Cerebral toxoplasmosis in a patient with systemic sclerosis under thalidomide treatment: A case report

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INTRODUCTION

Toxoplasmosis is an opportunistic infection that arises from primary exposure or reactivation of latent forms of Toxoplasma gondii. The parasite has an estimated seroprevalence rate between 15% and 22% in the United States.[1] The manifestation of toxoplasmosis is influenced by individual immune responses. Immunocompetent hosts often remain asymptomatic or present with mild flu-like symptoms. Conversely, immunocompromised individuals may have severe manifestations including meningoencephalitis commonly due to the reactivation of a dormant infection.

Several cases of cerebral toxoplasmosis have been reported in patients with inflammatory disorders treated with immunosuppressive treatment, including tumor necrosis factor- α inhibitors (TNF-α) or other biologic agents.[2]

Despite the prevalence of anti-*T. gondii* antibodies documented in a large systemic sclerosis (SSc) patient cohort, to the best of our knowledge, only 1 case of toxoplasmosis in a SSc patient has been recorded.[3] We herein describe a case of cerebral toxoplasmosis in a patient with limited cutaneous SSc receiving thalidomide, a known inhibitor of TNF-α production.[4]

Abbreviations used:

SSc: systemic sclerosis
TNF-α: tumor necrosis factor- α inhibitors

CASE REPORT

A 49-year-old woman presented with progressive wood-like changes and hardness of bilateral legs 6 years ago. Physical examination revealed distinct, well-demarcated, wood-like changes in her legs, extending from knees down to ankles and encompassing the dorsal surface of both feet. She experienced painful induration, reduced strength, and limited flexibility in lower legs, with a stocking distribution pattern. Additionally, telangiectasis, Raynaud's phenomenon, and abnormal nailfold capillaries were observed during the examination.

She was diagnosed with limited cutaneous SSc based on clinical and serological findings, including positive anti-RNA polymerase III antibodies (26 units, positive reference range: 20.0-39.0 units).

Her baseline pulmonary function test and echocardiogram and urine protein/creatinine ratio were within normal limits. She was prescribed mycophenolate mofetil (2g daily) and hydroxychloroquine

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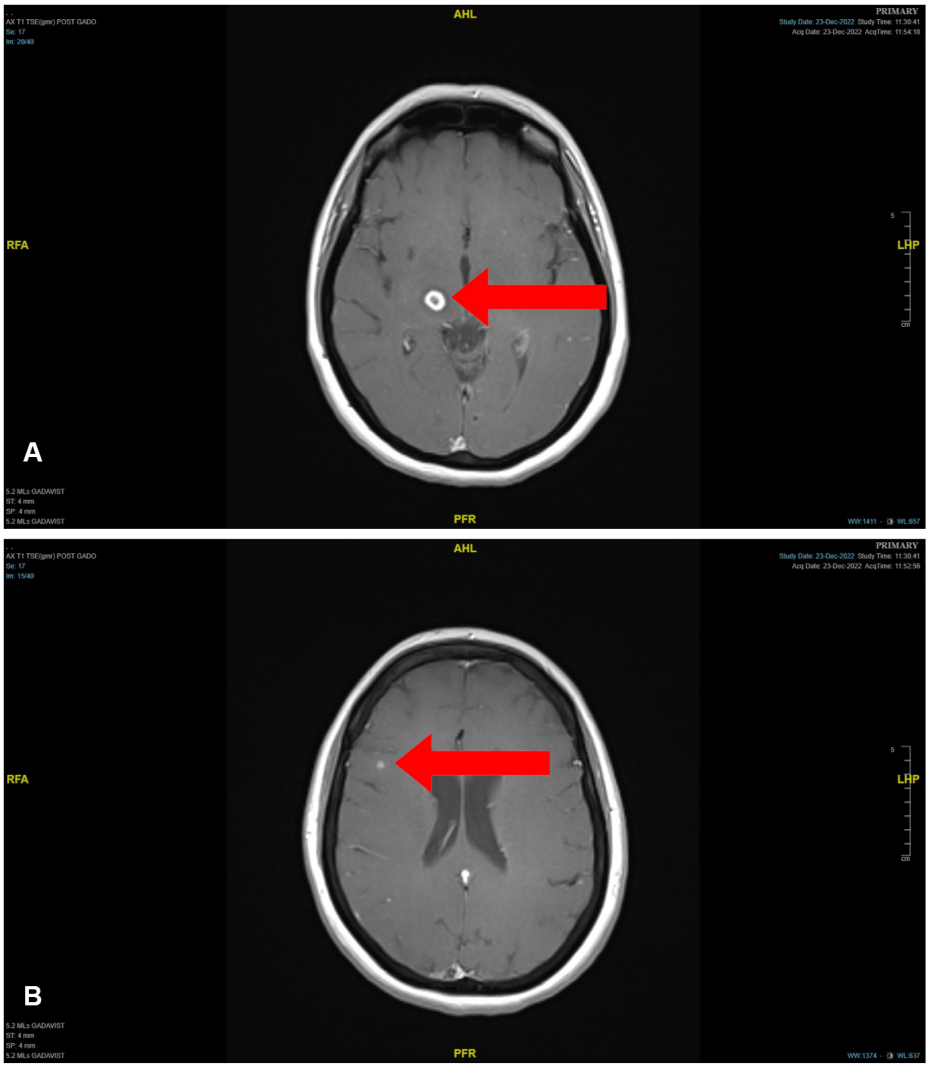

Fig 1. Axial T1-weighted magnetic resonance imaging shows 10 mm ring enhancing lesion (*red arrow*) (**A**) in the right thalamic with surrounding edema. The 4 mm nodular enhancement (*red arrow*) (**B**) is present in the right frontal lobe gyrus.

(400 mg daily). However, despite combined therapy for a year, she experienced a partial response. Tocilizumab was considered as an alternative, but it was not covered by her insurance. Additionally, she started complaining of oral ulcers. Thalidomide at a dosage of 50 mg daily was added to her treatment, while hydroxychloroquine was discontinued. After 2 months of thalidomide therapy, the patient reported a significant reduction in pain and increased range of motion in her ankles. Mycophenolate mofetil was subsequently discontinued.

Three years after initiating thalidomide, the patient presented to the emergency room with sensations of left-sided numbness and tingling occurring for 2 weeks. She had not been receiving any medications other than thalidomide. The patient denied owning cats but mentioned a history of occasionally feeding her neighbor's cats. Furthermore, there were no other identifiable risk factors for toxoplasmosis.

Brain magnetic resonance imaging (Fig 1, *A* and *B*) revealed rim-enhancing lesions within the thalamus and nodular enhancing lesion within the frontal lobe. Laboratory tests were noncontributory. Diagnostic lumbar puncture revealed 277 nucleated cells (0-5/CMM) with negative cultures. The patient had a negative human immunodeficiency virus antigen and antibody screen as well as a normal T cell count. However, serologic testing was positive for anti-toxoplasma immunoglobulins M and G with a toxoplasma IgG index (>33 IU/ml = positive), and a toxoplasma IgM index of >4

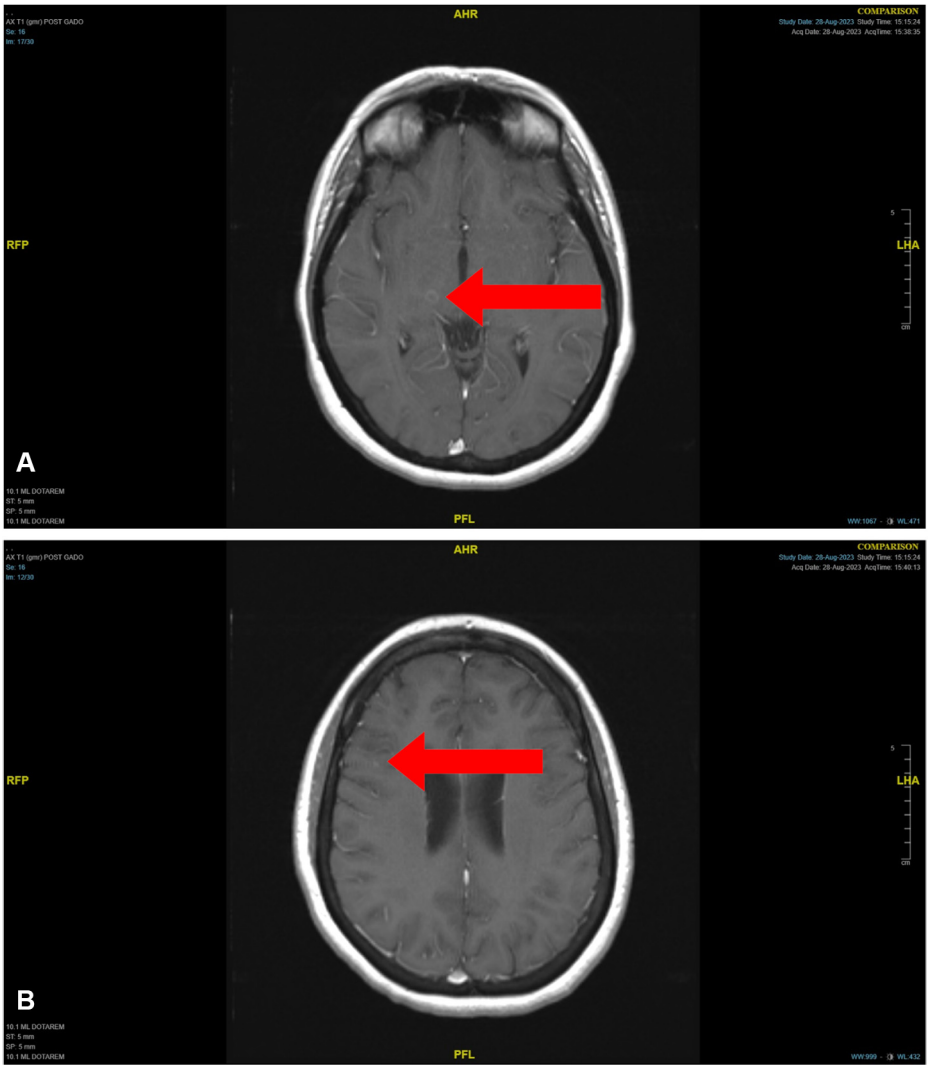

Fig 2. Two months later, repeat axial T1-weighted follow-up magnetic resonance imaging shows resolution of edema and a decreased size of the previously 10 mm ring enhancing lesion (*red arrow*) (**A**) and the 4 mm nodular enhancement (*red arrow*) (**B**).

AI (>0.8 = positive). Toxoserology confirmed the radiological diagnosis of central nervous system toxoplasmosis.

Thalidomide was discontinued and treatment with sulfadiazine and pyrimethamine was initiated for 6 weeks, followed by trimethoprim-sulfamethoxazole for maintenance. Two months later, a control brain magnetic resonance imaging (Fig 2, *A* and *B*) showed a decreased size of the rim-enhancing and nodular enhancing lesion and edema.

Nine months later, a new active lesion of limited cutaneous SSc with debilitating symptoms, including difficulty walking, was detected on her feet/lower leg. This prompted the initiation of subcutaneous tocilizumab treatment after appealing to the patient's insurance company, to which she responded after 2 months of use.

DISCUSSION

Cases of toxoplasmosis have been reported in patients with autoimmune diseases following immunosuppressive treatment. The risk of infection in patients with autoimmune diseases is high because the prolonged necessity for immunosuppressive treatments, and the increased usage of biologics.[2] Additionally, the high seroprevalence of toxoplasmosis among patients with autoimmune diseases has been previously reported, further contributing to their increased susceptibility to infection.[5]

A multicenter study identified toxoplasmosis rates in patients with autoimmune disease undergoing immunosuppressive treatment and determined that cerebral toxoplasmosis constituted the majority (49.2%) of cases.[2] Our case similarly showed the presence of cerebral toxoplasmosis, aligning with the study findings.

Despite the extensive use of immunomodulatory drugs in the treatment of SSc, no therapy has demonstrated complete effectiveness in managing or reversing SSc-related fibrosis. This has prompted ongoing exploration for novel treatments. Thalidomide and its analogs, known for their immunomodulatory properties on proinflammatory and profibrotic cytokines, as well as their antiangiogenic effects, have been considered as a potential treatment for skin fibrosis in SSc.[6] Thalidomide is capable of inhibiting TNF-α production, a cytokine involved in the immune response against intracellular pathogens like *T. gondii*.[4] Increased risk of severe infections in patients with multiple myeloma treated with thalidomide have been reported.[7] However, to the best of our knowledge, the association between thalidomide use and toxoplasmosis has not been previously described. The absence of findings in the patient's immunologic workup, coupled with no history of other immunosuppressive medications, supports the hypothesis that inhibition of TNF-α might have been a predisposing factor in this particular case of cerebral toxoplasmosis.

While evidence supports thalidomide's TNF-α immunomodulatory effects and its association with increased susceptibility to infections, direct evidence linking thalidomide to toxoplasmosis is limited. This proposed mechanism suggests a potential relationship between thalidomide-induced TNF-α suppression and increased vulnerability to opportunistic infections like toxoplasmosis. Additionally, reports have linked thalidomide usage to bacterial pneumonia, cytomegalovirus, herpes simplex virus, and varicella zoster virus infections.[8]

Further research is needed to establish standardized guidelines for the treatment of patients undergoing immunosuppressive therapy for autoimmune diseases. While there is no universally accepted protocol for screening or prophylaxis against toxoplasmosis in such patients, individualized assessments based on patient risk factors and treatment regimens should guide clinical decisions.

Though rare, cerebral toxoplasmosis should be considered in the differential diagnosis of patients with autoimmune diseases receiving immuno-suppressive treatment who present with neurological manifestations to allow for prompt intervention and improved patient care.

Conflicts of interest

Dr Abrar A. Qureshi is a consultant for OM1 and Incyte. Dr Betul Macit reported receiving grant from European Academy of Dermatology and Venereology Society outside the submitted work. Aakash Arora has no conflicts of interests to declare.

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