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Multiresistant Tuberculosis and Its Paradoxical Manifestations

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Dear Editor:

I read with interest the case report of disseminated multiresistant tuberculosis involving the brain published in your journal [1]. The patient was completely evaluated and properly treated, and the favorable outcome confirms excellent care. I would like to comment on the paradoxical cerebral manifestations observed during treatment of tuberculosis. The first case of tuberculosis was published in 1974 before the availability of computed tomography (CT) and documented using cerebral scintigraphy. Brain biopsy specimens demonstrated acid fast stain positivity, but negative culture results [2]. In subsequent reports, an a inconsistent consistent clinical pattern was observed: young women with miliary or disseminated tuberculosis presented after weeks or months of antituberculous drug treatment with new or additional neurological symptoms such as headache, seizures, or motor deficits. Brain CT showed lesions that were not initially present or increased in size or number during treatment [3]. If recovered in sputum cultures, *Mycobacterium tuberculosis* (MTB) generally shows no resistance to primary antituberculous drugs and is not detected in cultures of brain lesions. In most cases, the administration of corticosteroids is sufficient for ameliorating cerebral edema while treatment for tuberculosis is continued. A previous study reported that the absence of co-morbidities, extrapulmonary tuberculosis, and a low basal lymphocyte count in blood with a large increase in lymphocyte count at the onset of a paradoxical response were significant factors when compared with patients without a paradoxical response [4]. Theories regarding the pathogenesis of tuberculosis propose that a paradoxical reaction occurs as the result of an exaggerated immune response to MTB antigens in patients receiving effective anti-tuberculosis treatment rather than due to progressive uncontrolled mycobacterial replication [5]. A number of mycobacterial lipid-rich, insoluble cell wall antigens are present in infected tissues and potently stimulate the response of mononuclear phagocytes, producing an exaggerated inflammatory reaction in the host [6]. In a recent prospective series of 41 HIV-negative patients with tuberculous meningitis from Malaysia, a paradoxical reaction occurred in 23 (56%), improvement occurred in 14, neurological deficits persisted in 3, and death in 6 patients [7]. The significant contribution of this case report [1] was the results of the early susceptibility testing for MTB isolates, according to which the antituberculous drug treatment was adjusted. The resolution of brain lesions occurred in a shorter period than that reported previously. The findings of this case report make us consider

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whether, in many of the previously reported cases of paradoxical responses in cerebral tuberculosis not documented via culture and therefore lacking primary antituberculous drug susceptibility test results, we were in fact observing masked tuberculosis resistance that eventually resulted in morbidity, prolonged disease course, or even death. This case report highlights the need to conduct universal drug susceptibility tests when possible for all new MTB isolates, as recommended by the WHO [8]. This is a difficult task in limited resource settings but may be the only route to achieve a better understanding of paradoxical worsening in pulmonary and extrapulmonary tuberculosis, which is necessary for optimal patient management. Therefore, this case report represents a significant contribution.

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