JMS 2022; 5(2):12-16
UDC:616.155.392.2:[602.9:616-089.843
DOI: 10.55302/JMS2252012t

CHRONIC LYMPHOCYTIC LEUKEMIA ARISING IN A PATIENT WITH HODGKIN LYMPHOMA TREATED WITH PERIPHERAL BLOOD STEM CELL TRANSPLANTATION - Case report

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Abstract

Post-transplant lymphoproliferative disorders (PTLDs) are lymphoid or plasmacytic proliferations. These disorders develop as a consequence of immunosuppression in a recipient of a solid organ, bone marrow or stem cell allograft. The development of PTLDs is usually associated with Epstein-Barr virus (EBV) and the disorder is also termed EBV-associated lymphoproliferative disorder (LPD). The development of PTLD is a rare complication in autologous bone marrow/peripheral blood stem cell transplantation.

In this study, we will present a case of LPD which developed following an autologous peripheral blood stem cell transplantation for relapsing Hodgkin's lymphoma.

Keywords: CLL, post-transplant lymphoproliferative disorders, Covid 19.

Introduction

Post-transplant lymphoproliferative disorders (PTLDs) are defined as lymphoid or plasmacytic proliferations. These disorders develop as a result of immunosuppression in a recipient of a solid organ, a bone marrow or a stem cell allograft. They are classified as immunodeficiency-associated lymphoproliferative disorders (LPDs) in the WHO classification [1].

The development of PTLD is usually associated with Epstein-Barr virus (EBV) and the disorder is also termed EBV-associated LPD. The risk of developing PTLD varies; patients receiving renal allografts have the lowest frequency of PTLD (<1%), those with hepatic and cardiac allografts have an intermediate risk (1-2%) and those with heart-lung, lung or intestinal allografts have the highest frequency (>5%) (2-4).

The recipients of peripheral blood, stem cell and bone marrow allograft have a low risk of PTLD (~1%) and PTLD is rare following an autologous bone marrow transplantation [2,3].

In this study, we will present a case study of a patient with LPD- Chronic lymphocytic leukemia that developed following autologous peripheral blood stem cell transplantation for relapsing Hodgkin's lymphoma.

Case report

In 2005 at the University clinic for haematology a 60 - years old male was presented with a painless tumour in the neck. This patient was of Macedonian origin and did not have a positive family medical anamnesis. His physical examination revealed several swollen lymph nodes in all peripheral regions without hepatosplenomegalia.

During the last two months the patient manifested B symptoms by sweating and weight loss. Biopsy of the lymph node confirmed a diagnosis of Hodgkin lymphoma - mixed cellularity. Computed tomography scan (CT) revealed Stage IIB without presence of the disease below the diaphragm. Laboratory blood tests and biochemistry findings were normal. Other discovered comorbidities were: Alcohol level was regularly in excess (50ml per day); High blood pressure (HBP); Diabetes mellitus type 2 and Coronary stents.

Following ABVD therapy with (adriamycin, bleomycin, vinblastine, dacarbazine), protocol 6 cycles were administrated. Control CT evaluation revealed complete remission. From 2006 to 2012 the patient was in complete remission with regular medical examinations.

In 2012 we conducted a biopsy of the lymph node from the neck and confirmed a relapse of Hodgkin lymphoma. CT evaluation revealed the advancement of the disease below the diaphragm i.e. stage IIIB. A high dose of DHAP therapy (dexamethasone, high-dose cytarabine (Ara-C), cisplatin (platinum) was administrated with two cycles. In 2013 an autologous transplantation was performed with conditioning regime BEAM (carmustine, etoposide, cytarabine, melphalan). The patient's body accepted the graft on day +10.

Concluding with day +100 we administered antibacterial, antiviral, antifungal, and antiparasitic prophylaxis. By 2015 remission was maintained with regular medical examinations.

In January 2022, after several years past without any medical examination, the patient returned to our clinic with high temperature 39.5^{o}C, a severe headache, cough, fatigue, shortness of breath and chest pain. Oxygen saturation on ambient air was 86%, hart rate 110/min with low blood pressure 90/60 mmHg. Our clinic could not perform the blood examination due to a positive Coronavirus disease 2019 (Covid-19) PCR test. The patient was admitted to the Clinic for Infectious Disease.

The patient had not been vaccinated for Covid 19. The patient had a severe form of Covid 19 infection. He was treated with corticosteroids, antibiotics, oxygen therapy, low molecular weight heparin (LMWH), and REGEN-COV (casirivimab and imdevimab) monoclonal antibody.

After 28 days of hospitalization the patient was discharged with a recommendation for further medical examinations by the hematologist. In February 2022, blood examination at the University clinic for Hematology revealed: Hemoglobin level of 138 g/l, White blood cells (WBC) 13.9 x 10^9/l, Absolute Lymphocyte count (ALC) was 9.4x 10^9/l and Platelet count was 199 x 10^9/l. Peripheral blood smear with presence of

94% lymphocytes, 6% neutrophils, and smudge cells were present (Figure 1). Investigations were initiated to confirm the presence of lymphoproliferative disease (CLL).

The University clinic for hematology conducted a flow cytometry analysis of the peripheral blood and reported the following results: The analyzed cell population of 75% was positive for CD45, CD5, CD19. Same population was positive for CD23, CD43, with low expression of lambda Ig light chain. Cell population was negative for CD200 and CD81, kappa.

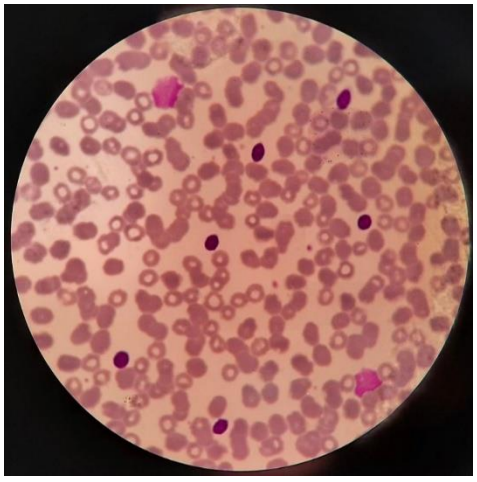

Figure 1. Peripheral smear from patient Z.S-light microscope - source University Clinic for Hematology.

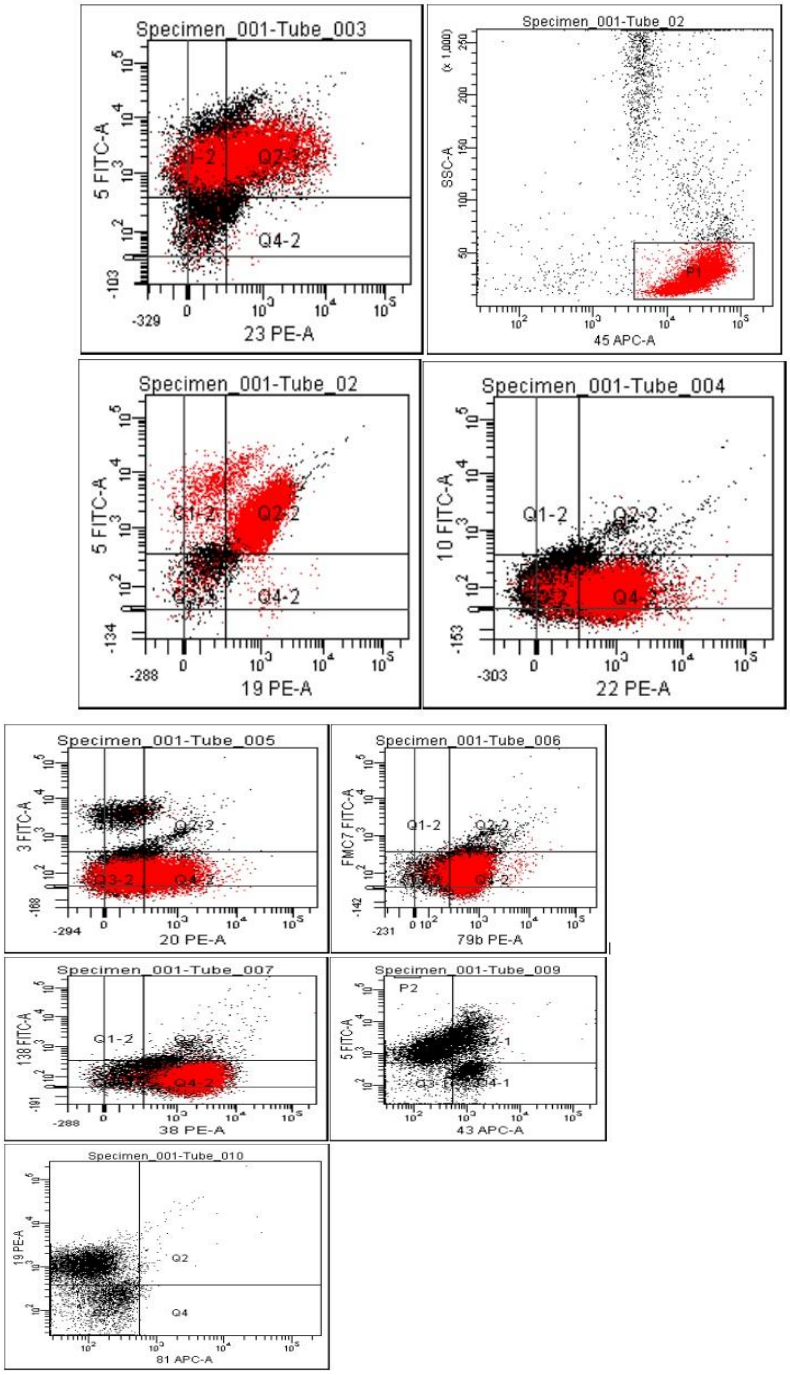

Figure 2. Flow cytometry results of patient Z.S - source unit for immuophenotyping University Clinic for Haematology.

The Biomolecular Pharmaceutical Analysis Center at the Faculty of Pharmacy in Skopje, North Macedonia conducted a mutational status of Immunoglobulin heavy chain variable region gene (IGHV). This status revealed a unmutated IGHV gene with the following profile: IGHV1-69*06 IGHD3-3*01 IGHJ4*01.

The multiplex ligation-dependent probe amplification (MLPA) applied to detect a copy number change did not reveal abnormalities affecting TP53 and other molecular prognostic markers. EBV DNA in the blood examined with PCR was negative.

Diagnosis was set CLL with stage Rai 0, Binet, and without any further treatment we chose to watch and wait. The computed tomography of the lungs revealed a pulmonary fibrosis as a consequence of a severe infection of Covid-19. The patient is presently receiving therapy with corticosteroids, bronchodilators, and oxygen.

Discussion

Is the appearance of Lymphoproliferative disease (CLL) a late complication nine years after the autologous transplantation at Hodgkin diseases or a de novo CLL?

Post-transplant lymphoproliferative disorders (PTLDs) are defined as lymphoid or plasmacytic proliferations that develop as a consequence of immunosuppression in a recipient of a solid organ, bone marrow or stem cell allograft and are classified as immunodeficiency-associated lymphoproliferative disorders (LPDs). The development of PTLD is usually associated with Epstein-Barr virus (EBV) and the disorder is also termed EBV-associated LPD.

The risk of developing PTLD varies from patients receiving renal allografts have the lowest frequency of PTLD (<1%), to those with hepatic and cardiac allografts have an intermediate risk (1-2%) and those with heart-lung, lung or intestinal allografts have the highest frequency (>5%) (2-4). Peripheral blood, stem cell and bone marrow allograft recipients have a low risk of PTLD (~1%) and PTLD is rarely expected following an autologous bone marrow transplantation.

Stephens MD et all.[4] published a large multi-centric study of Hodgkin Lymphoma (HL) in patients with chronic lymphocytic leukemia after an autologous transplantation. In this retrospective analysis, Stephens MD et all. reported a multi-centric group of patients with HL from CLL. Clinical outcomes, including survival, were higher in the group of patients with HL than what has previously been reported for this patient population and strikingly similar to what is historically expected in elderly patients with de novo HL [5].

Hauke RJ at all. published cases of two patients who developed post-transplant lymphoproliferative disorders (PTLD) following autologous transplantation [6].

One case had stage IIA nodular sclerosing Hodgkin's disease treated with autologous BMT and radiotherapy. On day +87, the male patient developed dyspnoea and bilateral pulmonary infiltrates. He was diagnosed with pneumocystis jirovecii pneumonia and CMV pneumonitis. He died on day +159. The autopsy revealed that he had disseminated polymorphous B cell PTLD involving the mediastinal, peri-gastric and peri-pancreatic lymph nodes as well as the pulmonary parenchyma.

Most individuals become infected with EBV and the virus persists within the body throughout their life in resting memory B cells. T lymphocytes control proliferating EBV-infected B cells. In a setting of decreased or impaired T-cell immune surveillance for EBV-infected B cells, as observed during immunosuppression in connection with the transplantation of solid organs or bone marrow, the unchecked replication of B lymphocytes may lead to polyclonal B-cell hyperplasia and/or the monoclonal proliferation of B cells [7].

In this case, the decreased or impaired immune surveillance for EBV-infected B cells may be correlated with the development of EBV-associated LPD due to chemotherapy and/or blood stem cell transplantation for relapsing Hodgkin's lymphoma.

Sakura Izumiya et all. published a case of EBV-associated LPD which developed following an autologous peripheral blood stem cell transplantation for relapsing Hodgkin's lymphoma [8]. Delayed immune reconstitution may play a role, although most patients who undergo autologous BMT do not develop PTLD.

Immunosuppression during Covid 19 infection may play a role at CLL development.It is noteworthy to say that there are no published cases of CLL following autologous peripheral blood stem cell transplantation. This is a case study of a chronic lymphocytic leukemia in a patient with Hodgkin lymphoma

that has been treated with autologous BMT. The patient had severe form of Covid-19 infection. The severity may be related to: unmutated IGHV, age, treatment, comorbidities, non-vaccinated status.

Chatzikonstantinou T. et all. [9] published an update of the international ERIC and Campus CLL study about Covid-19 severity and mortality in patients with CLL. The risk factors for case fatality rate (CFR), disease severity, and overall survival (OS) were investigated. Age, CLL-directed treatment, and cardiac failure were significant risk factors for OS.

Untreated patients had a better chance of survival than those on treatment or recently treated. Their findings suggest that in senior patients with CLL and Covid-19 confers a worsening prognosis with increased mortality. Our new-diagnosed CLL patient has two risk factors affecting OS: Age and Cardiac Disease.

Mutational status of IGHV was not investigated as risk factor for OS. Future studies are needed to address the impact of CLL related intrinsic factors such as IGHV mutation status on severity of the clinical picture and the survival of patients with CLL and Covid 19 infection.

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