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SHORT COMMUNICATION

Effect of the COVID-19 pandemic on disease activity in multiple sclerosis patients treated with hematopoietic stem cell transplantation

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Abstract

Background and purpose: It is still debated whether the COVID-19 pandemic affected disease activity in people with autoimmune diseases, including multiple sclerosis (MS). The aim of this study, therefore, was to explore the impact of COVID-19 in people with MS (pwMS) not receiving continuative disease-modifying therapy (DMT) after previous treatment with autologous hematopoietic stem cell transplantation (AHSCT).

Materials and methods: We included pwMS treated with AHSCT who were in disease remission without receiving DMTs during the pandemic and who were followed up at our centre during the study period. Data on SARS-CoV-2 infection and vaccination were recorded, with details of adverse events and clinical-radiological disease activity.

Results: A total of 36 pwMS (31 females; 86%) were included, of whom 23 (64%) had relapsing-remitting (RR-MS) and 13 had secondary progressive MS (SP-MS). Thirty-three pwMS (92%) received anti-SARS-CoV-2 mRNA vaccines. Thirteen patients (36%) developed mild to moderate COVID-19 a median (range) of 58 (4–224) months after AHSCT; seven (54%) of these patients were not yet vaccinated. Transient neurological symptoms after vaccination or infection were reported in 9% and 36% of the patients, respectively. The rate of new inflammatory events (relapses or asymptomatic magnetic resonance imaging [MRI] activity) after AHSCT increased from 0.006 (one asymptomatic new lesion/159 patient-years) before the pandemic to 0.083 (five relapses plus two cases of asymptomatic MRI activity/84 patient-years) since the pandemic start ($p = 0.004$).

Conclusions: People with MS with a history of highly active disease, who are untreated or receiving moderate-efficacy DMTs might be more vulnerable to disease reactivation, possibly elicited by exogenous triggers. Careful monitoring and further investigation are warranted to ascertain whether special precautions are needed in these cases.

Alice Mariottini and Antonio Lotti contributed equally to this work.

The present work was carried out at Azienda Ospedaliero-Universitaria Careggi, Largo Brambilla 3, Florence 50134, Italy.

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KEYWORDS
COVID-19, hematopoietic stem cell transplantation, multiple sclerosis, SARS-CoV-2, vaccination

INTRODUCTION

COVID-19 may trigger the onset or relapse of autoimmune diseases, including multiple sclerosis (MS) [1]. These events were reported also after anti-SARS-CoV-2 vaccination, with no indication of a causal relationship [2], and with partially conflicting results across studies [3, 4], which may be due to heterogeneity in inflammatory activity and variable use of high-efficacy disease-modifying treatments (DMTs). In this study, longitudinal changes in MS activity during the COVID-19 pandemic were explored in the absence of such confounders, focusing on a special population of people with (pw)MS who were in disease remission without any DMTs after having received autologous hematopoietic stem cell transplantation (AHSCT). AHSCT is a hematological procedure endorsed by the European Society for Blood and Marrow Transplantation (EBMT) guidelines as a standard of care for the treatment of relapsing-remitting (RR-) MS refractory to conventional DMTs [5]. AHSCT induces the "reprogramming" of the individual immune system with the restoration of immune tolerance [6]. Following AHSCT, pwMS do not routinely receive any DMTs, thus making disease remission somehow more vulnerable to potential triggers.

MATERIALS AND METHODS

Study design

This was a retrospective monocentric study aimed at exploring whether the COVID-19 pandemic affected MS activity in pwMS treated with AHSCT.

Patient population

People with MS diagnosed according to the McDonald criteria and treated with AHSCT for highly active or aggressive MS at our centre, who were in remission from inflammatory disease activity without any DMTs after AHSCT and had a follow-up assessment during the study period (January–December 2022), were included.

Autologous hematopoietic stem cell transplantation procedure

The AHSCT procedure was performed at the Cell Therapy and Transfusion Medicine Unit of the Careggi University Hospital in Florence, Italy, in collaboration with the MS Regional Referral Centre of the same hospital. The same AHSCT protocol was applied for all patients. Peripheral blood hematopoietic stem cells were mobilized with cyclophosphamide and granulocyte colony-stimulating factor, and the myeloablative intermediate-intensity conditioning regimen BEAM (carmustine, etoposide, cytarabine, and melphalan) plus rabbit anti-thymocyte globulin (ATG) was then administered [5]. The study was approved by the local ethics committee.

Clinical examinations and outcomes

Information on MS history, SARS-CoV-2 infection, and vaccination was recorded. Routine post-AHSCT follow-up included at least yearly brain magnetic resonance imaging (MRI) and neurological examination. MRI activity was re-baselined at Month 6 after AHSCT. The date of the pandemic start in Italy was set as February 25, 2020.

Statistical methods

Baseline patient characteristics are reported as median and range, or number and frequency, as appropriate. The statistics software used was SPSS version 25 (Windows). A two-tailed p value <0.05 was taken to indicate statistical significance.

RESULTS

Patient characteristics

Thirty-six pwMS were included (Table 1). All the patients had been in clinical-radiological inflammatory disease remission since undergoing AHSCT without DMT administration, except for one RR-MS patient who showed one asymptomatic new T2 lesion at brain MRI taken 11 years after AHSCT, but had no further clinical or radiological disease activity over the subsequent 5 years. AHSCT was performed before the pandemic start in 29/36 patients (81%; Figure 1).

Anti-SARS-CoV-2 vaccination and COVID-19

Thirty-three pwMS (92%) received a primary vaccination cycle, consisting of two doses of either Spikevax (COVID-19 Moderna mRNA −1273) or Comirnaty (Pfizer BioNTech BNT162b2 COVID-19 vaccine), except for those previously infected by SARS-CoV-2 who received a single dose of vaccine, according to the national regulations. Patients treated with AHSCT in the last 2 years were counselled on anti-SARS-CoV-2 vaccination according to the EBMT recommendations [7]. Vaccination occurred after AHSCT in all patients but

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TABLE 1 Clinical-demographic characteristics of the multiple sclerosis population at the start of the SARS-CoV-2 pandemic ($N = 36$).

	Median	(Range)
Age, years	45.5	(28–56)
Disease duration, years	17	(3–32)
Time between AHSCT and pandemic start, months	34.5	(−20; + 223)
Number of DMTs received before AHSCT	3	(1–7)
EDSS score	4.0	(1.0–9.0)
Relapses in the year before AHSCT	1	(0–4)
Relapses in the 2 years before AHSCT	2	(0–5)
	Number	**%**
Gender: female	31	86
RR-MS	23	64
SP-MS	13	36

Abbreviations: AHSCT, autologous hematopoietic stem cell transplantation; DMT, disease-modifying treatment; EDSS, Expanded Disability Status Scale; RR-MS, relapsing-remitting multiple sclerosis; SP-MS, secondary progressive multiple sclerosis.

one, with a median time interval of 52.5 (4–239) months. Nineteen patients (53%) received a third administration (either one dose of Comirnaty or a half-dose of Spikevax) at least 4 months after the primary cycle.

Thirteen patients (36%) tested positive for SARS-CoV-2 a median of 58 (4–224) months after undergoing AHSCT. COVID-19 occurred before the vaccination in seven patients (54%). It was mild to moderate in all the patients, without hospitalization in any case.

Transient neurological symptoms

Transient neurological symptoms during SARS-CoV-2 infection were reported in 13 patients (36%), mostly consisting of worsening of limb paresthesia during fever with spontaneous resolution within 24 h. One patient, who had three episodes of COVID-19, experienced a worsening of right-sided hemiparesis during the last infection, persisting for several days, with no new activity in the brain and spinal cord MRI; this was interpreted as a pseudo-relapse.

Three of 32 patients (9%) who were vaccinated after AHSCT experienced transient paresthesia, all occurring within a few days after vaccination.

New clinical or MRI inflammatory activity

After AHSCT, no relapses were observed over 159 patient-years of observation in the pre-pandemic period, whereas five episodes of new-onset neurological symptoms suggestive of MS relapse, verified by objective changes on neurological examination, occurred in four patients over 84 patient-years after the pandemic start (Figure 1), the latter corresponding to an annualized relapse rate of 0.06. Three of these patients also showed new T2 lesions (1–2 each) at MRI compared to a previous examination taken 6–12 months earlier. In the remaining patient, a lesion congruous to the new-onset symptoms was observed in the spinal cord MRI, but a previous recent examination was not available for comparison. Clinical disease activity occurred within 18 months of AHSCT in two patients, and after 8 years in the remaining two patients. These patients were all female and aged 42–47 years; three had RR-MS and one had SP-MS. Three patients were vaccinated with two to three doses of either Spikevax or Comirnaty after AHSCT, and did not report symptomatic COVID-19. One patient was vaccinated before AHSCT only, as she contracted a COVID-19 infection 4 months after AHSCT. In two patients, MS relapse occurred 4 and 10 weeks after the latest dose of vaccine, respectively.

Two further patients showed new asymptomatic activity on the brain MRI (two new T2 lesions, and one millimetric gadolinium-enhancing lesion, respectively) compared with the most recent previous MRI, taken 1 year before and when the pandemic had already started. In the 12-month interval between the two scans, both the patients were vaccinated, and one of them became infected with COVID-19.

The rate of new inflammatory events (relapses or new asymptomatic MRI activity) after AHSCT increased from 0.006 (1/159 patient-years) before the pandemic to 0.083 (7/84 patient-years) since the pandemic start ($p = 0.004$).

DISCUSSION

Multiple sclerosis relapse following AHSCT with myeloablative conditioning regimens is a rare event, estimated to occur in fewer than 20% of treated patients at 10 years of follow-up [8]. Based on our experience [9] and other published data on BEAM-based AHSCT [10], the rate of new inflammatory activity observed in this study during the pandemic period was unexpectedly high. Furthermore, despite the same schedule of post-AHSCT clinical and MRI assessments being adopted both before and after the pandemic start, new inflammatory disease activity appeared to be clustered over the relatively short pandemic period, in contrast to only one asymptomatic MRI reactivation being observed in the almost twofold longer pre-pandemic follow-up. In our opinion, this suggests that people with highly active disease who had achieved MS remission following immunoreconstitutive therapies, such as AHSCT, and who are untreated thereafter might be more vulnerable to potential triggers of disease reactivation, especially shortly after the treatment. The first 2 years after AHSCT are indeed crucial for the reconstitution of a tolerogenic environment, and an encounter with definite agents inducing the expansion of specific T-cell clones may affect neurological outcomes [11].

Furthermore, lack of treatment with DMTs may confer a higher susceptibility in this population, as recently suggested by the association between a higher risk of MS relapse following anti-SARS-CoV-2

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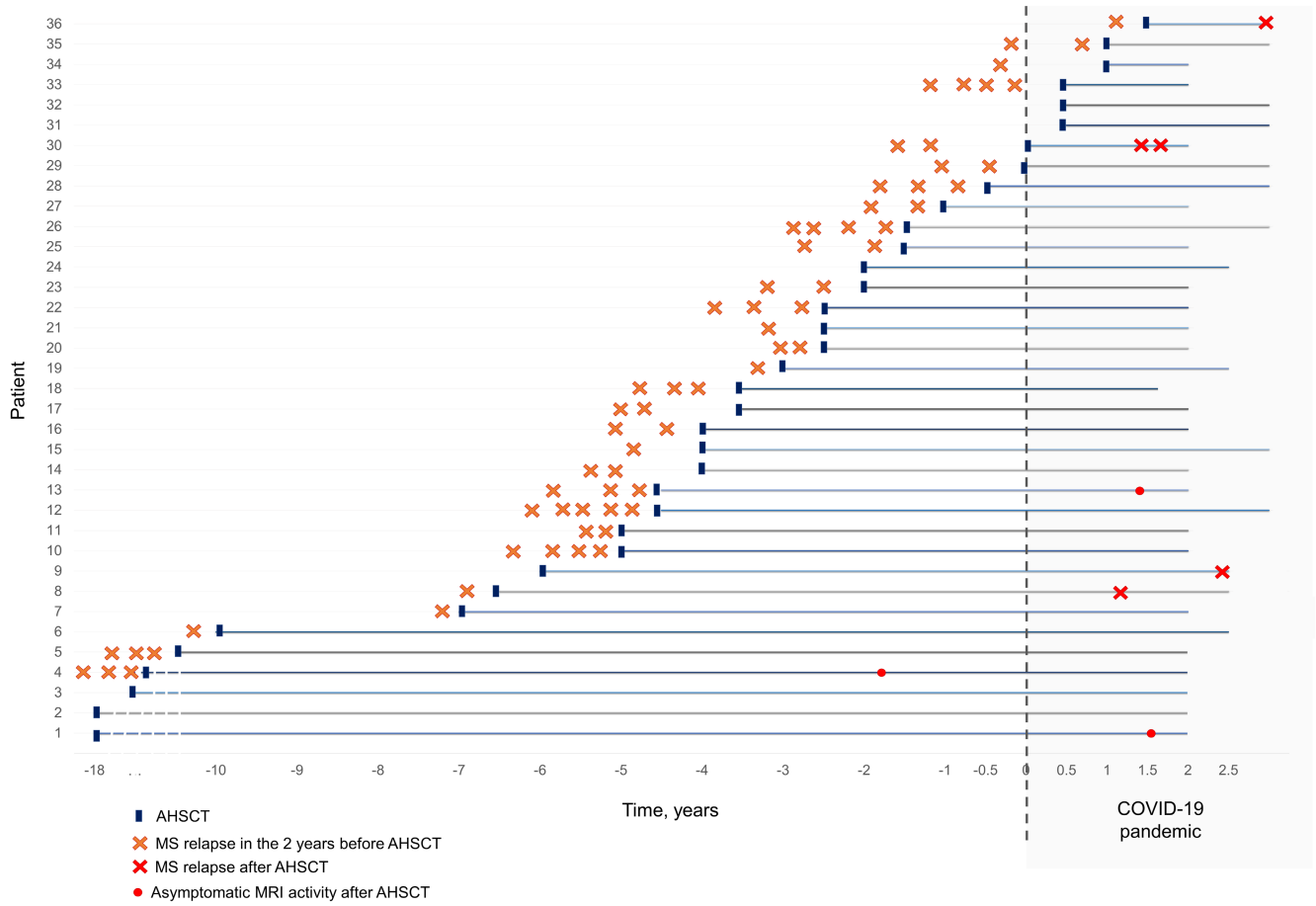

FIGURE 1 Episodes of new neurological symptoms (red crosses) or asymptomatic magnetic resonance imaging (MRI) inflammatory activity (red dots) observed after autologous hematopoietic stem cell transplantation (AHSCT) in the 36 people with multiple sclerosis (MS) included, numbered in progressive order according to the date of transplant. MS relapses occurring in the 2 years prior to AHSCT are also reported (orange crosses). Time of AHSCT is represented as a rectangle, and follow-up after transplant is in thick line. The reference year (0) was set at the pandemic start in Italy (February 25, 2020). Combined new inflammatory activity (relapse or new asymptomatic MRI activity) after AHSCT clustered over the 2-year period of the COVID-19 pandemic, from one event/159 patient-years of observation in the pre-pandemic period to seven events/84 patient-years since the pandemic start.

vaccination and absence of treatment with DMTs, along with younger age, relapsing course, and inflammatory activity in the recent past [12].

The picture is complicated further by the chance of experiencing SARS-CoV-2 infection multiple times despite previous vaccination/COVID-19 (although with a milder course), and by subclinical SARS-CoV-2 infections. These may produce a complex interplay of potential triggers of disease activity, based on high immunogenicity and putative molecular mimicry with nervous system antigens (including myelin proteins), the latter suggested for both SARS-CoV-2 [13] and the SARS-CoV-2 spike protein from mRNA vaccines [14]. In this scenario, it could be argued that the type and schedule of vaccination should be tailored to the evolving COVID-19 pandemic and the individual risk profile [15]. Finally, if a causal relationship was ascertained between these cases of MS reactivation and the putative trigger, this could have relevant implications for the long-term management of such patients, and stringent monitoring may be needed.

The main limitations of this study include the small sample size due to the low number of AHSCT-treated pwMS, and the lack of analysis of anti-SARS-CoV-2 antibodies, although their protective role is still debated. It is unknown whether the risk of MS reactivation in this setting would have been lower using a more intensive conditioning protocol. As the study is exploratory, these results should be confirmed in wider cohorts to exclude the possibility that this was a spurious finding.

In conclusion, a higher propensity to experience disease reactivation during the COVID-19 pandemic may be present for certain categories of patient, including pwMS who have had highly active disease and are currently untreated, or pwMS receiving low-efficacy DMTs. This issue requires further investigation to ascertain whether special precautions are needed in these cases.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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