

Chronic myeloid leukemia following liver transplantation: A case report

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Abstract. Long-term utilization of immunosuppression in organ transplant recipients leads to decreased immune-mediated tumor surveillance and increased risk of developing malignant tumors. However, chronic myeloid leukemia (CML) following living donor liver transplantation (LDLT) is rarely reported. The current case report presents a 42-year-old male patient who developed CML 14 months following LDLT. The patient achieved complete hematologic remission and early molecular response at 3 months imatinib treatment and major molecular response at 12 months imatinib treatment. The pathogenesis, risk factors, treatment and prognosis for CML following liver transplantation are unclear. Therefore, further analysis through accumulation of cases will be of great importance to prevent and treat this rare complication following liver transplantation.

Introduction

Recent advances in the long-term survival of organ transplant recipients have led to an increased incidence of malignant tumors after transplantation (1). The incidence of de novo tumors has been reported to be ranging from 2.6 to 11.5% in liver transplant recipients (2). The most common malignancy diseases after transplantation are solid tumors, including lymphoproliferative disease, skin cancers and sarcomas (3). However, chronic myeloid leukemia (CML) is a rare complication after liver transplantation. The first case of CML after liver transplantation was reported in 2007 (4), after that two cases of post transplantation CML has been reported (5,6).

Here we report a 42-year-old male patient who developed CML 14 months after liver transplantation.

Case report

A 42-year-old male patient presented with a hepatitis B virus related acute liver failure, was admitted to our hospital on October 1, 2014. Blood tests at the diagnosis revealed: white blood cell (WBC) $7.4 \times 10^9/l$, with 17.4% lymphocytes, 71.9% neutrophils and no immature cells. Liver function test showed: ALT 1287 U/l, AST 1063 U/l, TBIL $327.2 \mu\text{mol/l}$, DBIL $244 \mu\text{mol/l}$, IBIL $83.2 \mu\text{mol/l}$. Conservative treatment was invalid. On November 21, 2014, the patient accepted a living donor liver transplantation (LDLT). After LDLT, the patient achieved normal liver function: ALT 23 U/l, AST 15 U/l, TBIL $14.2 \mu\text{mol/l}$, DBIL $8.86 \mu\text{mol/l}$, IBIL $5.3 \mu\text{mol/l}$. The immunosuppressive therapy comprised tacrolimus, mycophenolate mofetil and prednisone. A biopsy of hepatic revealed chronic severe hepatitis accompanied nodular cirrhosis.

In December 2015, 12 months after transplantation, the patient's blood test revealed leukocytosis at $12.45 \times 10^9/l$. At 14 months posttransplantation, his white blood cell (WBC) increased to $37.49 \times 10^9/l$, with 79.2% neutrophils, 8.7% lymphocytes, 4.8% monocytes, 3.1% eosinophils, 4.2% basophils and 22.7% immature granulocyte. Liver function test revealed normal limits: ALT 16 U/l, AST 30 U/l, TBIL $11.1 \mu\text{mol/l}$, DBIL $2.6 \mu\text{mol/l}$, IBIL $8.6 \mu\text{mol/l}$. Bone marrow (BM) aspirate showed massive infiltration of neutrophils, eosinophils and basophils, which confirmed the diagnosis of chronic myeloid leukemia (CML) in chronic phase. Genetic testing revealed BCR-ABL (P210) positive by polymerase chain reaction (PCR). The quantitative of BCR-ABL transcript was 31.763%. The mutation of BCR-ABL kinase region was negative. Chromosome analysis showed 46, XY, t (9;22) (q34; q11.2) (Fig. 1). A diagnosis of chronic myeloid leukemia (CML) in chronic phase was made.

The patient received imatinib 400 mg once daily. After 1 month treatment, the WBC count decreased to $3.81 \times 10^9/l$. The patient achieved complete hematologic remission (CHR) after 3 months imatinib treatment, and continuous CHR thereafter. Liver function test was within normal limits: ALT 14 U/l, AST 20 U/l, TBIL $15.9 \mu\text{mol/l}$, DBIL $6 \mu\text{mol/l}$, IBIL $9.9 \mu\text{mol/l}$. At 3 months post imatinib treatment, the quantitative of BCR-ABL transcript had decreased to 2.7838%, consistent with early molecular response (EMR). 12 months

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after imatinib treatment, the patient's BCR-ABL transcript had been $<0.1\%$, consistent with major molecular response (MMR). At 30 months posttransplantation, the patient is alive with no graft rejection. He remains CHR 13 months after the diagnosis of CML. His current therapy includes imatinib, tacrolimus, mycophenolate mofetil and prednisone.

Discussion

With the increasing number of long-term survivors of transplantation, the incidence of malignancy disease post transplantation is higher. The most common malignancy diseases after solid organ transplantation are solid tumors, including lymphoproliferative disease, skin cancers and sarcomas (3). While the subsequent malignancy diseases after HSCT are solid tumors, post-transplant lymphoproliferative disease (PTLD) and hematologic malignancies (7). The annual incidence of CML ranges from 0.35 to 0.55 per 100,000 in Chinese population (8). There was no report about the incidence of CML post LDLT, just few case reports, so CML is a rarely complication after LDLT.

There were many hypotheses regarding the development of malignancies in LDLT recipients. Immunosuppressive medications were regarded as the most important risk factor for malignancies after transplantation (9). The role of immunosuppressants in the leukemogenesis has not been elucidated. Mycophenolate mofetil is an inhibitor of hypoxanthine nucleotide dehydrogenase highly expressed in the leukemia, which can develop an anti-leukemia effect (10). Our patient received Mycophenolate mofetil as immunosuppressive therapy. Whether Mycophenolate mofetil can reduce the incidence of leukemia after transplantation needs to be studied further. Moreover, viral infections have been reported to be associated with malignancies after transplantation, such as Epstein-Barr virus, human herpes virus-8, and Papillomaviruses (11). The correlation between hepatitis virus infection and CML deserved further investigation. Some reported cases of leukemia after transplantation have associated chromosomal abnormalities, for example trisomy 8, monosomy 7, $t(15;17)$, $inv(16)$ and $t(9;22)$ (12,13). Our patient had chromosomal abnormalities involving Philadelphia chromosome.

The most common presentation is leukocytosis or thrombocytosis in the chronic phase of CML. Our patient presented with leukocytosis for two months with no clinical symptoms. Once the diagnosis of CML was confirmed, the patient promptly received imatinib treatment. Effective immunosuppressive therapy greatly reduced the incidence of graft rejection and improved survival time, however, cancer and infections may increase. Some authors reduced tacrolimus to the minimized dosage to maintain stable liver function during acute leukemia chemotherapy (14). Imatinib had been used as a first-line treatment for newly diagnosed CML. However, several cases of hepatotoxicity, including acute liver failure have been reported in the long term imatinib therapy (15). Imatinib-induced acute liver failure is a rare and serious complication of imatinib therapy. Our patient received the same dosage of immunosuppressants during imatinib treatment, and his liver function was normal. The early diagnosis and timely treatment of leukemia post transplantation may significantly reduce mortality (16).

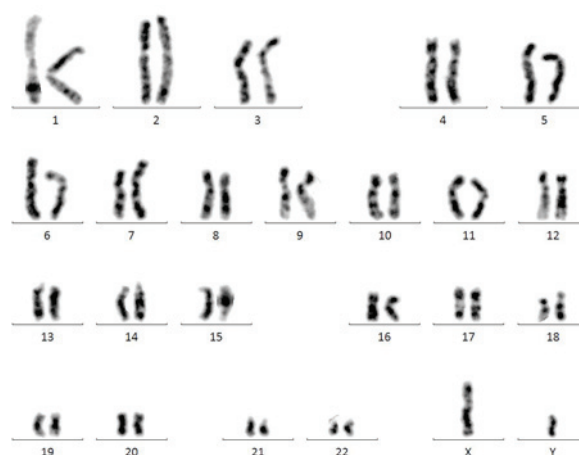


Figure 1. Chromosome karyotype analysis showed 46, XY, $t(9;22)(q34;q11.2)$.

The pathogenesis, risk factors, treatment and prognosis for CML post liver transplantation are unclear. Therefore, further analysis through accumulation cases will be of great importance to prevent and treat this rare complication after liver transplantation.

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