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Newly onset cytopenias not always indicate a relapsing AML after allogeneic HSCT, a case of non-destructive post transplant lymphoproliferative disorder

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ABSTRACT

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains an effective option for the treatment of intermediate and high-risk Acute myeloid leukemia (AML). Post-transplant lymphoproliferative disorder (PTLD) is related to the intensity of post-transplant immunosuppression. Although Epstein-Barr virus (EBV) seropositivity and reactivation can be a major risk factor for PTLD. A few PTLDs could be EBV negative. There are a very limited number of PTLD cases following HSCT in patients with AML. We present a differential diagnosis of cytopenias after allo-HSCT. This is the first report of an AML patient developing bone marrow EBV-negative PTLD relatively late in their post-transplant course.

1. Introduction

Acute myeloid leukemia (AML) is a highly heterogenic disease caused by abnormal proliferation of clonal myeloid stem cells due to chromosomal rearrangements and multiple gene mutations [1]. Achieving remission on AML is considered to be relatively hard, on the other hand, relapses are still a significant challenge for patients and allogeneic hematopoietic stem cell transplant (allo-HSCT) is considered to be one of the best therapy options for intermediate and high-risk AML [2]. Although the risk of disease relapse gets lower with allo-HSCT, increased morbidity such as chronic graft versus host disease (GVHD) or secondary malignancies and the elevated risk of non-relapse mortality must be considered and must be weighed against the risk of treatment failure and relapse when providing post-remission therapy [3].

One of the most serious complications of HSCT and solid organ transplant (SOT) are post-transplant lymphoproliferative disorders (PTLDs) [4]. PTLDs associated with Epstein-Barr virus (EBV) are seen in the early post-transplant period whereas late onset lymphomas are usually EBV-negative. A spectrum of histological presentations from nondestructive lesions to destructive polymorphic or more aggressive monomorphic PTLDs can appear as a result of the uncontrolled B cell proliferation [5]. The role of EBV in PTLD evolution is well identified; however, the development of PTLD in EBV-negative patients is also not uncommon. On the other hand, PTLDs as a result of T-cell proliferation are seen much less commonly and the majority are EBV-negative [6].

A very limited number of post allo-HSCT PTLD cases have been reported in patients with AML. Herein, we present a case of EBV-negative PTLD in a patient with a history of AML who remained in remission for two years after the allo-HSCT.

2. Case report

A 46-year-old male patient with a past medical history of pulmonary tuberculosis and gastroesophageal reflux, was diagnosed with intermediate risk AML following bone marrow biopsy and flow cytometry in a local hospital in August 2019. He presented with leukocytosis, anemia, malaise, fever and excessive sweating complaints. No numerical structural anomalies were detected in the chromosomal analysis, and at the same time no prognostic and therapeutically significant variant was detected in the next-generation sequencing panel. He commenced first line therapy with 7 + 3 induction chemotherapy regimen (cytarabine continuous infusion for 7 days plus idarubicine for 3 days). Bone marrow

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biopsy results after induction therapy revealed less than 5% residual blast count. He received two cycles of high-dose cytarabine as consolidation therapy. His second consolidation chemotherapy course was complicated with acute appendicitis and he underwent an emergency appendectomy operation. He had two matched sibling donors and he was referred to our center for allo-HSCT. Following the conditioning regimen with fludarabine and busulfan the patient underwent allo-HSCT in December 2019 from a full matched sibling donor. GVHD prophylaxis consisted of methotrexate and cyclosporine. The patient's neutrophils and platelets were engrafted on +12 and +17 days respectively. Peripheral blood chimerism on day +90 post-transplant demonstrated a successful engraftment, with 99% donor cells, and a bone marrow biopsy showed complete remission (CR). On day +98 skin biopsy was performed on his neck and was reported compatible with a grade 2 GVHD, which was treated with prednisone, cyclosporin and photopheresis. On day +120 he was admitted to hospital because of a CMV DNA positivity for which he got treated with ganciclovir. He was followed up in CR for 2 years, but he was admitted to the hospital with anemia and severe thrombocytopenia (28 × 10^3/ul) in December 2021. Bone marrow biopsy performed and demonstrated morphological CR with minimal residual disease (MRD) negativity by flow cytometry and biopsy, donor chimerism in the bone marrow was at% 99, unfortunately reported to be consistent with non-destructive PTLD. In situ hybridization showed that the PTLD was EBV-negative. His EBV deoxyribonucleic acid polymerase chain reaction results were negative. Of note, serum EBV viral capsid antigen-Immunoglobulin G (VCA-IgG) was positive in the recipient and donor in the pre-transplant period. PET-CT showed no abnormalities. For PTLD, he was treated with rituximab administered once a week for 4 weeks at a dosage of 375 mg/m^2 and eltrombopag was given for severe thrombocytopenia. He responded well to the therapies; bone marrow biopsy performed in the 3rd month of rituximab treatment confirmed a CR. Eltrombopag was continued. The patient is still on his regular follow-ups with full hematological response and has shown no relapse thus far.

3. Discussion

The estimated incidence of PTLD in allo-HCST is about 2% and the risk is much higher in SOT patients with an estimated incidence of 10–15% [7]. Nevertheless, PTLD after HCST carries a greater risk of mortality and disseminated disease. PTLD incidence after HCST is mainly influenced by seronegativity of the patient for EBV at the time of transplant. Patients who acquire EBV infection after transplantation are subject to a greater risk for PTLD development. Other risk factors for PTLD are HLA mismatch and type and intensity of T-cell depleting therapy used pre- and post-transplant. The risk related to HLA mismatch is greater in the transplants from a mismatch unrelated donor and lowest in those from a matched related donor. Some of the particular antilymphocyte agents related with higher risks of PTLD are anti-thymocyte globulin (ATG), anti-CD3 monoclonal antibodies and azathioprine [5]. Relatively lower incidences of PTLD are observed in patients who received non-specific antilymphocyte agents which deplete both B and T-cells [6].

Diagnosis of PTLD remains a challenge and requires a high clinical suspicion, while the signs and symptoms are non-specific and can be attributed to more common problems related to transplant procedure. Symptoms of PTLD include but not limited to fever, weight loss, anorexia, night sweats and allograft dysfunction [5]. For instance, Dutta et al. has reported a rare case of EBV + PTLD in a patient with AML presenting with pulmonary complaints such as dry cough and bibasilar consolidations on chest computed tomography (CT) which may indicate a broad spectrum of differentials including pneumonia and GVHD [8]. Our patient also was admitted to hospital with anemia and severe thrombocytopenia, which both are non-specific manifestations for PTLD.

The mainstay of the treatment of PTLD is reducing the immunosuppression (RI) while monitoring the allograft function against an acute rejection and even complete cessation of immunosuppression may become necessary [6]. In addition to RI, surgical intervention, rituximab monotherapy, chemotherapy, immunochemotherapy, antiviral therapy, localized radiation therapy and stem-cell transplantation are available options for the treatment of PTLD [4]. Rituximab is a standard therapeutic agent in PTLD and can be added to treatment plan for nondestructive, polymorphic and monomorphic diffuse large B-cell lymphoma-like subtypes of WHO classification of PTLD [6]. For PTLDs unresponsive to RI and rituximab, chemotherapy is indicated. Our patient has remained in remission with rituximab monotherapy, to the date.

To the best of our knowledge, this is the first report of an AML patient developing bone marrow EBV-negative PTLD relatively late in their post-transplant course. He remains in complete remission over 13 months following rituximab monotherapy. It should be kept in mind in the differential diagnosis of patients presenting with cytopenias after allo-HSCT.

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Author contributions

Süreyya Yiğit Kaya and Ömür Gökmen Sevindik were the treating physicians and participated in the study design and writing of the manuscript. Abdullah Emre Askin and Sebnem Bektas contributed to the writing of the manuscript and discussion of the case with the literature review. Ömür Gökmen Sevindik reviewed the manuscript. Aslı Çakır participated in the pathological analyses. All authors have read and approved the final manuscript

Institutional review board statement

Not applicable.

Informed consent statement

Written informed consent was obtained from the patient for publication of this case report. All authors have reviewed the manuscript and approved it for publication.

Data availability

The data that support the findings of this study are available on request from the corresponding author.

Declaration of Competing Interest

The authors declare that they have no conflict of interest

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