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Nonhealing Wound Due to *Rhodococcus equi* in an Apparently Immunocompetent Patient, Revealing CD8$^+$ T-Lymphocyte Deficiency$^{\nabla}$

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We describe a case of a nonhealing wound due to *Rhodococcus equi*. Failure of the wound to heal led to immunological investigations and the discovery of a previously unknown CD8$^+$ T-lymphocyte deficit responsible for the chronic infection. The infection was cured after a 3-month course of a combination of antibiotics.

CASE REPORT

Our 58-year-old patient injured her right leg with a previously cut branch while gardening in a private garden. She had no notable medical history and no history of chronic or recurring infections. She disinfected the wound, and her general practitioner (GP) prescribed antibiotics (amoxicillin, 1 g twice a day for 10 days) 6 days after the incident because of local tenderness and inflammation. One month later, her leg was still swollen. Three nodules, approximately 1 cm in diameter, appeared above the wound, spaced approximately 2.5 cm apart, with a zone of induration between them. Her GP then prescribed doxycycline (100 mg twice a day for 10 days), with no improvement. One month later, the wound and nodules were unchanged, and a skin biopsy of the upper nodule was performed. Histology revealed an inflammatory granuloma with macrophages, multinuclear cells, altered polynuclear cells, and fragments of malphigian cells. This was diagnosed as a macrophagic granuloma. No treatment was prescribed, and 1 month later, a bacteriological sample of the wound revealed the presence of *Rhodococcus equi*. The bacterium was sensitive to all antibiotics tested except fosfomycin, clindamycin, and quinupristin-dalfopristin. No other bacterium grew on this sample. Chest radiography performed 3 months after the onset of skin lesions was normal.

The patient was referred to our department after a 4-month evolution of the lesions. Physical examination revealed an unhealed wound approximately 1.5 cm in diameter surrounded by induration and the biopsy scab (Fig. 1A). There were no abnormalities of the lungs, heart, abdomen, or lymph nodes, and she was apyrexial. She was prescribed a combination of rifampin (600 mg twice a day) and ofloxacin (200 mg twice a day) orally since the infection was localized and there was no sign of systemic involvement. After 2 months of antibiotics, the wound had partially healed (Fig. 1B). Induration was still present around the initial wound, but the nodules and induration between the wounds had disappeared. There was persistent pain around the initial wound, and epithelialization was incomplete. Because of side effects (joint pain) of rifampin, another antibiotic combination was prescribed for a further month (ofloxacin, 200 mg twice a day, plus azithromycin, 250 mg once a day, after a loading dose). One month later, the induration had disappeared, the wound had completely healed, and epithelialization was complete (Fig. 1C). Treatment was then stopped. There was no sign of relapse after 3 months' follow-up.

Since the patient did not have any obvious immunosuppression due either to disease or to treatment, an immunological assessment was carried out. Her total white blood cell count ($5{,}600 \times 10^9$/liter) was normal, as were her neutrophils (61.9%; $3{,}334 \times 10^9$/liter) and lymphocytes (26.3%; $1{,}420 \times 10^9$/liter). Protein electrophoresis did not reveal any abnormalities, and levels of immunoglobulin isotypes (IgA, IgG, and IgM) were normal. However, there was a quantitative deficit of CD8$^+$ T lymphocytes. The first count was 159 cells/mm^3, which represents 10.4% of total T lymphocytes. Normal values range from 500 to 900 cells/mm^3 and from 30 to 40% of T lymphocytes. One month later, the infection was cured but her CD8$^+$ T lymphocytes were still low: 201/mm^3 (11.2% of T lymphocytes). Six months later, we again checked her CD8$^+$ T lymphocytes. There was no change, since their level was 162/mm^3 (12.1% of T lymphocytes). Her CD4$^+$ T lymphocytes were normal on all occasions, as were the numbers of natural killer cells. Unfortunately, we were not able to perform a functional test on these CD8$^+$ T cells.

Infections due to *Rhodococcus equi* are uncommon, especially in immunocompetent individuals. Infection in these individuals most often involves the lungs (13), and skin involvement is rare. Subcutaneous abscesses have been reported only in immunosuppressed patients with AIDS (5) or in heart transplant recipients (1). To our knowledge, only two cases of chronic wound infection due to *R. equi* have been reported; one was in a female with self-destructive behavior and a leg ulcer (6), and the other was in an immunosuppressed gardener

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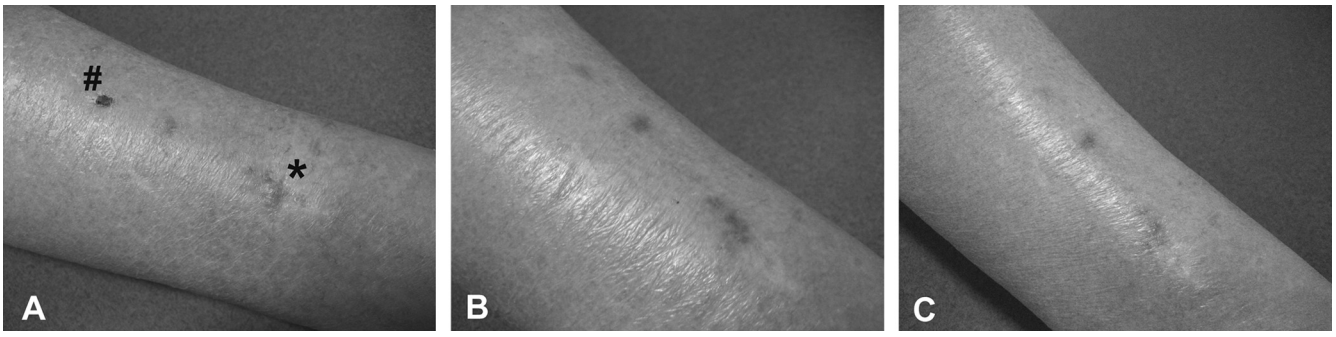

FIG. 1. Evolution of the wound. (A) After 4 months and before antibiotic treatment. *, initial wound; #, biopsy scab on the upper nodule. (B) After 2 months of antibiotics. Epithelialization is incomplete. (C) After 3 months of antibiotics. The wound has completely healed.

who had undergone a renal transplant (9). We report the first case of a nonhealing wound due to *R. equi* in a woman who was previously considered to be immunocompetent.

R. equi is a Gram-positive soil organism and was first described as a zoonotic infection, since it is carried in the gut of many herbivores, in particular horses and foals. Human infection is uncommon and occurs mainly in patients with AIDS (5, 8, 2, 18) but also in immunocompromised patients with cancer (3), leukemia, diabetes mellitus, or lymphoma and after solid-organ transplantation (1, 19). Typically, the infection is localized in the lungs (7, 8), since the bacteria are acquired orally. However, some cases present as subcutaneous infections (1–3, 5, 9, 10), probably due to traumatic inoculation or superinfection of wounds.

To our knowledge, skin infection with this organism has never been found in an immunocompetent individual. In a review of 19 immunocompetent patients, this type of infection was not reported (13). One patient with a renal transplant, taking prednisone and azathioprine, presented with a recurrent skin infection due to *R. equi*, which was treated with a long course of amoxicillin (9). Subcutaneous abscesses due to *R. equi* have been described only for immunosuppressed patients with AIDS (1, 2, 5), cancer (3), or liver cirrhosis with severe liver failure (10). This type of presentation is probably due to the absence of an immune response.

The main immune defense against *R. equi* is cell mediated (12, 18). $CD4^+$ T lymphocytes and $CD8^+$ T lymphocytes are the major cells involved in bacterial clearance in both murine and equine models (11, 16, 17), and $CD8^+$ T lymphocytes play a major role in immunity to *R. equi* (16, 17). In our case, the $CD8^+$ T-lymphocyte deficit could partly explain the persistence of *R. equi* in the skin. Indeed, this impairment was then compensated for by granuloma formation, whereby the immune system could control the bacteria without destroying them. Granuloma formation cannot occur or is limited in immunosuppressed patients, since cell-mediated immune mechanisms are deficient, allowing the infection to evolve into an abscess.

In contrast, granulomas have previously been found in immunocompetent patients during chronic infection with *R. equi* (4, 14). These granulomas exhibited caseating necrosis. In our case, no caseating granulomas were observed, but granuloma formation was a manifestation of the immune response to this chronic infection. In the other cases reported with granulomas (4, 14), no investigations of a potential CD8 deficit were carried out. The search for this type of deficit is not performed routinely, and it might therefore be present but go unrecognized. This might have been the case with the immunocompetent patients described by Kedlaya, where no investigation of the immune system was carried out (13).

There was no clinical sign of an ongoing infection, either bacterial or viral, which could have explained the low level of $CD8^+$ T cells. Doxycycline has been shown to induce T-lymphocyte apoptosis (15); however, in our case there was a period of almost 2 months between the prescription of doxycycline and the first dosage of $CD8^+$ T lymphocytes. Thus, the role of doxycycline in the deficit can be excluded.

Our case highlights the fact that some "apparently immunocompetent" patients might have a slight immune deficit which can remain silent for a long period of time. Furthermore, this deficit might be expressed in some circumstances depending on the host-pathogen relationship. Defining an immunocompetent patient is therefore difficult. Our patient was immunodeficient in terms of her response to *R. equi* but immunocompetent against other pathogens, since she had never had any other severe infections in the past.

The antibiotic regimen for *R. equi* in immunocompetent patients is not well established due to the rarity of these infections. Some combinations have been proposed based on a review of the literature (13). Combination therapy is recommended to prevent the emergence of antibiotic resistance. Since the bacteria may be localized intracellularly, some authors suggest that the combination should include at least one antibiotic with intracellular activity, such as macrolide, rifampin, or ciprofloxacin. The length of antibiotic treatment is also unclear, but clinical success has been reported with courses in immunocompetent subjects that are shorter than those used in immunosuppressed individuals (13). In our case, 3 months' treatment was sufficient to cure the infection.

This report is the first description of a chronic wound infection caused by *R. equi*. Granuloma formation was successful at limiting the infection, but mild immunosuppression led to a chronic infection. This is the first time that a deficit in $CD8^+$ T lymphocytes has been reported as the possible cause of chronic infection due to *R. equi* in a patient previously thought to be immunocompetent. This type of deficit should always be investigated before asserting that the patient is immunocompetent. A short course (3 months) of a combination of two antibiotics

with intracellular activity was effective in our patient, and this is an argument for shortening the course of antibiotics in immunocompetent patients with localized infections, even if the overall duration of therapy is unclear.

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