

Cat Scratch Disease as a Mimicker of Malignancy

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Cat scratch disease (CSD) infrequently mimics malignancy. We reviewed 11 such cases at MD Anderson Cancer Center and an additional 36 reported from the literature. Breast cancer, sarcoma, and lymphoma were the most commonly suspected malignancies. Most patients were young, female, had prior cat exposure, and had no systemic symptoms. Regional lymphadenopathy was the most common finding.

Keywords. *Bartonella henselae*; cat scratch disease; malignancy; mimickers.

Cat scratch disease (CSD) is a relatively common zoonotic infection acquired from cats (cat fleas) caused by a fastidious gram-negative bacterium, *Bartonella henselae* [1, 2]. The most common clinical presentation of CSD is lymphadenopathy proximal to the site of inoculation with or without fever, weight loss, and systemic involvement (eg, hepatosplenic lesions) [3, 4]. Atypical manifestations such as neuroretinitis, osteomyelitis, and soft tissue masses mimicking malignancy have been rarely described in isolated case reports [5, 6] (Supplementary Tables 1 and 2 and Supplementary References). To that end, we sought to describe our experience with CSD mimicking malignancy at MD Anderson Cancer Center (MDACC) and reviewed the reported cases in the literature.

METHODS

We retrospectively reviewed all consecutive cases of CSD mimicking malignancy (November 2015 to January 2020) at MDACC in adults and children who presented to our institution with a

suspicion of cancer. Diagnosis of CSD was made if at least 3 of 4 of the following criteria were met: (1) cat contact with or without a scratch or inoculating lesion in skin, eye, or mucous membranes; (2) positive serology for *B. henselae* (Bartonella Antibody Panel, immunoglobulin G [IgG] and immunoglobulin M [IgM], Mayo Clinic; immunofluorescence assay) with an IgG titer >1:64 or positive IgM ($\geq 1:20$); a 4-fold rise in convalescent titer (definitive); (3) compatible laboratory/radiology findings such as negative mycobacterial purified protein derivative or serologies for other causes of lymphadenopathy, positive *Bartonella* polymerase chain reaction (PCR) assay (BARRP real-time PCR, Mayo Clinic), ultrasound (US) or computed tomography (CT) scan with liver/spleen lesions; (4) pathology: granulomatous inflammation findings consistent with CSD with or without identification of bacteria on Warthin-Starry stain [4]. Patients diagnosed with CSD previously at an outside facility were not included. Data were collected on demographics, history of animal contact, symptoms, signs, laboratory findings, histopathology, radiological studies, treatment, outcomes, and malignancy mimicked. The study was approved by our institutional review board. In addition, we also performed a comprehensive search of the literature between 1952 and October 2020 with the assistance of a qualified medical librarian (R. S. H.). Medline (Ovid), Embase (Ovid), Scopus (Wiley), and Google Scholar were queried using both natural language and controlled vocabulary terms for CSD and malignancies. Articles not in the English language were excluded.

RESULTS

We identified 11 patients at MDACC (Table 1). Average age was 34 years. Ten of 11 (91%) patients were female, with 5 of 11 (45%) being ≤ 18 years of age. Only 2 of 11 (18%) patients reported fever and 1 had night sweats. On evaluation none of the patients had weight loss, skin lesions, conjunctivitis or hepatosplenomegaly. Ten of 11 (91%) patients had history of exposure to a cat. All patients had regional lymphadenopathy on evaluation, with axillary and inguinal regions being the most common (3 each) and 2 with epitrochlear lymphadenopathy. None of the patients had an atypical presentation (eg, Parinaud oculoglandular syndrome, neuroretinitis, encephalopathy, osteomyelitis, pneumonia, or thrombocytopenic purpura). All patients had positive *Bartonella* serology. Nine of 11 (82%) patients had IgG titers $\geq 1:512$ while 3 of 11 (27%) had positive IgM titers. Nonnecrotizing granulomas were the most common finding, seen in 4 of 8 (50%) patients who had a biopsy. None of the 5 patients tested showed presence of the organism with Warthin-Starry staining of specimen. Both patients with PCR testing in blood for *Bartonella* were negative. US or CT of chest, abdomen, pelvis, or extremities showed only isolated mass/

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regional lymphadenopathy but no visceral or bony involvement. Similarly, positron emission tomography (PET) scans were done in 3 patients, revealing localized lymphadenopathy in different regions without visceral organ involvement (Table 1). Eight patients were treated with a short course of azithromycin. Among 10 patients with follow-up, 1 had persistent fever while the others showed resolution or improvement. Malignancies suspected in these 11 patients were lymphoma (n = 3), breast (n = 2), sarcoma (n = 2), unknown malignancy (n = 3), and skin cancer (n = 1).

We identified 36 additional cases reported in the literature of CSD simulating malignancy (Table 1; Supplementary Tables 1 and 2; Supplementary References). Average age was 33 years, and 21 of 36 (58%) cases were female. Four of them had a prior history of cancer. History of cat exposure was reported in 27 of 30 (90%) cases. Lymphadenopathy was the most common symptom/sign/imaging finding described in 33 of 36 (92%) cases with the axillary region being most common (11 of 36 [31%]). Fever was not common, reported in 13 of 36 (36%) cases. Atypical presentations were seen in 5 of 36 (14%) cases (2

Table 1. Summary of 47 Cases of Cat Scratch Disease Mimicking Malignancy

Parameter	MDACC (n = 11)	Published Cases (n = 36)	Total (N = 47)
Age, y			
Mean	34	33	...
Median	21	29	...
Sex, female	10	21	31
Fever	2	13	15
Skin lesions	0	10	10
Lymphadenopathy (clinical, imaging)			
Axillary	3	11	14
Cervical	2	5	7
Inguinal	2	0	2
Epirochlear	2	1	3
Multiple	2	10	12
Other ^a	0	6	6
None	0	2	2
Unknown	0	1	1
Visceral involvement			
Liver	0	5	5
Spleen	0	6	6
Bone ^b	0	3	3
Biopsy findings ^c			
Necrotizing granulomatous lymphadenitis/inflammation	0	20	20
Nonnecrotizing granulomatous lymphadenitis/inflammation	4	5	9
Nonspecific inflammatory infiltrate ^d	3	4	7
Abscess/microabscess	1	5	6
Unknown/insufficient information	0	5	5
Not performed	4	5	9
Warthin-Starry stain positivity	0	10	10
History of cat exposure			
Yes	10	27	37
No	1	3	4
Unknown	0	6	6
Malignancy mimicked			
Other ^e	5	13	18
Breast cancer	2	11	13
Lymphoma ^f	2	9	11
Sarcoma	2	3	5

Data are presented as No. unless otherwise indicated.

Abbreviation: MDACC, MD Anderson Cancer Center.

^aSplenic hilum, retroperitoneal, abdominal.

^bAbnormal bone scan or positron emission tomography findings.

^cPatients may have >1 finding.

^dHistiocytes, lymphocytes, lymphoreticular proliferation, plasma cells, lymphadenitis.

^eIncludes metastatic skin cancer, unknown malignancies, neuroblastoma, pancreatic cancer, hypopharyngeal cancer, chest wall malignancy, parotid cancer, etc.

^fIncludes splenic lymphoma, T-cell lymphoblastic lymphoma, Hodgkin lymphoma, large cell lymphoma.

with Parinaud oculoglandular syndrome, 3 with bony involvement). In 17 cases with reported serological testing, IgG was positive in 13 (76.5%) and IgM alone was positive in 2 (11.8%). Antibody titers when reported were $\geq 1:512$ in 4 of 5 (80%) cases. Seven patients had positive PCR testing for *B henselae* in blood or tissue.

US or CT of chest, abdomen, pelvis, or extremities showed hepatomegaly or splenomegaly in 4 of 11 (36%) cases, hepatic or splenic hypodensities, and/or hypoechoic lesions in 8 of 10 (80%) cases. Four patients had PET scans done, with all showing lymphadenopathy and 1 with cervical and thoracic vertebrae involvement (Supplementary Reference 24). Necrotizing granulomatous lymphadenitis was the most common finding on histopathology in 20 of 36 (56%) specimens, with Warthin-Starry stain positive in 10 of 18 (56%) specimens.

Macrolides were used most frequently as treatment (9 cases) and 3 patients received fluoroquinolones and tetracyclines. Rifampin was used as an adjunct in 3 cases. Outcome was favorable in all 26 cases reporting for follow-up.

Similar to our own experience, malignancies mimicked most commonly were breast (n = 11), lymphoma (including recurrences; n = 9), sarcoma (n = 3), and "other" (n = 13) (Table 1; Supplementary Tables 1 and 2).

DISCUSSION

To our knowledge, this is the first systematic evaluation of CSD mimicking malignancy. Several observations arose from our study. A variety of solid tumors, especially breast, sarcoma, and lymphoma, were the main diagnostic consideration in both our series and the literature.

Affected patients at our institution were young (mean age, 34 years) with a clear female sex predominance. History of exposure to cats was seen in 91% in our cohort and 90% from the published cases. Regional lymphadenopathy was the most common presentation, noted in the vast majority of patients. Our patients seen at MDACC reported no constitutional symptoms and did not have visceral involvement or other atypical manifestations of CSD. By contrast, in published cases, systemic symptoms (fever, weight loss, night sweats; 39%) and atypical manifestations (14%) were more commonly reported, likely reflecting a publication bias. Necrotizing granulomas on biopsy (56%) were also more common in the published cases potentially due to a small number of cases in our cohort. High serological titers (IgG $\geq 1:512$) were seen in 82% of our cases and 80% in the published cases, consistent with the reported frequency of positive serology in a large series of CSD [7]. While interpreting serological data, one should be mindful that IgG can be positive (up to 25% cases) after 2 years since initial

infection [8]. A subgroup of patients both in our experience and the literature had PET scans done as part of evaluation of suspected malignancy with fluorodeoxyglucose avid lesions. This experience suggests that a positive PET scan should not exclude CSD as a possibility in the appropriate setting [9, 10].

We acknowledge the limitations of our review. In addition to small numbers and heterogeneity of data, the lack of a denominator makes it impossible to calculate the frequency of CSD as a mimicker of malignancy. Some of our findings may be prone to referral biases of patients seeking a diagnosis of cancer at MDACC. Finally, it is quite possible that our cases and the ones from the literature are an underrepresentation of the frequency of CSD as a mimicker of malignancy, as some cases initially considered to be malignant may have been missed given the self-limiting nature of CSD.

In conclusion, CSD can mimic a variety of malignancies. A high index of suspicion needs to be maintained, especially in young patients who present with lymphadenopathy. History of exposure to cats, *Bartonella* serology, and biopsy are crucial for the diagnosis.

Supplementary Data

Supplementary materials are available at the *Journal of The Pediatric Infectious Diseases Society* online (<http://jpid.oxfordjournals.org>).

Notes

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Patient consent statement. This retrospective study was approved by our institutional review board. As this retrospective study posed no more than minimal risk to patients, informed consent was not required.

Potential conflicts of interest. All authors: No reported conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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