

Variable Morphology of Human Immunodeficiency Virus-Associated Lymphomas With C-MYC Rearrangements

By H.J. Delecluse, M. Raphael, J.P. Magaud, P. Felman, the French Study Group of Pathology for Human Immunodeficiency Virus-Associated Tumors, I. Abd Alsamad, G.W. Bornkamm, and G.M. Lenoir

Burkitt lymphoma (BL) and immunoblastic lymphoma (IL) are the most frequent lymphoid tumors encountered in human immunodeficiency virus (HIV)-infected patients. Tumors with a morphology intermediate between BL and IL, and the existence of Burkitt's type translocations in some IL cases makes the classification of these tumors sometimes unclear. We have studied 14 cases of BL and IL in HIV-seropositive individuals with regard to clonality, Epstein-Barr virus (EBV) association, and the presence of *c-myc* rearrangement. Of seven tumors with morphology of BL, all were monoclonal, six showed a *c-myc* rearrangement and four were associated with EBV. Five tumors

with morphology of IL were associated with EBV and devoid of *c-myc* rearrangement. Three were polyclonal representing EBV-driven lymphoproliferations similar to those observed in transplant recipients. Two tumors, one with a morphology of IL and the other intermediate between IL and BL were monoclonal, associated with EBV, and harbored a *c-myc* rearrangement. We propose that these last two tumors represent cases of BL that have adopted an immunoblastic morphotype in the context of acquired immunodeficiency syndrome (AIDS), reflecting the morphologic evolution of Burkitt lymphoma cells observed in culture. © 1993 by The American Society of Hematology.

MALIGNANT B-cell proliferations including non-Hodgkin's lymphomas (NHL) are well known complications of human immunodeficiency virus (HIV) infection.¹⁻⁶ These are intermediate- and high-grade malignant NHL, according to the international working formulation.⁷ Large-cell lymphomas, of the immunoblastic or of the large noncleaved type, peripheral or involving the central nervous system,^{2,8} and small noncleaved cell lymphoma of the Burkitt type constitute the majority of these tumors.⁹ Peripheral polyclonal lymphomas not associated with Epstein-Barr virus (EBV),¹⁰ and atypical undifferentiated large-cell lymphomas have also been reported.¹¹

Occurrence of NHL in HIV-infected patients has been initially attributed to the state of immunodeficiency, as observed in patients with primary immunodeficiency or after organ transplantation.^{12,13} Posttransplant lymphomas have been proposed to be the consequence of the uncontrolled proliferation of EBV-infected cells giving rise to proliferations of extremely variable morphology.¹⁴⁻¹⁷ Large-cell lymphomas of the immunoblastic type are particularly frequent in cardiac transplant recipients.¹⁸ Lymphoproliferations in

transplant recipients usually do not possess chromosomal Ig/*c-myc* translocations.^{16,19,20} They may be either polyclonal or monoclonal, as suggested by immunophenotyping or by Ig gene rearrangement analysis.^{17,21-24}

However, in addition to immunoblastic lymphomas, HIV carriers have also a high risk of small noncleaved cell lymphomas principally of the Burkitt type (BL), a complication only exceptionally identified to date in congenital or acquired immunodeficiencies other than acquired immunodeficiency syndrome (AIDS).^{1,3} BL is characterized by its monoclonality and one of the typical t(8;14), t(2;8), or t(8;22) translocations affecting the *c-myc* locus. However, association with EBV is not a constant feature.^{25,26}

Several studies have pointed out the different characteristics of these two types of lymphomas in the context of HIV infection. Immunoblastic lymphoma (IL) and large-cell lymphomas occur usually in patients with severe immunodeficiency with an extremely low count of CD4⁺ lymphocytes. These tumors do not respond to chemotherapy and have a poor prognosis.³ In contrast, BL generally occurs in patients with less severe immunodeficiency, is often preceded by a generalized reactive lymphadenopathy, and responds better, at least initially, to chemotherapy.^{1,3} Previous studies on the presence of EBV in BL among HIV carriers have described a viral association in about one-half of the cases.^{1,3,27-32} These tumors display the characteristic chromosomal translocations affecting the long arm of chromosome 8 (8q24).^{29,31-34}

However, analysis of tumors from HIV-infected patients has shown the existence of Ig/*c-myc* translocations in cases of IL.^{31,35} The pathologic diagnosis of these tumors in HIV-positive individuals is sometimes difficult, with presence of numerous atypical morphologic features and existence of tumors with morphologies intermediate between IL and BL.^{36,37}

For these reasons we have undertaken a combined molecular and morphologic analysis of 14 of these tumors to precisely distinguish between IL and BL in the context of HIV infection. Our results suggest the possibility that in the course of the HIV infection, BL cells may adopt morphologic characteristics of IL cells in vivo, a phenomenon also observed when BL cells are explanted in vitro in culture.

From the Centre International de Recherche sur le cancer, Lyon, France; CHU Pitié-Salpêtrière, Département d'Hématologie, Paris, France; Hopital Ed. Herriot, Lyon, France; Centre hospitalier Lyon Sud, Laboratoire central d'hématologie B, Lyon, France; and the Institut für Klinische Molekularbiologie und Tumorgenetik, München, Germany.

A complete list of the participants is given in the appendix.

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Address reprint requests to H. J. Delecluse, MD, Institut für Klinische Molekularbiologie und Tumorgenetik, GSF, Marchioninistraße 25, 8000 München 70, Germany.

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MATERIALS AND METHODS

Pathologic Samples

Tumoral biopsies obtained from patients infected by HIV were used for simultaneous morphologic and molecular analyses. Cases with partial tumoral infiltration were systematically excluded from our study. Tumors from 14 patients satisfied the conditions cited above.

Part of material was formalin-fixed and embedded after standard procedures. DNA was extracted from the rest of the primary material, with the exception of case 1 and 2 where in vitro cultured cell lines established from the initial tumors were used (IARC BL 115 and IARC BL 134).

These tumors were diagnosed and classified, according to the international working formulation (Table 1). All pathologic findings, except cases 1 and 2, were reviewed by the members of the "French Study Group of Pathology for HIV-Associated Tumors." Cases 1 and 2 were diagnosed and typed in Lyon (Centre Léon Bérard).

DNA Isolation and Southern Blotting

Total cellular and viral DNA was prepared by sodium dodecyl sulfate (SDS) cell lysis, proteinase K digestion, phenol/chloroform extraction, and ethanol precipitation.

Ten micrograms of DNA were digested with 50 IU of the appropriate endonucleases (Bethesda Research Laboratories, Bethesda, MD).

Digested DNAs were electrophoresed on a 0.7% to 0.9% agarose gel in TBE (0.045 mol/L Tris-Borate 0.001 mol/L EDTA) buffer, hydrolyzed for 15 minutes in 0.25 N HCl, denatured for 30 minutes, and renatured before being transferred onto Hybond N filter (Amersham, Amersham, UK) according to Southern analysis. Probes were labeled with ³²P by multiple random priming (Amersham) and hybridized with the filter at 65° in 0.5 mol/L NaH₂PO₄, pH 7.2, 1% bovine serum albumin (BSA), 7% SDS.

Filters were washed at 60°C for 30 minutes in 2× SSC, 0.1% SDS, for 15 to 30 minutes in 0.2× SSC (0.15 mol/L NaCl, 0.0157 sodium citrate), 0.1% SDS, and autoradiographed using intensifying screens (Quanta III; Dupont, Wilmington, DE).

DNA Probes

Rearrangements of the *c-myc* gene were studied by hybridization of *Bam*HI-, *Eco*RI-, *Hind*III-, or *Xba*I-digested DNAs to probes

representative of the first or third exon of the *c-myc* gene³⁸ (Fig 1A). Rearrangements 3' of *c-myc* in pvt-1 or bvr-1 regions were analyzed using the probes 455 and 550.³⁹ These genomic probes represent parts of the bvr-1 and pvt-1 loci, respectively situated 140 and 260 kb 3' of the *c-myc* locus, which are frequently involved in the t(2;8) and t(8;22) variant translocations³⁹⁻⁴¹ (Fig. 1A). The search for rearrangements 5' of *c-myc* was performed using the probe p380j9 0.8 SS (kindly provided by F. Haluska) situated at 175 kb 5' of *c-myc*.^{42,43}

The organization of the IgH locus was analyzed by hybridization of *Bam*HI-, *Eco*RI-, *Hind*III- and *Xba*I-digested DNA to probes specific of the joining region (JH) and of the C_μ gene (Fig 1B). The κ light chain was studied using a 2-kb J κ and a 2.5-kb C κ fragment.

Search for EBV DNA was done using a probe specific for the *Bam*HI-W internal repeats of the virus,⁴⁴ and the 1.9-kb *Xho*I fragment located near the right end of the linear viral genome.⁴⁵

RESULTS

Patients and Pathologic Characteristics

Table 1 summarizes the main clinical and pathologic characteristics of our cases. Fourteen tumor samples were collected in four French hospitals (Hôpital Pitié-Salpêtrière, Paris; Hôpital Beaujon, Paris; Hôpital d'Argenteuil; Centre Léon Bérard, Lyon). Seven patients were homosexual, four were heterosexual with multiple partners, one came from an endemic country, and two were intravenous (IV) drug users. Ages ranged from 22 to 50 (mean, 38) years.

Pathologic examination was performed by members of the "French Study Group of Pathology for HIV-Associated Tumors." Tumors typed as IL or BL according to the international working formulation were selected for molecular analysis. All tumors were B-cell lymphomas, according to immunologic studies performed on frozen sections using monoclonal antibodies to detect B-cell antigens and Ig heavy and light chains (data not shown). Seven tumors (cases 1 through 7) were diagnosed as small noncleaved cell lymphoma of Burkitt type. Six tumors were IL, of which 5 (cases 9 through 13) showed marked plasmacytic differentiation. One sample (case 14) was typed as lymphoproliferation with plasmacytic differentiation (LP) according to the initial description of Nalesnik et al²² in posttransplant lymphoproliferative diseases. Case 8 was diagnosed as intermediate between IL and BL. This tumor possessed features of small noncleaved cell lymphoma of the Burkitt type. The architecture was composed mainly of large cells with interspersed macrophages, giving rise to a "starry sky" pattern. A high level of apoptosis and a strong cohesiveness of the cells were observed. However, there was a polymorphism in the size of the tumor cells with presence of an important percentage of small cells (Fig 2). Most of the large cells possessed a large unique nucleolus, as seen in IL in contrast to the multiple and paracentral nucleoli of the small cells.

The majority of the cases had a nodal presentation. Extracapsular presentation was observed in 5 patients: 1 had a subcutaneous mass, 3 had buccal involvement, and 1 had splenomegaly. Four patients had bone marrow (BM) involvement at diagnosis (Table 1). Two patients (cases 5 and 8) have developed a generalized reactive lymphadenopathy before onset of the lymphoma.

Patients received polychemotherapy, except for two: one

Table 1. Pathologic Diagnosis and Clinical Characteristics of the HIV+ Patients with NHL

Case No.	Sex/Age	Risk Factor	Major Location	Diagnosis	Treatment	Survival (mo)
1	M/45	Het/xPart	Marrow	BL	PC	Dead (9)
2	M/22	IVD	LN	BL	PC	Dead (8)
3	M/31	Ho	LN	BL	PC	Dead (7)
4	M/46	Het/xPart	LN	BL	PC	Dead (8)
5	M/36	Ho	LN	BL	PC	Dead (18)
6	M/39	Ho	SCM	BL	PC	Dead (13)
7	M/40	Ho	LN	BL	PC	Dead (50)
8	M/48	Het/xPart	LN	IL	—	Dead (2)
9	M/32	Ho	IB	IL	—	?
10	M/30	Ho	IB	IL	PC	Dead (5)
11	F/44	IVD	IB	IL	PC	Dead (5)
12	M/43	Ho	LN	IL	PC	Dead (9)
13	M/36	Endemic	LN	IL	PC	Alive (6)
14	M/30	Het/xPart	Spleen	LP	PC	Dead (1)

Abbreviations: Het/xPart; heterosexual with multiple partners; Ho, homosexual; IVD, intravenous drug user; LN, lymph node; SCM, subcutaneous masses; IB, intra-buccal; BL, Burkitt's lymphoma; IL, immunoblastic lymphoma; LP, lymphoproliferation with plasmacytic differentiation; PC, polychemotherapy.

died shortly after diagnosis and the other could not be observed.

Detection of myc Rearrangements

In eight tumors, we identified rearrangements within the *c-myc* gene (Fig 3A). Because genetic polymorphisms in the *c-myc* gene are extremely rare, we interpret these as a result of chromosomal rearrangements. In case 9, with a diagnosis of IL, a faint rearranged *c-myc* fragment was observed. Therefore, the Southern analysis was repeated using *EcoRI* and *HindIII*, confirming the initial result (Fig 3B). In one tumor classified as BL, a rearrangement on chromosome 8 could neither be detected by Southern blotting using a *c-myc*, *pvt-1* or *bvr-1* probe, nor using a probe detecting rearrangements in the region carrying a cluster of *t(8;14)* translocation breakpoints at a distance 175 kb 5' of *c-myc*.^{39,42,43} The failure to detect all Burkitt translocations by conventional Southern blotting is consistent with the findings that the breakpoints can be scattered over a distance of more than 700 kb.^{39,46}

Chromosome 14 Breakpoints

S μ . Breakpoints were assumed to be located within the switch μ region if two criteria were fulfilled: (1) hybridization of the JH and C μ probes to different *EcoRI* and *BamHI* fragments indicating a noncontiguous configuration of JH and C μ , and (2) comigration of fragments visualized by a C μ and a *c-myc* exon 3 probe after digestion with *BamHI*, *EcoRI*, and *HindIII*.⁴⁷ According to these criteria, 3 of the 8 cases with *c-myc* gene rearrangement (cases 2, 5, and 9) had a breakpoint within the μ switch region (Table 2).

JH. In two cases (cases 4 and 8) C μ and JH probes hybridized to identical *BamHI* and *EcoRI* fragments, indicating a contiguous configuration of JH, S μ , and C μ on both alleles. However, hybridization with JH showed a third fragment different in size from the nonrearranged JH gene provided by the stromal cells. This third rearranged JH fragment did not hybridize to a C μ probe. Visualization of a third fragment was taken as an indication that the joining region is transected on one of both Ig heavy-chain alleles⁴⁷ (Fig 4). The most likely explanation is that one heavy chain is functionally rearranged and that the other is fused to chromosome 8 sequences within the region covered by the JH probe.

Breakpoints in the IgH gene locus of the three other tumors could not be localized by this method (Table 2), probably because the rearrangements affected the genes of other Ig heavy-chain isotypes that have also been shown to participate in *c-myc* translocations.⁴⁸

Study of Clonality

Southern blot analysis of Ig genes permits to discriminate between monoclonal or polyclonal proliferations. In the case of a monoclonal proliferation, neoplastic cells present one or two identical rearrangements in all cells corresponding to a rearrangement on one or both Ig alleles. Thus, monoclonality is shown by the presence of one or two bands in a position different from that of the unrearranged germline configuration as exemplified in Fig 4.

In contrast, polyclonal proliferations are composed of neoplastic cells carrying different Ig rearrangements. Each is expected to give a discrete band but the signal is too weak to be identified, and in fact nothing but the germline band can be identified by Southern blot analysis. Using the C μ and the JH probes and at least two enzymes, all BL were monoclonal, whereas IL or LP were composed of monoclonal or polyclonal proliferations (Table 3). The Southern blot hybridization of two polyclonal proliferations using three different enzymes and the C μ and JH and J κ probes is presented in Fig 5.

Presence of EBV Sequences

The presence of EBV was detected in all cases of IL and LP and in 4 of 7 BL using the *BamHI*-W and the 1.9-kb *XhoI* probe (Table 3). The intensity of the signals obtained after hybridization was higher in monoclonal, than in polyclonal cases (Fig 6) with the exception of case 4 (not shown). For the three polyclonal cases, comparison with a cell line containing two copies of EBV DNA (Namalwa) indicated the presence of about one to two copies per cell.

Fusion of the terminal repeats gives rise to the episomal conformation of the EBV genome in lymphoid tumors. The number of terminal repeats, and thus the size of the fused terminal fragment, is variable in different infected cells. Southern blot hybridization using the 1.9-kb *XhoI* probe has been used to study the clonality of EBV-carrying tumors.⁴⁵ A single fused terminal fragment is interpreted as evidence for monoclonality, the presence of two or more terminal fragments is taken as evidence for oligoclonality or polyclonality.^{45,49-51}

Seven of the 8 monoclonal proliferations were monoclonal according to the criteria described above (Fig 6A). However, one case (case 1, Fig 6B) showed one or two additional bands after digestion with *BamHI*, *HindIII*, and *XbaI*. The monoclonality of this case is beyond any doubt. The molecular analysis of Ig and *c-myc* rearrangement was performed on an established cell line and clearly showed monoclonality. Therefore, the detection of more than one band with the terminal-repeat probe is not definitely conclusive for oligoclonality or polyclonality (see also Discussion).

In one of the cases with polyclonal proliferation as defined by Ig gene rearrangement, oligoclonality or polyclonality was confirmed using the EBV terminal repeat probe and the restriction enzymes *BamHI* and *EcoRI* (case 14, Fig 6C). The restriction enzyme *HindIII* generates very large fragments spanning the termini that cannot be resolved by conventional electrophoresis in case of polyclonality. All other cases showed one major band on the background of a smear, as exemplified for case 12 in Fig 6C. This type of pattern is not conclusive for either monoclonality or polyclonality, as detailed in the Discussion. Therefore, diagnosis of monoclonality or polyclonality is based on the unequivocal results obtained by the analysis of Ig gene rearrangements.

DISCUSSION

t(8;14), *t(8;22)*, and *t(2;8)* translocations leading to rearrangements between the *c-myc* and the Ig loci are a constant

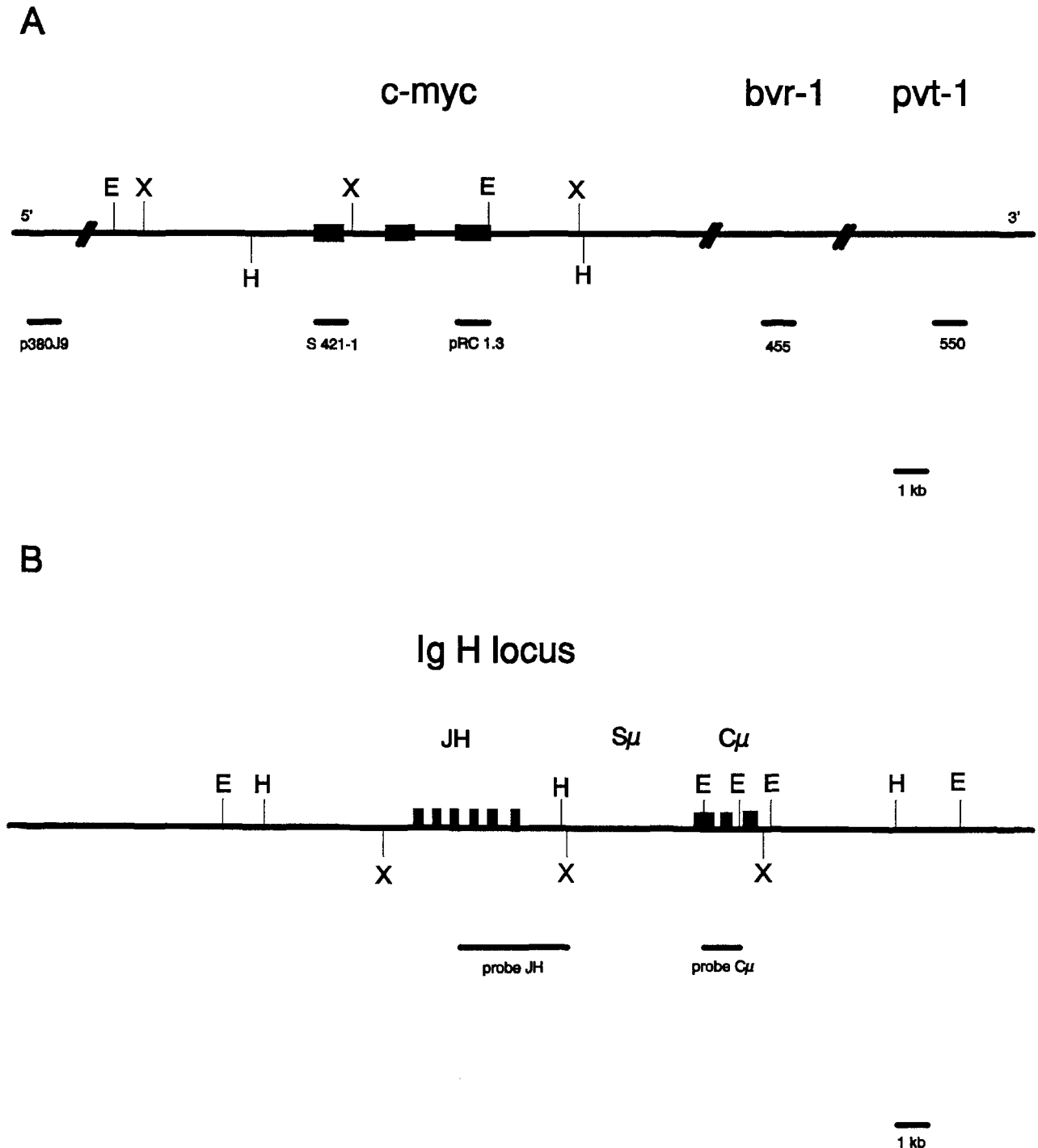


Fig 1. Diagrams of the human *c-myc* (A) and IgH (B) genes, indicating position of the probes used. Restriction sites: E, *EcoRI*; H, *HindIII*; X, *Xba I*; C, *Cla I*; P, *Pvu II*.

characteristic of BL,^{26,52} a tumor composed of small non-cleaved cells with high mitotic activity.⁷ The so-called "small noncleaved nonBurkitt lymphoma", made of small cells with a pleomorphism in size and shape and with unique central nucleoli, has also been found to harbor one of the typical BL translocations, and is considered as a vari-

ant of BL.⁵³⁻⁵⁶ The small to medium size of these tumors, as well as the high nuclear cytoplasmic ratio, clearly differentiate these tumors from immunoblastic lymphomas that represent a monotonous proliferation of large cells with a large nucleus with a central unique nucleolus and a large amount of cytoplasm.⁵⁴

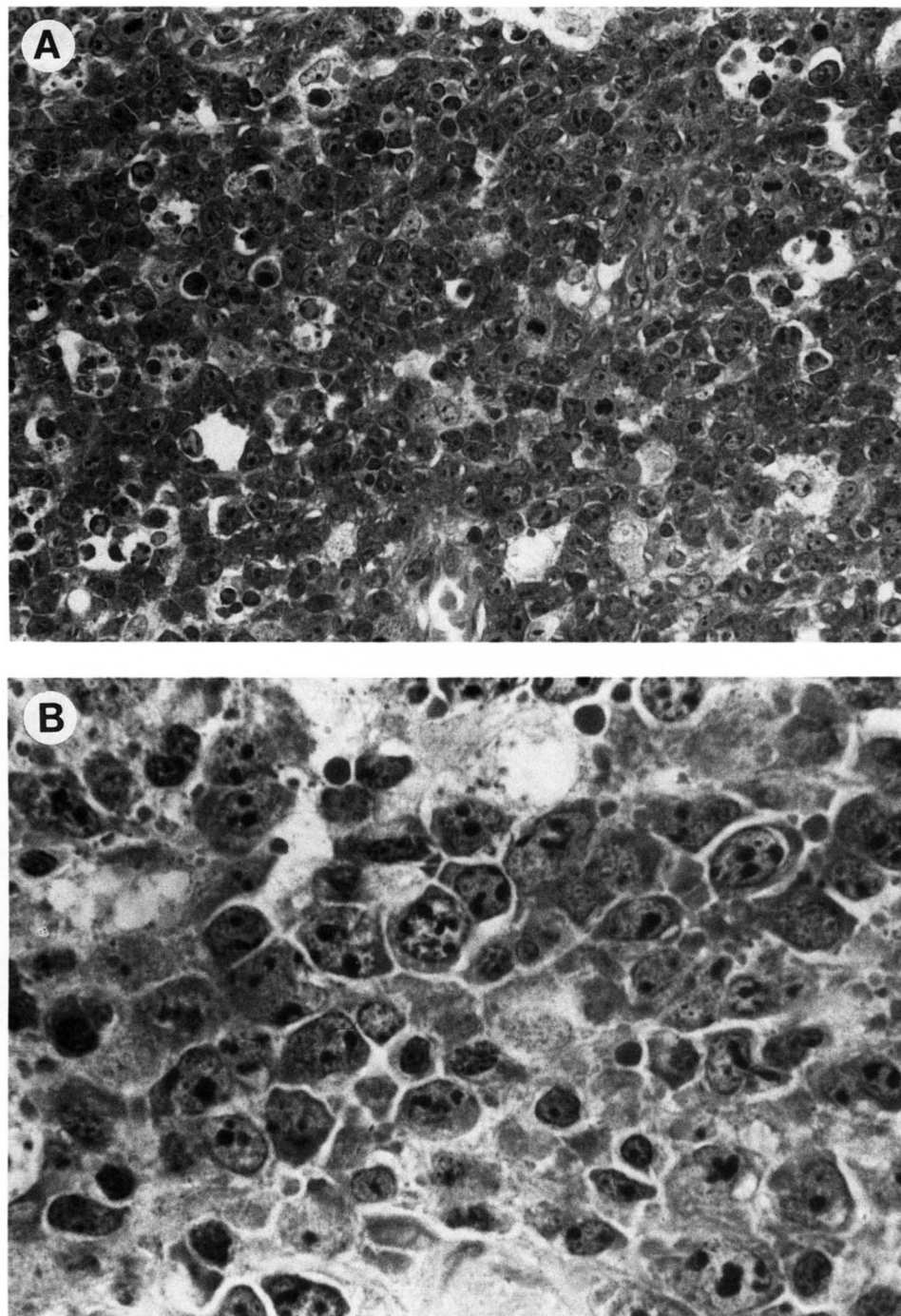


Fig 2. (A) Lymphomatous proliferation from case 8, composed of large cells with regularly disposed macrophage cells, giving rise to a starry sky pattern. Giemsa staining, original magnification $\times 400$. (B) Small part of the same tumor proliferation showing cells of various sizes. One can observe large cells with large central nucleoli and chromatin reminiscent of BL cells. Smaller cells resemble small noncleaved cells of Burkitt type. Giemsa staining, original magnification $\times 1,000$.

Among the 14 tumors studied here, 7 had the characteristic morphologic features of BL. All 7 tumors were of monoclonal origin; 6 showed a *c-myc* rearrangement and 4 harbored EBV DNA sequences. Case 1 was clearly monoclonal with regard to Ig and *c-myc* rearrangements. However, it showed more than one band after hybridization with the 1.9-kb *Xho* I probe. This shows that additional bands detected by this probe have to be interpreted with caution. They are not indicative for oligoclonality or polyclonality per se. There is a number of reasons why monoclonal tu-

mors may harbor more than one EBV-terminal fragment. One obvious reason is the coexistence of episomal and integrated copies as recently reported for Burkitt's lymphoma cells.⁵⁷ Another possibility that is difficult or impossible to exclude is homologous recombination among individual episomal genomes. Finally, reinfection of cells carrying already EBV genomes has been reported to occur in vitro.⁵⁸

Our data confirm previous studies showing the presence of EBV in about one-half of the BL cases in HIV⁺ individuals^{1,28,31} (Table 3). Remarkably, neither of the patients with

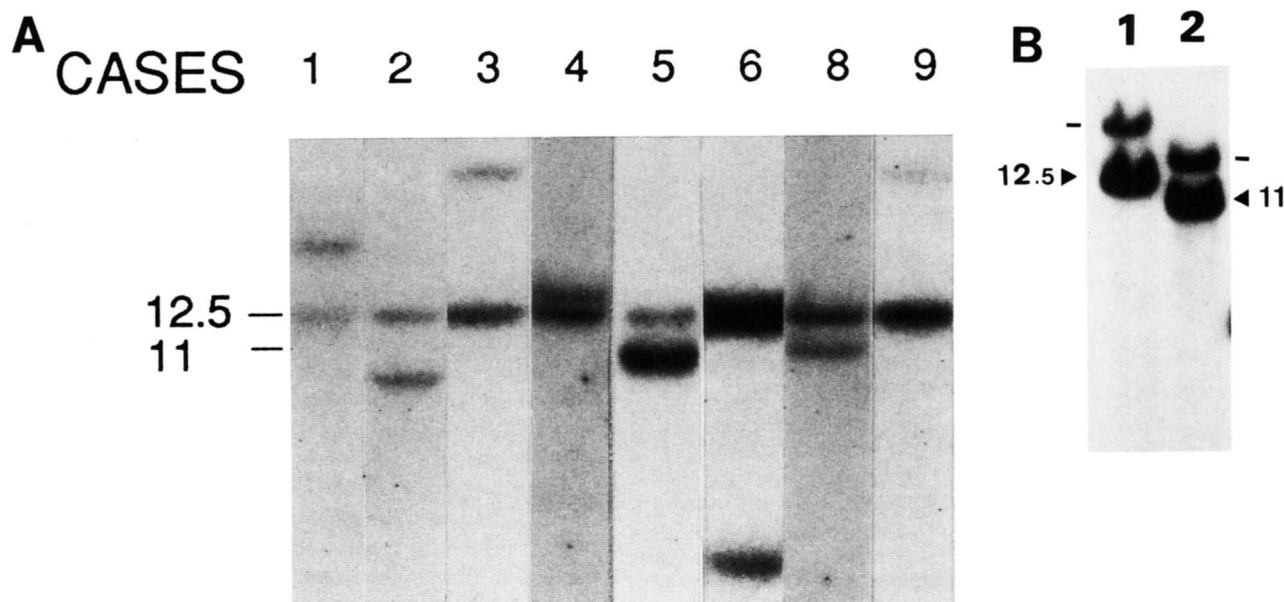


Fig 3. *c-myc* rearrangements. (A) DNA of all cases except case 5 were digested with *Eco*RI. DNA of the case 5 was digested with *Hind*III. After digestion, DNA was separated by electrophoresis and hybridized with a 1.3-kb *Cla*I-*Eco*RI *c-myc* exon 3 probe. Fragment sizes are given in kilobases (kb). (B) Southern blot analysis of case 9. DNA was digested with *Eco*RI (lane 1) and *Hind*III (lane 2), separated by electrophoresis and hybridized with a *c-myc* exon 3 probe. Arrows indicate germline configuration. Dashes indicate rearranged fragments. Fragment sizes are given in kilobases (kb).

BL presented with opportunistic infections or Kaposi sarcoma at the time of diagnosis (Table 3). This is in line with the observation of Kalter et al³ that BL is often an early or even the first manifestation of AIDS.

Four of 6 lymphomas with morphologic features of IL as well as the case diagnosed as lymphoproliferation were associated with EBV and were devoid of *c-myc* rearrangement. Three of them were polyclonal and 2 were monoclonal according to the analyses of the Ig gene rearrangements. The polyclonal cases exhibited a comparatively small number of viral genome copies per cell and it remains an open question as to whether in fact all cells carried the viral DNA within the pathologic lesions. However, even if the EBV load is low in these lymphoproliferations compared with the monoclonal cases including EBV⁺ Burkitt lymphomas, the detection

of viral sequences within a clinical specimen by conventional Southern blotting is indicative of an EBV-associated lymphoproliferation. In 50 HIV⁺ patients with persistent generalized lymphadenopathy, it has not been possible to detect EBV by conventional Southern blotting.⁵⁹ EBV has only been detected in persistent generalized lymphadenopathy from HIV-infected patients by polymerase chain reaction (PCR).⁶⁰

Clonality was studied not only by Ig gene rearrangement analyses, but also using an EBV terminal repeats specific probe. Analyses of two of the polyclonal cases with the terminal repeat probe of EBV showed a smear with one band predominating (Fig 6C). At first sight, this suggested the presence of a minor occult clonal population within the polyclonal lymphoproliferations that remained undetected by Ig gene rearrangement analysis. However, this conclusion is unlikely to be correct for the following reasons. Herpes viruses carry quite variable numbers of terminal repeats at the ends of their linear viral genome. However, the variation in terminal repeat copy number is much smaller if the number of terminal repeats from the left and right end of individual linear DNA molecules is compiled.^{61,62} The reason is probably that only DNA molecules within a given range of length can be packaged. Circular genomes contain the terminal repeats from both ends. Therefore, the number of repeats is less variable than the number of repeats from individual ends. Because the number of repeats follows a Poisson distribution, molecules with an average number of repeats will predominate. This is exactly what has been observed by us and others, ie, a minor band in the middle of a smear (Fig 6C).⁵⁰ Therefore, the existence of a band on the

Table 2. Chromosomal Breakpoints of Rearranged Tumors

Case No.	<i>c-myc</i>	IgH Locus
1	+	ND
2	+	S μ
3	+	ND
4	+	JH
5	+	S μ
6	+	ND
8	+	JH
9	+	S μ

Abbreviations: +, rearrangement within the 12.5-kb *Eco*RI fragment carrying *c-myc*; JH, breakpoint occurs probably in the JH region of the IgH locus; S μ , breakpoint occurs in the S μ region of the IgH locus; ND, breakpoint has not been identified by Southern analysis.

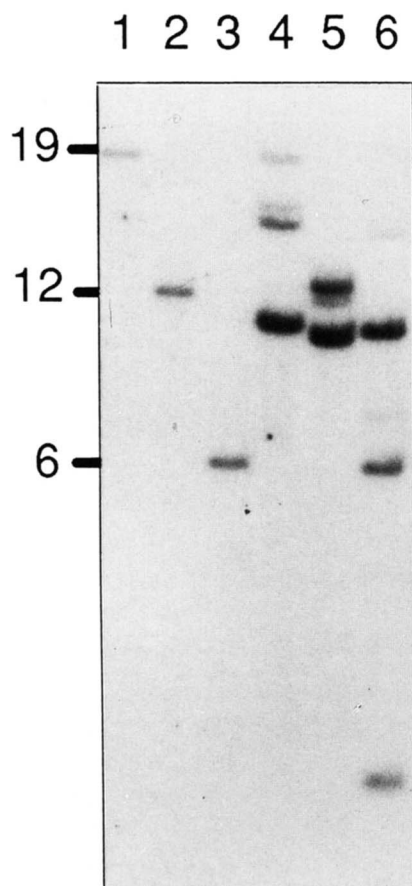


Fig 4. Southern blot analysis of case 8 using the JH gene as a probe. Fibroblasts are used as control. DNAs were digested with *EcoRI* (lanes 1 and 4), *HindIII* (lanes 2 and 5), and *Xba I* enzymes (lanes 3 and 6), and hybridized with a 3.1-kb *EcoRI-HindIII* JH probe. Lanes 1, 2, 3 represent the germline configuration (fibroblasts). Lanes 4, 5, 6 represent DNA digestions of case 8. Fragment sizes are given in kilobases (kb).

background of an homogeneously distributed smear cannot be taken as definite evidence for the existence of an occult clonal population, even though this interpretation has been proposed and cannot be formally ruled out.⁵⁰ As a result, the analysis of Ig gene rearrangements is more reliable and remains the method of choice.

The two monoclonal cases of IL developed in highly immunosuppressed patients: case 10 occurred in a patient with AIDS symptoms, whereas the other monoclonal case occurred in a patient with an extremely low count of CD4⁺ peripheral blood lymphocytes (33/mm³). The two polyclonal IL cases and the case of lymphoproliferation (case 14) are very similar to lymphoproliferations in transplant recipients in which EBV-infected B cells proliferate in vivo, as a consequence of severe immunosuppression.

Two lymphomas associated with EBV and typed as IL possessed rearrangements of the *c-myc* gene. These rearrangements were confirmed using several enzymes excluding a restriction polymorphism. One case was composed of immunoblastic cells, whereas the other was composed of a

tumor sharing features of BL and IL. The development of this tumor was preceded by a generalized reactive lymphadenopathy, as often reported for BL.^{1,3} These two lymphomas were the only tumors with a rearranged *c-myc* gene that appeared in patients with extremely advanced immunodepression (Table 3).

Only few large studies have investigated the presence of chromosomal translocations and/or *c-myc* rearrangement in immunoblastic lymphomas in the nonimmunosuppressed population. The overall frequency of t(8;14) (q24;q32) translocations in IL was reported to be 1 in 42 cases at the Fifth International Workshop on Chromosomes in Leukemias and Lymphomas,⁵² although two reports in the literature described higher frequencies.^{63,64} No data were presented on the HIV status of these cases. Within a large series of diffuse large-cell lymphomas for which karyotypic as well as *c-myc* rearrangement data were available, two cases of immunoblastic B-cell lymphomas with t(8;14) translocations and *c-myc* rearrangement were described.³⁵ Of these, one arose in an HIV-infected individual. For the second, the HIV status was not presented. Furthermore, association with EBV has not been studied. Another case of an immunoblastic lymphoma with *c-myc* rearrangement and associated with EBV was described in an AIDS patient.³¹

Taking into account the additional two cases of monoclonal immunoblastic lymphomas with *c-myc* rearrangement presented here, we may conclude that immunoblastic lymphomas with *c-myc* rearrangement can be detected to a small although significant percentage in HIV⁺ individuals, but are exceptional outside the context of HIV infection.

Two hypothesis can be proposed to explain the pathogene-

Table 3. Immune Status of Patients at the Time of Diagnosis and Characteristics of the Tumors

Case No.	OI	KS	CD4	Diagnosis	Clonality*	<i>c-myc</i>	EBV†
1	—	—	ND	BL	M	R	+
2	—	—	ND	BL	M	R	—
3	—	—	669	BL	M	R	—
4	—	—	ND	BL	M	R	+
5	—	—	224	BL	M	R	+
6	—	—	230	BL	M	R	—
7	—	—	150	BL	M	G	+
8	+	—	ND	IL	M	R	+
9	+	—	33	IL	M	R	+
10	+	+	7	IL	M	G	+
11	—	—	297	IL	P	G	+
12	—	—	ND	IL	P	G	+
13	—	—	33	IL	M	G	+
14	—	—	348	LP	P	G	+

CD4⁺ lymphocytes: (N) 729 ± 253/mm³.

Abbreviations: OI, opportunistic infections; KS, Kaposi sarcoma; BL, Burkitt's lymphoma; IL, immunoblastic lymphoma; LP, lymphoproliferation with plasmacytic differentiation; R, rearranged; G, germline; M, monoclonal; P, polyclonal; ND, not done.

* Results on clonality are based on Southern blots hybridized with JH, C_μ, and C_κ probes, which in all cases gave concordant results.

† Analyzed with an *Bam*HI-W as well as the 1.9-kb *Xho*I probe.

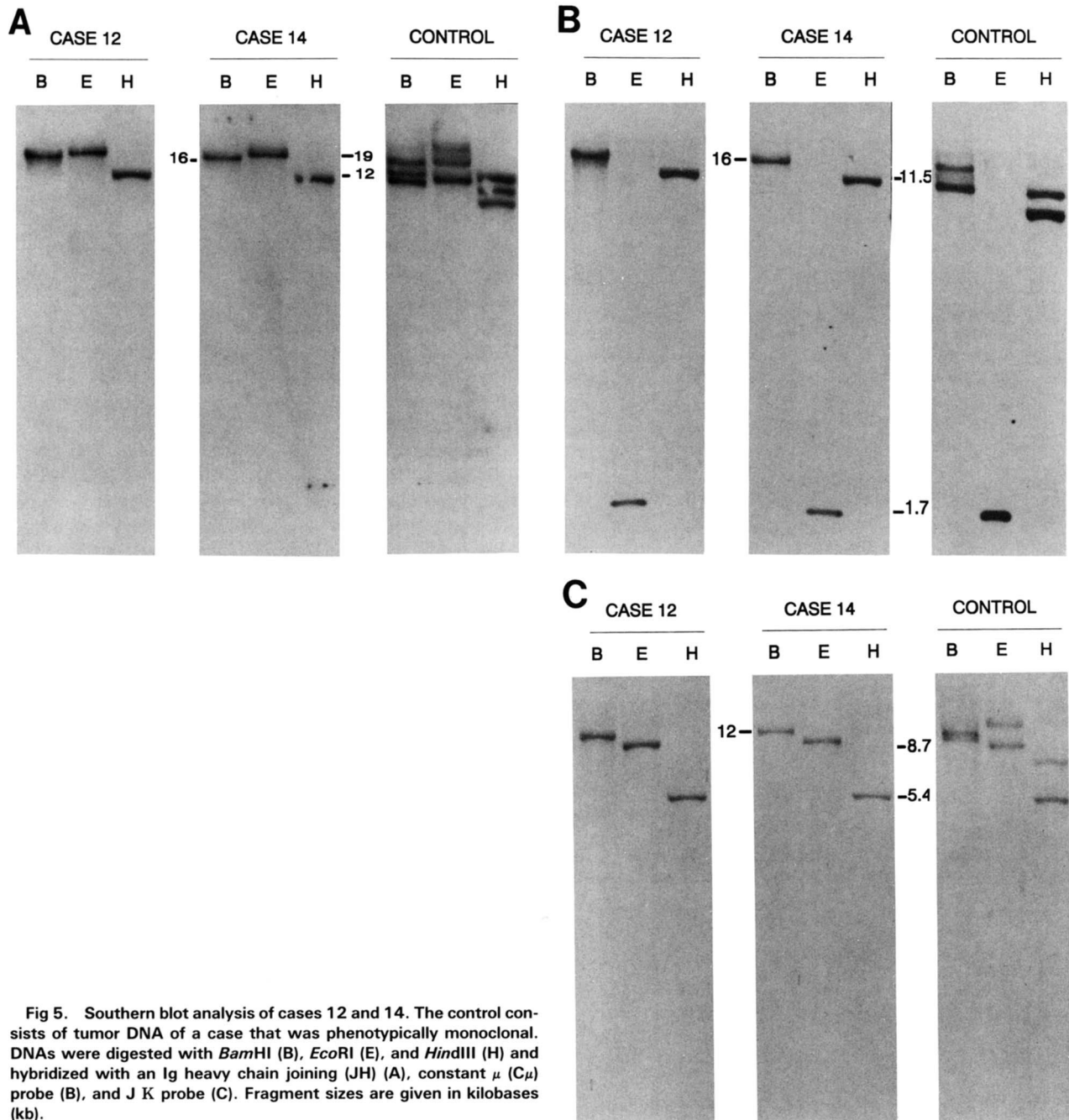


Fig 5. Southern blot analysis of cases 12 and 14. The control consists of tumor DNA of a case that was phenotypically monoclonal. DNAs were digested with *Bam*HI (B), *Eco*RI (E), and *Hind*III (H) and hybridized with an Ig heavy chain joining (JH) (A), constant μ ($C\mu$) probe (B), and J K probe (C). Fragment sizes are given in kilobases (kb).

sis of these tumors. They may represent a new disease entity of HIV-infected patients, as proposed for the EBV⁻ peripheral polyclonal lymphomas,¹⁰ or they may represent a modification of tumors also encountered in patients without AIDS. We favor the latter hypothesis for the following reasons. In vitro, studies have clearly shown that BL cells have the potential to progress towards different morphotypes. Tumor cells, suspended from a biopsy and seeded into culture, present as a uniform population of small cells. However, after only a few passages in culture, they may give rise to cells with quite different morphology.⁶⁵ Some tumors re-

tain the typical morphology of BL in vitro, others evolve towards a morphology indistinguishable from IL. EBV⁻ cell lines were more stable in culture in maintaining small size (16 of 19 EBV⁻ cell lines), whereas EBV⁺ lines displayed a much higher tendency to develop in large cells (19 of 33 cell lines). Of the cases with large irregular morphology, 7 of 8 were EBV⁺, and progression to the immunoblastic morphology has been observed exclusively within EBV⁺ cases. This finding suggests an active role of the virus in in vitro, cultured cells for morphologic progression towards increased cell size and irregular or immunoblastic morphotype. The

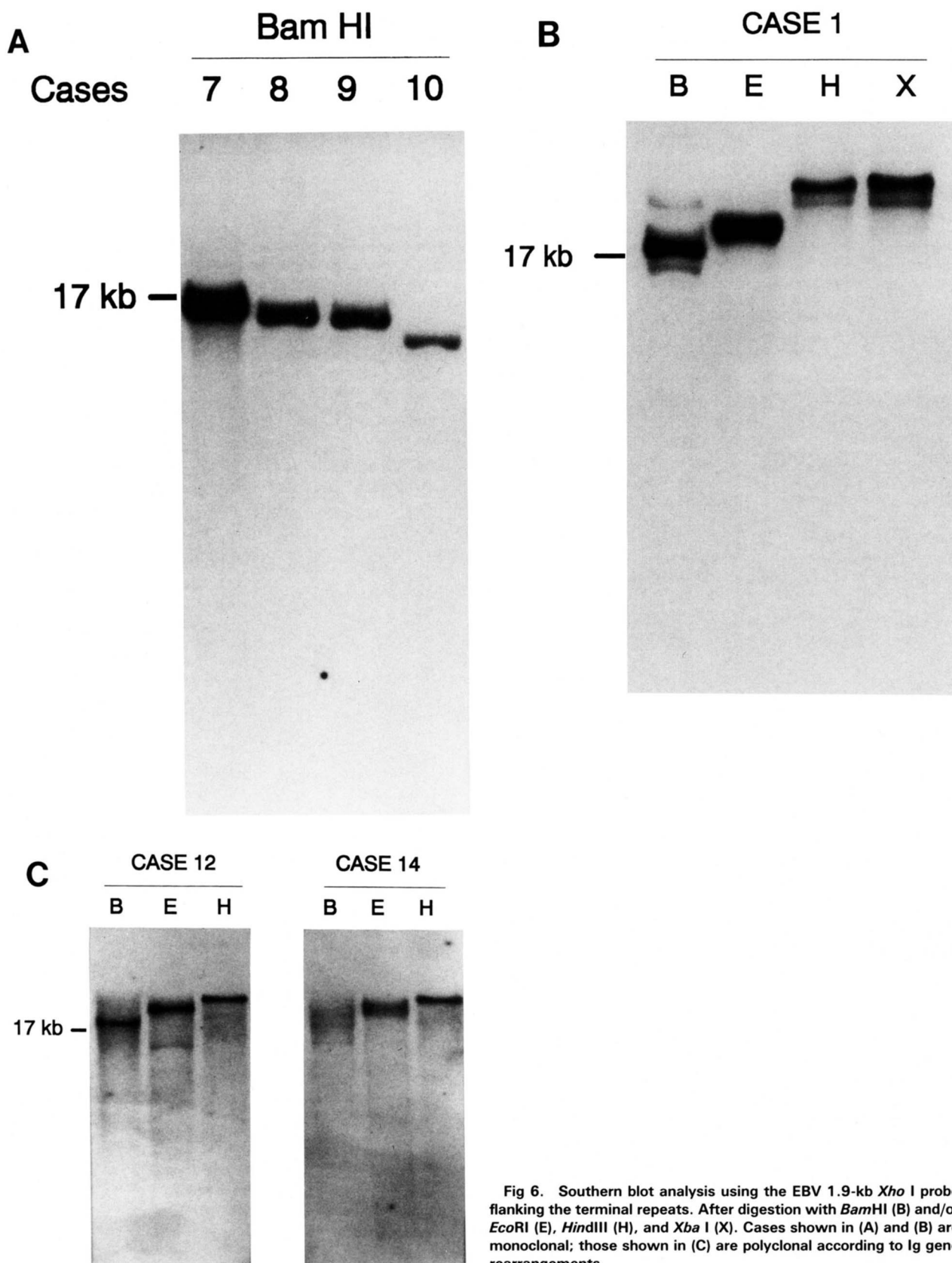


Fig 6. Southern blot analysis using the EBV 1.9-kb *Xho* I probe flanking the terminal repeats. After digestion with *Bam*HI (B) and/or *Eco*RI (E), *Hind*III (H), and *Xba* I (X). Cases shown in (A) and (B) are monoclonal; those shown in (C) are polyclonal according to Ig gene rearrangements.

change in morphology most likely reflects the change in the phenotype of Burkitt lymphoma cells after explantation of the tumor cells into culture described by Rickinson et al.⁶⁶⁻⁶⁹

Thus, we hypothesize that the two EBV⁺ tumors with a *c-myc* rearrangement have adopted morphologic features of IL caused by the severe perturbation of the immune system in these patients. Immunohistologic analyses are in progress to correlate the morphologic features of these tumors with the pattern of cell-surface antigen as well as viral-gene expression. Another interesting correlation has recently been observed between morphology and interleukin-6 (IL-6) expression in lymphomas that had developed in HIV seropositive and negative patients.⁷⁰ A high number of IL-6 producing stromal cells has been observed in IL but not in BL. Remarkably, the case with a morphology intermediate between IL and BL reported here has been included in this study and was found to harbor a high number of IL-6-expressing cells. This raises the question as to whether IL-6 is responsible for morphologic transformation towards immunoblasts. IL-6 receptor has been reported to be expressed in immunoblasts. It will also be interesting to see whether EBV can modulate expression of this receptor.

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APPENDIX

Members of the French Study Group of Pathology for HIV-Associated Tumors. Groupe hospitalier Pitie-Salpetriere, Paris: D. Henin, J. F. Foncin, L. Marelle, M. Raphael; Hopital de l'Hotel-Dieu, Paris: J. Diebold, J. Audoin, S. Prevot; Hopital Edouard Herriot, Lyon: O. Gentilhomme, F. Berger, P. A. Bryon; Hopital Cochin, Paris: M. Tulliez; Institut Curie, Paris: J. Dumont; Hopital Henri Mondor, Paris: P. Gaulard; Hopital A. Morvan, Brest: J. Briere; Institut Paoli-Calmette, Marseille: N. Horshowski; Hopital Necker, Paris: N. Brousse; Hopital St Andre, Bordeaux: J.P. Merlio; Hopital Purpan, Toulouse: G. Del-sol.

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HJ Delecluse, M Raphael, JP Magaud, P Felman, IA Alsamad, GW Bornkamm and GM Lenoir

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