Lymphadenitis Caused by *Scedosporium apiospermum* in an Immunocompetent Patient

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A case of lymphadenitis caused by *Scedosporium apiospermum* in a 25-year-old immunocompetent woman had been misdiagnosed as tuberculous lymphadenitis. Clinical response to itraconazole therapy was obtained in 6 months; to our knowledge, this is the first report of lymphadenitis caused by *S. apiospermum* in humans.

Pseudallescheria boydii and its anamorph, *Scedosporium apiospermum*, are ubiquitous soil-inhabiting fungi. *S. apiospermum* has occasionally been reported to cause localized infections of the lung and other deep organs as well as disseminated infections. However, *S. apiospermum* has not been implicated as an etiologic agent of lymphadenitis in an immunocompetent host. We describe a patient who had long-standing lymphadenitis that was caused by *S. apiospermum* and that had been misdiagnosed as tuberculous lymphadenitis, and who experienced failure of antituberculous therapy.

Case report. A 25-year-old woman presented with cervical and submandibular lymphadenopathy. She had been prescribed antibiotics for the treatment of enlarged cervical lymph nodes (diameter, 0.5–1 cm) 10 years earlier, but she did not respond to them. There was no change in her condition until 3 years before presentation, when she noticed further enlargement of her cervical lymph nodes. The findings of physical examination were unremarkable, except for the discovery of bilateral multiple mobile and painless lymph nodes, the largest of which was 2 cm in diameter, in the anterior and posterior cervical chains, and the presence of a posttraumatic scar, which she had received 12 years earlier, on her right hemiface. Biopsy of her lymph nodes was done, and histopathologic examination showed granulomatous lesions surrounded by multinucleated giant cells. Although the results of microscopic examination and cultures were negative for *Mycobacterium tuberculosis,* a presumptive diagnosis of tuberculosis was made on the basis of the histopathologic findings and purified protein derivative positivity. She was given isoniazid, ethambutol, and rifampin for 9 months with no response. Physical examination performed 3 months after the initiation of antituberculous treatment revealed an increase in the number and size of enlarged cervical lymph nodes. In addition, bilateral axillary and right epitrochlear lymphadenopathy were detected. Results of CT of the thorax and abdomen were negative. The patient's hemoglobin level, WBC count, and differential, lymphocyte subsets (T cell, B cell, and NK cell), and immunoglobulin and complement levels were within normal ranges. The phagocytic activity and burst activity of neutrophils and monocytes were also normal.

Lymph node biopsy was repeated. Histopathologic examination of a biopsy specimen stained with Grocott–methenamine silver showed an inflammatory infiltrate with branched septate fungal hyphae in tissue (figure 1). Biopsy material was cultured onto Sabouraud's glucose agar that was supplemented with chloramphenicol; it was then incubated at 30°C. Numerous cottony colonies were noticed after 5 days; they were initially white but became greenish and brownish gray. Microscopic examination showed septate hyaline hyphae with conidia borne on a single terminal on simple or branched conidiophores or laterally on hyphae. The conidia were ovoid, with a distinct brown wall, and they appeared to be cut off at the base. The isolate failed to produce sexual state on either corn meal agar or potato dextrose agar. The fungus was identified as *Scedosporium apiospermum.*

Antifungal susceptibility testing was done by use of a macrobroth dilution test, in accordance with the National Committee for Clinical Laboratory Standards guidelines [1]. RPMI 1640 with L-glutamine but without sodium bicarbonate (Sigma), buffered to pH 7.0 with 0.165 *M* of morpholinepropanesulfonic acid, was used as the test medium for all agents. The inoculum was prepared by diluting a stock conidial suspension to obtain a final inoculum of $\sim 0.4 \times 10^4$ to 5×10^4 cfu/mL. The tubes were incubated at 35°C for 70–74 h. The MIC was defined, for amphotericin B, as the lowest concentration that resulted in no growth and, for flucytosine and azoles, as a ⩾50% reduction in growth. Itraconazole showed the highest in vitro activity (MIC, 0.25 μg/mL) against the isolate. The MICs of ketoconazole, miconazole, amphotericin B, fluconazole, and flucytosine were 2, 4, 8, 32, and >64 μg/

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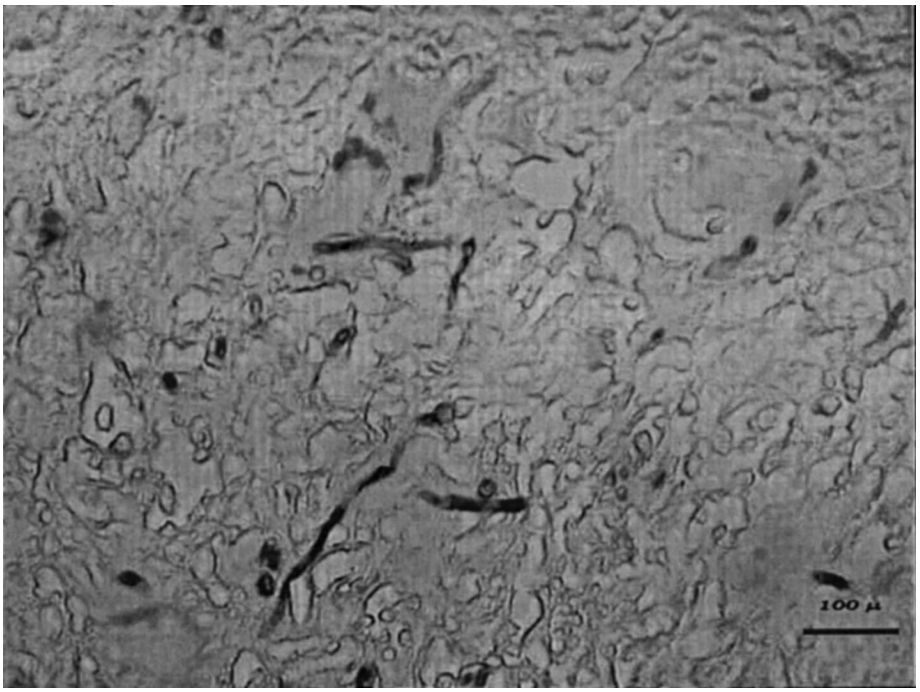

Figure 1. Section of lymph node biopsy sample stained with Grocott methamine silver. Septate hyphal and conidial elements are shown.

mL, respectively. We used *Candida parapsilosis* ATCC 22019 as a control isolate, and the MIC values for this reference organism were as follows: for amphotericin B, 0.5 μg/mL; fluconazole, 4.0 μg/mL; itraconazole, 0.12 μg/mL; ketoconazole, 0.25 μg/mL; and flucytosine, 0.5 μg/mL [1].

The patient was given oral itraconazole, 200 mg t.i.d. Regression in the diameter of lymph nodes was noticed within 6 months, and clinical cure was obtained within 1 year.

Discussion. *S. apiospermum* and its teleomorph *P. boydii* are found in nature ubiquitously and are often recovered from sewage and polluted water. They occasionally have been reported to cause systemic infection in immunocompromised patients. Localized infections, such as sinusitis [2], brain abscess [3], meningitis [4], arthritis and osteomyelitis [2, 5, 6], endophthalmitis [6, 7], corneal infection, [8] and mycetoma [9, 10], may occur after traumatic introduction of the fungus or its dissemination from the lungs. Although the majority of disseminated infections occur in immunosuppressed patients, especially those with neutropenia or who have received organ transplants, immunosuppression is not a prerequisite for invasive infection.

Skin is the most common portal of entry for *S. apiospermum* [11–13]. Traumatic implantation of the organism into subcutaneous tissue leads to the formation of a mycetoma. The lesion starts as a painless subcutaneous swelling that enlarges and ruptures through the surface through sinus tracts. Adjacent tissue and bone become involved later. Lymphadenitis after trauma, however, has not been reported.

Our patient is unique in several respects. First, she developed a chronic infection of the lymph nodes that has not been previously described. Second, the organism appears to have remained indolent for years. Although no histological or cultural evaluation was made before the current evaluation, it is likely that the patient had been infected for years. Her symptoms began 10 years prior to presentation, and we suppose that the infection was acquired as a result of a facial trauma that had happened 2 years before her first symptoms occurred. Liu et al. [12] reported a similar protracted course in a patient who had a 13-year history of faciocervical infiltrative erythema. An acceleration in the clinical course was noted only after 7 years of latency. The factor(s) that led to this acceleration remains unknown in this case.

Rapid and true diagnosis of *S. apiospermum* infection is very difficult because of clinical and histopathological similarities to other filamentous fungi, such as *Aspergillus* species, *Fusarium* species, and *Sporothrix schenckii.* The infection also resembles tuberculosis in its pulmonary form. Although underlying cavitating disease is a major factor that predisposes a patient to colonization by *S. apiospermum* [14], invasive pseudallescheriasis associated with tuberculosis is an unusual finding [15]. Skin involvement may also be mistaken for tuberculosis [12]. Our patient's condition was misdiagnosed as tuberculosis, and she showed no response to therapy with antituberculous agents. In fact, her disease progressed during that period. This case provides additional evidence that correct diagnosis requires clinical suspicion as well as proper histopathologic examination and cultures for fungi.

The optimal treatment for *S. apiospermum* infection is un-

clear. Amphotericin B is considered to be ineffective, and in vitro studies have shown that the levels of the drug that are required are clinically unachievable [16, 17]. Miconazole, ketoconazole, and itraconazole are active in vitro, and successful outcome has been observed in certain patients, especially those with localized infections [18–20]. However, a protracted course should be anticipated, as was the case with our patient. Voriconazole, a new monotriazole antifungal agent that is active against a wide spectrum of fungi, appears to be promising in the treatment of severe cases [21].

In conclusion, *S. apiospermum* must be considered in the etiologic diagnosis of long-standing lymphadenitis in immunocompetent patients. Differential diagnosis is particularly important in regions where tuberculosis is endemic.

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