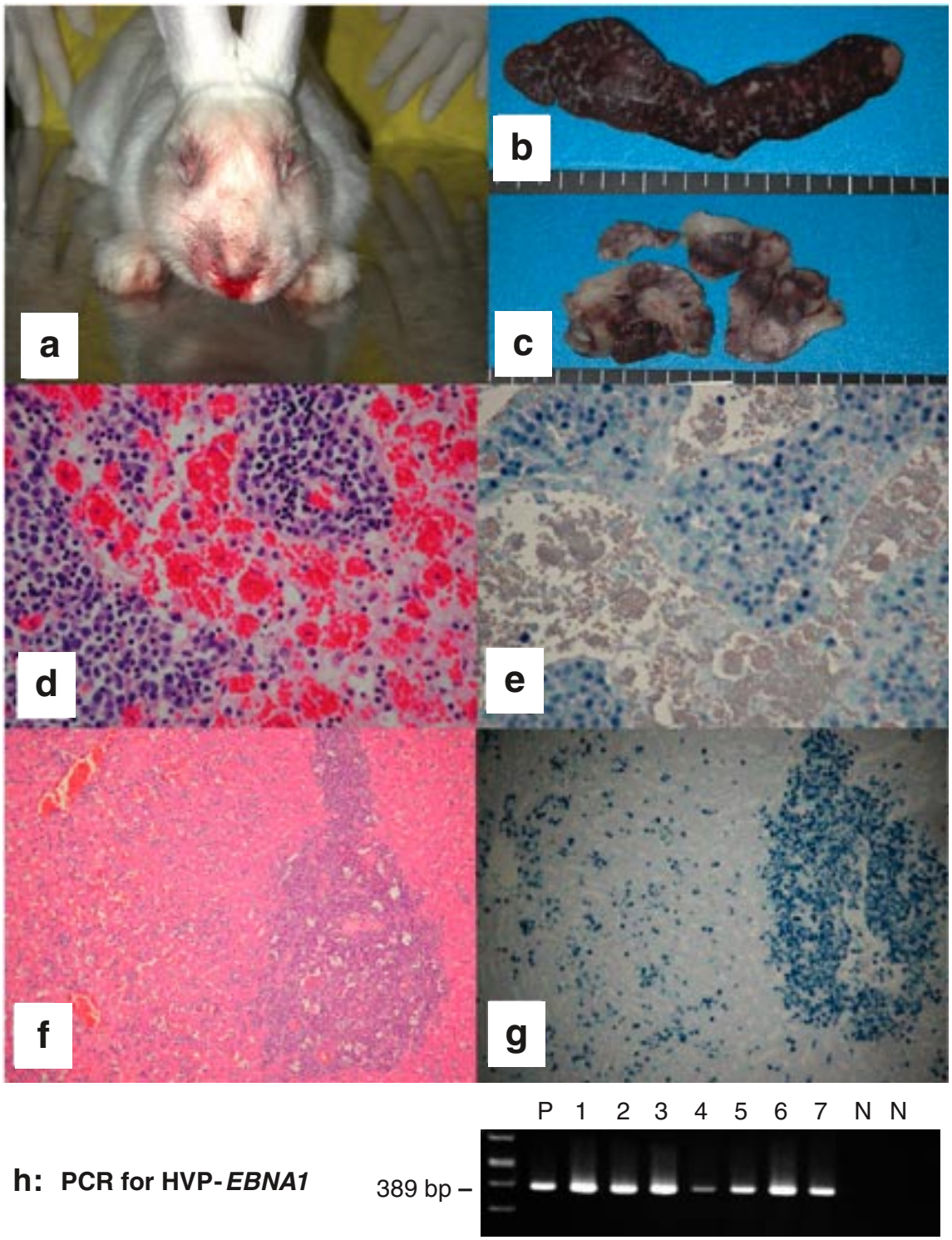

Fig. 4. Baboon-EBV (HVP)-induced lymphoproliferative diseases with hemophagocytosis in rabbits. Rabbit nasal bleeding due to bleeding tendency (**a**). Splenomegaly (**b**) and lymph node swelling with hemorrhage (**c**). Atypical lymphocyte infiltration and marked hemophagocytosis in lymph nodes (hematoxylin and eosin stain) (**d**) and HVP-EBER-1 (*in situ* hybridization) (**e**). Atypical lymphocyte infiltration in the liver (hematoxylin and eosin stain) (**f**) and HVP-EBER-1 (*in situ* hybridization) (**g**). (**h**) Detection of HVP-*EBNA1* DNA by PCR. HVP-*EBNA1* DNA was amplified in the positive control (lane P) and HVP-infected rabbit tissues (lanes 1 through 7) but not in the negative controls (lane N).

PCR for the HVP-EBNA-1 region was carried out using the primer pair HPNA-1S: 5'-CTG GGT TGT TGC GTT CCA TG-3' and HPNA-1A: 5'-TTG GGG GCG TCT CCT AAC AA-3'. Amplified DNA of the expected size of 389 bp was demonstrated in the positive control (594S) and 594S (HVP)-induced rabbit LPD lesions (Fig. 4h) as well as in peripheral blood from the infected rabbits. PCR analysis revealed the presence of HVP-DNA in all six rabbit cell lines established from HVP-infected rabbits. Clonality analysis using the HVPTR2 probe revealed monoclonal or oligoclonal bands in 594S (HVP)-induced rabbit LPD lesions (data not shown).

On the latency of EBV infection, while cross-reactive EBNA-2 expression by immunofluorescence test was detected in 594S cells, neither EBNA-1 nor LMP-1 cross-reactivity was observed. HVP-*EBNA1* and HVP-*EBNA2* mRNAs were detected by reverse transription-PCR in 594S cells and HVP-induced rabbit LPD lesions, suggesting the latency type III. HVP-*LMP1* transcripts were detected in 2 of the 4 *in vivo* samples. However, reverse transription-PCR revealed mRNA expression of both HVP-EBNA1 and HVP-LMP1 but not of HVP-EBNA2 in rabbit T cell lines (data not shown), suggesting the latency type II.

I consider that this rabbit model of fatal LPD with VAHS induced by primary infection of HPV is a useful animal model for fatal childhood EBV-AHS (Kikuta et al., 1993; Su et al., 1994, 1995; Chen et al., 1997). Those results mentioned above suggested that the clinicopathologic features of the rabbit model were similar to those of fatal childhood EBV-AHS described by Su et al. (1994, 1995).

To determine the nature of HVP-induced rabbit LPD, it is important to determine if the atypical lymphocytes in rabbit LPDS were reactive or neoplastic, that is, whether or not they exhibited clonal cytogenetic abnormalities. Both oligoclonal and monoclonal expansion of HVP-infected rabbit lymphoid cells in rabbit LPD *in vivo* was observed by Southern blot analysis of EBV termini. However, chromosomal analysis revealed normal rabbit karyotypes in cells from all 10 *in vivo* LPD lesions from 5 rabbits examined, and in 5 of the 6 IL-2 dependent rabbit cell lines (Hayashi et al., 2003a). This suggested that most *in vivo* rabbit LPD cells were non-neoplastic in nature. In addition, the rabbits with HVP infection usually died within a short time of VAHS. Based on these results, it is possible that most HVP-infected rabbits die relatively quickly of severe LPD and VAHS with bleeding in the presence of oligoclonal LPD, before the development of completely monoclonal neoplastic lymphoma. However, it is also possible that these rabbit LPD lesions may contain some small components of neoplastic or pre-neoplastic cells with HVP infection.

Therapeutic trials with vidarabine or CHOP* for a rabbit model of EBV-AHS were not succeeded (Hayashi et al., 2003b).

Comparative analysis of the rabbit models with human EBV-associated LPD

Four rabbit models using simian EBV-like viruses have been reported (Table 2). Three of them using Cynomolgus-EBV, HVMA and HVMNE are animal models for human EBV-associated malignant lymphoma. Cynomolgus-EBV- or HVMNE-induced rabbit malignant lymphoma showed T-cell phenotype, while phenotype of HVMA-induced rabbit malignant lymphoma was not determined. It is very interesting that Cynomolgus-EBV (Si-IIA-EBV and HVMF1) and HVMA were isolated from the simian cell lines infected with retroviruses such as HTLV-II, SIV or STLV, respectively. Among these three viruses, Cynomolgus-EBV can induce rabbit lymphoma the most frequently (90%) and is the only one kind to be demonstrated to transmit to rabbits by natural peroral infection and to result in rabbit lymphoma development. The latency type I/II of Cynomolgus-EBV induced rabbit T-cell lymphoma is compatible with that of human EBV-associated T-cell lymphoma. However, sim-

* CHOP, combination chemotherapy consisting of cyclophosphamide, hydroxydaunomycin, oncovin and prednisone.

ian EBV-like viruses (Cyno-EBV, HVMA and HVMNE) infection of rabbits resulted in T-cell lymphomas several months of latent period after primary infection, while the latency period between the primary EBV infection and human EBV-associated T-cell lymphoma development is considered more than 30 years. The direct causative relation between primary simian EBV-like viruses and subsequent rabbit T-cell lymphomas is very clear. However, additional events such as some genetic alterations must be needed to develop human EBV-associated T-cell lymphomas during long latent infection of EBV after the primary EBV infection. If possible, I need to develop some animal models with long latent virus infection and subsequent T-cell lymphomas for human EBV-associated T-cell lymphomas.

As the clinicopathologic features of HVP-infected rabbit model are very similar to those of fatal childhood EBV-AHS with T-cell LPD (Su et al., 1994) or fulminant EBV-positive T-cell LPD following acute/chronic EBV infection (Quintanilla-Martinez et al., 2000), I suggest that this rabbit model of fatal LPD with VAHS, induced by a primary natural route of HPV infection, represents an animal model for fulminant EBV-positive T-cell LPD with VAHS due to primary EBV infection. This system may be useful for the study of human EBV-AHS pathogenesis, prevention and treatment.

Perspectives on animal models of EBV-associated diseases

In spite of the many investigations into the role of EBV infection in the pathogenesis of EBV-associated diseases, a direct causal relationship between EBV infection and these tumors has been established only in primary EBV infection related diseases including infectious mononucleosis and EBV-AHS in childhood and the opportunistic LPDs arising with a relatively short latency period in immunocompromized hosts. However, most EBV-associated tumors arise with a very long latency in long-term EBV carriers. This suggests the multistep oncogenesis by risk factors and malignant transformation from a single cell within the EBV-infected pool (Rickinson and Kieff, 2001). It is generally accepted that risk factors such as genetic background, ethnicity, environmental factors including nitrosamines in foods, economic status and malarial or helicobacter pylori infection and the mutation or deletion of genes like *p53* are needed for the development of the other EBV-associated tumors. EBV contributes to the malignant phenotype, such as growth in low serum concentration, anchorage-independent growth in soft agar, and tumorigenicity in nude mice (Shimizu et al., 1994), and oncogenic role of EBERs and resistance to apoptosis by EBERs are also demonstrated in Burkitt's lymphoma cell line Akata (Komano et al., 1999; Ruf et al., 2000). Insulin-like growth factor 1 induced by EBERs acts as an autocrine growth factor for EBV-positive gastric carcinoma (Iwakiri et al., 2003). On the other hand, there are different hypotheses that EBV is only an innocent bystander virus or that EBV just infects the tumor cells after the malignant transformation of EBV-non-infected cells and EBV does not contribute to the oncogenic process (Ohshima et al., 1998).

The direct causative relationship between infection by EBV-related virus and the subsequent development of malignant lymphoma is very clear in this rabbit experimental model by EBV-related virus, reinforcing the assertion that EBV has the significant role in the development of EBV-associated tumors. According to the comparative overview data of EBV-associated lymphomas in human and rabbits (Tables 1 and 2), these rabbit LPDs induced by EBV-like viruses are very good models for the fatal lymphoproliferative disease seen in fatal infectious mononucleosis/fatal LPD with a virus-associated hemophagocytic syndrome and EBV-positive T cell lymphoma. In addition, new animal models developing after long latent infection are needed for human T-cell lymphoma with a very long latency in long-term EBV carriers. In view of the scarcity and expense of non-human primates, these rabbit models are very useful and inexpensive alternative experimental models for studying the biology and pathogenesis of EBV,

especially in relation to human EBV-related lymphomas. Rabbit models with Cynomolgus-EBV or HVP can also be used for studying the mechanism of the natural oropharyngeal route of infection by EBV-related virus.

On the present animal models *in vivo* of EBV infection and EBV-associated diseases, all animal models are useful for studying EBV-associated LPD or EBV-related lymphomas, and most of them are acute or subacute models with short latency and develop by primary virus infection. Mouse models using murine gamma-herpesvirus is the only one for EBV-related lymphoma with a very long latency in long-term gamma-herpesvirus carriers. Rhesus monkey model using LCV-naïve rhesus monkeys infected with rhesus LCV is a very excellent one for natural primary EBV infection and subsequent latent EBV infection, because essentially the same virus-host interactions have been maintained in this system. However, rhesus LCV-related tumors without immunodeficiency have not been detected yet. These animal models in vivo also provide a means of studying prophylactic regimens such as recombinant vaccines and CTL epitope peptide-based vaccines. These are useful *in vivo* system to test novel therapies including new drugs, CTL-based immune therapy and gene therapy directed against the EBV-positive LPD or lymphomas which are usually refractory to conventional chemotherapy (Franken et al., 1996; Barnes et al., 1999). However, it is noteworthy that there have been no animal models *in vivo* for EBV-infected epithelial tumors such as a set of nasopharyngeal carcinoma or gastric carcinoma, because the cases of EBV-associated gastric carcinoma (6.7% or 4.7–11.2% of gastric carcinoma cases) (Tokunaga et al., 1993; Koriyama et al., 2001, respectively) is the largest in number among EBV-related tumors in Japan. To elucidate the detail pathogenesis of EBV-associated diseases using animal models, sequential follow-up studies and clarifying functions of the oncogenes of EBV or EBV-like viruses are needed. Animal models infected with defected EBV-like virus deleting some important oncogenes will be also useful for the function of the oncogenes. Why rabbits are so highly susceptible to lymphomagenesis induced by simian EBV-like viruses is not clear. I could not demonstrate the lymphomagenesis in some strains of mice, rats and hamsters (unpublished data). The mechanism of cross-species virus transmission should be elucidated.

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