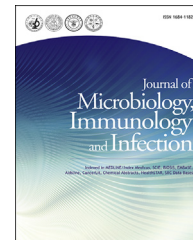




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## CASE REPORT

# Erythema nodosum associated with *Staphylococcus xylosum* septicemia



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### KEYWORDS

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*Staphylococcus xylosum* is a coagulase-negative staphylococcus. It is a commensal bacterium associated with skin and mucous membranes and occasionally it can cause human infections. We report the first case of erythema nodosum developed in a young woman with *S. xylosum* septicemia and specific serum antibody response.

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## Introduction

On October 13, 2010, a 27-year-old woman was admitted to our Department of Internal Medicine, Endocrine and Metabolic Diseases of the University of Siena, because of continuous fever, arthralgia, and painful red nodules on her legs that appeared 6 days before her admission. She works as a bank clerk, was born in Chiusi and lives in Sarteano, two little towns in the province of Siena. Her family and personal history were unrevealing, she does not own domestic animals, and she does not take any medication,

including oral contraceptive pills and antimicrobial drugs. The only note referred by the patient was that she was bitten by mosquitos, in particular on the legs, a few days before the onset of the clinical manifestations. Symptoms included arthralgia and fever, followed by the sudden onset of symmetrical, tender, erythematous, warm nodules located on her legs. She did not have cough, ocular discomfort, hemoptysis, or abdominal pain; no urinary symptoms were referred. At home, she started to use paracetamol, without a significant decrease of fever, osteoarticular pain, and skin lesions.

On examination, the patient's general condition was satisfactory. Her body temperature was 38.5°C, blood pressure was 110/80 mmHg, pulse 105 per minute, and respiration 20 breaths per minute. Her throat was clear and physical examination of the heart, chest, and abdomen was unremarkable. She did not have enlarged lymph nodes,

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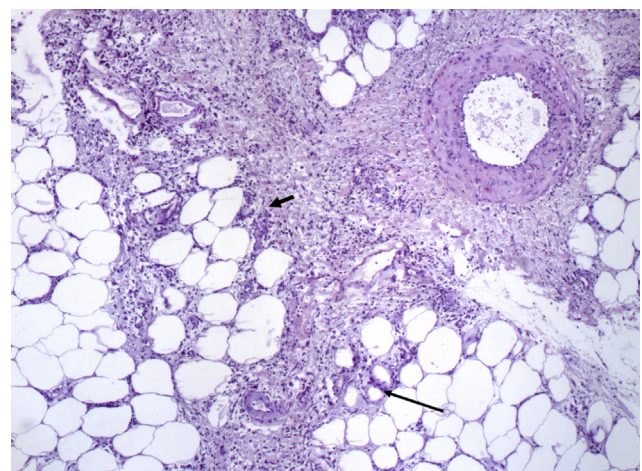
hepatomegaly, or splenomegaly. No sign of osteoarticular involvement was noted. There were multiple painful, erythematous papular-nodular, mild, tender skin lesions on both legs; lesion borders were poorly defined; the lesions were not suppurate or ulcerate and varied from 1.8 to 6 cm. The clinical examination allowed us to confirm the diagnosis of erythema nodosum (EN) (Fig. 1). Treatment was started with oral aspirin (3 g/day) and amoxicillin (2 g/day).

Abnormal laboratory test parameters were as follows: white blood cells 13,020/mm<sup>3</sup> (normal range: 4000–10,000 per mm<sup>3</sup>); neutrophils 82.5%; erythrocyte sedimentation rate 99 mm/hour; C-reactive protein 9.30 mg/dL (normal range <0.5 mg/dL). The results of the first-level laboratory investigations showed that glucose, transaminases, urea, creatinine, uric acid, sodium, potassium, calcium and phosphate, alkaline phosphatase, and urine analysis were in the normal range. Moreover, rheumatoid factor (latex test and Rose-Waaler test), anticyclic citrullinated protein antibodies, antinuclear antibodies, antidouble stranded DNA antibodies, antiextractable nuclear antigen antibodies, and antineutrophil cytoplasmic antibodies were negative. Serum immunoglobulins, C3-C4 levels, lactic dehydrogenase, chitotriosidase, and angiotensin-converting enzyme appeared to be in the normal range. Serologic investigations for B and C hepatitis viruses, human immunodeficiency virus, herpes simplex virus, cytomegalovirus, echo and coxsackie A and B viruses, Epstein-Barr virus, parvovirus B19,  $\beta$ -hemolytic streptococcus, *Brucella* spp, *Salmonella* spp., *Campylobacter* spp, *Yersinia enterocolitica*, *Chlamydia* spp, *Leptospira* spp, *Mycobacterium tuberculosis*, *Toxoplasma gondii*, *Helicobacter pylori*, and *Borrelia* spp infections were negative. Throat swab, urine and stool cultures, and parasitic examination of the same specimens were negative. Chest

X-ray, echocardiography, and complete abdominal echography were normal. The patient also underwent skin biopsy. At histology, a septal panniculitis was evident, with a predominantly mononuclear infiltrate partly extending into the lobular fat. There were no signs of vasculitis. Histochemical stains for mycetes as well as for bacteria were negative (Fig. 2). On the second day after the admission, due to high fever of 39.2°C, blood cultures were taken. After 24 hours, two of the three blood cultures performed were positive for Gram-positive, coagulase-negative bacteria, subsequently identified as *Staphylococcus xylosus*. The organism was identified by Gram stain, catalase and coagulase tests, and the API Staph System (Biomérieux, S.p.A., Florence, Italy). An antibiotic susceptibility test was determined by agar disc diffusion (Kirby-Bauer method).<sup>1</sup> The isolated pathogen was sensitive to the most common antimicrobial agents, except for beta-lactam antibiotics. Because *S. xylosus* is a common inhabitant of the human skin and mucous membranes, in order to dispel the possibility that the blood cultures were contaminated with the patient's or the environment's bacteria, we determined the presence of specific antibodies using a *S. xylosus* strain provided by the Culture Collection of the University of Gothenburg, strain CCUG 7324 (the patient's own strain was no longer available). Paired serum samples were collected during the 3rd day after her admission and after 5 weeks. Twofold serial serum dilutions in buffered saline pH 7.4 were performed, using U-shaped microtiter plates. Bacterial suspensions were added to each dilution at the final concentration of approximately 10<sup>9</sup> organisms per mL. We used a whole cell suspension and a suspension of bacteria boiled for 2 hours to destroy the protein antigens. Plates were incubated at 37°C for 24 hours; then they were inspected: the agglutination titer was the highest serum dilution at which a complete agglutination was observed. Tests were performed in duplicate. Agglutinating titer to the antiheat-labile and heat-stable antigens



**Figure 1.** Multiple erythematous, papular-nodular skin lesions on both legs.



**Figure 2.** Skin biopsy showing the presence of inflammatory cells (mostly lymphocytes) largely confined to the septa (long arrow) of subcutaneous adipose tissue that are thickened with absence of vasculitis. Miescher radial granuloma is indicated by the short arrow (hematoxylin and eosin staining; magnification, 50 $\times$ ).

was <1:2 for the "acute phase" serum and 1:16 and 1:64, respectively, for the "convalescence phase" serum specimens. Seroconversion to the bacterial proteins and polysaccharides confirmed that the patient had septicemia by *S. xylosus*.

On the basis of blood cultures and the identification of *S. xylosus*, treatment with teicoplanin (400 mg/day, intravenously) and levofloxacin (500 mg/day, orally) was started. The patient improved rapidly: fever decreased 1 day after the onset of antibiotic treatment and disappeared completely on the second day without any relapse episode. The skin lesions gradually resolved and completely disappeared over the next 10 days. Teicoplanin was stopped after 10 days from the beginning, levofloxacin after 14 days. Blood cultures taken 1 week after the start of the antibiotic treatment were negative. All the abnormal laboratory findings returned to normal limits within 2 weeks and the patient was discharged. Afterward, she was examined three times at 1-month intervals and remained in excellent health.

## Discussion

We report the first case of EN that developed in a young woman with *S. xylosus* septicemia. The diagnosis of EN was made by clinical examination and confirmed by the skin biopsy, which showed the typical findings of the disease: a septal panniculitis with a predominantly superficial and deep perivascular inflammatory mononuclear infiltrate, partly extending into the lobular fat (Fig. 2). EN is the most common form of panniculitis.<sup>2</sup> It is a cutaneous reaction pattern characterized clinically by the presence of erythematous tender nodules and raised plaques. They tend to be symmetrical in distribution and are usually located on the lower extremities, particularly on the anterior tibial surface, although they may also involve the ankles, the lower parts of the thighs, and the forearms. Although EN usually has no specific documented cause, it is imperative to investigate possible triggers. Streptococcal infections, tuberculosis, inflammatory bowel disease, drug reactions, infective endocarditis, and sarcoidosis are the most common causes in children and adults.<sup>2</sup> EN is considered to be a hypersensitivity response to a wide variety of inciting factors. The variability of possible antigenic stimuli that can induce EN indicates that this disorder is a cutaneous reactive process and that the skin has limited responses to different provoking agents. EN probably results from the formation of immune complexes and their deposition in and around venules of the connective tissue septa of the subcutaneous fat. However, a type IV delayed hypersensitivity reaction is not totally excluded in the pathogenesis of the disorder.<sup>2</sup>

On the basis of the patient's history, clinical examination, and laboratory and instrumental findings, we excluded all the above-mentioned causes of the disease. The identification of *S. xylosus* in blood culture and the seroconversion to the bacterial proteins and polysaccharides confirmed that our patient had septicemia by *S. xylosus*, a species of bacteria belonging to the genus *Staphylococcus*.<sup>3</sup> It is a Gram-positive bacterium that forms clusters of cells. Like most staphylococcal species, it is coagulase-

negative and resides as a commensal on the skin of humans and animals and in the environment. It appears to be far more common in animals than in humans. The dominant skin flora of animals (including pigs, horses, cows, chickens, dogs, laboratory mice, and pigeons) are coagulase-negative staphylococci, particularly *S. xylosus* and *Staphylococcus sciuri*. In contrast, the normal skin flora of humans is mainly composed by *Staphylococcus epidermidis* (63.8%), *Staphylococcus warneri* (28.8%), and *Staphylococcus hominis* (13.8%).<sup>3</sup> *S. xylosus* is a source of proteolytic enzymes commonly used in food processing.<sup>4</sup> *S. xylosus* has occasionally been identified as a cause of human infection, but in some cases it may have been misidentified. Currently the literature has reported few conditions indicating the pathogenetic role of *S. xylosus*; acute endocarditis,<sup>5</sup> acute pyelonephritis and urinary tract infection,<sup>6</sup> secondary root canal infection,<sup>7</sup> corneal/external infections,<sup>8</sup> otogenic brain abscess,<sup>9</sup> orthopedic implant infections,<sup>10</sup> erosive esophagitis,<sup>11</sup> and filarial lymphedema superinfection<sup>12</sup> have been described. Coagulase-negative staphylococcal species (and among them *S. xylosus*) were isolated from patients affected by nosocomial bacteremia<sup>13</sup> and human immunodeficiency virus/acquired immunodeficiency syndrome,<sup>14</sup> as well as from various clinical specimens (blood, tracheal aspiration, and urine).<sup>15</sup> Staphylococci generally have a commensal relationship with the host. However, under certain situations, they can gain entry into the host tissue and may behave as a pathogen. Currently we are not able to explain the route of transmission of *S. xylosus* infection in our patient. We underline what was revealed to us: the episode of mosquito bites before the onset of EN. It might be that bites and scratching are responsible for the germ penetration. In any case, this report may amplify the spectrum of the infectious agents causing EN. To the best of our knowledge, the association between EN and *S. xylosus* has not been previously reported in the literature.

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