Am J Transl Res 2023;15(11):6632-6643
www.ajtr.org /ISSN:1943-8141/AJTR0152016

Case Report

Clinical analysis of malignant lymphoma secondary to transplantation: the notorious lymphoproliferative disease

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Received July 2, 2023; Accepted October 26, 2023; Epub November 15, 2023; Published November 30, 2023

Abstract: As one of the worst complications after solid organ transplantation (SOT) or hematopoietic stem cell transplantation (HSCT), post-transplant lymphoproliferative disorder (PTLD) usually progresses rapidly and accompanies with a high mortality rate, which is the most notorious adverse event threatening long-term survival of organ transplant recipients. PTLD is generally characterized by malignant clonal proliferation of lymphocytes, so the location of the disease is uncertain, the clinical symptoms and signs are very complex, lack of specificity, and it is easy to miss diagnosis and misdiagnosis in clinical practice, which will lead to low survival of patients after transplantation. To this end, the clinical data of two patients with PTLD were retrospectively studied, and characteristics of medical history, clinical manifestations, treatment process, curative effect and prognosis of the patients with PTLD were systematically analyzed and discussed, with a view to improving the novel understanding of PTLD in the field of hematology and oncology.

Keywords: Post-transplant lymphoproliferative disorder, organ transplantation, extranodal lymphoma, differential diagnosis, prognosis

Introduction

Post-transplant lymphoproliferative disorder (PTLD) is a kind of clinically rare malignant clonal disease of lymphocytes or plasma cells induced by long-term immunosuppressive therapy after solid organ transplantation (SOT) or bone marrow hematopoietic stem cell transplantation (BM-HSCT). Due to the variable location of the disease, it is usually in the extranuclear location, and Epstein-Barr virus (EBV) plays an important role in the occurrence and development of PTLD [1]. The fourth edition of WHO's Classification of Hematopoietic and Lymphoid Tumors which was revised in 2017, classifies PTLD into four categories [2]: Non-destructive PTLD (ND-PTLD, including three subtypes), polymorphic PTLD (P-PTLD), monomorphic PTLD (M-PTLD, including B cell and T/NK cell types), and classical Hodgkin lymphoma PTLD (HL-PTLD). Due to the low incidence of PTLD, its clinical rarity, poor efficacy and poor prognosis, it is easy to miss diagnosis and misdiagnosis in the course of diagnosis and treatment, which affects the long-term survival of patients after transplantation. Nowadays, the clinical or academic research on PTLD is relatively simple and limited, lacking retrospective studies and systematic discussions, so it is very challenging to reach a consensus on diagnosis and treatment of PTLD. In view of this, a retrospective analysis of the detailed medical history, diagnosis and treatment, and prognosis of two patients with PTLD is expected to provide

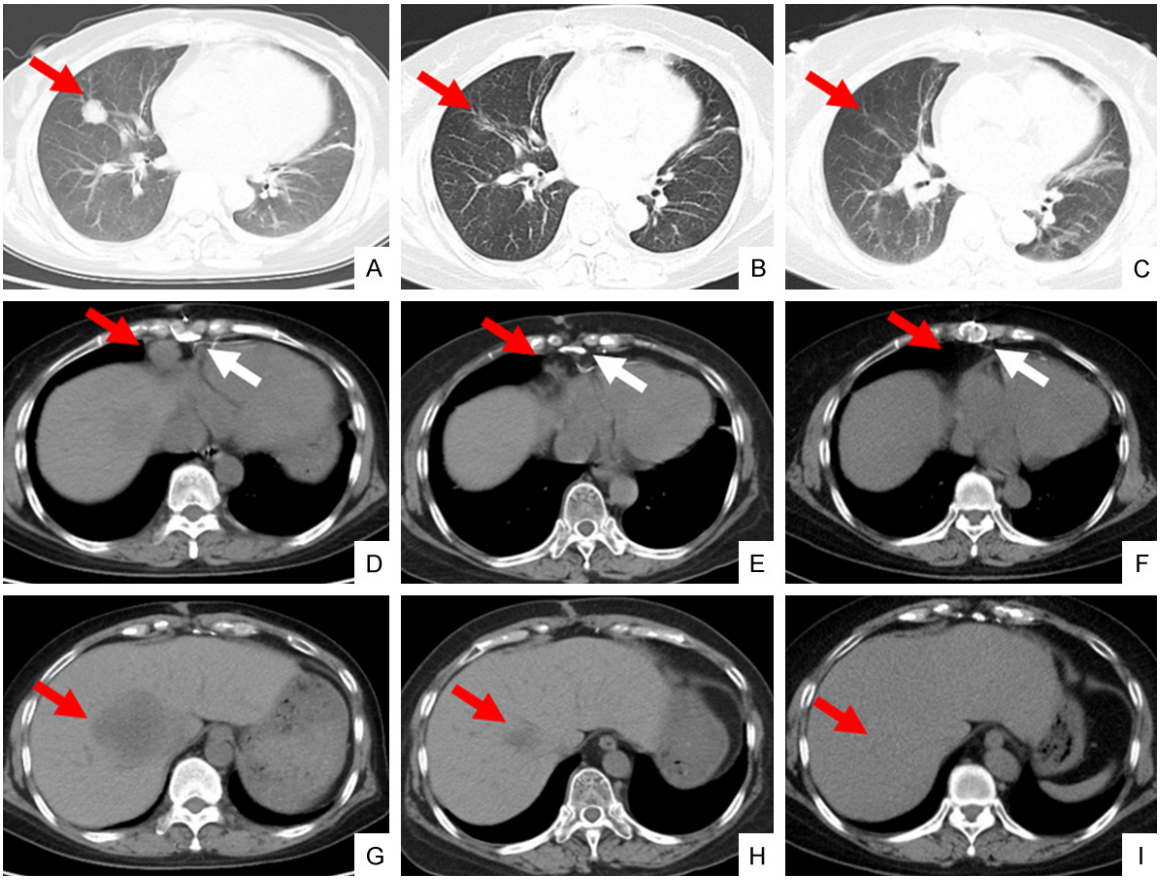

Figure 1. CT images of chest and abdomen before and after treatment. A. The red arrow indicated the space-occupying mass lesion; B, C. The red arrow indicated the disappearance of the space-occupying lesion after treatment; D. The red arrow indicated the enlarged lymph nodes in the heart and phrenic angle, and the white arrow indicated the postoperative imaging lesions of heart transplantation; E, F. The red arrow indicated the disappearance of enlarged lymph nodes, and the white arrow indicated postoperative changes of the sternum after heart transplantation; G. The red arrow indicated the liver mass and low-density lesions at the time of initial diagnosis (malignant tumor possible); H, I. The red arrow indicated the liver low-density lesions gradually decreased after treatment and disappear.

novel strategies and ideas for the prevention and treatment of PTLD in the fields of transplantation, oncology, and hematology.

Clinical presentation

Case 1

A 54-year-old female patient was admitted to our hospital with the chief complaint of "finding vulvar masses for half a month". The patient underwent "allograft orthotopic heart transplantation" in Fujian Medical University Union Hospital in July 2017 due to "dilated heart disease and grade III heart function", regularly took "mercaptopurine, tacrolimus and prednisone" after surgery, and considering that the cardiac insufficiency has not fully recovered, the patient still had asthma feelings after climbing three floors. However, the main complaint of the patient admitted this time was the vulvar mass appeared half a month before admission without obvious inductions and causes. Blood routine tests showed WBC 5.7×10^9/L, Hb 121 g/L, and PLT 89×10^9/L. Color ultrasound of urinary system showed: 1. Hypoechoic mass of right liver; 2. Hypoechoic nodules in the upper part of the right kidney (malignant tumor?); 3. Hypoechoic tubercles in the middle of the left kidney. Lung CT showed (**Figure 1**): 1. Nodules in the middle lobe of the right lung (cancer possible); 2. Cardiac phrenic horn lymph node enlargement; 3. Postoperative sternal changes, bilateral pleural thickening; 4. Liver mass with low density (malignant tumor possible); 5. Left adrenal tubercle, alert for metastasis. Pathological biopsy of the vulvar mass showed (**Figure 2**): Combined with clinical history, it was

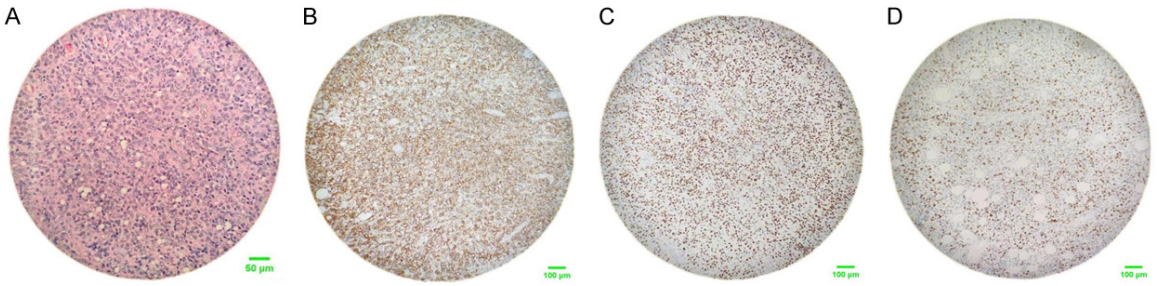

Figure 2. Immunohistochemical (IHC) staining of pathological biopsy of the vulvar mass from patient 1. Note: (A) HE staining 400×, (B) CD20 (+), (C) Ki-67 (about 60%+), (D) EBER (+). (B-D) are 200×.

consistent with monomeric post-transplantation lymphoproliferative disease (diffuse large B-cell lymphoma, non-germinal center activated B-cell). The immunohistochemical staining (IHC) showed positive CD20, Pax-5, CD23, Mum-1, about 70% positive Bcl-2, about 40% positive c-myc, and about 50% positive CD30. About 60% of Ki-67 cells were positive, Bcl-6, CD10, TdT, CD3, CD5 and CyclinD1 were negative, and Epstein-Barr Early RNA (EBER) cells were positive with in situ hybridization. Routine findings of bone marrow: 1. No lymphoma cells were detected; 2. Hyperplastic anemia. Bone marrow pathology showed that lymphoma involved bone marrow with insufficient evidence for diagnosis.

Based on the above medical examination results, the patient was diagnosed with diffuse large B-cell lymphoma (non-GCB, stage IVA, IPI 3). The elderly female patient was treated with CHOP (Cyclophosphamide 1.16 g qd d1, Doxorubicin hydrochloride liposome 40 mg d1, Vindesine 4 mg qd d1, Dexamethasone 20 mg qd d1-5) regimen for 6 courses of treatment from June to November 2016, and the process of chemotherapy was successful. PET-CT assessment of the condition showed (**Figure 3**): 1. Changes after heart transplantation; 2. Imaging of diffuse large B-cell lymphoma, residual film shadow of right lung lesion, inhibition of activity, liver S8 segment residual active lesion smaller than before. Therefore, the patient received two courses of "CHOP" regimen (same as before) in December 2016 and February 2017, and the chemotherapy was successful. From March 2017 to September 2018, no significant abnormalities were found in laboratory examinations such as blood routine and blood biochemistry during monthly review. Imaging examinations such as pulmonary CT, systemic superficial lymph node ultrasonography and whole-abdominal ultrasonography were reviewed every 3 months, indicating that the lymph nodes were more consistent than before and did not show the disease progression. Then the patient was asked to follow up regularly.

Subsequently, the patient returned to our hospital in December 2018 with the chief complaint of "right neck lymph node enlargement without obvious causes". Multiple lymph nodes could be touched in the right neck, bilateral axilla, and groin duiring physical examination, the largest of which was located in the right neck, about 1.5×1 cm in size, the texture of lymph nodes is tough, with clear boundary, good range of motion, and no tenderness. No obvious abnormalities were found in blood routine examination, blood biochemistry, coagulation analysis and other examinations. R-CHOP regimen (Rituximab 0.6 g qd d0, Cyclophosphamide 1 g qd d1, Doxorubicin hydrochloride liposome 40 mg qd d1, Vindesine 4 mg qd d1, Dexamethasone 10 mg qd d1-5) was given again. The process of chemotherapy was successful. After discharge, the patient was asked to periodically review blood and imaging examinations. Cervical thoracoabdominal CT scan plus enhanced scan in November 2019 showed: 1. Multiple small lymph nodes in bilateral neck, supraclavicular, mediastinum, peritoneal mesenteric region, and retroperitoneal region; 2. Changes after heart transplantation; 3. Nodules of posterior upper lobe of right lung. Then the patient was treated with "R regimen" (Rituximab 0.6 g) for 1 course of chemotherapy, and the chemotherapy was successful. After discharge, the patient's disease was under control and no new lesions appeared.

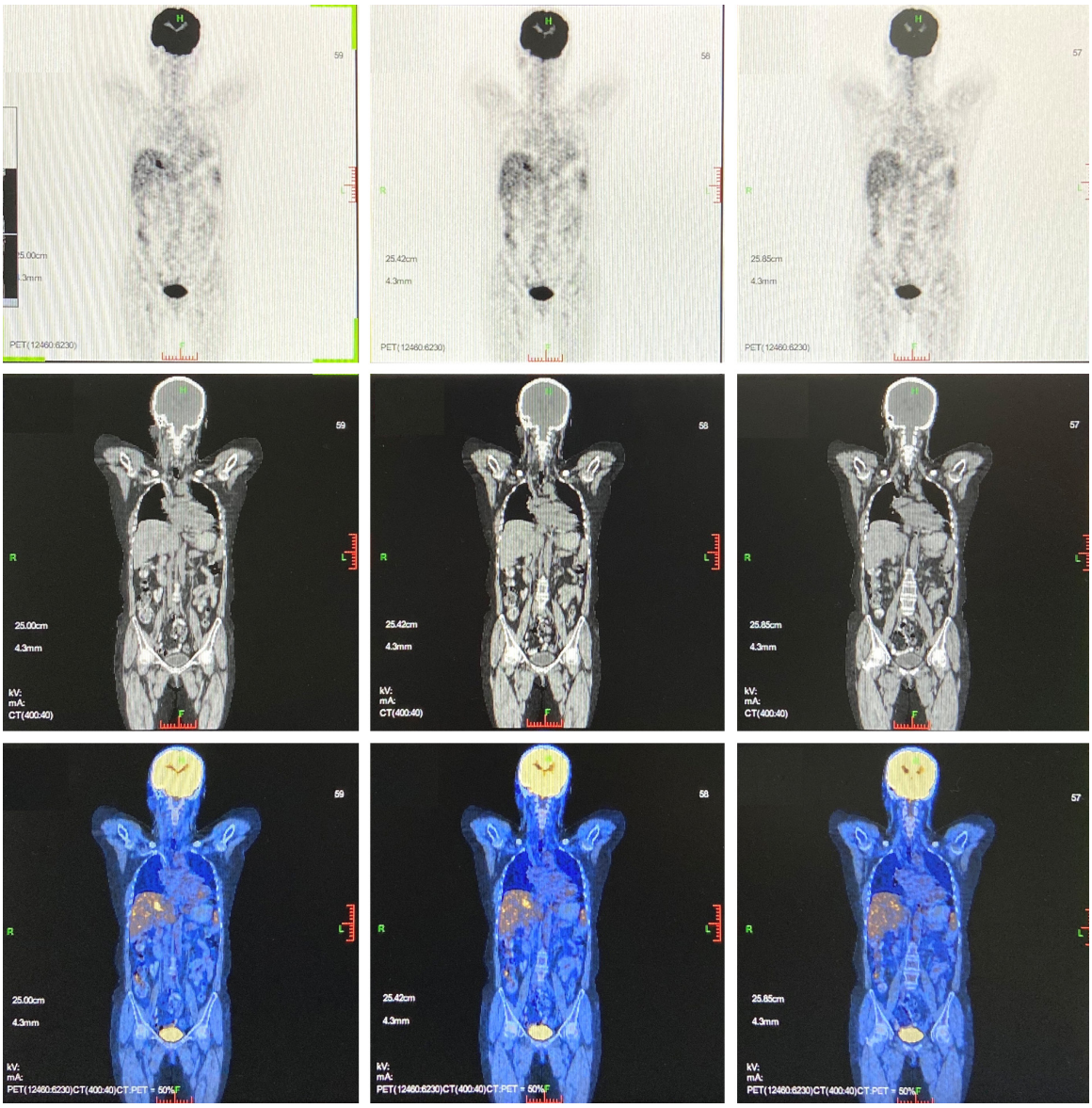

Figure 3. The PET-CT image of patient 1 after chemotherapy for assessment of condition. PET-CT showed: 1. Changes after heart transplantation; 2. Diffuse large B-cell lymphoma imaging, residual flakes in the right lung lesions, activity was suppressed, and the residual active lesions in the S8 segment of the liver were smaller than before.

Case 2

A 51-year-old male patient was admitted to our hospital with "repeated multiple systemic lymph node enlargement for more than 7 years". The patient was admitted to Fujian Provincial Hospital due to the presence of neoplasms in the nasopharynx, right neck, and left groin seven years ago without obvious causes, and the neoplasms gradually increased. The hospital completed the cervical lymph node biopsy pathology and showed that it was consistent with reactive hyperplasia of lymph nodes, with obvious hyperplasia in the T-zone, accompanied by dysplasia, which was related to EBV infection. IHC showed that CD2, CD3, CD5, CD7, CD4 and CD8 were positive, Ki-67 was positive about 40%, CD20, CD10, Bcl-6 and CD30 were negative. In situ hybridization: EBER positive of tumor cells. Nasopharyngeal biopsy showed diffuse large B-cell lymphoma, and IHC showed CD20, Pax-5, Bcl-6, c-myc, Mum-1, CD56 positive, CD30 positive about 40%, Bcl-2 positive about 60%, Ki-67 positive

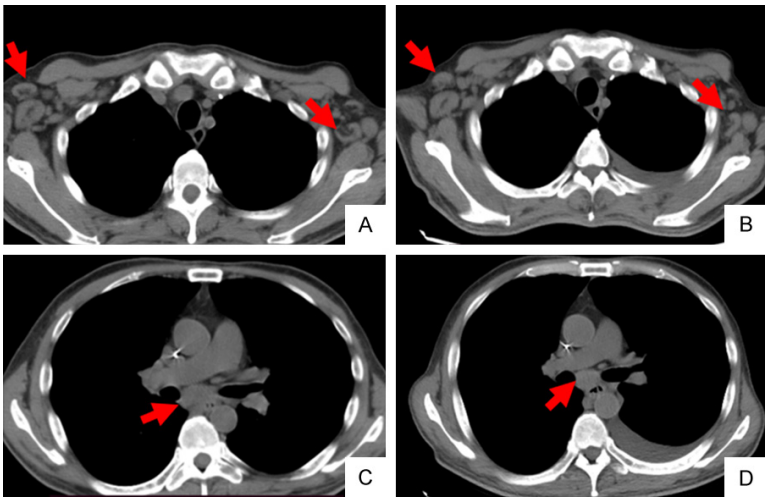

Figure 4. Lung CT image of the patient 2. A, C. Multiple enlarged lymph nodes in the mediastinum, bilateral supraclavicular area and bilateral axilla; B, D. The CT scans of the patient who was automatically discharged from the hospital. It shows multiple enlarged lymph nodes in the mediastinum, bilateral supraclavicular area and bilateral axilla.

about 40%, and CD10, CD3, CD5, TdT, CyclinD1 were negative, in situ hybridization: tumor cells EBER positive. No abnormalities were found in bone marrow routine and pathology. PET-CT showed: 1. Mucosa thickened and metabolism increased in posterior and left wall of nasopharyngeal apex; 2. Multiple hypermetabolically enlarged lymph nodes in the left parapharyngeal space, bilateral neck, supraclavicular fossa and left groin; 3. Mild enlargement of the spleen, multiple high metabolic focus, lymphoma infiltration considered.

According to the above medical examination results, the hospital diagnosed the patient with "diffuse large B-cell lymphoma (non-GCB, stage IIIB, aaIPI 3 high-risk group)". From December 2013 to April 2014, the patient received 5 courses of chemotherapy with R-CHOP regimen (Rituximab 0.6 g d1, Epirubicin 0.14 g d2, Vindesine 2 mg d2, Dexamethasone 15 mg D2-6). And in May 2014, the patient was given R-DHAP (Rituximab 0.6 g d1, Cisplatin 0.16 g d2, Cytarabine 3.4 g d2, Dexamethasone 40 mg d2-5) for mobilization, and then underwent autologous hematopoietic stem cell transplantation in the hospital in June 2014, with a total amount of about 480 ml, and no adverse reactions after transplantation. Lymph nodes did not enlarge again, and the disease control was acceptable. Then in early 2016, due to a history of "chronic hepatitis B" before, the patient took traditional Chinese herbal medicine orally by himself (the specific prescription is unknown), which later led to "late subacute liver failure", and went to Fuzhou General Hospital for "allograft total liver transplantation" and long-term oral "Tacrolimus" for immunosuppression and anti-graft rejection after transplantation. In October 2019, the patient went to Fujian Provincial Hospital again for medical treatment due to the reenlargement of left cervical lymph nodes. After completing pathological biopsy of left cervical lymph nodes, the hospital diagnosed the patient as "post-transplantation lymphoproliferative disease (T-cell tumor stage)". From November 2019 to February 2020, the patient received 4 courses of chemotherapy with "ECDOP regimen (Cyclophosphamide 1.2 g d1, Doxorubicin hydrochloride liposome 20 mg d2-3, Vincristine 2 mg d1, Etoposide 150 mg d1, Dexamethasone 15 mg d1-5)", and PR was evaluated in the interim. After that, the patient was given another 2 courses of chemotherapy with "ECDOP regimen" (same as before) from March to April 2020, and was given long-term treatment with "Chidamide 30 mg biw" after discharge.

Unfortunately, the patient developed progressive enlargement of right neck and right axillary lymph nodes again in September 2020 without obvious cause, and was then referred to our hospital. Subsequently, we performed CT examination on the patient, which indicated (**Figure 4**): 1. Multiple enlarged lymph nodes in both lungs, whose nature was undetermined; 2. Multiple enlarged lymph nodes in mediastinum, bilateral supraclavicular region and bilateral axilla. Bone marrow routine showed reduced proliferation of nucleated cells, and bone marrow pathology showed insufficient evidence of lymphoma infiltrating bone marrow. The flow cytometric immunoassay of bone marrow showed no significant abnormality. Pathological findings of cervical lymph node biopsy (**Figure 5**): Combined with clinical history, considering "post-transplantation lymphoprolif-

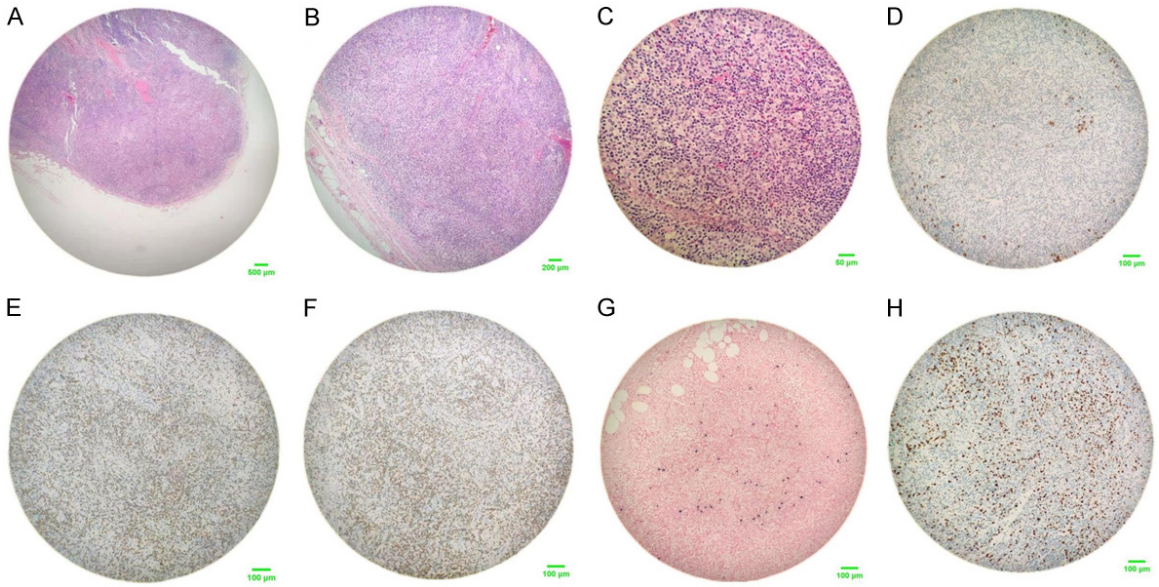

Figure 5. IHC staining of pathological biopsy from the patient 2. Note: (A-C) HE staining 40×, 100×, 400×, (D) CD20 (+), (E) CD3 (+), (F) CD5 (+), (G) EBER (+), (H) Ki-67 (about 30%+). Images of (D-H) are 200×.

erative disease (pleomorphic) with EBV infection", IHC showed positive CD20 B cells, positive CD2, CD3, CD5, CD7, CD4 and CD8 T cells, CD21 showed FDC network, about 30% Ki-67 positive, and CD10, CD30, PD-1, CXCL13 were negative, in situ hybridization: EBER positive. No abnormality was found in TCR, Ig and IGHV gene rearrangement. The patient was diagnosed with "post-transplantation lymphoproliferative disease (pleomorphic) with EBV infection" in our hospital, and he received two chemotherapy courses of "RP-Gemox regimen (Rituximab 0.6 g d1, Gemcitabine 1.78 g d1, Oxaliplatin 178 mg d1, Pegaspargase 3750 u d2)" from October to November 2020. In January 2021, the "RP2-Gemox regimen (Rituximab 0.6 g d1, PD-1 200 mg d2, Gemcitabine 1.78 g d1, Oxaliplatin 178 mg d1, Pegaspargase 3750 u d2)" was given one course of chemotherapy. At the 3rd week after discharge, the patient returned to the clinic due to "abdominal distension for more than 1 week", and blood routine examination showed white blood cell (WBC) 2.49×10^9/L, hemoglobin (HGB) 60 g/L, and platelet (PLT) 11×10^9/L. Blood biochemistry showed albumin (ALB) 26.9 g/L, total bilirubin (TBIL) 22.7 μmol/L, direct bilirubin (DBIL) 8.7 μmol/L, alanine transferase (ALT) 77 IU/L, aspartate aminotransferase (AST) 66 IU/L, uric acid (URIC) 739 μmol/L, lactate dehydrogenase (LDH) 469 IU/L, procalcitonin (PCT) 20.34 ng/ml, and C-reactive protein (CRP) 24.98 mg/L. Coagulation function showed activated partial thromboplastin time (APTT) 57.9 s, and fibrinogen (FIB) 1.01 g/L. Whole-abdominal color ultrasonography showed: 1. Hepatomegaly and splenomegaly; 2. Multiple calcification foci in prostate; 3. Multiple abdominal and retroperitoneal nodules (malignant tumor?); 4. Gallbladder display is unclear; 5. Bilateral pleural and abdominal effusion. According to the relevant medical examination results of the patient and the previous diagnosis and treatment process in our hospital, considering the progress of the disease, the patient received one course of chemotherapy with "ZBR regimen (Rituximab 0.6 g d1, Obutinib 150 mg, Bendamustine 100 mg d2-3)" in February 2021. The patient developed fever during hospitalization, and the CT examination showed: 1. Multiple small irregular nodules in both lungs were newly added. 2. Multiple enlarged lymph nodes in mediastinum, bilateral supraclavicular region and bilateral axilla were similar to those before. At the same time, blood culture for the patient was conducted. While the serious infection could not be controlled after the anti-infection treatment such as Ceftazidime, Cefoperazone sodium and sulbactam sodium, Ertapenem and so on, the patient's family requested discharge in such a sad situation, and unfortunately the patient died on the fourth day after discharge.

Discussion

Post-transplantation lymphoproliferative disease (PTLD) is a series of diseases that range from benign proliferation of lymphoid tissue to aggressive malignant lymphocytic tumors. PTLD is the most serious complications after SOT or HSCT. It usually progresses rapidly, with a poor prognosis and a high mortality rate, and is the adverse event that poses the greatest threat to the long-term survival of organ transplant recipients [3]. The main risk factors associated with the occurrence and development of PTLD are the cumulative burden of immunosuppression and the carcinogenic effect after EBV infection, and the latter is the key factor for the continuous evolution of PTLD. PTLD is often characterized by malignant clonal proliferation of lymphocytes, and the clinical symptoms and signs of PTLD are complex and lack specificity, which often requires pathological biopsy for diagnosis [4]. Among the two patients included in this study, the first case was extranodal malignant lymphoma caused by long-term use of immunosuppressive drugs after heart transplantation, while the other case had a history of lymphoma, which was well controlled after multiple courses of chemotherapy combined with autologous hematopoietic stem cell transplantation, and the disease of lymphoma recurred and progressed rapidly due to long-term use of anti-graft rejection drugs after liver transplantation. It is consistent with the characteristics of PTLD.

Generally speaking, patients after organ transplantation need to take anti-graft rejection drugs or immunosuppressants for a long time, and in the state of long-term immunosuppression, SOT or HSCT recipients are very likely to develop malignant tumors characterized by malignant clonal proliferation of lymphoid tissue or plasma cells, which also belong to other iatrogenic immunodeficiency associated lymphoproliferative diseases (OIIA-LPD) [1]. The incidence of PTLD after SOT is as high as 20%, with the highest incidence in intestinal and multi-organ transplantation (5-20%), followed by lung and heart transplantation (2-10%), and then kidney and liver transplantation (1-5%) [5]. The high incidence of PTLD in heart, lung, intestine and multi-organ grafts is due to the clinical use of high-dose immunosuppressive drugs to protect patient graft survival [6, 7]. In addition, among children with SOT, the incidence of PTLD for kidney transplantation is about 2.2%, while the incidence of PTLD for lung transplantation is about 15% [8]. In contrast, the incidence of PTLD after HSCT is about 4% [9]. However, previous studies [10, 11] have found that the mortality rate of SOT-related PTLD is 50-70%, while that of HSCT is as high as 70-90%.

Given that PTLD is highly heterogeneous and includes multiple histological/pathological types, each disease form has different biological characteristics and clinical manifestations or features. It is worth noting that about 70% of PTLD is closely related to EBV infection [12], and PTLD can be divided into EBV-associated PTLD (EBV-PTLD) and non-EBV-associated PTLD according to whether it is accompanied by EBV infection. Relevant studies [13, 14] have shown that, due to the application of anti-graft rejection drugs, the highest probability of EBV-related PTLD occurs within one year after transplantation, with the highest immunosuppressive effect on human body, and the total incidence can reach 1% to 20%. In this study, the detection of EBV-encoded small RNA (EBER in situ hybridization) in both patients was positive, indicating that EBV may play an important role in the occurrence and progression of PTLD, which is consistent with the conclusions of previous studies.

EBV is a DNA virus, and its only host is human. EBV often invades human B cells and oropharyngeal/nasopharyngeal epithelial cells. People infected with EBV are mostly in a “virus carrying” state without special clinical symptoms, but a few people can spread EBV in the body due to low immunity, and then cause fever, liver and spleen or lymph node enlargement, and in some severe cases, it can also cause damage to organ function [15]. EBV is generally transmitted by droplets, and for transplant recipients, it may also be acquired by a donor of EBV (+) or by transfusion of blood products with no white blood cell component removed [16, 17]. Generally, B cells can cause clonal proliferation after infection with EBV, and the body can regulate their proliferation and apoptosis process through the triggering mechanism of B-cell apoptosis induced by EBV-specific cytotoxic T cells (EBV-CTL) when immune function is normal. However, the above biological regulatory mechanism is interfered or even inhibited due

to immunosuppressive treatment of transplant recipients. Furthermore, the balance between B cell proliferation and immune regulation induced by EBV is destroyed, and then abnormal B cell malignant clonal proliferation is caused, ultimately leading to the occurrence and development of PTLD [18, 19]. Therefore, long-term monitoring of EBV viral load is extremely important for the prevention and treatment of PTLD.

As mentioned above, the pathologic types of PTLD after SOT and HSCT transplantation are complex, and PTLD often occurs at the extranodal site. Therefore, prior to the diagnosis of PTLD, it is necessary to exclude the primary and prodromal history such as infectious diseases or potential malignant tumors, and conduct the EBV detection, blood routine, bone marrow examination and imaging examination as soon as possible, and it will be beneficial to the diagnosis and staging of PTLD disease. However, pathological biopsy is still the gold standard for the diagnosis of PTLD [20]. As early as 2008, WHO classified PTLD into four types: early-stage PTLD, polymorphic PTLD, monomorphic PTLD and classical Hodgkin lymphoma PTLD. This classification reflected the gradual evolution of PTLD lesions from polyclonal to monoclonal, and the increasing aggressiveness, and the final outcome is a progressive and continuous process of progression to lymphoma [21]. Until 2016, WHO updated the classification of PTLD, which subdivided early lesions into plasmacytoproliferative PTLD, infectious mononucleosis like PTLD, and energetic follicular proliferative PTLD, while remaining classifications remained unchanged [2]. Generally, polymorphic PTLD is common in children, while adult PTLD is common in monomeric B-cell lymphoma, the most common pathological type of which is diffuse large B-cell lymphoma (DLBCL), which needs to be combined with CD20 expression, Ki-67 positive rate and EBER in situ hybridization to determine its prognosis [22]. According to the Hans model, DLBCL can be divided into germinal B-cell-like type (GCB) and non-GCB type, which also has guiding significance for disease diagnosis and prognosis assessment. However, it is frustrating that compared with common malignant lymphoma, PTLD has poor efficacy and prognosis, and low long-term survival rate [23].

It is worth noting that not all PTLD patients can be accurately classified into the corresponding subtypes, even though the pathological types of the same patient after biopsy at different lesion sites may still be different, and even different histological types of PTLD may appear in the same site of the patient [24]. As in case 2 of our study, the patient was diagnosed with T-cell lymphoma in monomorphic PTLD in an outside hospital, but with polymorphic PTLD in our hospital. Therefore, such patients should be combined with imaging examinations (such as PET/CT) to confirm the presence of multiple lesions, and multi-site puncture biopsy may have important practical significance for accurate treatment and prognosis assessment. It is of concern that PTLD is very challenging to diagnose in clinical practice and often requires invasive surgery to complete the corresponding pathological biopsy. Analysis of circulating free DNA (cfDNA) isolated from plasma is minimally invasive and effective for tumor genome analysis. It has been found that it is feasible to analyze, screen, and diagnose PTLD using cfDNA, namely low-coverage whole genome sequencing (lcWGS) to detect copy number variation (CNV), and targeted next generation sequencing (NGS) was used to identify Epstein-Barr virus (EBV) DNA payload and somatic single nucleotide variation (SNV) plasma from cfDNA [25].

For the prevention and treatment of PTLD, EBV testing is required for both donors and recipients of SOT or HSCT, and antiviral drugs or immunoglobulin can be used prophylactically if necessary [26, 27]. For people at high risk of PTLD, the dosage of immunosuppressants can be reduced and EBV DNA load can be monitored as appropriate [28]. Due to the high heterogeneity of PTLD and the lack of clinical prospective trials, the academic community has not yet formed a unified treatment standard for PTLD. In clinical practice, the treatment of PTLD still follows the treatment methods and standards of primary malignant lymphoma, but due to the lack of specific clinical manifestations in the early stage, the disease progresses rapidly, and the mortality rate of patients with PTLD is extremely high if it is not treated in time. There is no doubt that the therapeutic goal of PTLD is to cure and alleviate it on the premise of ensuring the transplantation function. Reducing the degree of immunosuppression has always been the main therapeutic

method [29], and the effectiveness of this method depends on the subtype of PTLD, the degree of disease and other prognostic indicators [30]. Less than 10% of patients can maintain the persistence of the response to the degree of immunosuppression and achieve the goal of cure [31, 32]. It is surprising that the antiviral drugs Ganciclovir and Acyclovir have been used to prevent and treat EBV-associated PTLD, and it has been confirmed that patients who receive antiviral drugs within 3 months during immunosuppressive therapy after organ transplantation have a lower risk of developing PTLD and can benefit patients [33].

Choquet et al. conducted the first prospective (Phase II) trial of Rituximab monotherapy and SOT-associated PTLD after RI failure, and the overall response rate (ORR) at 1 year was 34% and the overall survival rate (OS) was 67% [34]. For patients with low risk or RIS failure, Rituximab monotherapy is still regarded as the first choice [35], and Rituximab alone as the initial response to induction therapy is also considered to be a prognostic factor for PTLD [36]. In patients older than 16 years, anthracycline-based chemotherapy regiments have shown considerable results for PTLD, and R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone) is currently the preferred regimen for B-cell PTLD with ORR up to 90% [37, 38]. For pediatric patients, RCP (Rituximab, Cyclophosphamide and Prednisone) regimen has shown acceptable results and is the preferred regimen for pediatric PTLD [39, 40]. It should be noted that PTLD is a common secondary malignant tumor after transplantation, and Hodgkin lymphoma (HL) type PTLD is the rarest of the four subtypes of PTLD, and there are still no treatment guidelines. HL-type PTLD includes classical HL-type PTLD (cHL-PTLD) and HL-like PTLD, and it has been confirmed that brentuximab vedotin (BV) combined with Sirolimus has shown considerable efficacy in patients with classical HL type PTLD, and can achieve lasting complete remission [41].

In summary, PTLD is a malignant proliferative tumor originating from lymphoid tissue that is secondary to transplantation which lacks specificity, has a poor prognosis and progresses rapidly. Imaging examination, pathological biopsy and EBV detection are reliable means for the diagnosis of PTLD. A personalized treatment plan based on the principles of "reasonable reduction of immunosuppression, chemotherapy targeting CD20 (Rituximab), radiation therapy, adoptive immunotherapy of EBV-specific cytotoxic T lymphocytes, and the above combination therapy" through multidisciplinary assisted treatment (MDT) is expected to maximize the prognosis of patients [42]. However, the choice of personalized treatment depends on the subtype of PTLD, the invasive transplant type of PTLD, and the patient's underlying conditions. The goal of treatment is to cure PTLD and preserve graft function. Despite the rarity of PTLD and the lack of consensus treatment options, acceptable and satisfactory outcomes can be also achieved with the standard regimen of malignant lymphoma in the first patient of our study. As for the long-term prognosis of PTLD patients and whether they can be accompanied by other adverse events, more in-depth clinical case studies are needed to explore new chemotherapy regiments and immunotherapies. The standardized diagnosis, treatment and therapeutic effect of PTLD still need to be supported and improved by new evidence-based medical evidence.

Acknowledgements

We would like to thank colleagues from Fujian Institute of Hematology and the First Affiliated Hospital of Gannan Medical University for their academic assistance in the publication of this paper. The study was supproted by the Science and Technology Research Project of Education Department of Jiangxi Province (No. GJJ220-1414); the Science and Technology Project of Jiangxi Provincial Administration of Traditional Chinese Medicine (No. 2022B072); and the Science and Technology Foundation of Jiangxi Provincial Health Commission (No. 20213-0697).

Written informed consent was obtained from the patient or the patient's family.

Disclosure of conflict of interest

None.

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