Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

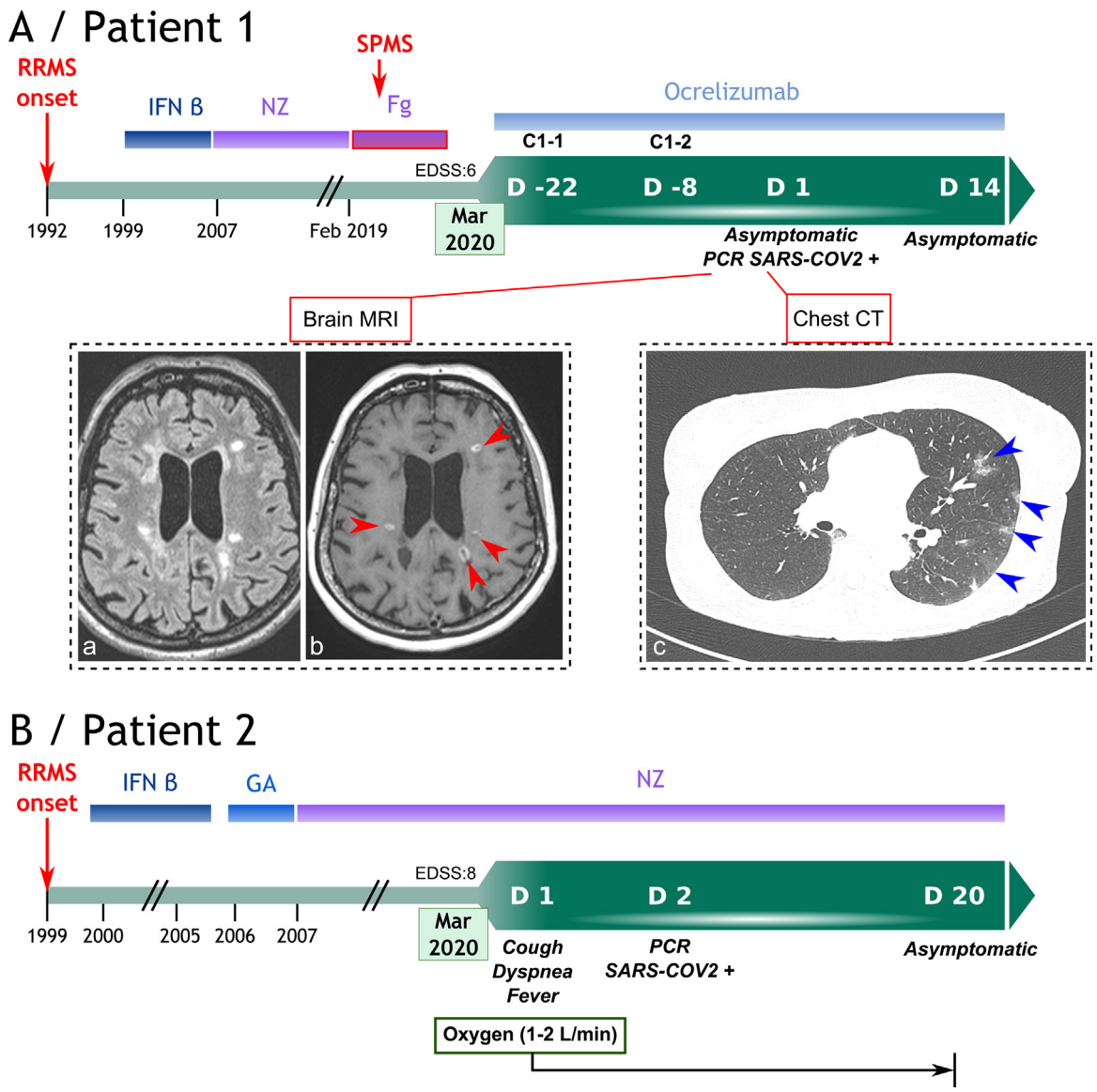

Fig. 1 – Timeline for both patients: multiple sclerosis onset and succession of disease modifying therapies, followed by COVID-19 diagnosis in March 2020. Days are noted from the diagnosis of COVID-19 (patient 1) or the first symptoms of COVID-19 (patient 2) (ex: D–22 corresponds to 22 days before COVID-19 diagnosis). (a) Fluid attenuation inversion recovery (FLAIR) sequence showing hyperintense MS lesions. (b) Post gadolinium T1 sequence showing gadolinium-enhanced lesions (red arrowheads) among a total of 16 supra- and infra-tentorial gadolinium-enhanced lesions. (c) Ground glass opacities (blues arrowheads) mainly located in lower lobes with moderate extent (10–25% of parenchyma). C1-1: First infusion of cycle 1 of ocrelizumab; C1-2: Second infusion of cycle 1 of ocrelizumab; EDSS: Expanded Disability Status Scale; RRMS: Relapsing remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis; IFNß: Interferon beta; GA: Glatiramer acetate; NZ: Natalizumab; Fg: Fingolimod.

included hypertension, acute pancreatitis and cholecystectomy. Body mass index was normal (20.8 kg/m^2). She was treated with natalizumab from 2007, switched by fingolimod in February 2019 after JC virus seroconversion. Despite fingolimod, the patient reported a progressive clinical worsening of the lower limb paresis, and cerebral MRI revealed several gadolinium enhanced-T1 lesions. This led to a switch for ocrelizumab. Before fingolimod discontinuation, the absolute lymphocyte count was 0.29 G/L (N: 1.0–4.0), raising up to 1.02 G/L at ocrelizumab initiation. EDSS was 6 on the day of the first ocrelizumab infusion. Two weeks after the first cycle of infusions (300 mg on March 5 and March 19 2020), in the middle of COVID-19 outbreak in France, the patient was referred to the hospital after a traumatic fall without loss of consciousness. Due to a mild inflammatory syndrome with elevation of C-reactive protein (19 mg/L, N < 5), a PCR for SARS-CoV-2 was performed and revealed the presence of the virus on March 27 2020. Thoracic CT

showed nodular and striped ground glass opacities. Grade 2 lymphopenia was noticed (absolute lymphocyte count: 0.52 G/L, N: 1.0–4.0). No respiratory symptoms, nor fever, nor anosmia nor flu-like syndrome were reported by the patient, and clinical examination did not detect respiratory dysfunction. At 14 days post-COVID-19 diagnosis, the patient remained asymptomatic.

2. Case 2

A 56-year-old woman, with relapsing remitting MS since 1999, was hospitalised in April 2019 in a long-term care unit because of severe MS disability. Her past medical history included severe comorbidities, such as a chronic obstructive pulmonary disease (COPD) related to smoking (more than 30 packs/years), and epilepsy since June 2017. Body mass index was normal (22.4 kg/m^2). She received natalizumab since 2007, last JC virus serology was controlled negative in October 2019. EDSS was 8, with tetraparesis and cognitive disorders. Last infusion of natalizumab (number 119) was performed on 14th February 2020. Her symptomatic treatment included venlafaxine, gabapentin, melatonin and bromazepam, anti-epileptic treatment included valproate. Biology revealed a mild increase of lymphocytes at 5.400 G/L (considered as related to natalizumab). One month after natalizumab infusion, mild fever (38.5 °C) and cough were reported, with non-bacterial pneumonia requiring oxygen support (2L/min). COVID-19 infection was confirmed on March 16 2020 (day 2) with PCR for SARS-CoV-2. Decrease of lymphocytes count to 2.11 G/L and of platelet count to 94 G/L (N: 150–400) were reported with moderate elevation of CRP (60 mg/L). Clinical recovery was complete with oxygen stop 20 days after the first COVID-19 symptoms.

3. Discussion

These two cases illustrate contrasting clinical phenotype of COVID-19 in patients with MS. The first patient had an incidental diagnosis, while recently treated with ocrelizumab, an anti-CD20 treatment targeting B-lymphocytes. This treatment is presumed to be at risk for COVID-19 for two reasons:

- B-lymphopenia persists for several months;
- several severe pulmonary infections have been reported in MS patients treated with anti-CD20 [3].

Several experts recommend considering a delay in the infusion of anti-CD20 during the period of COVID-19 outbreak, depending on the risk-benefice balance. The second case shows a classic clinical form of COVID-19 presenting as hypoxemic pneumonia, in a patient with previous pulmonary comorbidity and treated with natalizumab, an anti-alpha4 integrin antibody, known to be at risk for JC virus infection.

Among few COVID-19 cases reported in patients treated with immunosuppressants, clinical outcome was heterogeneous, from successful recovery [4] or pauci-symptomatic forms in 13 patients with rheumatoid arthritis [5] to death in patients with kidney or bone marrow transplant [6] or cancer [7].

Many initiatives including national and international registries have emerged to collect epidemiological data from MS patients with COVID-19. These registries will make it possible to identify the demographic characteristics of MS patients with COVID-19, to compare them with those of the general population and to determine whether immunosuppressive treatments significantly influence the clinical expression and severity of COVID-19, among known risk factors such as age, neurological disability, hypertension, obesity and pulmonary diseases. Meanwhile, it seems reasonable to discuss treatment options individually, considering MS activity and known risk factors for severe COVID-19. National recommendations have been issued [8] and will be updated upon the results from epidemiological and immunological studies about COVID-19 in MS population.

Disclosure of interest

The authors declare that they have no competing interest.

REFERENCES

[1] Brownlee W, Bourdette D, Broadley S, Killestein J, Ciccarelli O. Treating multiple sclerosis and neuromyelitis optica spectrum disorder during the COVID-19 pandemic. Neurology 2020. http://dx.doi.org/10.1212/WNL.0000000000009507.
[2] Giovannoni G, Hawkes C, Lechner-Scott J, Levy M, Waubant E, Gold J. The COVID-19 pandemic and the use of MS disease-modifying therapies. Mult Scler Relat Disord 2020. http://dx.doi.org/10.1016/j.msard.2020.102073.
[3] Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. N Engl J Med 2017;376:209–20. http://dx.doi.org/10.1056/NEJMoa1606468.
[4] Zhu L, Xu X, Ma K, et al. Successful recovery of COVID-19 pneumonia in a renal transplant recipient with long-term immunosuppression. Am J Transplant 2020. http://dx.doi.org/10.1111/ajt.15869.
[5] Monti S, Balduzzi S, Delvino P, Bellis E, Quadrelli VS, Montecucco C. Clinical course of COVID-19 in a series of patients with chronic arthritis treated with immunosuppressive targeted therapies. Ann Rheum Dis 2020. http://dx.doi.org/10.1136/annrheumdis-2020-217424.
[6] Huang J, Lin H, Wu Y, et al. COVID-19 in post-transplantation patients – report of two cases. Am J Transplant 2020. http://dx.doi.org/10.1111/ajt.15896.
[7] Zhang L, Zhu F, Xie L, et al. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. Ann Oncol 2020. http://dx.doi.org/10.1016/j.annonc.2020.03.296.
[8] https://www.arsep.org/fr/actualites/coronavirus_covid_19.html and https://sfsep.org/conseils-a-propos-du-covid-19-pour-les-personnes-atteintes-de-sep/.

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