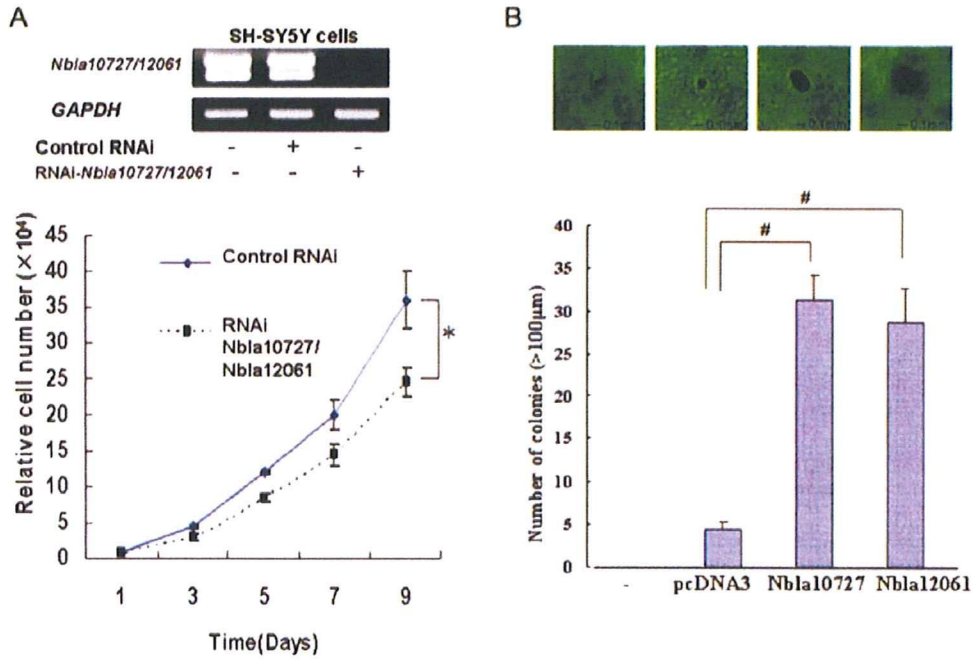

Figure 3. *ncRAN* is involved in inducing enhancement of cell growth in neuroblastoma cells and transformation of NIH3T3 cells. A, Knockdown of *ncRAN* suppress cell growth in SH-SY5Y neuroblastoma cells. SH-SY5Y cells were transfected with expression plasmid for siRNA against *ncRAN* termed pMuni-si*Nbla10727* or with the empty plasmid. On day 2, total RNA was prepared from the cells and subjected to RT-PCR. The expression of two splicing variants of *ncRAN* was knocked-down. At the same time, transfected cells were spread onto 24-well plates and the numbers of the cells at indicated time points were counted using hemocytometer and expressed as the mean ± SEM (n=3). *p<0.05. B, Overexpression of *ncRAN* promotes the malignant transformation of NIH3T3 cells. NIH3T3 cells transfected with pcDNA3, pcDNA3-*Nbla10727* and pcDNA3-*Nbla12061* were used to carry out the soft-agar assay as described in Materials and methods. Blank and mock-transfected NIH3T3 cells served as negative controls. #p<0.01.

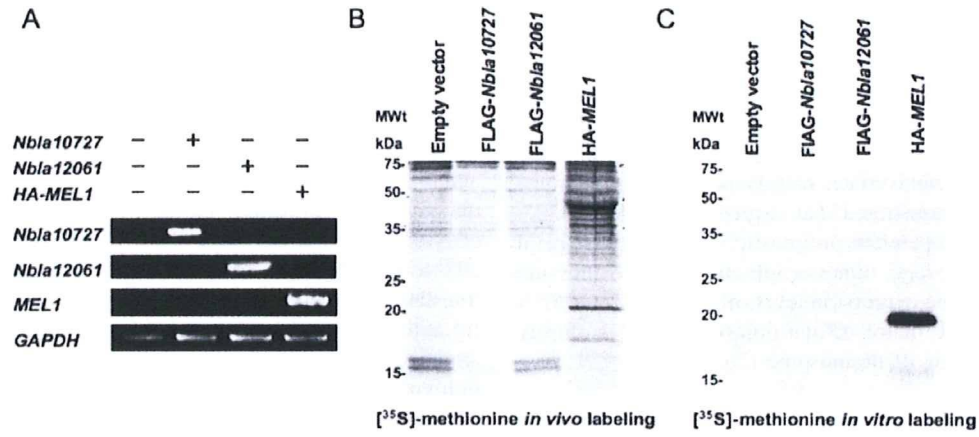

Figure 4. *ncRAN* is a non-protein-coding RNA. A, Ectopic expression of *ncRAN* transcripts in COS7 cells. The *ncRAN* expression vectors were transfected into COS7 cells and total RNA was subjected to RT-PCR. pcDNA3-HA-*MEL1* was used as a positive control. B, *In vivo* [^{35}S]-methionine labeling experiment. COS7 cells transfected with the indicated expression vectors were maintained in fresh growth media without methionine for 2 h and then cultured in the media containing [^{35}S]-methionine overnight. Cells were lysed and subjected to immunoprecipitation with anti-FLAG antibody. Immune complex was washed extensively, resolved by SDS-PAGE and detected by autoradiography. Cell lysate prepared from COS7 cells transfected with pcDNA3-HA-*MEL1* were immunopricipitated with anti-HA antibody. C, *In vitro* translation assay. *In vitro* translation was performed in the presence of [^{35}S]-methionine according to the manufacturer's instructions. pcDNA3-HA-*MEL1* was used as a positive control.

suggest that *ncRAN* might be an evolutionally developed non-coding RNA.

Finally, previous studies have shown that certain large non-coding RNAs are relevant to host RNAs that harbor small RNAs such as microRNA (miRNA) (18). Therefore, we made a search for sequences of known miRNAs in conserved regions within the *ncRAN* locus, but none were identified. These results inferred that the *ncRAN* transcript might not be

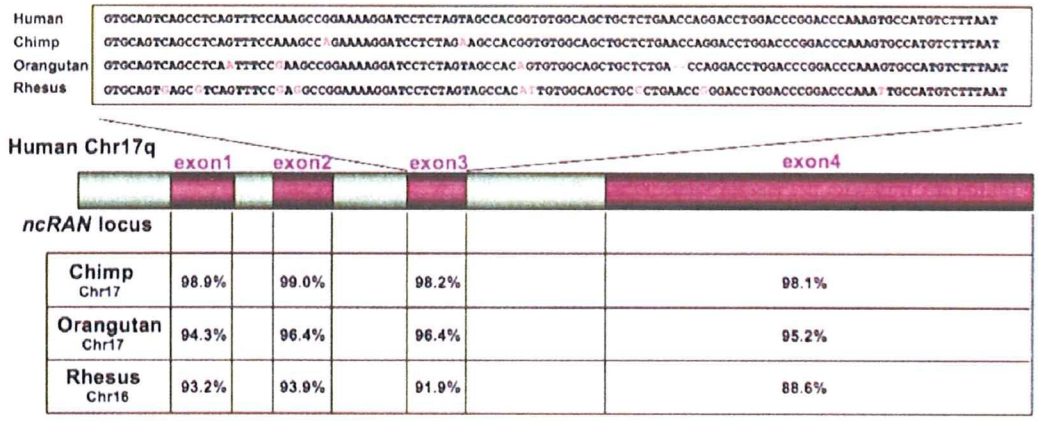

Figure 5. Schematic representation of *ncRAN* sequence conservation in primates. Sequence conservation in *ncRAN* gene locus among human and primates is indicated. Nucleotide sequences of exon3 of *ncRAN* in primates are indicated by numbers in brackets. Genomic sequences within the highly conserved sequence are marked black; mismatches are marked pink. % identities to humans are shown below for each exon. Other lower species, such as mouse, rat, dog, cow, horse, zebrafish, or *C. elegans*, do not have *ncRAN* in their genomes.

Table II. Multivariate analyses of *ncRAN/Nbla10727* mRNA expression as well as other prognostic factors in primary neuroblastomas.

Factor	n	p-value	q-value	H.R.	C.I.
Age (>12-month vs. <12-month)	45 vs. 25	0.0096		3.4	(1.2-9.9)
ncRAN expression	n=70	0.0015	0.0281	3.6	(1.7-7.9)
Age (>18-month vs. <18-month)	40 vs. 30	0.0150		2.9	(1.2-7.1)
ncRAN expression	n=70	0.0023	0.0361	3.5	(1.6-7.8)
Stage (1, 2, 4s vs. 3, 4)	42 vs. 28	<0.0001		8.0	(2.9-14)
ncRAN expression	n=70	0.0457	0.3151	2.4	(1.0-5.6)
Origin (adrenal vs. non-adrenal)	27 vs. 43	<0.0001		9.1	(2.6-33)
ncRAN expression	n=70	0.0107	0.1335	2.8	(1.3-6.1)
MYCN expression	n=70	0.0003		2.0	(1.4-2.8)
ncRAN expression	n=70	0.0035	0.0470	3.3	(1.5-7.3)

n, number of samples; H.R., hazard ratio; C.I., confidence interval. The q-value denotes estimated false discovery rate if all genes whose p-values are equal to or smaller than that of *ncRAN* are discovered as significant (17).

processed to one or more small RNAs. In addition, database search did not identify genes with anti-direction to *ncRAN*, excluding the possibility that *ncRAN* is an antisense gene for certain known genes. Collectively, these results strongly suggested that the *ncRAN* transcript functions as a novel large non-coding RNA.

Discussion

In the present study, we used the combination of array-CGH (5) and gene expression profiling by using an in-house neuroblastoma-proper cDNA microarray (10) to identify genes that strongly correlate with chromosome 17q gain in aggressive neuroblastoma. Our array CGH analysis demonstrated three major genomic groups of chromosomal aberrations such as silent (GGS), partial gains and/or losses (GGP), and whole gains and/or losses (GGW). Correlation analysis revealed that the global feature of the aberrations was maximally correlated with the gain of the long arm of chromosome 17 and with the gain of a whole chromosome 17, therefore the genomic groups GGP and GGW were defined by the status of aberration, by 17q gain and 17 whole chromosomal gain occurred in chromosome 17, respectively (5). Survival analysis for each genetic group suggested that 17q gain was a characteristic and prognosis-related event in primary neuroblastomas. Therefore, we searched for genes that were expressed significantly higher in primary neuroblastomas of GGP compared to that of GGS and GGW and finally found a novel gene *ncRAN* mapped on 17q25.1. The level of its mRNA expression was strongly correlated with the status of chromosome 17 (Table I and Fig. 1B) as well as with patient survival (Table II and Fig. 2).

To our surprise, our results suggested that *ncRAN* is a large non-coding RNA. Non-coding RNA is a general term for functional and untranslatable RNAs. Increasing evidence has shown that they play important roles in a variety of biological events such as transcriptional and translational gene regulation, RNA processing and protein transport (18,19). Recently, the numerous miRNAs, a class of small non-coding RNAs, have been identified, and miRNA-expression profiling of the human tumors has identified signatures in relation to diagnosis, staging, progression, prognosis and response to treatment (19). On the other hand, another class of non-coding RNAs named as the large non-coding RNA, which are usually produced by RNA polymerase II and lack significant and utilized open reading frame, receives relatively little attention. However, recently, increasing number of studies have provided evidence that large non-coding RNAs also play important roles in certain biological processes of the cancers, such as acquisition of drug resistance, transformation, promoting metastasis and inhibition of tumor development (19). In addition, certain candidate non-coding RNAs were isolated from the tissue- and stage-specific libraries, suggesting a possible involvement of non-coding RNAs in development and tumor cell differentiation (20). Given that *ncRAN* was identified from the cDNA libraries generated from different subsets of primary neuroblastomas, it is possible that *ncRAN* might be involved in carcinogenic processes as well as development and differentiation of normal neurons.

In conclusion, we identified a novel large non-coding RNA transcript, *ncRAN*, mapped to the region of 17q gain frequently observed in aggressive neuroblastomas. The levels of *ncRAN* expression are relatively low in normal nerve tissues including adrenal gland, whereas they are upregulated in advanced neuroblastomas with gain of chromosome 17q. From our functional analyses, *ncRAN* appears to act like an oncogene. Notably, knockdown of *ncRAN* with siRNA was able to significantly repress the cell growth in SH-SY5Y neuroblastoma cells with 17q gain as well as high endogenous level of *ncRAN*. Considering emerging evidence on the large non-coding RNAs regulating transcription of other genes (19), the present results not only contribute to further understanding of the molecular and biological mechanism of neuroblastoma genesis, but also provide a potential target for new diagnostic and therapeutic intervention in the future.

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CASE REPORT

Pediatric post-transplant diffuse large B cell lymphoma after cardiac transplantation

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Abstract Post-transplant lymphoproliferative disorders (PTLDs) occur in 3.5–9% of patients after pediatric cardiac transplantation. Caution is needed when treating patients with PTLD because of the risk of allograft rejection frequently caused by withdrawal of immunosuppression. In this report, we describe a 47-month-old boy who developed PTLD as an ileocecal mass 29 months after cardiac transplantation. Immunosuppressive therapy with cyclosporine A (CyA) had been reduced due to an elevation of Epstein-Barr virus (EBV) titer for 8 months before development of PTLD. Histology of the tumor was diffuse large B cell lymphoma. EBV was detected by in situ hybridization assay. Cytogenetic analysis revealed *t*(8;14)(q24;q32) and Southern blot analysis detected a *c-Myc* rearrangement. He was treated with rituximab and combination chemotherapy with excellent response. CyA dose was maintained at reduced levels during chemotherapy and later minimized with introduction of everolimus. The child is free of both PTLD and allograft rejection 41 months after the diagnosis of PTLD.

Keywords Cardiac transplantation · Diffuse large B cell lymphoma · Pediatric · Post-transplant lymphoproliferative disorder

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1 Introduction

Post-transplant lymphoproliferative disorders (PTLDs) are an important cause of morbidity and mortality after pediatric cardiac transplantation. Although its pathological range is quite diverse, from monomorphic to polymorphic proliferation, the majority are B lymphocyte disorders and associated with Epstein-Barr virus (EBV) [1, 2]. Withdrawal of immunosuppression for management of PTLD can often lead to allograft rejection and transplant coronary artery disease [1]. We report a child with EBV-associated post-transplant diffuse large B cell lymphoma (DLBL) after cardiac transplantation who was successfully treated with rituximab and combination chemotherapy.

2 Case report

A 17-month-old boy underwent successful cardiac transplantation for dilated cardiomyopathy in October 2002. He received cyclosporine A (CyA), initially with azathioprine and later with mycofenolate mofetil for post-transplant immunosuppression. He was EBV-seronegative pre-transplant (VCA-IgG: <tenfold) and his donor was EBV-seropositive pre-transplant (VCA-IgG: 320-fold). In November 2003, his EBV antibody titer for VCA-IgG increased to 2,560-fold. In August 2004, 21 months

post-transplant, CyA dose was reduced and mycophenolate mofetil was stopped due to an increase in EBV titers (92,813 copies/DNA 1 μg; Fig. 1); no lymph node swelling or fever was observed; and no abnormalities were detected on CT scan or gallium scintigraphy. He also received ganciclovir or valganciclovir, and IV immunoglobulin with high titer of antibodies against EBV to prevent the development of PTLD. In April 2005, at 47 months of age and 29 months post-transplant, he developed abdominal pain. CT scan revealed an ileocecal mass (Fig. 2a). An open biopsy of the tumor established a diagnosis of monomorphic PTLD, DLBL (Fig. 3a). Immunoblasts were $CD20^+$ (Fig. 3b), $CD79a^+$, and $CD3^-$. In situ hybridization for EBV early RNA (EBER) showed reactivity in lymphoid cells (Fig. 3c). Conventional cytogenetic analysis revealed 46, XY, *t*(8;14)(q24;q32). Southern blot analysis detected a *c-Myc* rearrangement in tumor cells in ascites (Fig. 4). At this point, EBV titer was increased to 15,000 copies/10^6 WBCs (normal value <20 copies). EBV antibody titers for VCA-IgG, VCA-IgM, EADR-IgG, and EBNA were 1,280-fold, <10-fold, <10-fold, and 40-fold, respectively. Laboratory studies showed a WBC count of 4,470 μL^{-1}, hemoglobin 9.9 g/dL, lactate dehydrogenase 1,261 IU/L, serum soluble interleukin-2 receptor (sIL-2R) level 1,947 U/mL (normal value 150–505 U/mL), and normal electrolytes and liver function.

The clinical course of this patient is summarized on Fig. 1. Immunosuppressive therapy with oral CyA was continued to maintain trough levels at 50–90 ng/mL. He received six courses of weekly rituximab (375 mg/m^2) with one course of cyclophosphamide (600 mg/m^2), and seven courses of combination chemotherapy. Combination chemotherapy was as follows: regimen A consisted of high-dose methotrexate, vincristine, cyclophosphamide, pirarubicin (THP-adriamycin), and dexamethasone; regimen B, methotrexate and cytosine arabinoside; and regimen C, cytosine arabinoside and etoposide. Excellent response was observed with resolution of tumor mass (Fig. 2b) and reduction of EBV titer (Fig. 1). Serum sIL-2R level decreased to 987 U/mL 2 weeks after the start of chemotherapy. After completion of chemotherapy, oral everolimus was started, followed by a further reduction of oral CyA to maintain trough levels at 30–60 ng/mL. EBV titer was moderately increased up to 1,000 copies/10^6 WBCs and serum sIL-2R level was maintained at <1,000 U/mL. He remains in complete remission 41 months following diagnosis of DLBL without allograft rejection.

3 Discussion

The incidence of PTLD has been reported to range from 3.5 to 9% after pediatric cardiac transplantation [1–4]. PTLD comprises two pathological types, i.e., polymorphic and monomorphic. Early-onset disease (≤3 years post-transplant) is frequently observed with polymorphic localized disease, while late-onset disease (>3 years post-transplant) is more often associated with monomorphic disseminated disease [1, 5]. Most cases were of B cell

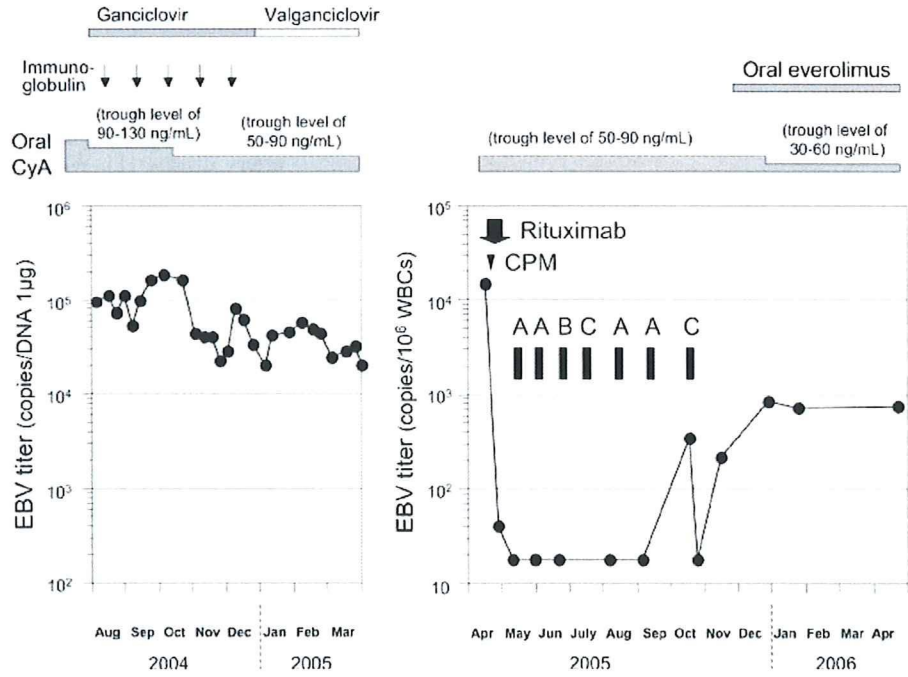

Fig. 1 Clinical course and changes in EBV titer. *CyA* cyclosporine A, *CPM* cyclophosphamide, *EBV* Epstein-Barr virus. **a**–**c** indicate combination chemotherapy regimens (details are shown in the text)

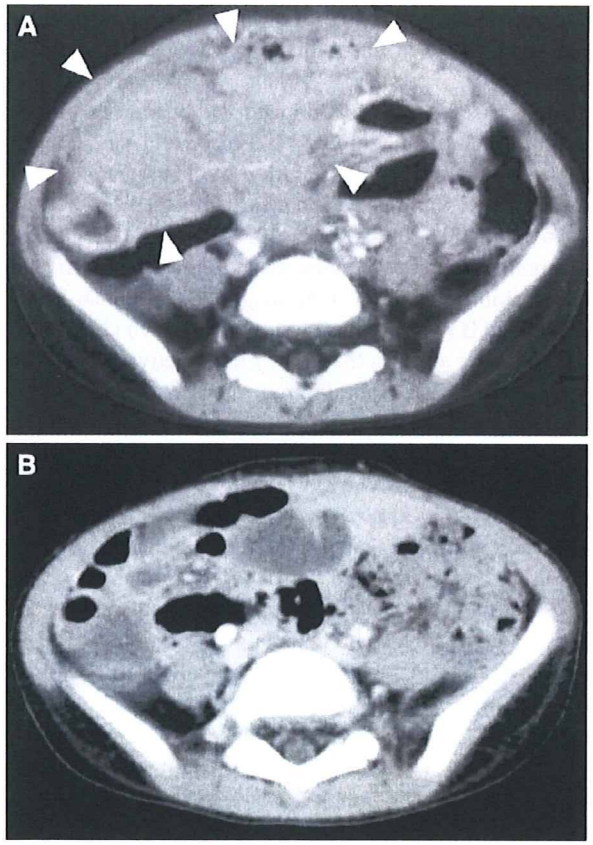

Fig. 2 CT scan images. Abdominal enhanced CT scan showing an ileocecal mass (*arrowheads*) at diagnosis (**a**) and dramatic disappearance after the first course of combination chemotherapy (**b**)

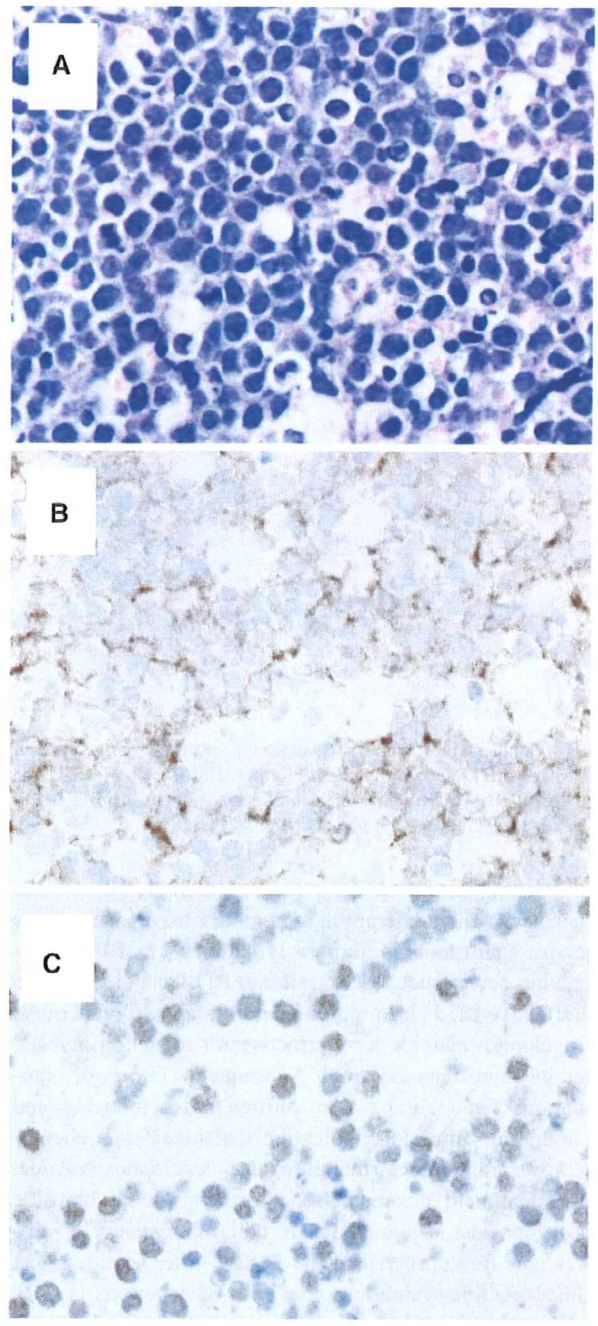

Fig. 3 Pathological studies. **a** Diffuse infiltration of large lymphocytes with clear nucleoli (H&E stain, ×400). **b** Tumor cells showing strong CD20 immunoreactivity stained brown (CD20 stain, ×400). **c** Tumor cells showing reactivity stained brown with the probe specific for EBER-RNA (EBER in situ hybridization, ×400)

origin and contained EBV in lesions [1, 2]. Polymorphic disease is manifested as reactive B cell hyperplasia or B cell lymphoma, while monomorphic diseases as diffuse large B cell lymphoma or Burkitt lymphoma [2, 4].

Our patient developed monomorphic PTLD, DLBL with *t*(8;14)(q24;q32) possessing *c-Myc* rearrangement, which strongly suggests the existence of immunoglobulin heavy chain (IgH)/*c-Myc* fusion. *t*(8;14)(q24;q32) has been detected not only in patients with Burkitt lymphoma but also in 5–15% of patients with de novo DLBL [6, 7]. This translocation results in overexpression of *c-Myc*, driving cell growth and proliferation, and expression of other genes involved in cell growth [8]. Extranodal lymphomas, particularly gastrointestinal lymphomas, as observed in our case, are more likely to carry *c-Myc* rearrangement than nodal lymphoma [7]. The role of chronic infection with EBV in the pathogenesis of a variety of tumors including Burkitt lymphoma is well documented. However, the mechanisms involved have not been completely defined. EBV might have an initiating role in which growth-transforming B cell infections establish a pool of target cells that are at risk of a subsequent *c-Myc* translocation [9].

Most patients with polymorphic disease are treated with lowered immunosuppression in most institutes: minor

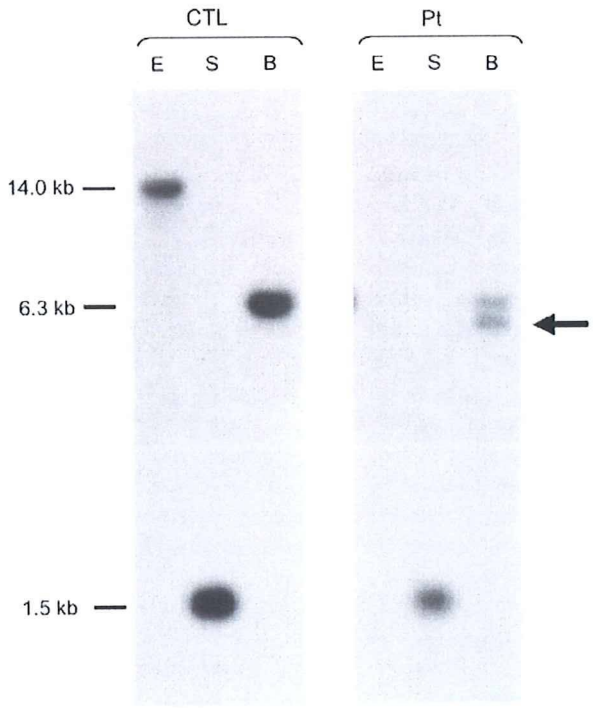

Fig. 4 Southern blot analysis. Rearrangement of the *c-Myc* gene in tumor cells in ascites by Southern blotting with *Eco*RI (E), Sac I(S) and Bgl II (B). The *arrow* indicates a rearrangement band of the *c-Myc* gene. *CTL* control, *Pt* patient

reduction or temporary complete cessation [1, 10]. On the other hand, chemotherapy is commonly used for first-line therapy against monomorphic lymphoma [1, 10]. Rituximab has been widely used for B cell PTLD and reported to be effective [2, 11]. In our case, rituximab and one course of cyclophosphamide were effective for reduction of EBV titer by more than two logs. Subsequent courses of combination chemotherapy were sufficient for inducing and maintaining remission, indicating that block-type chemotherapy containing methotrexate, cyclophosphamide, pirarubicin and dexamethasone, or cytosine arabinoside and etoposide, designed for B cell malignancy, is also effective for post-transplant DLBL after solid organ transplantation, which is in line with other reports [1, 10].

Webber et al. [1] reported 42 cases with pediatric PTLD after cardiac transplantation, of which 16 patients died from progressive PTLD ($n = 7$), acute rejection ($n = 3$), coronary artery disease ($n = 3$), PTLD with acute rejection ($n = 1$), PTLD with sudden death ($n = 1$), and graft failure ($n = 1$). This report also indicated that death from graft loss is a serious issue during PTLD treatment. A fine balance between management against PTLD and preserving allograft from rejection is therefore highly important. With respect to this standpoint, chemotherapy may be useful for maintaining an immunosuppressed state to prevent allograft rejection [1, 10]. Lower rejection rates have been reported when chemotherapy was used as primary therapy [1].

In our case, CyA was continued without further reduction during the treatment of PTLD to protect the allograft from rejection. Following cessation of chemotherapy, oral everolimus was initiated with a further reduction of CyA dose to maintain trough levels at 30–60 ng/mL. Everolimus, an immunosuppressive mammalian target of rapamycin (mTOR) kinase inhibitor, inhibits growth of human EBV-transformed B lymphocytes in vitro and in vivo [12]. Thus, it is promising agent in that it may be effective in both the prevention of PTLD and allograft rejection. In our case it might have contributed to protection against PTLD relapse as well as allograft rejection. Further studies are needed with this agent in this clinical setting.

In summary, we present a child who was successfully treated for post-transplant DLBL after cardiac transplant. The disease was associated with *c-Myc* rearrangement and EBV. Rituximab and combination chemotherapy were effective in inducing and maintaining remission. PTLD should be carefully managed to prevent allograft rejection.

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