Erythema nodosum and sarcoid granulomas — letting the cat out of the bag

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Abstract

A 41-year-old woman presented with a violaceous papule on the dorsum of the hand, large ipsilateral axillary lymphadenopathy, and tender, erythematous, subcutaneous nodules on the legs. Accompanying signs included fever, ankle swelling, and bilateral red eye. She recalled having a previous exposure to kittens one month before and had a positive family history for sarcoidosis. Histological examination of the hand lesion showed sarcoidal granulomas with positive Bartonella henselae DNA, whereas a biopsy done on the leg nodules was compatible with erythema nodosum. Cat scratch disease (CSD) typically presents as a tender regional lymphadenopathy preceded by an inoculation papule with spontaneous resolution occurring between 8-16 weeks. Cutaneous manifestations of CSD are rare, with erythema nodosum accompanying only 0.6% of cases. Although speculative, the background of a positive family history for sarcoidosis may explain the atypical presentation of this case, with red eye, persistent arthralgia, and associated sarcoidal granulomas.

Keywords: sarcoidal granulomas, cat scratch disease, erythema nodosum

Introduction

There are several infectious zoonoses induced by cats. Cat scratch disease is caused by *Bartonella henselae* [1]. Typically, it presents as a tender regional lymphadenopathy preceded by a papule at the site of inoculation [2]. The lymphadenopathy usually resolves within 2-4 months, although it is not unusual for it to resolve in 6-12 months [3]. About half of the patients experience systemic symptoms. Skin eruptions are uncommon, with erythema nodosum present in only 0.6% of the cases [4-5].

Case Synopsis

A 41-year-old woman, with irrelevant past medical history, was admitted to our hospital with fever (38ºC) and myoarthralgias (elbows and ankles). She complained of large tender right axillary lymphadenopathy, a violaceous papule on the dorsum of the right hand (**Figure 1**), and bilateral red eye for 3 weeks. On the day before the admission, she

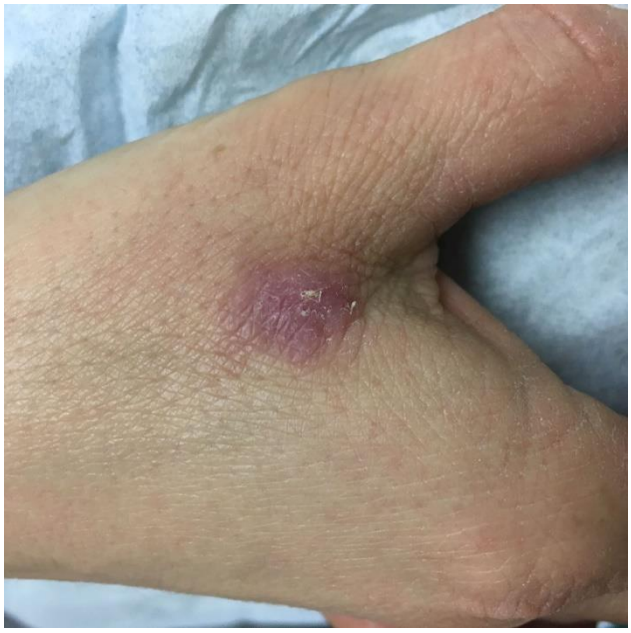

Figure 1. *Inoculation papule on the dorsum of the right hand.*

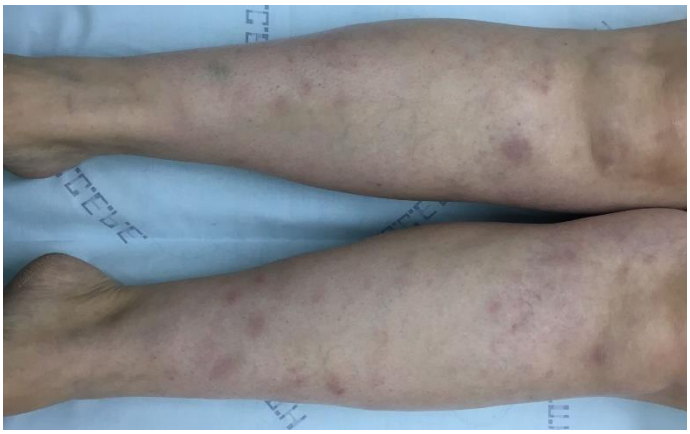

Figure 2. *Painful, erythematous, subcutaneous nodules on the lower legs.*

had developed a pustular eruption on her arms and painful, erythematous, subcutaneous nodules on the shins and thighs (**Figure 2**). She denied night sweats or weight loss. She reported a previous exposure to kittens, 6 weeks before. Her family history was significant for sarcoidosis (mother).

Laboratory workup revealed a slight elevation of inflammatory parameters (high C-reactive protein and leukocytosis) with no other abnormalities. Ultrasonography confirmed a right axillary lymph node of 3.6cm and chest X-ray and abdominal ultrasound were normal.

Blood and urine cultures were negative, as well as viral serologies and serologies for toxoplasmosis, syphilis, *Brucella, Rickettsia, Coxiella* and *Borrelia*. Quantiferon assay for *M. tuberculosis* was negative. Serologies for *Bartonella* were positive IgG (>128g/l) and negative for IgM. Chemistry panel, including serum LDH, calcium and serum angiotensin-converting enzyme were within normal levels. Ophthalmology examination excluded uveitis.

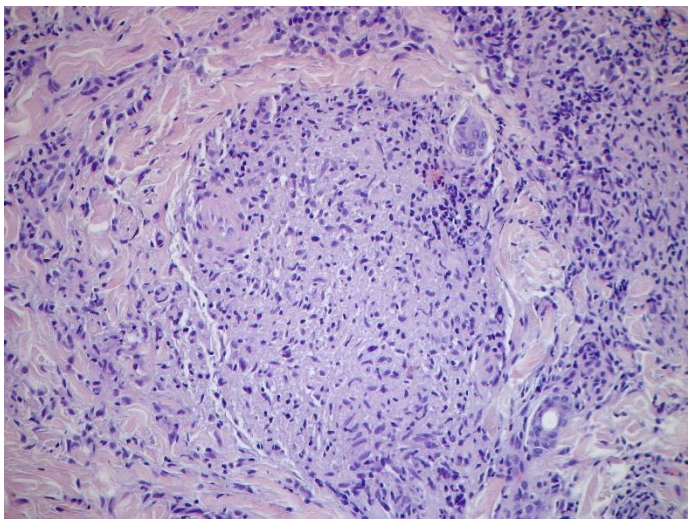

Figure 3. *Skin biopsy, the hand lesion - granulomatous reaction pattern with sarcoidal granulomas. H&E, 40×.*

A skin biopsy was performed on the hand lesion, revealing a granulomatous reaction pattern involving the superficial and deep dermis, characterized by sarcoidal granulomas: granulomas composed of epithelioid histiocytes and giant cells with a paucity of surrounding lymphocytes and plasma cells ("naked granulomas"), (**Figure 3**). Histopathology examination of a subcutaneous nodule of the leg showed a predominantly septal panniculitis with mixed cellular infiltrate, compatible with erythema nodosum (**Figure 4**). DNA of *B. henselae* was found in the biopsy of the inoculation lesion.

Five weeks after admission, the patient still displayed tibio-tarsal arthritis, faded erythema nodosum lesions, and palpable lymphadenopathy. As such, further investigation included a thoracic computed tomography (CT) and a positron emission tomography (PET) that confirmed right axillary lymphadenopathy (2.9cm) with high metabolic activity. Excisional biopsy of the affected lymph node was performed and histopathology demonstrated necrotizing granulomatous lymphadenitis.

The differential diagnosis included atypical bacterial infections and neoplastic lymphadenopathy, both of

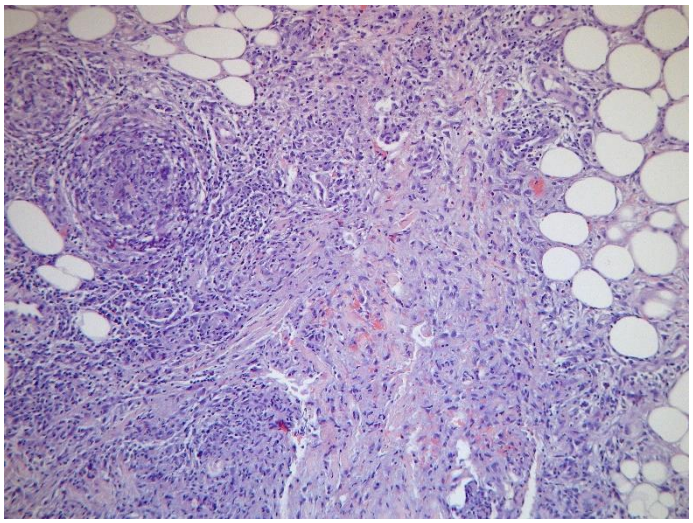

Figure 4. *Skin biopsy, subcutaneous nodule of the leg - predominantly septal panniculitis with mixed cellular infiltrate. H&E, 25×.*

which were excluded based on serologies, cultures, and histopathology. Considering the clinical picture of fever, arthralgias, red eye, erythema nodosum, and sarcoidal granulomas, combined with a positive family background, sarcoidosis was also in the differential.

Sarcoidosis is a diagnosis of exclusion, as other causes of granulomas must be ruled out. In this case, with *B. henselae* DNA being found in the inoculation papule — a highly specific finding — a diagnosis of CSD can be made. Furthermore, no other organ involvement was seen in the PET and CT scans making sarcoidosis less likely.

On admission, the patient was started on doxycycline 100mg twice daily and azithromycin 250mg daily, empirically, bearing in mind the possibility of atypical bacterial infection or cat scratch disease. Later, a short course of oral prednisolone 0.5mg/kg/day with rapid tapering was started to relieve the persistent symptoms.

After 6 months of follow-up, the patient was asymptomatic, with no further cutaneous lesions, but residual axillary lymph node still palpable. Currently, she displays no palpable lymph nodes or further symptoms.

Case Discussion

CSD can be diagnosed on the basis of a compatible clinical picture, positive serologies, and ideally, the presence of *B. henselae* DNA in an inoculation papule or regional lymph node. Erythema nodosum, persistent arthralgia, and conjunctivitis are uncommon findings. In fact, only 5% of cases display cutaneous manifestations other than the inoculation papule.

Erythema nodosum is, by definition, a hypersensitivity reaction with the inflammatory reaction occurring in the panniculus. A wide range of precipitant factors has been linked to erythema nodosum, with infectious causes being the most common. In CSD in particular, erythema nodosum is described in no more than 0.6% of the cases [6].

In typical CSD cases, a lymph node biopsy is not indicated. However, it must be considered in cases of atypical presentation, in which other diagnoses, such as possible malignancy, are entertained [7]. Histopathologically, CSD is usually characterized by suppurative granulomas and necrotizing granulomatous lymphadenitis. For most patients with mild disease only conservative treatment is recommended and the use of antibiotics is controversial [8]. Antibiotics can be used in cases of atypical presentation with systemic disease or significant symptoms, and first-line agents include rifampin, ciprofloxacin, and azithromycin.

In our review of the literature we could not find an association between CSD and sarcoidal granulomas, but it is known that in other infections, such as in secondary syphilis or herpes zoster-affected dermatomes, this type of granulomatous reaction can occur, especially with older lesions. Indeed, sarcoidal disease is characterized by an exaggerated immune response against an unknown antigen in a genetically predisposed individual, resulting in typical non-caseating granulomas [9].

Cutaneous sarcoidal granulomas can be generalized or occur as isolated lesions. Isolated lesions tend to develop especially if there is a localized immune imbalance induced by antigen stimulation in association with local dysfunction of lymphatic drainage, abnormal neuroimmune signaling, or focally deranged immune feedback mechanisms [10].

The existence of familiar predisposition to sarcoidosis is well known, with correlation between specific class 2 MHC alleles and the disease (i.e. HLA-DRB1*03, HLA-DRB1*11, HLA-DRB1*12, HLA-DRB1*14, and HLA-DRB1*15). There is also an association with non-HLA genes [11]. Therefore, it is interesting to note our patient with a genetic background of sarcoidosis who developed an exaggerated granulomatous immune response after a confirmed *Bartonella* infection, presenting with atypical clinical and pathologic aspects that resembled Löfgren syndrome.

Conclusion

This unique case should alert the clinician to the wide spectrum of manifestations possible with CSD. To

the best of our knowledge, it is the first report of a confirmed CSD displaying sarcoidal granulomas on histology and a sarcoidosis-like clinical picture. Interestingly, it may have occurred in the background of an immunological profile that favors this pattern of reaction.

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