadenopathy in EBV-IM. Transverse scans of the largest neck mass in a 1.7-year-old boy (case 4; A) and a 4-year-old-girl (case 5; B) demonstrate multiple enlarged nodes measuring 5 to 15 mm in diameter in a single neck mass.

EBV-IM ($P < .01$, respectively, by the Mann-Whitney test). There were no significant differences in both neutrophil counts and CRP levels between the patients with KD and those with presumed bacterial cervical lymphadenitis.

DISCUSSION

In this study, we demonstrated that ultrasonograms of cervical lymph nodes in KD patients showed a characteristic pattern that looks like a cluster of grapes. There have been no previous reports of the use of ultrasonography to examine cervical lymphadenopathy in KD. It has previously been reported that there were no specific findings in a computed tomographic evaluation of KD patients with cervical swelling and fever.[7] The sonographic echotexture is more suitable for providing high-quality images of hypoechoic lymph nodes than are the density-dependent images obtained by CT in general.

Cervical lymphadenopathy is 1 of the major criteria for KD. It is usually unilateral but can sometimes be bilateral. The lymph nodes are usually firm and tender. Clinically, these nodes are often mistaken for bacterial lymphadenitis when patients are early in the course of their illness and the other features of KD have not yet appeared. This can sometimes lead to unnecessary treatment with antibiotics and delay the administration of IVGG.[5] Little is known about the pathogenesis of the cervical lymphadenopathy in KD. In search of clues as to the cause of KD, Ka-

wasaki and colleagues[8,9] performed cervical lymph node biopsies and found that the single, palpable mass usually consisted of multiple nodes. Our study confirmed this observation. Histologic examination of the lymph nodes revealed swelling of the endothelial cells of postcapillary venules and hyperplasia of reticulum cells.[8,9] Other investigators have described nonspecific changes that included focal areas of necrosis with microthrombi in adjacent small vessels, hyperplasia of T-zones, and macrophage infiltration of B-zones.[10–12]

The feature of the ultrasonography of cervical lymph nodes in KD is similar to that of EBV-IM but different from that of presumed bacterial lymphadenitis. Ultrasonography is well-known to be valuable for differentiating between nonsuppurative adenopathy and abscess caused by suppurative lymphadenitis.[13] It is important for clinical management to differentiate between KD and other infectious diseases, such as suppurative lymphadenitis and IM, early in the course of the illness. In our series, patients with EBV-IM could be easily differentiated from the other clinical categories based on laboratory data. In patients with suppurative lymphadenitis; however, laboratory data showed a pattern similar to that in patients with KD, ie, an increase in neutrophils and CRP. In our study, the combination of laboratory examinations and ultrasonography of cervical lymph nodes might be a valuable method for diagnosing KD in patients who initially presented with only fever and cervical lymphadenopathy. Ultrasonography is an appealing technique for use with children. It is noninvasive, rapid, and easy to perform and allows diagnostic examination of pediatric patients who may not cooperate or who may cry for any small reason.

The shortcomings of our presents study were as follows: 1) the number of patients was small; and 2) some patients with bacterial cervical lymphadenitis were diagnosed by clinical criteria. A new, multicenter study with a large number of patients will be needed for the next step in this line of investigation.

CONCLUSION

Ultrasonographic features of cervical lymph nodes of KD patients were different from those of presumed bacterial lymphadenitis. Ultrasonographic evaluation may be useful for diagnosis of KD patients having cervical lymphadenopathy at an early stage of the disease.

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