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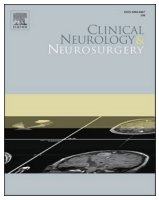

Case report

Chronic cavitary pulmonary aspergillosis in a teriflunomide-treated multiple sclerosis patient

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1. Introduction

Teriflunomide is a once-daily oral therapy approved for the treatment of relapsing forms of multiple sclerosis. Teriflunomide has been shown to reduce relapse rate and disability progression [1]. Its efficacy presumably results from of a selective and reversible inhibition of dihydro-orotate dehydrogenase (DHODH), a mitochondrial enzyme essential for de novo pyrimidine synthesis, and inducing a reduction of activated T and B cells without compromising mechanisms of adaptive immunity [2]. Although long-term risk of lymphopenia and infections is low in teriflunomide treated patients, monitoring lymphocyte counts is required [3]. We herein describe the case of a 55-year-old male patient with MS who developed pulmonary aspergilloma while receiving teriflunomide treatment.

2. Case presentation

The patient is a 55-year-old Caucasian man, ex-smoker, with history of relapsing-remitting multiple sclerosis (RRMS) and urinary diversion with ileal conduit but no previous respiratory disorders. RRMS was formally diagnosed in 1989. He had been treated by first-line injectable (interferon beta-1a) between 2001–2014. In 2014, treatment was switched to teriflunomide for convenience. The patient remained clinically (Expanded Disability Status Scale (EDSS) 6.0; walking 100 m with a stick) and radiologically stable during teriflunomide treatment, which was well tolerated.

The patient presented in July 2018 with a 2-month history of non-productive cough and asthenia without chest pain or dyspnea. He did not report fever or haemoptysis. On admission, cardiopulmonary auscultation was normal. Neurological examination did not reveal new deficits but walking performances were reduced (bilateral assistance needed; EDSS 6.5). Routine blood tests showed slightly elevated C-reactive protein levels (19 mg/L; N < 10 mg/L) and a reduced level of lymphocytes (1098/mm^3; N 1500–4000/mm^3). Spirometry showed a forced expiratory volume in 1 s of 86 % predicted. Chest computed tomography demonstrated a cavitary lesion in the right upper lobe, suggestive of aspergilloma (Fig. 1). The patient subsequently had a bronchoscopy which was macroscopically normal and showed histologically normal bronchial mucosa, with no malignant cells. To obtain a definitive histological diagnosis, a thoracotomy with right upper lobe wedge resection was performed. Histology demonstrated a cavity filled with inflammatory material and septate fungal hyphae consistent with Aspergillus (Fig. 2). There was no evidence of malignancy. Teriflunomide was stopped and intravenous voriconazole was started (6 mg/kg for day 1, followed by 4 mg/kg every 12 h.) He ultimately died due to massive gastrointestinal bleeding 6 weeks later.

3. Discussion

We report herein an additional case of fatal pulmonary aspergilloma in a teriflunomide treated MS patient, in the setting of mild lymphopenia (grade 0 according to the World Health Organization -WHO). Chronic

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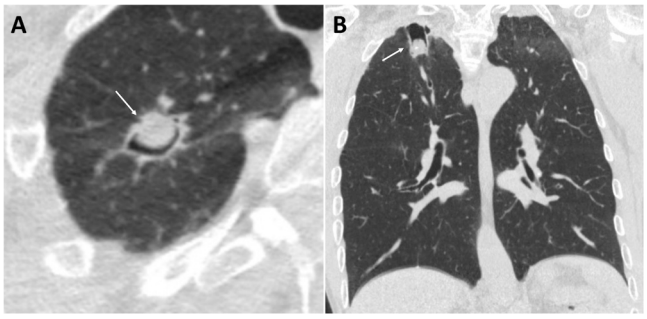

Fig. 1. Chest computed tomography in axial (A) and coronal (B) view showing a cavitary pulmonary in the right upper lobe (arrows).

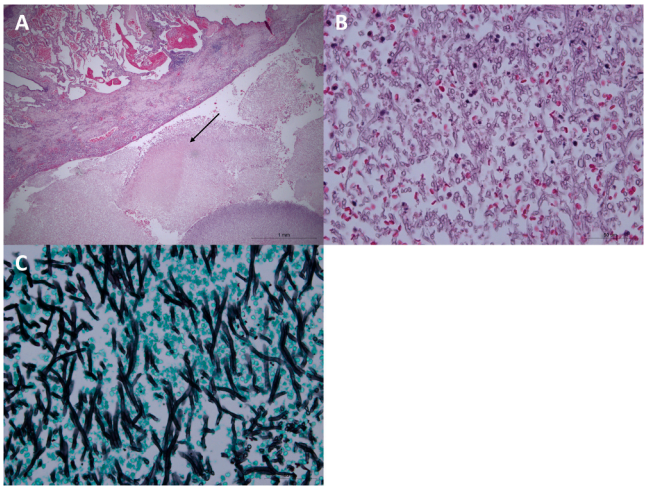

Fig. 2. Histopathological examination of the cavitary lesion (black arrow) showing fungal hyphae in the lumen, with 45-degree-angle branching, morphologically consistent with *Aspergillus* species (A, Hematoxylin-eosin staining, x2,5; B, Hematoxylin-eosin staining, x40; C, Grocott staining, x40).

pulmonary aspergillosis is a severe fungal infection usually seen in immunocompetent or mildly immunosuppressed patients with underlying respiratory disorders. Surgical resection and triazole therapy are the cornerstone of treatment although recommendations are based on low-quality evidence from cohort studies [3]. The current patient had no history of opportunistic infections. To date, teriflunomide-treated patients are not considered as highly susceptible to opportunistic infections. In a pooled analysis of 4 clinical trials on teriflunomide in MS, no increased risk of serious infections was observed in teriflunomide-treated patients without lymphopenia in comparison with placebo- and interferon beta-1a-treated patients (respectively 3.0 %, 2.2 % and 1.2 %) [4]. Based on this analysis, the long-term risk of lymphopenia and infections in patients treating with teriflunomide is currently considered as low [4]. After searching in the literature using PubMed and Scopus, we found only one confirmed case of pulmonary aspergilloma developed in a 56-year-old woman treated for 10 months with teriflunomide for MS [5]. However, when we checked VigiBase (http://www.vigiaccess.org/), the WHO global database for adverse drug reactions, we found 8 reported cases of bronchopulmonary aspergillosis. Also, 2 cases of pulmonary aspergillosis in rheumatoid arthritis patients receiving leflunomide, prodrug of teriflunomide have been previously reported [5]. In our patient, a potential role of lymphopenia, presumably induced by teriflunomide, in the occurrence of aspergillosis cannot therefore be ruled out.

4. Conclusion

So although there is currently no direct evidence confirming causality of teriflunomide, this observation advocates the need for continued vigilance in teriflunomide-treated patients, especially in patients older than 50 years who appear to be more susceptible to opportunistic infections and malignancies due to the effects of natural immunosenescence in conjunction with long-term effects of teriflunomide on the immune system. This also underscores the importance of gathering real world evidence on the long-term safety of MS patients on disease-modifying treatments.

Informed consent

Informed consent was obtained from the patient, prior to death.

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Conflict of interest

No potential conflict of interest was reported by the author(s).

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