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RESEARCH ARTICLES

Could other viruses cause pediatric posttransplant lymphoproliferative disorder?

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Abstract
Introduction Posttransplant lymphoproliferative disorder (PTLD) constitutes a heterogeneous group of diseases. We summarize the experience of our hospital, one of Spain's largest series of renal (294), liver (47) and allogeneic stem cell transplants (67), where four cases of PTLD have developed related to complex viral infections.
Methods Case 1 was a 24-month-old boy diagnosed with acute lymphoblastic leukemia who underwent allogeneic stem-cell transplantation (SCT). He was seropositive for Epstein-Barr virus (EBV) and developed an aggressive B-cell non-Hodgkin's lymphoma (B-NHL) related to EBV reactivation and human herpesvirus 6 (HHV-6) infection. Cases 2, 3, and 4 developed after kidney transplantation and were all EBV seronegative. Case 2 had associated cytomegalovirus (CMV) and EBV infection. Cases 3 and 4 only revealed EBV viral load. Cases 1, 3, and 4 progressed rapidly, with fatal outcome. Global incidence of PTLD in our series is 1.1%.
Conclusion PTLD is a rare but life-threatening condition. Although EBV plays a clear role in its pathogenesis, other associated viral infections could trigger this situation. Current therapies include rituximab, decreasing immunosuppressive drugs. and conventional chemotherapy.

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Introduction

Posttransplant lymphoproliferative disorder (PTLD) constitutes an infrequent disease with marked clinical and histological heterogeneity. Its incidence ranges from 1% to 2% in published series of solid-organ (SOT) or allogeneic hematopoietic stem-cell transplantations (HSCT) [1–3]. Ebstein-Barr virus (EBV) plays an important role in its pathogenesis, although the responsibility of other infectious agents has not been cleared yet. Other risk factors include immunosuppressive agents [cyclosporine, antithymocyte globulin (ATG)], EBV seronegative status, and T-cell depletion of the graft have been described to date. [2, 4].

We summarize the experience of our children's hospital, one of Spain's largest series, including 294 renal transplants (from 1974 to 2006), 67 allogeneic HSCT (from 1990 to 2005), and 47 liver transplants (from 1997 to 2007). We retrospectively reviewed medical records of patients diagnosed of PTLD regarding viral infections, risk factors, histology and outcome.

Case reports

Case 1

A 9-month old boy was diagnosed of pro-B, MLL positive acute lymphoblastic leukemia (ALL) and received chemotherapy according to the Very High Risk – SHOP 99 Spanish collaborative protocol, achieving his first complete morphological and molecular remission (CR) after 1 month from induction. He had no available sibling donor, and 6 months later, he underwent autologous HSCT in CR1. Seven months

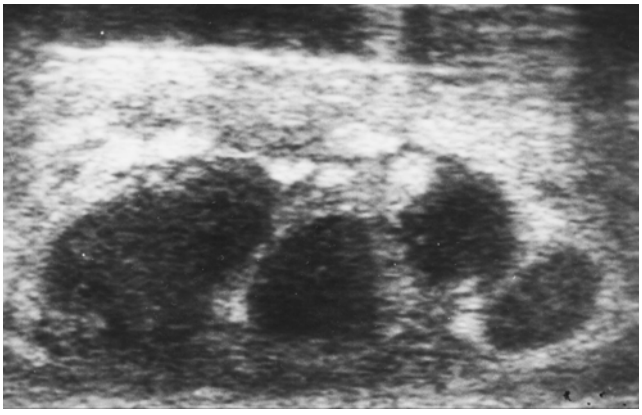

Fig. 1 Case 4: A 4-year old boy with polycystic kidney disease who received renal transplant and 9 years afterward developed posttransplant lymphoproliferative disorder. Ultrasound showed partially necrosed left cervical lymph nodes

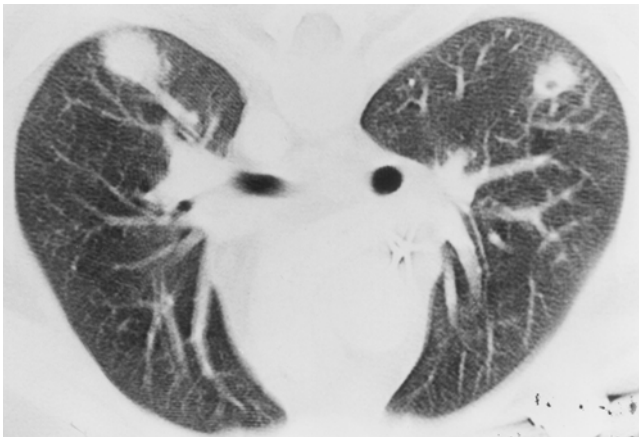

Fig. 2 Case 4: A 4-year old boy with polycystic kidney disease who received renal transplant and nine years afterwards developed post-transplant lymphoproliferative disorder. Computed tomography scan shows basal lung nodes

later, he developed an isolated hematological relapse and received ALL LMB 96 protocol, achieving second morphological and molecular CR. Then he received an unrelated, 8/8 human leukocyte antigen (HLA)-matched, peripheral blood allogeneic HSCT including cyclosporine, low-dose methotrexate, and rabbit ATG as graft-versus-host-disease prophylaxis.

On day +50, he developed fever, supraclavicular and laterocervical lymph nodes, progressive hepatomegaly, jaundice and deranged liver function tests. One supraclavicular lymph node was biopsied and showed monomorphous B-cell non-Hodgkin's lymphoma (B-NHL). Human herpesvirus 6 (HHV-6) deoxyribonucleic acid (DNA) was identified in the biopsy by polymerase chain reaction (PCR) and EBV DNA was isolated in serum by PCR. Immunosuppressive drugs were tapered, but the patient worsened rapidly and died of multiorgan failure (MOF) 24 h after the diagnosis of PTLD.

Case 2

A 10-year-old boy received a renal transplant from a nonrelated, non-HLA-matched cadaver donor due to end-stage renal failure secondary to grade III vesicoureteral reflux. He also had chronic liver disease secondary to hepatitis B virus (HBV) infection. Pretransplant immunoglobulin G (IgG) was negative for EBV and positive for cytomegalovirus (CMV). He also received cyclosporine, mycophenolate mofetil (MMF), prednisone, and basiliximab. Five months later, he developed febricula, abdominal pain, and decreased glomerular filtration rate. Abdominal ultrasound and computed tomography (CT) scan showed small retroperitoneal adenopathies and homogeneous small-bowel enlargement. Histological examination revealed monomorphic $CD20^+$ B-NHL. EBV DNA was detected by PCR in biopsy specimen and peripheral blood. CMV DNA was also present in peripheral blood. HBV could not be detected but was possibly present as well. He received rituximab and ganciclovir, immunosuppression was tapered, and symptoms resolved. He was alive 26 months later.

Case 3

A 10-year-old boy developed meningococcal sepsis 2 days after severe head injury, with associated renal failure requiring hemodialysis. One year later, he received a kidney transplant from a nonrelated, non-HLA-matched cadaver donor. The patient was seronegative for EBV before transplant and received cyclosporine, azathioprine, prednisone, and tacrolimus.

Four years after transplant, he presented acute sinusitis, fever, peripheral adenopathies, and pancytopenia. Bone marrow aspirate showed 5-10% lymphomatoid infiltration of polymorphous $CD20^+$ B-NHL. EBV DNA was found in serum and bone marrow samples by PCR. Ultrasound and CT scans showed mucosal enlargement of maxilla sinuses, enlargement of submaxilla glands, cervical adenopathies, pleural effusion, and homogeneous hepatosplenomegaly. Despite acyclovir and IV immunoglobulin and decreasing immunosuppressive drugs, he developed progressive renal failure, edema, pleural effusion, respiratory distress, and massive lung hemorrhage, dying of multiorgan failure 20 days after the diagnosis of PTLD.

Case 4

This patient was diagnosed at neonatal stage of polycystic kidney disease that led to chronic renal failure. At the age of 4 years, he received kidney transplant from a nonrelated, non-HLA-matched cadaver donor, receiving cyclosporine, prednisone, azathioprine, and tacrolimus.

Nine years later, he presented fever and cervical adenopathies. CT scan showed bilateral lung effusion with paratracheal, perihilar, and carinal enlarged lymph nodes, with homogeneous liver and spleen enlargement. A cervical lymph node biopsy revealed a polymorphic $CD20^+$, B-NHL. EBV DNA was detected in tissue material and peripheral blood by PCR. According to LMB 89 protocol for stage III B-NHL, he started chemotherapy and IV immunoglobulins and acyclovir, achieving complete remission. He relapsed 9 months later. CT scan and ultrasound showed left cervical lymph nodes (Fig. 1), basal lung nodes (Fig. 2), and parietal enlargement of small bowel. He started on rituximab, prednisone, and cidofovir, with clinical improvement, although lymph nodes persisted. Five months later, he presented progressive deterioration with fever and hepatomegaly and refractory shock, dying of multiorgan failure 7 months after relapse of PTLD.

Discussion

Global incidence of PTLD after pediatric kidney transplant or HSCT at our institution is 1.1%, similar to that reported previously by other authors [2, 3, 5]. Most cases of PTLD

Table 1 Clinical and histological characteristics of patients who developed posttransplant lymphoproliferative disorder (PTLD) from 1964 to 2004 at La Fe Children's Hospital, Valencia

Case	Previous disease	Age at transplant	Transplant	Recipient's EBV status	Lapse of time to PTLD	Clinical manifestations of PTLD	Histology/ virology	Treatment	Response/Present time situation
1: 1st SCT	pro-B, MML+, ALL	15 months	Autologous SCT						
1: 2nd SCT	Relapse after 7 months	28 months	Allogeneic non T-cell depleted	+	50 days	Fever, hepatomegaly, cervical and supraclavicular adenopathies	B-NHL, EBV-monomorphic/ blood EBV DNA: +	1. Decrease of IS 2. Prednisone	NR – died after 24 h of diagnosis of PTLD
2	CRF due to grade 3 vesicoureteral reflux	10 years	Kidney: nonrelated, non-HLA matched cadaver donor	–	5 months	Fever, hepatomegaly, adenopathies, abdominal mass	B-NHL, EBV+ monomorphic/ blood and BM EBV DNA: +	1. Surgery 2. Anti-CD20 3. Decrease of IS	CR – Free from illness for 26 months
3	CRF due to meningococcal sepsis and MOF	11 years	Kidney: nonrelated, non-HLA matched cadaver donor	–	54 months	Fever, hepatosplenomegaly, adenopathies, sinusitis	B-NHL, EBV+ polymorphic/blood and BM EBV DNA: +	1. Decrease of IS 2. Acyclovir 3. γ-globulin	NR – died after 20 days of diagnosis of PTLD
4	CRF due to polycystic kidney disease	4 years	Kidney: nonrelated, non-HLA matched cadaver donor	–	108 months	Fever, hepatomegaly, adenopathies, lung nodes	B-NHL, EBV+ polymorphic/ blood and BM EBV DNA: +	1. Acyclovir 2. γ-globulin 3. Chemotherapy (LMB 89)	PR – relapse after 9 months. Second treatment: rituximab, prednisone, cidofovir. NR – died 16 months after relapse

SCT stem cell transplant, *ALL* acute lymphoblastic leukemia, *MML* myelomonocytic leukemia, *CRF* chronic renal failure, *MOF* multiorgan failure, *IS* immunosuppression, *Ab* antibody, *B-NHL* B-cell non-Hodgkin's lymphoma, *EBV* Epstein-Barr virus, *BM* bone marrow, *DNA* deoxyribonucleic acid, *NR* no response, *CR* complete remission, *PR* partial remission

develop within 1 year of transplant, although the risk persists for more than 10 years afterward.

Most cases of PTLD have been linked to uncontrolled proliferation of EBV-infected B cells, related to the suppression of immunosurveillance mechanisms by potent immunosuppressive therapy. Children have an incidence of PTLD four times higher than adults, probably because a larger proportion of children are EBV-naïve pretransplant [6], and the incidence of PTLD has been reported to be 25–50 times higher in EBV-naïve pediatric recipients. In our series, EBV was detected by qualitative PCR in all biopsies and peripheral blood specimens. The role of other viral infections as triggers or coinfectors has not been established. To date there are no reports of HHV 6 infection and PTLD, but it seems possible that this virus could have enhanced the proliferation of latent EBV, inducing disturbance of the patient's immune response, as previously described for CMV [7]. In fact, primary CMV infection in solid-organ recipients has been linked to higher incidence of EBV-related PTLD [8], although in our series, CMV DNA was detected in blood and bone marrow samples only in case 2. We could not demonstrate any responsibility for HBV infection in patient 2.

Other known risk factors for PTLD are immunosuppressive drugs, T-cell depletion of the graft [4], and ATG therapy [9]. We would emphasize the aggressive behavior of PTLD that developed after the non-T-cell-depleted HSCT from unrelated donor (case 1) compared with renal transplant recipients. We believe that intense immunosuppressive therapies as well as HHV 6 infection played an important role in this outcome.

New microbiological techniques such as real-time quantitative PCR will evaluate the role of coinfections in PTLD pathogenesis. Monitoring viral load with current methods can be used to monitor response to therapy.

Current therapies for PTLD include rituximab (anti-CD20 monoclonal antibody), reducing immunosuppression, and conventional chemotherapy when NHL does not respond to rituximab [10]. Currently, rituximab may be used preemptively in allogeneic HSCT, when EBV viral load increases before developing PTLD. National collaborative protocols have been initiated in a few European countries to collect all available information on this rare but life-threatening complication posttransplant. A high index of suspicion, early diagnosis, and therapy are essential for survival.

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