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Infectious complications during immunochemotherapy of post-transplantation lymphoproliferative disease—can we decrease the risk? Two case reports and review of literature

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Abstract

BACKGROUND

Post-transplant lymphoproliferative disease (PTLD) is a heterogeneous group of diseases that develop after solid organ and hematopoietic stem cells transplantation related to intensive immunosuppression regimen, T-cell depletion and Epstein-Barr virus infection. Despite the improvement in the management of PTLD, the prognosis remains poor. Here we report the management of two transplanted patients with PTLD and infections during immunochemotherapy (ICTH).

CASE SUMMARY

Of 65-year-old woman 11 years after kidney transplantation (first case) presented with diffuse large B-cell lymphoma (DLBCL) CS III and started ICTH according to R-CHOP protocol. Despite the secondary prevention of neutropenic fever, the patient developed grade 4 neutropenia with urinary and pulmonary tract infections after the fifth cycle. ICTH was continued in reduced doses up to 7 cycles followed by involved-field radiation therapy of the residual disease. The second case presents a 49-year-old man, 8 years after liver transplantation due to cirrhosis in the course of chronic hepatitis B, who started ICTH for DLBCL Burkitt-like CS IV. The patient received four cycles of ICTH according to R-CODOX/R-IVAC protocol, with reduced doses. In both cases initially undertaken reduction of immunosuppression was ineffective to prevent infectious complications. Despite one incomplete ICTH treatment due to recurrent infections, both our patients remain in complete remission.

CONCLUSION

Reduction of immunosuppression and the doses of chemotherapeutics may be

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insufficient to prevent infectious complications during ICTH in PTLD patients.

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Core Tip: Post-transplant lymphoproliferative disease (PTLD) is a heterogeneous group of diseases in transplanted patients related to immunosuppression regimen, T-cell depletion and Epstein-Barr virus infection. Immunochemotherapy (ICTH) increases already high incidence of bacterial infections in transplanted patients related to the immunosuppression therapy. We report the successful management of two solid organ transplanted patients with PTLD and urinary and pulmonary tract infections during ICTH that developed regardless of the reduction of immunosuppression therapy, doses of chemotherapeutics and G-CSF used in the prevention of neutropenic fever. We show that all these interventions may be insufficient to prevent infectious complications, but they are manageable.

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INTRODUCTION

Post-transplant lymphoproliferative disease (PTLD) is a heterogeneous group of diseases that develop after solid-organ and hematopoietic stem cells transplant^[1]. 2016 WHO classification distinguished several subcategories: Plasmacytic hyperplasia, infectious mononucleosis, florid follicular hyperplasia, polymorphic (P-PTLD), monomorphic (M-PTLD) and classical Hodgkin lymphoma PTLD^[2]. Most P-PTLD cases are EBV positive and develop shortly after transplantation. About half of M-PTLD is associated with EBV infection, and most cases are large B-cell lymphoma (DLBCL), less often Burkitt's lymphoma (BL)^[3]. The highest rate of PTLD occurs after small bowel (20%), lung (10%), and heart (6%) transplant. Liver and kidney transplantations are associated with much lower risk, accounted for 2.8% and 2.3%^[4].

The main risk factors for PTLD are the intensity of immunosuppression regimen, T-cell depletion and Epstein-Barr virus (EBV) infection^[1]. Transplant patients who are EBV-negative before transplantation have a higher risk of PTLD. Both primary and reactivated EBV infections are potent risk factors for PTLD^[5]. The infections are often asymptomatic, with a high rate of latency^[5].

Clinically, PTLD is hardly distinguishable from aggressive B-cell lymphoma^[6]. Immunosuppression reduction (IR) is the first step in PTLD management with overall response rate (ORR) of 45%, in the retrospective analysis^[7]. The prospective study has shown response in 1 out of 16 patients (ORR-6%)^[7]. Due to the rare occurrence of PTLD, there are currently no guidelines based on hard scientific evidence for further management of patients with PTLD.

Here we report the management of two patients with PTLD and infections during immunochemotherapy (ICTH).

CASE PRESENTATION

Chief complaints

Case 1: A 65-year-old woman with an extensive medical history including end-stage kidney disease, subtotal parathyroid gland removal for severe hyperparathyroidism and subtotal thyroidectomy, renal osteodystrophy, hypertension and atherosclerosis;

received a kidney transplant from a deceased donor after four years of hemodialysis therapy (2006). The donor Epstein-Barr virus (EBV) status was unknown (pre-2008 donors and recipients were not routinely screened for EBV serostatus)^[8]. The immunosuppressive regimen consisted of mycophenolate mofetil and cyclosporine A.

Case 2: Forty-nine-year old man 8 years after liver transplantation for end-stage chronic hepatitis B, treated with tacrolimus and mycophenolate mofetil, was admitted to the neurological ward due to severe headache on the right side with nausea and vomiting, accompanied by the numbness of his cheek, which lasted for two weeks (October 2015). The patient reported a weight loss of 8-10 kg during the last 6 mo and presented with fever.

History of present illness

Case 1: Eleven years since transplantation (2017) the patient was referred to the transplant ward with persisting night sweats and fatigue. There was no fever and weight loss.

Case 2: The patient was admitted to neurological ward due to the cheek numbness. Head magnetic resonance imaging revealed the infiltration of right pterygoideus medialis muscle. He was then referred to the transplant ward, with the suspicion of neoplastic changes. After histological examination, the patient was referred to the oncology department.

History of past illness

Case 1: The patient had a history of end-stage kidney disease with hemodialysis treatment started in 2002 and bilateral nephrectomy in 2004 followed by kidney transplantation two years later.

Case 2: HBV infection, which led to chronic B hepatitis and cirrhosis, followed by liver transplantation in 2006.

Personal and family history

Case 1: There was long-lasting history of hypertension. Family history was unremarkable.

Case 2: The patient had hypertension and reported *Helicobacter pylori* stomach infection. Family history was unremarkable.

Physical examination

Case 1: There was no lymphadenopathy in physical examination. Liver and spleen were not enlarged.

Case 2: Physical examination revealed pleural effusion in the right cavity and symmetric ankles oedema.

Laboratory examinations

Case 1: Serologic tests for EBV were positive for IgG-class and EBNA, IgM-class was negative. The fine needle biopsy of the submandibular gland revealed monomorphic subtype of PTLT-DLBCL, the most frequent type of PTLT^[9]. The patient was referred to the oncological ward for further diagnostic work-up. The blood tests showed leukocytosis 21.65 G/L without thrombocytopenia, mild anaemia (Hb 10.6 g/dL) increased activity of LDH (291 IU/L), and high concentration of β 2-microglobulin (13.5 mg/L). The graft function was impaired (eGFR 24 mL/min/1.73m² without proteinuria).

Case 2: Histological examination of stomach biopsy gave the diagnosis of aggressive (Burkitt-like) DLBCL with CD20 (+), CD10 (+), bcl-6 (+), bcl-2 (-), MUM-1 (+/-), cyclin D1 (-), CD30 (-), CD5 (-), Ki67-almost 100%. Location of the lesions on both sides of the diaphragm in symptomatic patients (loss of weight), was corresponding to the clinical stage was IVB (IPI 3/5). HBV DNA in the blood was not detected. The patient was IgM seronegative but IgG seropositive for both cytomegalovirus (CMV) and EBV. The patients' immunosuppression regiment was modified-mycophenolate mofetil was switched to everolimus for its anticancer properties but did not prevent DLBCL progression.

Imaging examinations

Case 1: The computed tomography (CT) examinations revealed numerous enlarged cervical, mediastinal, axillary, retroperitoneal and inguinal lymph nodes on both sides with a predominance on the left (Figure 1) as well as slight hepatosplenomegaly.

Case 2: CT scan of the brain was normal, while lumbar puncture revealed elevated LDH activity in cerebrospinal fluid. The patient was referred to the transplantation ward with suspicion of neoplastic infiltration. CT scan of the thorax and abdomen revealed numerous hypovascular structures in the liver and kidneys, massive infiltration of mucosa of the stomach and two nodule changes close to the left subclavian vein, below the sternocleidomastoid muscle (Figure 2).

FINAL DIAGNOSIS

Case 1: Taking into account all the symptoms and tests, a diagnosis of PLTD was made.

Case 2: Taking into account all the symptoms and tests, a diagnosis of PLTD was made.

TREATMENT

Case 1: The patient signed informed consent for ICTH and started R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), as initial rituximab monotherapy increases the risk of recurrence and usually does not bring complete remission in monomorphic PTLT^[9]. Beyond slight, local upper limbs oedema, the patient tolerated the applied ICTH quite well. Night sweats subsided after the second R-CHOP cycle. Neutropenia and anaemia (requiring transient blood transfusion) were manageable. An episode of atrial fibrillation occurred after the second cycle. The immunosuppression, as well as the doses of chemotherapeutics, were reduced (mycophenolate mofetil was discontinued) due to episodes of prolonged pancytopenia. The G-CSF treatment (filgrastim) in the secondary prevention of neutropenic fever (NF) was used. Regardless of the use of G-CSF and Pneumocystis jiroveci prophylaxis (with co-trimoxazole), after the fifth cycle, the patient developed grade 4 neutropenia with symptoms of febrile neutropenia. There was an increase in the concentration of inflammatory markers: CRP 217 mg/L and procalcitonin 40.1 ng/mL. Empirical antibiotic therapy with ciprofloxacin was started. After one week, regardless of neutrophil recovery, inflammatory parameters were still elevated and the symptoms (fever, weakness and dysuria) persisted. Blood culture showed a growth of Staphylococcus aureus (sensitive to ciprofloxacin) and Klebsiella pneumoniae ESBL (+) (resistant to ciprofloxacin and co-trimoxazole, but sensitive to carbapenems and aminoglycosides). Broad-spectrum antibiotic therapy with meropenem (1 g for every 12 h) and amikacin (500 mg once a day) was administered. Three days later, there was a worsening of dyspnea, cough and decreased oxygen saturation of 88%-90%, without an increase in the concentration of inflammatory markers. Pneumocystis jiroveci infection was suspected and a smear from the epiglottis was taken for the examination. Additionally, co-trimoxazole was administered intravenously at a dose of 960 mg twice daily. Few days later, a significant improvement of the patient's clinical condition with a decrease of inflammatory markers concentration (CRP 14.8 mg/L and PCT 0.4 ng/mL) was observed. The patient recovered, however with persisting impaired graft function. The doses of ICTH were reduced by 30% in the next 2 cycles. Despite dose reduction, the therapy had been terminated because of grade 4 neutropenia.

PET-CT performed after the seventh cycle revealed active lesions in sub- and infraclavicular area with the avidity of 4 points in the Deauville five-point scale. The patient started involved-field radiation therapy (3D-IMRT, Dc = 30 Gy/df = 3) of the residual disease.

Case 2: The patient signed informed consent for ICTH with 4 cycles of R-CODOX (rituximab, cyclophosphamide doxorubicin, vincristine, cytarabine) followed by R-IVAC scheme (rituximab, ifosfamide, cytarabine, methotrexate) and started the treatment. After the 1st cycle of R-CODOX therapy, symptoms of neutropenic fever appeared. The presence of multi-drug-resistant bacterias was found in the blood

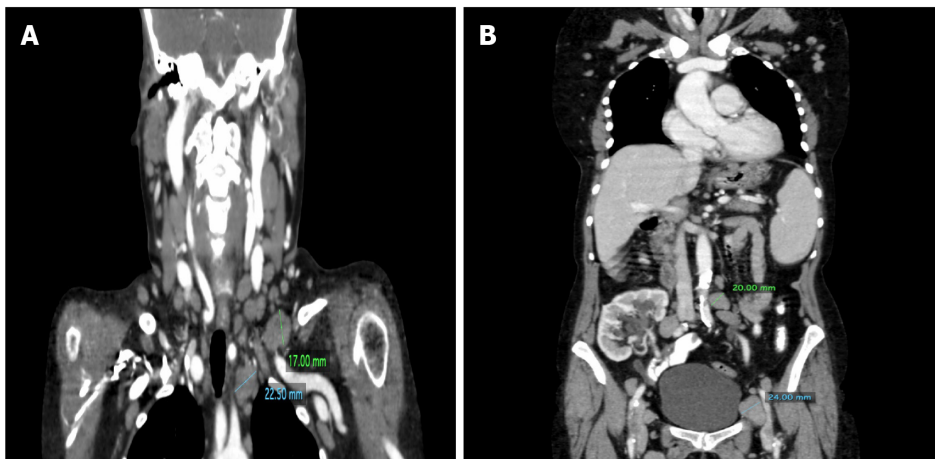


Figure 1 The head and neck computed tomography scan of a 65-year-old woman. A: Numerous cervical lymph nodes and enlarged lymph nodes in the left supraclavicular region and upper mediastinum; B: The computed tomography of the same patients' abdomen and pelvis showing enlarged retroperitoneal and inguinal lymph nodes and kidney transplant in the lower abdomen on the right.

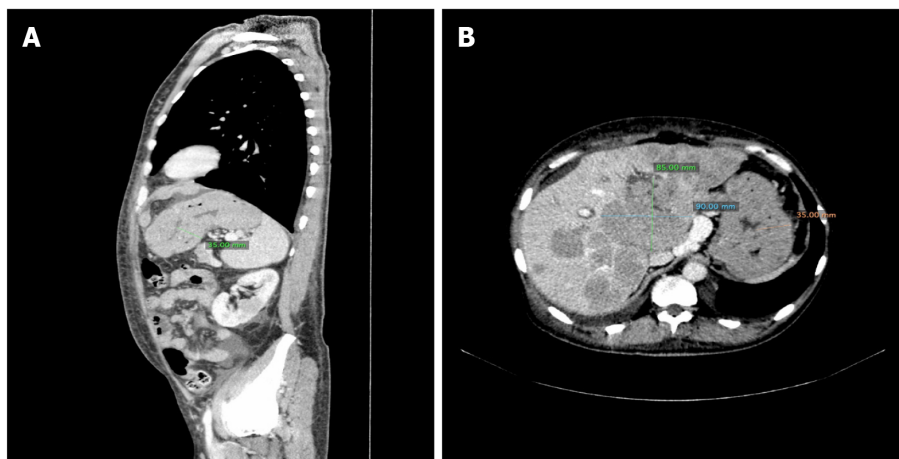


Figure 2 The computed tomography scan of a 49-year-old man. A: The stomach wall thickening and hypodense lesions in the left kidney; B: Multiple hypodense lesions forming conglomerates in the liver of the same patient.

cultures. The first blood culture revealed *Stenotrophomonas maltophilia* and ESBL *Escherichia coli* (resistant to beta-lactams, cephalosporins and co-trimoxazole but sensitive to carbapenems) and 5 d later the second blood culture showed MRCNS *Staphylococcus lentus* and MRCNS *Staphylococcus hominis* (resistant to beta-lactams, carbapenems, cephalosporins but sensitive to aminoglycosides). CRP level was 164 mg/L. After therapy with meropenem (1 g every 8 h) and amicin (500 mg daily) for ten days, CRP level decreased to 6.0 mg/L. Subsequently, ICTH was continued with reduced doses and after the second R-IVAC cycle, neutropenia developed with negative blood cultures (performed 3 times). Because of the clinical symptoms (fever, dyspnoea, weakness) and high CRP level 173 ng/mL intravenous therapy with vancomycin (2 g every 8 h) was started. As there was no clinical improvement (repeated negative blood cultures), after 7 d, colistin was administered intravenously (2 mL units every 8 h) with a good clinical response (CRP 15.8 mg/L). During the whole ICTH the patient received red blood cells transfusions (14 units in total) because of grade 4 anaemia.

OUTCOME AND FOLLOW-UP

Case 1: The treatment was complicated by neutropenia and anemia, but followed by complete remission (CR). After two years the patient remains in CR with stable, however poor allograft function (eGFR 21.8 mL/min/1.73 m²). The patient remains under the care of an oncologist and a clinical transplantologist. The timeline of the information presented in this case report is presented in [Table 1](#).

Case 2: ICTH was complicated by neutropenia and anemia, but followed by CR in CT scans of the neck, thorax, abdomen and pelvis as well as trephine biopsy (March 2016). After 4 years the patient remains in CR with regular check-up every 6 mo in the oncology outpatient clinic. [Table 2](#) presents the information from this case report organized into a timeline.

DISCUSSION

According to 2019 NCCN guidelines^[10], the first-line treatment always includes the reduction of immunosuppressive drug regime. Further management depends on PTLT subtype and patient's response to changes in the immunosuppression. In both reported cases the reduction of immunosuppression regiment was ineffective, however safe, and was not followed by acute rejection or progressive deterioration in graft function^[9]. Currently, the standard of care in case of this type of lymphomas is the initial administration of rituximab as monotherapy and depending on the response to treatment, its continuation or the implementation of CHOP chemotherapy^[9-11]. These recommendations are based on the results of the largest prospective study so far-PTLT-1. According to this trial, about 25% of PTLT patients may not require chemotherapy^[11]. Also, after sequential therapy low treatment mortality rate was observed (13%) in comparison to upfront CHOP chemotherapy (26%) described in the literature^[12]. Because of the fast progression of the disease and no response to IR we decided to start ICTH upfront but with reduced doses. Besides single-centre experience reports, there is no clinical trial with BL after solid organ transplantation. The role of CNS prophylaxis is unclear.

Despite the immunosuppression therapy reduction, both our patients developed severe infections during ICTH. Immunosuppression therapy in transplanted patients per se is associated with an increased incidence of bacterial infections of the urinary and respiratory tracts. Urinary tract infections were reported to occur almost twice more frequently than in non-transplant patients (7% *vs* 4.4%)^[13]. The occurrence of pneumonia depends on transplanted organs and ranges from 7.3% in the kidney^[14], 22% in the liver^[15], up to 36% in the lung graft recipients^[16] during the first post-transplant year. Infectious complications in kidney transplant patients are associated with significant morbidity and mortality^[17], highest in developing countries associated with low socioeconomic profile^[18-20], and severity of immunosuppression regimen^[21]. Prophylactic use of antibiotics decreased the prevalence from 6.3% to 2.2% at the end of the first year after transplantation^[22]. Trappe *et al*^[9] noticed grade 3 and grade 4 infections in about 41% of patients and grade 3 and grade 4 leukopenia in 68% of patients during PTLT chemotherapy^[7].

Neutropenic fever is a common adverse event during R-CHOP treatment of DLBCL with the incidence estimated at 5%-40%^[22-24], usually occurring after the first cycle of ICTH^[25]. There is no data on the frequency of NF in PTLT patients. Our kidney transplant patient presented with NF in the fifth cycle despite using G-CSF prophylaxis, which is a standard in NF prevention^[26]. NF was successfully treated with antibiotics, however, associated with deterioration of the kidney graft function.

We confirm that *Pneumocystis carinii* prophylaxis should be utilized in each PTLT patients during ICTH and consisted of 960 mg co-trimoxazole orally 3 times a week^[8]. The prophylaxis is recommended as the infection occurs in one-third of treated PTLT patients^[9].

Despite the improvement in the management of PTLT, related mainly to the introduction of rituximab in B-cell lymphoproliferative disorders^[27], the prognosis remains generally poor^[1,28], with 55% 3-year overall survival^[1], median OS 64 mo^[29]. Until now both our patients remain in clinical remission, despite one of the patients had not received complete ICTH treatment due to recurrent infections.

It is worth to be mentioned that PTLT may be linked to other viruses presence, such as HCV, HHV-8 and CMV^[1]. Although it has been reported that after liver transplant, HBV reactivation plays an important role in PTLT occurrence^[30], even 12 years after transplantation^[31]. In the case of our patient, the disease onset was late (8 years after

Table 1 Timeline of the diagnostic procedures and treatment of the first case

Date	Procedure
November 1, 2002	Dialysis initiation
August 2, 2004	Laparotomy with bilateral nephrectomy
July 18, 2006	Kidney transplantation
October 5, 2006	Thyroid and parathyroid resection
July 28 to August 10, 2017	Hospital stay at the nephrology ward
July 31, 2017	Retrieval of the submandibular node
August 7, 2017	Chest CT scan
August 28 to September 8, 2017	1 st hospital stay at the oncology department
August 31, 2017	Abdominal CT scan
September 4 and 5, 2017	Chemotherapy I
September 25 to October 9, 2017	2 nd hospital stay at the oncology department
September 25 and 26, 2017	Chemotherapy II
September 29, 2017	Blood transfusion-2 units
October 16 to 25, 2017	3 rd hospital stay at the oncology department
October 18 and 19, 2017	Chemotherapy III
October 19, 2017	Abdominal CT scan
November 8 to 24, 2017	4 th hospital stay at the oncology department
October 8 and November 8, 2017	Chemotherapy IV
November 11, 2017	Chest CT scan
December 15, 2017 to January 24, 2018	5 th hospital stay at the oncology department
December 15 and 16, 2017	Chemotherapy V
January 23, 2018	Chemotherapy VI
February 28 to March 7, 2018	6 th hospital stay at the oncology department
March 1, 2018	Chemotherapy VII
April 10, 2018	Positron emission tomography (PET scan)
April 12 to 27, 2018	7 th hospital stay at the oncology department
June 28 to July 11, 2018	Radiation therapy
July 12 to 17, 2018	8 th hospital stay at the oncology department

CT: Computed tomography; PET: Positron emission computed tomography.

liver transplant), and the patient HBV DNA remains undetectable, therefore the PTLT (DLBCL) seems unrelated to hepatotropic viruses.

CONCLUSION

In summary, ICTH on the tope of immunosuppression therapy increases the risk of infectious complications in PTLT patients. Reduction of immunosuppression and the doses of chemotherapeutics may be insufficient to diminish the risk of infectious complications during ICTH.

Table 2 Timeline of the diagnostic procedures and treatment of the second case

Date	Procedure
2006	Liver transplantation
October 24, 2015	Head CT scan
October 24, 2015	Lumbar puncture
October 26, 2015	Head MRI scan
October 27, 2015	Discharge from the neurological ward
October 27 to November 9, 2015	Hospital stay at the transplantation ward
October 29, 2015	Chest CT scan
November 3, 2015	Stomach biopsy
November 9, 2015 to March 14, 2016	Hospital stay at the oncology department
November 10, 2015 to February 18, 2016	Chemotherapy
March 9, 2016	Chest CT scan
March 11, 2016	Trephine biopsy

CT: Computed tomography; MRI: Magnetic resonance imaging.

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