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Case report

Disseminated *Rhodococcus equi* infection in a patient with diffuse large B-cell lymphoma treated with immunotherapy

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ABSTRACT

Immunotherapies can lead to an immune compromised state that can allow for opportunistic pathogens such as *Rhodococcus* to flourish. The vast majority of *Rhodococcus* infections occur in immunocompromised hosts. Here we describe disseminated *Rhodococcus equi* infection in a patient with diffuse large B-cell lymphoma treated with immunotherapy. Infection with *Rhodococcus* can be diagnosed with the aid of cytomorphology and histochemical findings and the organism confirmed by sequencing. In conclusion, *Rhodococcus* should be considered in the differential of granulomatous inflammation in immunocompromised individuals treated with immunotherapies.

Case report

As immunotherapies such as chimeric antigen receptor (CAR)-T cell therapy, monoclonal antibodies, and bispecific antibody therapy become more popular in the treatment of hematologic malignancies, opportunistic pathogens will seize the opportunity. In the treatment of B-cell lymphomas, many of the new medications target B cells and can lead to further immunocompromise. The immunocompromised state that this produces provides the chance for opportunistic infections to take their toll.

Rhodococcus equi is widely present in the environment. It was originally isolated as a veterinary pathogen in 1923 from foals with pneumonia [1]. The first human case was reported in 1967 [2]. The vast majority of infections occur in immunocompromised hosts, most classically in those with defects in cell-mediated immunity [3]. In cancer patients, it is often associated with biofilms on central intravascular lines. Within macrophages, the bacteria are able to resist degradation by the phagolysosome, which allows for intracellular proliferation and escape from the cells [3]. Disease due to *R. equi* most commonly presents as a cavitary upper lobe pneumonia and can become disseminated in the immunocompromised host [3].

The patient was a 68-year-old male with a past medical history of relapsed, transformed marginal zone lymphoma/diffuse large B-cell lymphoma. Originally, marginal zone lymphoma was diagnosed in a hilar lymph node. The following year, diffuse large B-cell lymphoma was diagnosed in a soft tissue mass in the right upper arm. He did not respond well to chemotherapy and was unable to undergo bone marrow transplantation. He thus underwent treatment with the CAR-T cell therapy with axicabtagene ciloleucel. He had a recurrence of diffuse large B-cell lymphoma in the right upper lobe of the lung and was treated with nivolumab as part of a research study. Two weeks after completing the study, he had a relapse of marginal zone lymphoma on the right buttock and was started on bendamustine, rituximab, and palliative radiation. Two months later, he then had diffuse large B cell lymphoma in a station 11 lymph node. He underwent chemotherapy with tafasitamab-cxix and lenalidomide. He then joined a study for odronextamab, which is a bispecific antibody for relapsed B-cell lymphoma.

He was hospitalized approximately half a year later for complications related to COVID and *Rhodococcus* bloodstream infection. His port was removed as it grew positive cultures. He underwent treatment with convalescent plasma, azithromycin, vancomycin, piperacillin-tazobactam, ending with a two-week home course of vancomycin. PET-CT was concerning for progressive lymphoma, but biopsy grew *Rhodococcus* on culture and *Rhodococcus* was detected on broad range 16 S rDNA bacterial PCR plus sequencing on tissue from the lung. Imaging showed pulmonary nodules and a pleural effusion. Histology showed inflammation with limited necrosis and numerous intracellular coccobacilli on Gram stain. He was then treated with trimethoprim-sulfamethoxazole and azithromycin. Repeat blood cultures were

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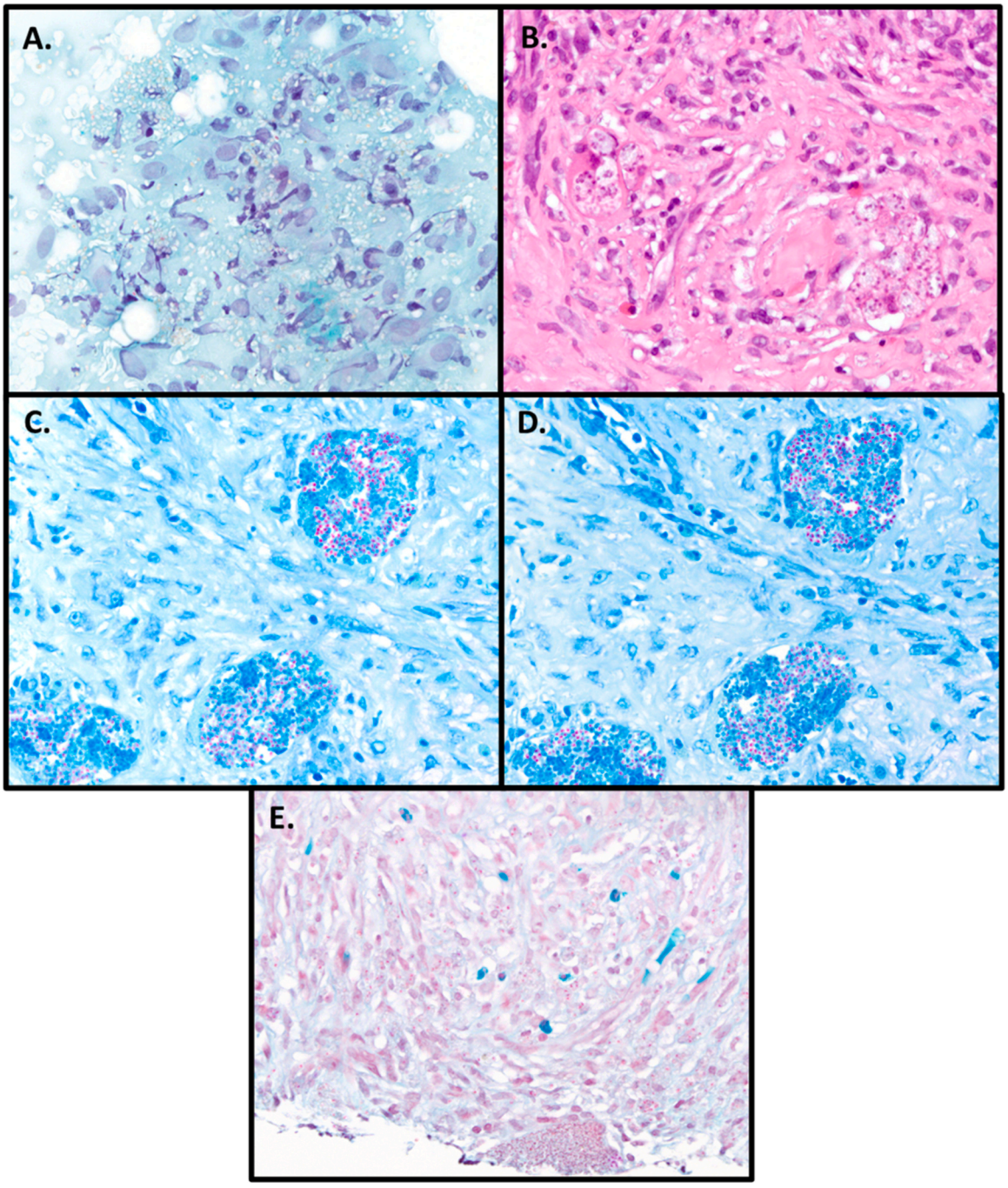

Fig. 1. *Rhodococcus equi* malakoplakia cytomorphology and histochemical findings. (A) Papanicolaou stain 600×. (B) Hematoxylin and eosin stain 600×. (C) Acid-fast stain 600×. (D) Fite acid-fast stain 600×. (E) Gram stain 600×.

negative. Repeat imaging showed mixed changes in the pulmonary nodules, resolution of the pleural effusion, mild enlargement of a solitary right hepatic lesion, multiple enhancing lesions of the left gluteal muscle concerning for disseminated infection versus HSV, and new prostatitis. Trimethoprim-sulfamethoxazole led to neutropenia, so after approximately a month antimicrobial therapy was changed to moxifloxacin. He was monitored by EKG for long QTc syndrome with a combination of azithromycin and moxifloxacin. Odronextamab was held since he developed the infections. The disseminated infection involved the lung, mediastinum, liver, presumably the adrenal, and possibly the prostate and sinus as well. He was switched to azithromycin, vancomycin, and imipenem two months later. He developed cholecystitis and a cholecystostomy tube was placed. A month after that he was switched to vancomycin, imipenem, plus minocycline and rifampin as he developed hearing loss on azithromycin. He underwent cholecystectomy and a liver wedge resection for enlarging abscess. PET scan also showed foci of infection presenting as subpleural nodules, skeletal muscle lesions, and a new right inguinal mass. He continued to have persistent hypogammaglobulinemia and CD4 lymphopenia. The groin lesion was favored to be small cell carcinoma. Gram stain of tissue from the lung nodule again showed gram-positive cocci with a morphology compatible with *Rhodococcus*. A few weeks later, he developed leukopenia with rifampin and imipenem. He was switched off rifampin and started on moxifloxacin. He had been hospititalized for several months and, given his ongoing infections, pancytopenia, and malignancy, he elected to enroll in hospice care and changed his status to "do not resuscitate."

Antimicrobials were discontinued. He passed away two weeks later on hospice care.

Histologically, *Rhodococcus* infections present as a necrotizing granulomatous pattern with numerous macrophages that contain coccobacilli (Fig. 1) [4]. Necrotizing granuloma producing infections similar to *Rhodococcus* include other members of the aerobic actinomycetes, *Corynebacterium*, and *Mycobacterium.* [3] *Rhodococcus* can stain positive on acid-fast stain (Fig. 1) [4]. Pulmonary cavitary lesions can also be caused by *Mycobacterium tuberculosis*, nontuberculous mycobacteria, *Blastomyces*, *Histoplasma*, *Coccidioides*, *Aspergillus*, and *Burkholderia pseudomallei.* [3] Histiocytic aggregates may be due to *Mycobacterium avium* complex, *Mycobacterium genavense*, *Histoplasma*, and *Cryptococcus neoformans*. The pathologic changes consisting of aggregates of histiocytes produced by *Rhodococcus* can be similar to those caused by *Tropheryma whipplei*, the bacterium that causes Whipple disease [5]. Features that help to differentiate *Rhodococcus* from other pathogens include the coccobacillary morphology of the organisms that can be visualized by Gram or silver stains (Fig. 1) [4]. *Rhodococcus* is classically gram-positive. (Fig. 1) [4].

Rhodococcus infections can present as malakoplakia. [4] Fine needle aspirations (FNAs) and bronchoalveolar lavage fluid may demonstrate sheets of macrophages with intracytoplasmic inclusions, malakoplakia [6]. Malakoplakia presents as a mass on imaging and can also be associated with gram-negative bacterial infections of the genitourinary tract [3]. Malakoplakia due to *Rhodococcus* may show periodic acid Shiff (PAS)-positive macrophages with cytoplasmic globules and inclusions called Michaelis-Gutmann bodies that are made up of the mineralized remains of incompletely digested bacteria [4].

On culture plates, *Rhodococcus* produces pink to red colonies on solid media [3]. MALDI-TOF and/or 16 S rRNA sequencing performed on colonies can be used to identify the bacterium [7].

Here we describe disseminated *R. equi* infection in a patient with diffuse large B-cell lymphoma treated with immunotherapy. Immunotherapies can lead to an immune compromised state that can allow for opportunistic organisms such as *Rhodococcus* to flourish. *Rhodococcus* infections can be diagnosed with the aid of cytomorphology and histochemical findings and confirmed by MALDI-TOF and/or 16SrRNA sequencing. In conclusion, *Rhodococcus* should be considered in the differential for individuals in an immunocompromised state treated with immunotherapies.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

CRediT authorship contribution statement

Judith Jebastin Thangaiah: Conceptualization, Data curation, Supervision, Writing – original draft, Writing – review & editing. **Catherine D. Zomok:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Jennifer M. Larson:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Audrey N. Schuetz:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Rosalie Sterner:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: RMS is an inventor on patents related to CAR-T cell therapy licensed to Humanigen through Mayo Clinic.

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