Rapid Resolution of *Mycobacterium marinum* Chronic Skin Infection during Lenalidomide Therapy for Chronic Lymphocytic Leukemia

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The immunomodulatory drug lenalidomide is currently being evaluated for its antineoplastic properties in treating hematologic malignancies. However, its potential role in augmenting immune reactions against opportunistic infections has not been explored. We report the rapid resolution of chronic *Mycobacterium marinum* infection in a patient following initiation of lenalidomide therapy for chronic lymphocytic leukemia.

Thalidomide is a synthetic glutamic acid derivative that was initially withdrawn from the market as an anti-emetic agent because of the occurrence of teratogenicity [1]. Thalidomide was later identified as a potent immunomodulatory agent, leading to its successful use in the treatment of erythema nodosum leprosum [2] and autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, and Behcet disease [1]. In recent years, thalidomide was found to be effective in the therapy of multiple myeloma [3], leading to renewed interest in the exploration of thalidomide and its derivatives as cancer therapy.

Lenalidomide is a thalidomide derivative that is 50,000 times more potent than thalidomide in the inhibition of macrophage TNF-α release [1]. Lenalidomide belongs to a class of compounds called immunomodulatory drugs. Immunomodulatory drugs have pleiotropic immune effects, including the modulation of IL-2, IFN-γ, and IL-12 production, the costimulation of T cells via the B7-CD28 pathway, the augmentation of natural killer cell–mediated immunity, and the enhancement of antigen-presenting cell function [1]. Lenalidomide has activity in treating hematologic malignancies, such as multiple myeloma [1], myelodysplasia [4], and chronic lymphocytic leukemia (CLL) [5]. However, whether its immunomodulatory activity may be effective in controlling infection has not been explored. We report the observation of potent antimycobacterial activity in a patient receiving lenalidomide for CLL therapy.

**Case report.** A 64-year-old man received a diagnosis of Rai stage 0 CLL during a routine annual physical examination, with a WBC count of $16 \times 10^9$ cells/L. After 2 years of observation, he developed progressive disease, was treated with 6 cycles of fludarabine, cyclophosphamide, and rituximab, and achieved a complete remission.

Five years later, the patient experienced relapse and was referred for therapy of recurrent CLL. At that time, he developed a sporotrichoid pattern of scabbed, tender nodules and violaceous papules on his right arm and hand several days after cleaning a fish tank. An excisional skin biopsy sample from 1 of the nodules had culture results positive for *Mycobacterium marinum*, and the patient initiated treatment with oral trimethoprim-sulfamethoxazole, clarithromycin, and ciprofloxacin. Despite intensive combination antibiotic therapy to which he was compliant, the patient’s arm lesions were slow to improve, and after 3 months, trimethoprim-sulfamethoxazole was changed to doxycycline. After a total of 9 months of antibiotic treatment, the patient’s skin lesions showed minimal improvement, with residual painful nodularity and scarring (figure 1A). Over the same period of time, his CLL was treated with rituximab, achieving a short-lived partial response.

The patient then received lenalidomide (10 mg daily) for the treatment of CLL progression. Unexpectedly, after 14 days of therapy, the areas of persistent *M. marinum* infection flattened, with marked improvement in the function of the arm. Over the next 3 months, the patient’s skin infection resolved completely, with residual scarring (figure 1B). The patient’s CLL exhibited a partial response while the patient was receiving lenalidomide, but he ceased lenalidomide treatment after 12 months because of gastrointestinal adverse effects. There was no evidence of recurrent mycobacterial infection after 18 months of follow-up.

Peripheral blood lymphocyte subset analysis prior to the commencement of lenalidomide therapy revealed T lympho-
cytopenia, with absolute CD4 and CD8 cell counts of 96 cells/µL and 42 cells/µL, respectively. The patient was known to be seronegative for HIV, and the T lymphopenia was attributed to the effects of prior purine analogue therapy. Eight weeks after commencement of lenalidomide therapy, an additional peripheral blood assessment revealed increased CD4 and CD8 cell counts of 2382 cells/µL and 1906 cells/µL, respectively. Natural killer cell counts were not assessed in this patient.

Discussion. *M. marinum* was first isolated from dead fish in an aquarium in Philadelphia, Pennsylvania, in 1926 and causes peripheral granulomatous disease in humans, also known as “swimmer’s granuloma” or “fish tank granuloma” [6]. *M. marinum* infection is an occupational hazard for aquarium cleaners, fishermen, and seafood handlers. The organism’s growth requires a low temperature, and therefore, infection is usually limited to the skin, with the hands being the most common site of infection [6]. The lesions usually appear as papules on the elbows, knees, or hands, progressing to shallow ulcers and scarring. Many patients develop ascending lesions that resemble sporotrichosis. At least 3 months of therapy is required for the treatment of soft-tissue infections [6], commonly with a combination of rifampin and ethambutol. Trimethoprim-sulfamethoxazole and tetracyclines have also been used with some success.

The presence of an intact immune system is essential for combating mycobacterial infection [7]. IFN-γ, IL-12, and TNF-α have important roles in the macrophage-mediated killing of mycobacteria [7]. TNF-α affects immune cell migration and localization within tissues in *Mycobacterium tuberculosis* infection and influences the expression of adhesion molecules, as well as the release of chemokines [8]. Because TNF-α activity is important for the formation of granulomas, its inhibition by lenalidomide may have accounted for the rapid resolution of chronic skin lesions in our patient. However, the absence of recurrent infection 18 months later confirms immune clearance of *M. marinum*, possibly related to lenalidomide’s effect in modulating T cell and natural killer cell responses [1]. In our patient, the onset of antimycobacterial and antitumor activity coincided with a ≥20 times increase in CD4 and CD8 cell counts. Although the resolution of the patient’s chronic infection may have been spontaneous, the association with lenalidomide therapy and the resultant increase in T cell subsets was
strongly suggestive of an immunomodulatory effect. In this regard, it is interesting to note that thalidomide has been reported to be effective as adjunct therapy for tuberculous meningitis, highlighting the role of immunomodulation in the treatment of mycobacterial infection [9–11]. Our case supports further exploration of lenalidomide as adjunct therapy for patients with chronic mycobacterial infection.

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References