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NOTE

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Analysis of data in 30 patients with cat scratch disease without lymphadenopathy

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Abstract The prominent clinical manifestation of cat scratch disease is regional lymphadenopathy at the site of the cat scratch or bite, associated with fever or general symptoms. A serological study of 540 patients with either lymphadenopathy, persistent fever, or pet ownership disclosed that 30 (16.1%) of the 186 patients with a serological diagnosis of cat scratch disease had no regional lymphadenopathy, and in these 30 patients, the absence of lymphadenopathy was closely related to the presence of persistent fever, fever of unknown origin, or systemic complications. Physicians should be alert to cat scratch disease that is not associated with lymphadenopathy to enable prompt diagnosis and treatment.

Key words Cat scratch disease · *Bartonella henselae* · Lymphadenopathy

Cat scratch disease (CSD), caused by *Bartonella henselae*, typically presents with localized lymphadenopathy associated with a brief period of fever and general symptoms.[1] Chronic lymphadenitis is the hallmark of CSD, most frequently affecting lymph nodes draining the site of inoculation. With the use of serological diagnosis, we have found that some CSD patients lacked regional lymphadenopathy, and the diagnosis and treatment of CSD were delayed. We analyzed clinical manifestations in CSD patients without lymphadenopathy.

Between May 1997 and April 2004, a total of 540 patients from 112 hospitals located in central and southwestern areas of Japan (409 children; 131 adults) suspected of having CSD, because of either lymphadenopathy, persistent fever, or fever of unknown origin and pet ownership were referred to us for the serological diagnosis of CSD. All the 540 patients were otherwise healthy.

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Serological diagnosis, using an indirect fluorescence antibody (IFA) method,[2,3] was made according to either elevated titers of IgM (≧1:20) or IgG (≧1:256) antibodies, or a fourfold rise in IgG titer in acute compared with convalescent sera. The sensitivity and specificity of our IFA method were 69% and 100%, respectively.[4] Polymerase chain reaction (PCR) with primers CAT1 and CAT2[5] and nested primers, designated as CAT1′ and CAT2′ (CAT1′; 5′-AATGATGTCCGTGATCTAGC-3′ CAT2′; 5′-CATCAGAAGGAGCAACAATC-3′) was positive for *Bartonella* DNA.

Of the 540 patients, 186 (150 children, 36 adults) were serologically positive for *B. henselae*, whereas the other 345 were serologically negative. Of the 186 seropositive patients, 156 (83.9%) had regional lymphadenopathy, and the other 30 (16.1%) had no lymphadenopathy (Table 1). The age of these 30 patients ranged from 11 months to 56 years (mean, 15.8 years); 24 (80.0%) were under 18 years of age. There were 15 males (11 children, 4 adults) and 15 females (13 children, 2 adults).

Of the 30 patients without lymphadenopathy, prolonged fever lasting for 7 days or more was observed in 25 patients (83.3%), that lasting for 7–13 days was seen in 10 (33.3%), and that lasting for 14 days or more was seen in 15 (50.0%). The duration of fever ranged from 0 to 70 days (mean, 14.8 days), and the maximum temperature ranged from 37.9°C to 42.0°C. General symptoms, including malaise, headache, convulsion, sore throat, otalgia, vomiting, and diarrhea, were observed in 22 patients (73.3%). Of the 30 patients, 29 patients a previous history of contact with a cat, and 1 had had contact only with a dog. PCR analysis was performed for 18 patients; the analysis confirmed bacteremia in 1 patient.

Fifteen of the 30 patients without lymphadenopathy had systemic complications, including neuroretinitis (5 cases), Parinaud's oculoglandular syndrome ($n = 2$), hepatosplenic granuloma ($n = 2$), hepatosplenic abscesses ($n = 2$), hepatosplenic low-echoic lesions ($n = 2$), juvenile rheumatoid arthritis ($n = 1$), and granuloma of the papilla ($n = 1$).

Table 2 shows the association of duration of fever with or without lymphadenopathy and complications in the 186

Table 1. Clinical features of 30 patients without regional lymphadenopathy

Patient	Age (years)/ Sex	Duration of fever (days)	Maximum temperature (°C)	General symptoms[a]	Contact with cat	Laboratory findings			Complications
						IFA titer		PCR	
						IgM	IgG		
1	16/F	0	36.9	–	+	640	2048	NT	Neuroretinitis
2	30/M	0	36.8	+	+	80	1024	NT	Neuroretinitis
3	3/F	2	37.9	+	+	–	256	–[c]	Parinaud's oculoglandular syndrome
4	50/M	4	38.7	+	+	40	1024	NT	
5	6/F	5	39.4	NT	+	–	2048	–[c]	
6	9/F	7	40.0	+	+	20	1024	–[c]	
7	48/M	7	39.0	+	+	–	1024	–[c]	Parinaud's oculoglandular syndrome
8	55/F	7	38.0	+	+	–	2048	+[d]	Bilateral papilledema, neuroretinitis, visual impairment of the right eye
9	17/M	7	40.0	+	+	160	2048	NT	Granuloma of the papilla, macular stars, visual impairment, narrowing visual field
10	11/M	7	NT	+	+	40	64	–[c]	
11	7/F	7	39.5	+	+	80	1024	NT	
12	12/F	8	40.3	+	+	40	512	NT	
13	10/F	10	39.0	+	–[b]	–	512	+[e,i]	Hepatic granuloma
14	9/M	12	40.0	+	+	80	2048	–[c]	
15	56/M	12	42.0	+	+	20	256	–[c]	
16	9/F	14	39.0	+	+	80	1024	+[c]	
17	25/F	14	40.0	+	+	80	1024	+[f]	Splenomegaly, splenic granuloma
18	9/M	14	40.0	+	+	320	2048	NT	
19	13/F	15	41.0	+	+	–	1024	NT	Hepatosplenic low-echoic lesions
20	1/M	15	39.8	+	+	–	512	–[c]	
21	8/F	15	40.0	NT	+	20	512	NT	
22	9/F	20	40.0	–	+	160	2048	NT	Neuroretinitis, granuloma-like lesion in the cornea
23	8/M	21	40.0	–	+	80	2048	–[c]	
24	8/M	21	40.0	–	+	80	4096	NT	Splenic low-echoic lesions, neuroretinitis
25	17/M	24	39.0	+	+	–	512	–[g]	Multiple liver abscesses
26	1/M	24	40.0	+	+	20	1024	NT	
27	4/F	25	40.0	+	+	–	4096	–[c]	Juvenile rheumatoid arthritis
28	9/M	26	40.0	–	+	40	1024	–[c]	Fundas albipunctatus, splenic low-echoic lesions
29	12/F	32	39.0	+	+	80	2048	–[d]	
30	11 months/M	70	39.4	–	+	–	256	–[h]	Splenic abscesses, subdiaphragmatic abscesses

NT, not tested
[a] Malaise, headache, convulsion, sore throat, otalgia, vomiting, and diarrhea
[b] Contact with a dog
[c] Peripheral blood cells
[d] Cerebrospinal fluid
[e] Specimen by liver biopsy
[f] Specimen by spleen biopsy
[g] Liver abscesses
[h] Splenic abscesses
[i] DNA sequence was compatible with *Bartonella hensellae*

Table 2. Association of duration of fever with or without lymphadenopathy and complications in 186 patients

Feature	No. of patients	Duration of fever (days)			Complications
		0–6	7–13	≧14	
Lymphadenopathy[a]	156 (83.9)	118 (75.6)	18 (11.5)	20 (12.8)	8 (5.1)
No lymphadenopathy	30 (16.1)	5 (16.7)	10 (33.3)	15 (50.0)	15 (50.0)

Figures in parentheses are percentages
[a] Lymphadenopathy was associated with short duration of fever ($P < 0.01$) and absence of complications ($P < 0.000015$)

seropositive patients. When the presence of lymphadenopathy was chosen as the target variable by stepwise multiple regression analysis (logistic regression analysis), it was closely associated with short duration of fever ($P < 0.01$) and absence of complications ($P < 0.000015$).

It is noteworthy that lymphadenopathy was negatively related to the duration of fever or the presence of systemic complications. A few reports of CSD without regional lymphadenopathy, but associated with prolonged fever or systemic complications, have been described previously.[6,7]

There may be two plausible explanations for the frequent coincidence of lack of lymphadenopathy and the presence of persistent fever or systemic complications. First, a regional lymph node may fail to react properly to the entry of the bacteria, thus allowing rapid systemic infection. Second, in immunocompetent patients as well as immunocompromised patients, the immune response at any lymph node may be ineffective for raising specific reactions to *B. henselae*, inevitably leading to systemic infection.

When a patient has a prolonged fever of unknown origin, the possibility of CSD without lymphadenopathy should be considered, and a search for pet ownership or pet contact and underlying systemic complications is recommended to enable prompt diagnosis and appropriate treatment.

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