

## “Doughnut” Granulomas from Erythema Nodosum in Acute Q Fever

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Q fever is a zoonotic infection caused by *Coxiella burnetii*. The disease has two forms, acute and chronic. The acute form usually manifests as pneumonia, hepatitis, a combination of the two, or a flu-like syndrome. Skin manifestations during the acute disease are uncommon. Diagnosis of Q fever is based on positive serology tests. Liver and bone biopsies may show characteristic “doughnut” granulomata [1-4]. We describe a patient with an acute *C. burnetii* infection, presented as fever, a large angry-looking skin lesion and a characteristic “doughnut” granuloma on skin biopsy.

### Patient Description

A 70 year old woman was admitted to our ward with a fever that had not abated for 1 week. There were no other symptoms of disease, no history of recent travel or contact with sick individuals, and there was no recall of animal contact. Since her past medical history included colon cancer treated by chemotherapy, we were concerned that her current symptoms might be associated with recurrence and admitted her for observation.

On admission, fever was 37.8°C. Physical examination was completely normal and there were no pathological skin manifestations. Blood test results were unremarkable except for C-reactive protein levels, which rose from 38 to > 100 mg/dl during hospitalization (normal range 0–5 mg/dl).

Investigation of fever origin included blood and urine cultures and serology tests for common viruses and other bacteria: all the results were negative. A computed tomography scan of the chest, abdomen and pelvis failed to reveal a source for the fever or the presence of

any other pathology, and the findings of a complete array of markers for an autoimmune disease were negative. One week after her admission, she developed a widespread skin rash on her right lower leg. The skin lesion was biopsied and a 1 week course of cloxacillin and ampicillin for possible cellulitis was started, but there was no improvement in her general condition, fever pattern or skin rash. Three weeks after her admission, the results of serology testing were positive for an acute *C. burnetii* infection.

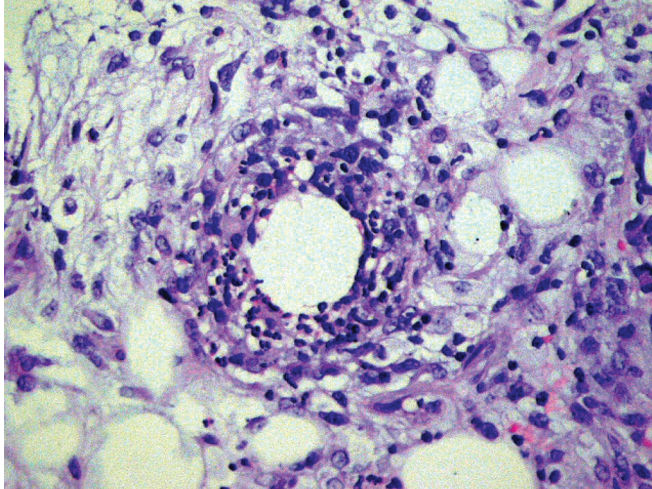
The first blood test that was performed on admission had shown negative titers for Q fever phase I and a 1:32 titers for Q fever phase II. The second test, taken 2 weeks later, showed a seroconversion, with a titer of > 1024 for Q fever phase II. The results indicated an acute infection. The samples were sent to an external laboratory whose results also revealed high titers. The skin biopsy taken from the patient’s lower leg demonstrated panniculitis, mainly localized to the subcutaneous septae, a finding typical of erythema nodosum (i.e., streptococcal, yersinia, mycobacteria and viral infections of the upper respiratory tract, drugs of the sulfa family, oral contraceptives, sarcoidosis and inflammatory bowel disease) were all eliminated. Larger magnification [Figure] demonstrated epithelioid histiocytic granulomas, some of them containing a central lipid vacuole and fibrin, compatible with a typical “doughnut” granuloma. Upon further questioning, the patient recalled having visited a friend who is a cat breeder, about 2 weeks prior to the onset of disease. *Coxiella burnetii* infection was diagnosed and a course of doxycycline was started. Response to treatment was

immediate: 2 days later she became afebrile and the erythema diminished and become dull in color, whereupon she was discharged. She was completely well and had no evidence of skin lesion at follow-up 1 month later.

### Comment

Q fever is a zoonotic infection caused by *C. burnetii*. This is a short (0.3–1.0 µm) pleomorphic rod, possessing a membrane similar to a gram-negative bacterium. While previously classified as a rickettsia, *C. burnetii* was assigned to the gamma subdivision of the Proteobacteria which are closer to legionella and francisella than to rickettsia. Humans are incidental hosts, with mammals, birds and arthropods being affected more often [1]. The most commonly identified sources of human infection are farm animals, such as cattle and goats, but household pets, including dogs, pigeons and cats, can serve as sources of urban outbreaks [2].

Cutaneous involvement in Q fever is uncommon. Maculopapules or purpuric rashes were seldom described, and erythema nodosum and erythema annulare are also rare [3]. Diagnosis is based on serological tests [1]. Histological studies of Q fever based on hepatic and bone marrow biopsies have demonstrated a variety of non-granulomatous histological changes and some types of inflammatory and necrotizing granulomas [4]. A distinctive type of granuloma in Q fever has also been reported, typically appearing as a “doughnut” granuloma characterized by a clean space surrounded by eosinophilic fibrinoid material with a border of polymorphonuclear leukocytes and epithelioid cells. These granulomas were found only in liver and bone marrow of patients with Q fever. The only descrip-



Large magnification of the skin biopsy, showing a typical “doughnut” granuloma.

tion of such a granuloma in the skin was reported by Galache et al. [5].

In our patient the acute Q fever was most probably caused by contact with cats. She developed a widespread

erythema nodosum on her leg, a very rare finding in this disease, and a characteristic “doughnut” granuloma was found in the biopsy of the lesion. We present this case report to raise the level of awareness to *C. burnetii* infection in the differential diagnosis of erythema nodosum in the context of infectious diseases, even in urban areas. A skin biopsy

can help with the diagnosis, even before serological tests become positive.

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