Annals of Clinical Case Reports

Case Report
Published: 20 Apr, 2022

Guillain-Barré Syndrome after Hematopoietic Transplantation

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Abstract

The Hematology Service at the University Hospital of Federal University of Juiz de Fora (HU-UFJF)/Brazil carried out a research project focused on assessing the toxicity and effectiveness of progressive Lomustine doses in association with Etoposide and Cyclophosphamide in the Autologous Hematopoietic Stem Cell Transplantation (AHSCT) conditioning regimen adopted for lymphoma patients. During the follow-up, a 31-year-old woman belonging to the 400 mg/m^2 Lomustine cohort evolved with neuromuscular complications 6 months after AHSCT. Initially, she experienced diffuse pain, mainly proximal weakness in the lower limbs; however, it got worse 10 days after vaccine protocol application. She evolved with rapidly ascending motor worsening, decreased ability to walk, foot paresthesia, binocular diplopia, areflexia, bulbar and dysautonomic symptoms such as sweating, tachycardia and postural hypotension. She experienced syncope episodes 72 h before being referred to intensive care unit at HU-UFJF.

Introduction

Lymphoma is a prevalent lymphoid tissue malignancy type which is seldom associated with Guillain-Barré Syndrome (GBS). It is more prevalent in non-Hodgkin lymphoma cases than in Hodgkin ones. The peripheral nervous system is mostly affected by GBS. Neurological manifestations overall do not often emerge until advanced disease stages. Neurological abnormalities are attributed to nerve invasion, radiotherapy and chemotherapy side effects, compression by mass or paraneoplastic syndrome [1].

GBS is a rare autoimmune polyradiculopathy featured by acute areflexic motor paralysis, as well as by different sensory impairment degrees, according to which the immune system attacks Schwann cells in the peripheral nervous system. GBS is associated with previous infections in several cases; however, nowadays, most cases present other etiologies, such as vaccines and hematological malignancy [2].

The Hematology Service at the University Hospital of Federal University of Juiz de Fora (HU-UFJF)/Brazil carried out a research project focused on evaluating the effectiveness and toxicity of progressive Lomustine doses, applied in association with Etoposide and Cyclophosphamide, in an Autologous Hematopoietic Stem Cell Transplantation (AHSCT) conditioning regimen adopted for lymphoma patients. This phase-1 study was based on the traditional 3+3 design and focused on determining the maximum tolerated Lomustine dose administered at D-5. Etoposide was also administered (1 gr/m^2) at D-5 as part of the conditioning regimen; it was followed by Cyclophosphamide (2 g/m^2) application for 3 days (D-4, -3 and -2), along with the corresponding MESNA dose [3]. The study was approved by the Research Ethics Committee of Federal University of Juiz de Fora - Brazil - under CAEE number: 16011019.7.0000.5133, in 2019.

Case Presentation

During the follow-up, a 31-year-old woman belonging to the 400 mg/m^2 Lomustine cohort evolved with neuromuscular complication 6 months after AHSCT. In 2018, the aforementioned patient was diagnosed with diffuse non-Hodgkin large B-cell lymphoma rich in T lymphocytes - stage IV B, which was associated with the following comorbidities: Grade-1 obesity, non-alcoholic fatty hepatitis, hypertension and generalized anxiety disorder. The first-line treatment comprised 8 R-CHOP cycles; however, after relapse, the patient underwent salvage chemotherapy with DHAP in February 2020. Enhanced ^{18}F-FDG-PET/CT Deauville 3 has shown full remission, and AHSCT was performed in May 2020. During the hospitalization period, there were no grade 3 or 4 adverse events based on the CTCAE criteria version 5 [4]. The patient only presented febrile neutropenia,

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Received Date: *23 Feb 2022*
Accepted Date: *08 Apr 2022*
Published Date: *20 Apr 2022*

Citation:
de Souza Leal CT, Cruzeiro MM, Hallack Neto AE. Guillain-Barré Syndrome after Hematopoietic Transplantation. Ann Clin Case Rep. 2022; 7: 2161.

ISSN: 2474-1655

Table 1: Tests results.

Tests results (reference values)	Hospital Admission	Hospital Discharge
Creatinine (0.6-1.2 mg/dl)	**1.9**	**0.83**
Urea (16–40 mg/dl)	**160**	**106**
Glucose (60-99 mg/dl)	**219**	**83**
Sodium (135-145 mmol/L)	**131**	**133**
Potassium (3.5–5.5 mmol/L)	5.4	4.7
Magnesium (1.7-2.6 mg/dl)	2.6	2.4
Ionic Calcium (4.6-5.4 mg/dl)	4.9	4.6
Troponin (<0.4 ng/ml)	0.013	-
Oxylacetic transaminase (5-40 UI/L)	**157**	**63**
Aspartate aminotransferase (7-56 UI/L)	**152**	**67**
Alkaline Phosphatase (35-104 UI/L)	**1018**	**168**
GGT (7-32 UI/L)	**1131**	**690**
Creatine phosphokinase (33-211 UI/L)	**430**	76
Lactate (10.8-18.9 mg/dl)	18	-
Hemoglobin	**9.59**	**10.7**
Leucometry global/Metamyelocytes/ neutrophils	9440/94/7269	6500/0/2730
Platelet	160000	162000
Ultrasensitive PCR (VR<1 mg/dl)	**16**	**5**

which was treated by following the institutional protocol. Neutrophil engraftment took place at D+9, whereas platelet engraftment at D+11. In October 2020, she started experiencing diffuse pain, mainly proximal weakness in the lower limbs, with progressive worsening. She has subjected to electroneuromyography and results indicated myopathy without signs of cell membrane irritation and CPK dosage was 1.623 UI/L but went back to normal levels within 30 days. The post-transplant vaccine protocol was implemented on November 20th; it comprised the following vaccines: Inactivated Polio Vaccine (IPV), MMR-meningococcal type C (first dose), Pneumococcal 13, Influenza and Hemophilus Influenza (first dose). Approximately 10 days after taking the vaccines, she evolved with rapidly ascending motor worsening, decreased ability to walk, foot paresthesia, binocular diplopia and bulbar symptoms (dysphagia for liquids, slurred speech and drooling) without fever. She presented dysautonomic symptoms such as sweating, tachycardia and postural hypotension with syncope episodes 72 h before hospitalization, which was followed to the intensive care unit at HU-UFJF. Two days later the patient presented with respiratory failure and was subjected to mechanical ventilation; vasoactive drugs were administered due to severe hypotension. Based on diagnostic criteria, Guillain-Barré Syndrome was the most likely diagnosis after the exclusion of other causes, such as recent viral illnesses. Lumbar puncture was performed, and her Cerebrospinal Fluid (CSF) presented normal results; other laboratory exams, such as SARS-CoV-2, did not show any factor capable of triggering an autoimmune response. Laboratory tests conducted at hospitalization time have evidenced compromised kidney function, mild hyponatremia, as well as elevated inflammatory markers and liver enzyme levels. Due to obesity and diabetes, as recently diagnosed, the patient presented changes in liver function before AHSCT (Table 1). ECG has only shown sinus tachycardia, although echocardiogram results were normal. She underwent plasmapheresis and supportive therapies, which enabled motor symptoms remission.

The patient still presented with proximal muscle weakness (grade 2) and global areflexia at hospital discharge. She was reassessed in the outpatient clinic in March 2021 and presented gait recovery, although she complained about chronic fatigue and weight gain. Her muscle strength went back to the normal level (grade 5), except for proximal grade 4 in the lower limbs and persistent global areflexia. The FACT/GOG-Ntx questionnaire version 4 (quality of life and functionality indicator including post-chemotherapy neurotoxicity) [5], duly licensed, was applied during outpatient assessment; the patient recorded a final score of 60% referring to impairment in physical, social, family, emotional and functional well-being. After the last ^{18}F-FDG-PET/CT was performed, in August 2020, Deauville 2 ruled out post-transplant recurrence as the likely cause of acute neuropathy.

Discussion

The patient had mild myopathy probably as a chemotherapy consequence. However, her evolution suggests the incidence of severe, although rare, complication after AHSCT, which may be associated with the reaction to the Influenza vaccine. It is known that lymphoma can trigger neurological manifestations and that it can emerge at any disease stage; however, ^{18}F-FDG-PET/CT ruled out lymphoma recurrence. Increased protein concentrations in CSF, along with moderate cellularity increases, support the GBS, although it could be normal [6]. No case of severe neurological toxicity caused by Lomustine, or even by Etoposide or Cyclophosphamide, was found in the literature, although it presented reports about neurotoxic effects of influenza vaccines, such as GBS and Giant Cell Arteritis [2].

GBS incidence after influenza vaccination was first reported in 1976 during a national vaccination program against the swine flu pandemic in the United States. Approximately 40 million people were inoculated with influenza A vaccine (influenza A vaccine, in New Jersey) during the pandemic; GBS incidence has increased by 8 times after this event (mainly at 2 to 3 weeks, or even more, after vaccination) [6]. Since then, studies have been conducted, and some of them have shown a small increase in the risk of GBS after inoculation with both the seasonal and 2009 H1N1 monovalent influenza vaccines [7]. The biological mechanism of GBS after influenza vaccination may involve synergistic effects of endotoxins and vaccine-induced autoimmunity [7,8]. Juurlink have investigated GBS association with influenza vaccines administered in Canada from 1992 to 2004; based on a self-controlled case series design, they found a small, although significantly increased, risk of GBS emergence within 6 weeks after influenza vaccination (Relative Risk [RR] 1.45; 95% Confidence Interval [CI], 1.05–1.99). Based on this evidence, the estimated risk of 1 additional GBS case per 1 million vaccinated persons was disclosed to the public and included in recommendations from the Advisory Committee on Immunization Practices, as well as in influenza vaccine Information Statements [8], which was likely what happened in the case addressed herein.

Acknowledgment

The authors would like to thank the patient for agreeing to participate in the current study.

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