Cavitary pulmonary disease in a patient treated with natalizumab

Pneumopathie cavitaire sous natalizumab

Natalizumab (Tysabri®) is a humanized monoclonal antibody, a selective adhesion molecule inhibitor. It inhibits binding of cells expressing α₄β₁ integrin and α₄β₇ integrin (e.g., lymphocytes) to vascular-cell adhesion molecule 1 and mucosal addressin-cell adhesion molecule 1 on endothelial cells. Thus, it reduces the migration of immunocompetent cells from peripheral blood into the target organs, i.e. the central nervous system of patients with multiple sclerosis (MS) and the intestinal tract of patients with inflammatory bowel disease [1]. Natalizumab is indicated in active remitting-relapsing MS and as second-line therapy for induction and maintenance of remission for moderate to severe Crohn’s disease. With the exception of progressive multifocal leukoencephalopathy (PML) due to JC polyomavirus [2], natalizumab does not appear to increase the risk of infection in clinical trials. We report a case of Mycobacterium intracellulare pneumonia in a MS patient receiving natalizumab.

Case report

This 28-year-old woman was followed in our department since 2001 for a remitting-relapsing MS. Subcutaneous interferon beta-1a (Rebif 22®) was given from February 2002 to March 2004, then she received intramuscular interferon beta-1a (Avonex®). Despite these immunomodulatory treatments, she experienced 3 relapses per year and her neurologic status worsened: in January 2008, before starting natalizumab, chest X-ray was normal. There was a 6 millimeters reaction to tuberculin skin test (BCG-vaccine status was positive) and HIV serology (ELISA assay) was negative. In May 2010, after a total of 29 infusions of natalizumab, she reported a neurologic improvement (EDSS 7.0), without new enhancing lesions on MRI. During natalizumab therapy, chest X-rays were systematically performed every year during the first 2 years and every 6 months after 24 infusions according to the local protocol in the absence of specific clinical guidelines. In June 2010, it revealed an excavated nodule in the right apex whereas the patient only reported asthenia, without evidence for fever, cough, weight loss, hemoptysis or dyspnea. High-resolution computed tomography of the chest confirmed the cavitary infiltrates of the right upper lobe (figure 1). Direct smear examination of the 3 first sputum did not show any acid-fast bacillus. A direct smear examination of a bronchoalveolar aspirate was negative again but one subsequent sputum smear revealed positive acid-fast bacilli which were identified as M. intracellulare by Genotype Mycobacterium® assay. Cultures in both solid and liquid medium of 7 respiratory specimens were positive within 7 weeks and confirmed Mycobacterium avium complex (MAC) infection. Direct smear examination and cultures of the bronchoalveolar aspirate were negative for other microorganisms. HIV serology and antigen detection were still negative. Natalizumab was withdrawn and changed for interferon beta-1a (Avonex®) together with monthly infusions of methylprednisolone (1000 mg each) until October 2010. Mycobacterial susceptibility testing was performed on the cultures and revealed new lesions. Natalizumab (300 mg intravenously every month) was started in January 2008. Before starting natalizumab, chest X-ray was normal. There was a 6 millimeters reaction to tuberculin skin test (BCG-vaccine status was positive) and HIV serology (ELISA assay) was negative. In May 2010, after a total of 29 infusions of natalizumab, she reported a neurologic improvement (EDSS 7.0), without new enhancing lesions on MRI.

Box 1
Score Extended Disability Status Scale (EDSS)

- The EDSS is a functional scoring system that is widely used to measure MS disability [3].
- This scale is currently used as primary end point in most therapeutic trials [4].
- It ranges in values from 0 to 10 with higher scores indicating a greater disease disability.
- A variation of at least 0.5 point in the EDSS is considered significant if the EDSS is between 6 and 9 [5].
Letter to the editor

in PML, the prevalence of non-tuberculous mycobacterial pulmonary infection suggests that other reservoirs might be involved [6]. As sputum was not well documented in most reported cases, some HIV-infected patients whereas the source of the contamination could rarely be associated with opportunistic pulmonary infections. MAC mainly occurs in immunocompromised patients or patients with underlying chronic lung disease such as chronic obstructive pulmonary disease or lung tuberculosis. In cases where MAC infection affects persons without predisposing conditions, particularly elderly women, its recognition is often delayed because of its indolent nature [8]. The treatment of MAC pulmonary infection remains long and difficult. For most patients with nodular/bronchiectatic disease, recommended treatment includes clarithromycin 1000 mg or azithromycin 500–600 mg, ethambutol 25 mg/kg, and rifampin 600 mg given three times weekly. A more aggressive treatment regimen for patients with severe and extensive or fibrocavitary disease, as reported herein, consists of daily clarithromycin or azithromycin, rifabutin or rifampin, ethambutol, and consideration of inclusion of either amikacin or streptomycin for the first 2 or 3 months of therapy. The optimal length of drug therapy, although not clearly established, is usually at least 12 months after negativation of the sputum cultures. In this case, rifabutin had to be stopped after 2 months of treatment due to intolerance, although official treatment guidelines recommend to keep a triple therapy regimen during the whole treatment course [6].

Our patient had no pharyngo-laryngeal involvement by MS, which could have led to false-passages, or respiratory problems which could have facilitated MAC growing. The role of mitoxantrone prescribed 4 years before is unlikely. Respiratory tract infections may occur but as a short-term adverse event caused by leukopenia. In addition, a large French cohort with at least 5 years of follow-up did not report any MAC pneumonia [9]. These findings, together with the evocative timing after the introduction of natalizumab, support the evidence for a direct role of natalizumab in the development of the infection, probably through a local cellular immunodeficiency. Natalizumab therapy has been associated with other opportunistic infections, such as PML, a rare, fatal or severely disabling infection of the oligodendrocytes by the JC polyomavirus. PML was first described in 2 patients in the phase III study of natalizumab in MS, concomitantly receiving interferon-β [10,11] and in one patient in a Crohn’s disease clinical trial [12]. Only one cryptosporidal gastroenteritis was reported in these phase III trials, other infectious side-effects being infrequent [13–15]. There was no case of tuberculosis or other mycobacterial infection reported in these studies. However, in the post-approval setting, 2 cases of lung tuberculosis [16] and one case of *Mycobacterium kansasii* pulmonary infection [17] have been described in recently published case reports. These cases, together with the present report, suggest that natalizumab could rarely be associated with opportunistic pulmonary infections, such as MAC infection.

susceptible phenotype. The patient was originally treated with oral clarithromycin 1000 mg 2 times a day, rifabutin 300 mg and ethambutol 1200 mg every day associated with intramuscular injections of amikacin 500 mg/day during the first month of treatment. Rifabutin had to be stopped after 2 months of treatment due to joint pain. The patient remained treated with clarithromycin and ethambutol. After 6 months of treatment, in January 2013, chest HRCT confirmed the good outcome with decrease of the right upper lobe cavity, thinning of the cavity walls, and clearing of the infiltrates. Clinical and radiological MS activity re-started in January 2013. Interferon beta-1a was therefore changed for fingolimod in August 2013 whereas she was still receiving rifabutin and ethambutol.

**Discussion**

In this case, facing the association of clinical signs, excavated pulmonary lesions, acid-fast bacilli positive smear examination and 7 positive respiratory specimens cultures, our patient met the criteria for diagnosing non-tuberculous mycobacterial lung disease in HIV-negative patients [6]. Other infectious causes for excavated pneumonia had been excluded by the negativity of bronchial wash cultures.

*M. intracellulare* (that belongs to the *Mycobacterium avium complex, MAC*) is an ubiquitous slow-growing non-tuberculous mycobacteria. Its reservoir is constituted by environmental sources, especially natural waters and soils. Airway contamination occurred through inhalation of infected water sources in some HIV-infected patients whereas the source of the contamination was not well documented in most reported cases, thus suggesting that other reservoirs might be involved [6]. As in PML, the prevalence of non-tuberculous mycobacterial pulmonary infections is extremely low in the general population (8.6/100,000) although up to 15% of the population may be exposed [7]. MAC mainly occurs in immunocompromised patients or patients with underlying chronic lung disease such as chronic obstructive pulmonary disease or lung tuberculosis. In cases where MAC infection affects persons without predisposing conditions, particularly elderly women, its recognition is often delayed because of its indolent nature [8]. The treatment of MAC pulmonary infection remains long and difficult. For most patients with nodular/bronchiectatic disease, recommended treatment includes clarithromycin 1000 mg or azithromycin 500–600 mg, ethambutol 25 mg/kg, and rifampin 600 mg given three times weekly. A more aggressive treatment regimen for patients with severe and extensive or fibrocavitary disease, as reported herein, consists of daily clarithromycin or azithromycin, rifabutin or rifampin, ethambutol, and consideration of inclusion of either amikacin or streptomycin for the first 2 or 3 months of therapy. The optimal length of drug therapy, although not clearly established, is usually at least 12 months after negativation of the sputum cultures. In this case, rifabutin had to be stopped after 2 months of treatment due to intolerance, although official treatment guidelines recommend to keep a triple therapy regimen during the whole treatment course [6].

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**Figure 1**

*High-resolution computed tomography. Cavitary infiltrates of the right upper lobe*

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Indeed, MAC infections are associated with impaired T-cell function, either in the setting of primary or of acquired immune deficiencies. The most common cause of acquired immune deficiency associated with mycobacterial infections is HIV infection in which non-tuberculous mycobacterial disease most often occurs when CD4 T lymphocytes count is less than 50/\text{mm}^2. Other acquired immune deficiencies leading to mycobacterial infections include drugs, mainly TNF-\alpha (tumor necrosis factor) inhibitors [18]: anti-TNF-\alpha monoclonal antibodies (infliximab, Remicade\textsuperscript{®} or adalimumab, Humira\textsuperscript{®}) and soluble TNF-\alpha receptor (etanercept, Enbrel\textsuperscript{®}). Finally, anti-IFN-\gamma (gamma interferon) antibodies have been identified in adult patients from Thailand or Taiwan with multiple mycobacterial opportunistic infections in the absence of HIV infection [19].

Primary immune deficiencies leading to increased mycobacterial susceptibility, called MSMD ( mendelian susceptibility to mycobacterial disease), are characterized by a genetic susceptibility to infections by low virulent mycobacteria, such as Mycobacterium bovis (bacille Calmette-Guerin, used for tuberculosis vaccination) and environmental non-tuberculous mycobacteria such as Mycobacterium avium. The identified mutations are located in genes involved in IFN-\gamma-mediated immunity (IFN-\gamma-secretion is stimulated by IL-12). Transmission may be autosomal ( IFNGR1, IFNGR2, STAT1, IL12B, IL12RB1 and IRF8 genes) or X-linked recessive ( NEMO and CYBB genes). These mutations alter IFN-\gamma secretion by T or natural killer (NK) lymphocytes or the signal induced by the binding of IFN-\gamma to its receptor. IFN-\gamma plays a critical role in the immune defenses directed against intracellular pathogens such as mycobacteria [20]. Both IFN-\gamma and TNF-\alpha are key cytokines produced by Th1 CD4 T cells.

Apart from these MSMD, GATA2 deficiency has recently been shown to lead to MonoMac (monocytopenia and mycobacterial infections) syndrome, that includes a predisposition to myelo-sclerosis vaccination) and environmental non-tuberculous mycobacterial disease), are characterized by a genetic susceptibility in the absence of HIV infection [19].

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References

Letter to the Editor

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