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Woman with necrotising granulomatous lymphadenitis: the key was in anamnesis and physical examination

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CASE PRESENTATION

A 48-year-old woman was referred to the internal medicine outpatient department (OPD) due to an enlarged lymph node in her left axilla. Before the consultation, a core needle biopsy (CNB) had been performed with a pathological diagnosis of necrotizing granulomatous lymphangitis (NGL). Polymerase chain reaction (PCR) of the sample for *M. tuberculosis* complex was negative. The pathologist recommended complete excision of the lymph node to obtain more tissue for analysis. The surgeon referred the patient to internal medicine OPD before performing the procedure.

Anamnesis and examination were conducted. The patient lived in a rural area in Spain. She worked in a kindergarten and had no toxic habits. Her past medical history was unremarkable. No allergies. Regarding her family history, a grandmother had had breast cancer and a cousin had Hodgkin's lymphoma. She takes care of two dogs and six cats at home and volunteered at an animal shelter. Her pets had had ticks but she did not remember having ever had any tick bite. She had not made any trips abroad. She was on tramadol, acetaminophen, cefecoxib, and omeprazole.

Current illness begins five months before the consultation, when a "lump" was noticed in the left axilla. The size of the mass has remained constant throughout this time. She did not have fever, constitutional syndrome, chills, headache, or arthromyalgia.

Physical examination: Body mass index of 40, blood pressure 129/94 mmHg, temperature 36.5°C and heart rate 70 beats per minute. She was in good condition. No jugular ingurgitation. Cardiopulmonary auscultation and abdomen exploration were normal. A small and painless mass could be palpated

at the left axilla, apparently not attached to deep layers. No other masses or enlarged lymph nodes were palpable at any other location. There were multiple cat scratches on the upper limbs (Figure 1). Examination of lower extremities was unremarkable.



Figure 1 Multiple cat scratches on the upper limbs

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Figure 2 The CT scan was normal except for the already known adenopathy in axilla.

In addition to the above-mentioned pathology data, the patient had a normal chest X-ray and mammography.

DIFFERENTIAL DIAGNOSIS

In summary, we have a patient without any type of general or infectious symptoms, with a family history of cancer and a single lymphadenopathy located in the left axilla with a pathological diagnosis that shows NGL. Regarding these data, the working diagnosis is based in two aetiologies of her condition: infectious and non-infectious.

Among the non-infectious causes it can be found sarcoidosis, a disease that can be paucisymptomatic and, although in most cases there are enlarged hilar lymph nodes, they can also occur in extrapulmonary territories such as the axilla. Others that should be taken into account would be haematological malignancies (Hodgkin and Non-Hodgkin lymphoma), berylliosis and tumor metastases, which rarely cause necrosis [1]. It should be noted that there was a necrotizing component in the adenopathy, which would make it necessary to include Kikuchi's disease, in which adenopathies are the most frequent sign although they are usually cervical and more typical in children and young people [2], and systemic lupus erythematosus [3], but there were no other signs or symptoms leading to this diagnosis.

As for infectious causes, the differential diagnosis is broader. We could further divide infectious entities in suppurative and non-suppurative causes. Among the former are tularemia, cat scratch disease, *Yersinia pestis* and fungal infections. Regarding the non-suppurative ones, the possibility of tuberculosis, non-tuberculous mycobacteria, toxoplasmosis, leprosy, syphilis, brucellosis and some types of fungi should be considered. Some of these diseases are highly unlikely, due to the almost complete lack of symptoms and location of the lymph node. For instance, *Y. pestis* infection would affect mesenteric lymph nodes, within a general picture of severe disease; in Epstein-Barr Virus infection (EBV), enlarged lymph

nodes are usually bilateral, predominantly cervical, and do not present granulomas [1].

To reach the diagnosis, the wounds on the arms and hands were crucial, what it would entail the loss of the integrity of the skin barrier. This finding reinforces the possibility of the infectious cause, and it may be due bacteria of the skin flora (bacterial adenitis due to *S. aureus*) or bacteria related to an occupational context. Let us remember that these wounds had been inflicted by cats, so the cat scratch disease, caused by *B. henselae* should be evaluated first, without forgetting other zoonoses such as those transmitted by fleas or ticks (Lyme disease, rickettsiosis, anaplasmosis, babesiosis or tularemia) [4].

PERFORMED TESTS AND CLINICAL EVOLUTION

In the OPD, it was requested a thoracoabdominal Computerized Tomography (CT) to search for other regions lymphadenopathy and a complete analysis with biochemistry, hemogram, peripheral blood morphology, proteinogram, immunoglobulins, inflammatory reactants, autoimmunity study (rheumatoid factor, Anti-nuclear Antibodies and Extractable Nuclear Antibody), Interferon-gamma release assays (IGRAs; *M. tuberculosis*) and serologies of *T. pallidum*, EBV, *T. gondii*, Cytomegalovirus, Hepatitis B and C Virus, Human Immunodeficiency Virus, *C. burnetii*, *B. henselae* and *Rickettsia* spp. The CT scan (Image 2) was normal except for the already known adenopathy in axilla. All blood studies were normal, including inflammatory reactants, except for serologies, being *Bartonella* spp. pathological, with results of: *B. Henselae* IgG, 1/4096 (pathological > 1/256); IgM, 1/80 (indicative of recent infection > 1/20). *B. quintana* IgG 1/256, IgM 1/20 (indicative of recent infection > 1/20), by indirect immunofluorescence. With a diagnosis of cat scratch disease, outpatient treatment was started with azithromycin 500 mg orally one day, followed by 250 mg orally daily for 4 more days. IgG titers for *B. henselae* were reduced by half two months later. The patient is currently asymptomatic.

DISCUSSION

To solve this case we started from a pathological diagnosis, but it was the anamnesis and examination that led us to diagnosis. We acknowledge that the order of action should have been inverse and that a PCR of *B. henselae* at the sample would have made the diagnosis.

NGL can be produced by various diseases that have been described above [1]. Granulomas are organized aggregates of macrophages and other immune cells that arise as biological structures in response to persistent (infectious or not) stimuli. Although they are defensive complexes, they can also transform into differentiated pathological structures. One of these would be necrosis, produced by macrophages. For reasons not entirely understood yet, some granulomas remain without necrosis (those caused by beryllium, sarcoidosis or Crohn's disease), while others, especially those caused by tuberculosis

and other infectious diseases (especially intracellular bacteria and fungi) do undergo it [5]. In a Danish study, 121 patients with lymphadenopathy with granulomatous inflammation in the neck and head were analysed. The most frequent diagnoses were sarcoidosis (26%), tuberculosis (22%), cat scratch disease (6%), non-tuberculous mycobacteria (7%), tumors (2%) and others (4%), with 33% of the patients without an established diagnosis. In the case of tuberculosis, the granulomas were normally necrotizing, being non-necrotizing in sarcoidosis [6]. However, a German study found that cat scratch diseases was present in 13.4% of the 454 patient with head and neck lymphadenopathy analysed, being reticular abscessed granuloma the most frequent pathological finding [7]. Diagnosis in the case of NGL can be challenging because the probability of tuberculosis is remarkable and the detection of bacilli may not be possible with conventional methods due to the low bacillary load in certain extrapulmonary territories, being necessary occasionally to confirm the diagnosis according to the response to anti-tuberculosis treatment [8,9].

Cat scratch disease is an infectious disease caused by *B. henselae*, a Gram-negative bacillus found in cats and fleas. It can be transmitted to humans through bites or scratches. The typical presentation is in children and usually presents with soft, enlarged and sometimes suppurative adenopathy, especially if there has been exposure to cats (mostly kittens, as happened in our case). One or two weeks after the inoculation wound, unilateral regional lymphadenopathies appear, which can persist for months. Other symptoms present may be malaise, arthromyalgia, anorexia, and low-grade fever. Visceral involvement has also been described, mainly hepatosplenomegaly with or without lymphadenopathy, as well as fever of unknown origin in children and occasionally meningoencephalitis, endocarditis and ocular involvement [10]. In immunosuppressed patients, *B. henselae* can cause bacillary angiomatosis, in which multisystem involvement can occur, especially skin, bone, liver and spleen [11,12].

Regarding epidemiology in Spain, seroprevalence in cats has been found in 29–78% of samples [13–15]. In humans, some studies have shown differences in seroactivity against *B. henselae*, especially considering the variable titers limit chosen to establish exposure or infection. We could find serological evidence of *B. henselae* in 8.7–13.55% [16,17] of healthy people, being higher in occupational jobs like veterinarians (37.1%) [18].

Diagnosis is serological, because *B. henselae* is difficult to culture. Titers less than 1:64 make the diagnosis unlikely; between 1:64 and 1:256 imply possible infection; greater than 1:256 make it very likely. IgM positivity suggests recent infection. It is important to highlight, as it happened in our case, that cross-reactivity frequently occurs in IgG titers between *B. henselae* and *B. quintana*. PCR tests can help to achieve diagnosis [10], although in our case the clinical history and the evaluation of the titers of both serologies were conclusive since, although *B. quintana* can cause trench fever and a similar clinical picture, is associated with the presence of lice and poor hygienic sanitary conditions [19].

Regarding treatment, there have been discrepancies classically in the literature about the use of antibiotics because in many cases cat scratch disease can be self-limited [10] although clinical practice guidelines recommend treatment in patients over 45 kg with 500 mg of azithromycin the first day followed by 250 mg per day for 4 more days. Patients weighing less than 45 kg (paediatrics) the dose would be 10 mg/kg the first day and 5 mg/kg the four following [20].

FINAL DIAGNOSIS

Cat scratch disease caused by *B. henselae*.

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CONFLICT OF INTERESTS

Authors declare no conflict of interests

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