Molecular Analysis of Immunoglobulin Genes in Primary Intraocular Lymphoma

Sarah E. Coupland, Michael Hummel, Hans-Henning Müller, and Harald Stein

PURPOSE. To analyze somatic hypermutations in clonally rearranged IgH chain variable (V) genes of primary intraocular lymphoma (PIOL), to identify the differentiation stage of B-PIOL cells.

METHODS. Sixteen cases of PIOL were diagnosed on the basis of morphology and immunohistology. In six patients, simultaneous cerebral lymphomatous involvement was known; stereotactic biopsy specimens were investigated in three cases. A polymerase chain reaction (PCR) was performed on DNA extracted from vitrectomy specimens or from paraffin-embedded sections, to amplify the clonally rearranged heavy-chain immunoglobulin (IgH) genes. The isolated PCR products were sequenced and compared with published VH germ-line segments to determine the VH usage and number of somatic mutations in the complementarity-determining region (CDR)2 and framework region (FR)3.

RESULTS. All tumors exhibited clonal IgH rearrangements. Of the eight sequenceable cases, four had the VH4-34 gene segment, two the VH3-23, one the VH3-7, and another the VH3-30. The pattern of somatic mutations indicated selection of PIOL cells for expression of a functional antibody. The mean frequency of somatic mutations detected for the IgH gene was very high (14.5%). In three oculocerebral lymphomas, the identical B-cell clone was demonstrated in ocular and cerebral tissues.

CONCLUSIONS. The data suggest that PIOLs (1) are derived from mature B-cells that have undergone the germinal center reaction and (2) are closely related to primary cerebral nervous system lymphoma (PCNSL), due to their high mutation frequency of VH region genes. The close relationship between PIOL and PCNSL is underlined by demonstration of the same VH segment (VH4-34) in three of six cases of oculocerebral lymphoma. (Invest Ophthalmol Vis Sci. 2005;46:3507–3514) DOI:10.1167/iovs.05-0401

Primary intraocular lymphoma (PIOL) is a high-grade malignant non-Hodgkin lymphoma (NHL) usually of B-cell type, which affects the retina, vitreous and/or the optic nerve.1 PIOL is considered a subtype of primary central nervous system lymphoma (PCNSL), due to their high mutation frequency of VH region genes. The close relationship between PIOL and PCNSL is underlined by demonstration of the same VH segment (VH4-34) in three of six cases of oculocerebral lymphoma. (Invest Ophthalmol Vis Sci. 2005;46:3507–3514)

From the Department of Pathology, Charité-University Hospital Berlin, Campus Benjamin Franklin, Germany.
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Corresponding author: Sarah E. Coupland, Department of Pathology, Charité-University Medicine Berlin, Campus Benjamin Franklin, Hindenburgdamm 30, D-12200 Berlin, Germany; sarah.coupland@charite.de.
To gain further insight into the nature of the IgVH
tations in the VH region of a patient with oculocerebral lym-
phomas,2 we reported the findings of an analysis of the somatic muta-
tions in PIOL.29 –32 Recently, we examined the VH genes in PIOL, we investigated 16 cases of PIOL using IgH-PCR.

Patients and Samples
Sixteen cases of PIOL were taken from the files of the Department of General Pathology and Reference Center for Hematopathology, Charité-University Medicine Berlin. These cases consisted of nine choroidal melanomas and seven vitrectomy specimens. In PCNSL,27 whereas an overrepresentation of VH gene families in peripheral DLBCL remains controversial.28

MATERIALS AND METHODS

Patients and Samples
Sixteen cases of PIOL were taken from the files of the Department of General Pathology and Reference Center for Hematopathology, Charité-University Medicine Berlin. These cases consisted of nine choroidal biopsy specimens at 500 rpm for 5 minutes and concentrating the cells onto glass slides. These were subsequently air dried and stained using conventional stains (e.g., May-Grünwald-Giemsa) and immunocytoLOGY.

ImmunocytoLOGY and Immunohistochemistry
The primary monoclonal antibodies used for immunocytoLOGY included CD79a and CD3 (Table 1). Polyclonal antibodies were used to test the expression of the Ig chains \( \kappa \) and \( \lambda \). The visualization of the antibodies was obtained using the alkaline phosphatase-antialkaline phosphatase (APAAP)25 and peroxidase-antiperoxidase (PAP)26 methods.

For immunostaining of paraffin-embedded tissues, sections (4 \( \mu m \)) were cut from paraffin blocks, dewaxed, rehydrated, and subjected to heat-induced epitope retrieval methods before incubation with the appropriate antibodies. Sections were immersed in sodium citrate buffer solution at pH 6.0 and were subsequently heated in a pressure cooker for antigen retrieval.37 After they were rinsed in running water and Tris-buffered saline, the sections were incubated with the primary antibodies listed in Table 1. Polyclonal antibodies were applied to examine the expression of IgH and IgL. The antibodies were made visible with an indirect immunoperoxidase method,30 for the antibodies to the heavy and light chains, whereas the APAAP method was used to demonstrate the binding of the remaining antibodies.39 Appropriate negative and positive tissue control experiments were performed with each investigation.

The tumor cells of PIOLs were considered (1) positive (+) when >75% of the tumor cells were immunoreactive for the examined antibody; (2) positive/negative (+/−) when 50% to 74% of the tumor cells were immunoreactive; (3) negative/positive (−/+ ) when 25% to 49% of the tumor cells showed immunoreactivity; and negative (−) when <24% of the tumor cells demonstrated immunoreactivity. The number of Ki-67-positive cells was determined by counting the number of cells with clear nuclear positivity for this marker per 100 cells in three high-power fields (HPFs; 40× objective, BH2; Olympus, Tokyo, Japan). The resultant mean of the three HPFs is expressed as a percentage, representing the growth fraction of the tumor.

Clinical outcome data were available for all samples (Table 2). An informed consent were obtained according to the Declaration of Helsinki. The research was approved by the institutional review board.

PCR Amplification Method
DNA was extracted after dewaxing of 20-\( \mu m \)-thick paraffin-embedded sections, as well as from the centrifuged vitreectomy specimens, with a DNA minikit (QiAmp; Qiagen, Hilden, Germany) according to the manufacturer’s recommendations. The IgH PCR was performed with the primer sets FR1, FR2, and FR3 (BioMed-2) in three separate single-step PCRs without reamplification, each consisting of 50 cycles (96°C for 15 seconds, 60°C for 40 seconds, and 72°C for 60 FR1, 45 FR2, and 30 FR3 seconds), as described previously.
Reactive tonsils and reactive vitritis specimens were used as the polyclonal control, whereas DNA from the B-cell lines Raji and Daudi served as the monoclonal control. Sufficient negative control samples were included. Reproducible dominant PCR products of the same size indicated monoclonality. The PCR products were analyzed on an automated DNA sequencer (model 310A; Applied Biosystems, Inc. [ABI], Foster City, CA) to allow a highly precise dose-by-dose separation of the amplificates. For this purpose, fluorescence (FAM)-labeled JH (JH22) oligonucleotides were used.

**DNA Sequence Analysis**

For DNA sequencing of the dominant IgH PCR products, a second PCR was performed in which the fluorescence-labeled JH22 primer was replaced by an unlabeled primer of the same sequence. The resultant unlabeled amplificates were isolated after gel electrophoresis by diffusion into distilled water overnight. The isolated PCR products were directly subjected to DNA sequencing with the two respective IgH PCR primers in two separate sequencing reactions. The sequencing reactions were run on an automated DNA sequencer (model 377; ABI) and analyzed. Sequences were compared with published VH germ line sequences with the help of the IMGT blast search (http://imgt.cines.fr:8104). Codons were numbered according to Kabat et al. The putative antigen selection in the tumor cell IgH rearrangements was determined by the ratio of replacement to silent mutations (R/S) in the CDR and FR regions. A rearrangement was considered to be antigen selected when the R-to-S ratio in the CDR2 region was higher than 2.9 and the R-to-S ratio in the FR3 region was lower than 1.5.

**RESULTS**

**Patient Group**

The patient group examined consisted of eight women and eight men with an age range of 40 to 84 years (mean, 65.0; Table 2). The clinical symptoms, treatment, and current status of the patients are summarized in Table 2. In seven patients, a vitreous aspirate only was performed to reach diagnosis. In eight patients, both a vitreous aspirate and a chorioretinal biopsy were performed within the same surgical procedure. In one patient, a chorioretinal biopsy only was performed.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Gender</th>
<th>CNS Involvement</th>
<th>Period between CNS and Ocular Lymphoma Manifestations</th>
<th>Symptoms and Signs</th>
<th>Treatment</th>
<th>Current Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55</td>
<td>M</td>
<td>Yes</td>
<td>8 Months (initial PCNSL)</td>
<td>Visual disturbances; decreased vision</td>
<td>HD MTX; Radiotherapy; HD-Ara-C</td>
<td>Deceased</td>
</tr>
<tr>
<td>2</td>
<td>71</td>
<td>F</td>
<td>Yes</td>
<td>20 Months (initial PCNSL)</td>
<td>Recurrent visual disturbances OD</td>
<td>Intraocular Triamcinolon; HD MTX; Topotecan Radiotherapy</td>
<td>Alive in PR</td>
</tr>
<tr>
<td>3</td>
<td>82</td>
<td>F</td>
<td>No</td>
<td>Not applicable</td>
<td>Decreased vision OD; steroid-resistant uveitis</td>
<td>Deceased</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>76</td>
<td>F</td>
<td>No</td>
<td>Not applicable</td>
<td>Unilateral steroid-resistant uveitis</td>
<td>Radiotherapy</td>
<td>Deceased</td>
</tr>
<tr>
<td>5</td>
<td>73</td>
<td>M</td>
<td>No</td>
<td>Not applicable</td>
<td>Steroid-resistant uveitis</td>
<td>HD MTX</td>
<td>Deceased</td>
</tr>
<tr>
<td>6</td>
<td>77</td>
<td>M</td>
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<td>Not applicable</td>
<td>Bilateral visual disturbances; vitritis; subretinal infiltrates</td>
<td>CHOP</td>
<td>Deceased</td>
</tr>
<tr>
<td>7</td>
<td>83</td>
<td>F</td>
<td>No</td>
<td>Not applicable</td>
<td>Pain OD; decreased vision</td>
<td>Trofofosfamid</td>
<td>Deceased</td>
</tr>
<tr>
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<td>65</td>
<td>M</td>
<td>Yes</td>
<td>24 Months (initial PCNSL)</td>
<td>Bilateral vitreous infiltrates</td>
<td>MTX</td>
<td>Alive in CR</td>
</tr>
<tr>
<td>9</td>
<td>52</td>
<td>M</td>
<td>Yes</td>
<td>17 Months (LA); 27 months (RA) (initial PCNSL)</td>
<td>Decreased vision OS; followed 10 months later with decreased vision OD</td>
<td>HD MTX; Ifosofamid</td>
<td>Alive in PR</td>
</tr>
<tr>
<td>10</td>
<td>81</td>
<td>F</td>
<td>Yes</td>
<td>35 Months (initial PCNSL)</td>
<td>Decreased bilateral vision</td>
<td>HD MTX</td>
<td>Alive in CR</td>
</tr>
<tr>
<td>11</td>
<td>76</td>
<td>M</td>
<td>No</td>
<td>Not applicable</td>
<td>Decreased bilateral vision; steroid-resistant uveitis</td>
<td>Trofofosfamid</td>
<td>Alive in CR</td>
</tr>
<tr>
<td>12</td>
<td>73</td>
<td>F</td>
<td>No</td>
<td>Not applicable</td>
<td>Decreased unilateral vision</td>
<td>Ifosofamid</td>
<td>Alive in CR</td>
</tr>
<tr>
<td>13</td>
<td>71</td>
<td>M</td>
<td>Yes</td>
<td>20 Months (initial PCNSL)</td>
<td>Decreased vision; steroid-resistant uveitis</td>
<td>Radiotherapy</td>
<td>Alive in PR</td>
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<tr>
<td>14</td>
<td>84</td>
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<td>HD MTX</td>
<td>Alive in PR</td>
</tr>
<tr>
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<td>58</td>
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<td>HD MTX</td>
<td>Alive in PR</td>
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<tr>
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<td>40</td>
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<td>No</td>
<td>Not applicable</td>
<td>Bilateral uveitis</td>
<td>HD MTX</td>
<td>Alive in PR</td>
</tr>
</tbody>
</table>

HD MTX, high-dose methotrexate; CHOP, cyclophosphamide, hydroxydaunorubicin (adriamycin), vincristine (Oncovin) and prednisone; CR, complete remission; PR, partial remission.

**Conventional Histology and Immunohistochemistry**

The 15 vitreous aspirates consisted of mature inflammatory cells, medium to large neoplastic lymphocytes, and lyric cells. The cells expressed the B-cell antigens CD79a, CD20, and PAX5/BSAP. Conventional histology of the nine chorioretinal...
biopsy specimens demonstrated an infiltrate of atypical lymphocytes in the retina and adjacent choroid. The neoplastic cells were medium to large, with basophilic cytoplasm, oval-shaped nuclei, and conspicuous nucleoli (Fig. 1). The tumor cells were positive for the above-mentioned B-cell antigens as well as for BCL2 (partial), BCL-6 (partial) and MUM1/IRF4 (Fig. 1). The tumor cells of three PIOLs expressed only CD10 (Table 3). A monotypical expression of an IgL and/or IgH was demonstrated in most cases, and a large growth fraction (average, 84%) using the MIB1 antibody was determined (Fig. 1; Table 3). The reactions against CD30 and Epstein-Barr virus (LMP1) were negative.

The three examined stereotactically obtained cerebral biopsy specimens (patients 8, 9, and 10) displayed diffuse and perivascular neoplastic infiltrates consisting of medium-sized blasts (Fig. 1D). These showed an immunophenotype similar to that of the respective PIOL infiltrates.

**PCR and Sequence Analysis**

In eight of the 16 PIOL samples, sufficient amount of PCR products was obtained allowing for sequencing. In the samples where monoclonal products were obtained with FR3 only, no sequencing was performed because of limited VH sequence data.

**TABLE 3. Morphological Subtype and Immunophenotype of the Investigated PIOL**

<table>
<thead>
<tr>
<th>Case</th>
<th>Biopsy Source</th>
<th>CD79a</th>
<th>BSAP</th>
<th>CD20</th>
<th>IgM</th>
<th>BCL2</th>
<th>BCL6</th>
<th>IRF4</th>
<th>CD10</th>
<th>CD30</th>
<th>Ki67</th>
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<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Neg</td>
<td>Neg</td>
<td>80%</td>
</tr>
<tr>
<td>2</td>
<td>V+R</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Neg</td>
<td>Neg</td>
<td>80%</td>
</tr>
<tr>
<td>3</td>
<td>V+R</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Neg</td>
<td>Neg</td>
<td>80%</td>
</tr>
<tr>
<td>4</td>
<td>V+R</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Neg</td>
<td>Neg</td>
<td>90%</td>
</tr>
<tr>
<td>5</td>
<td>V+R</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Neg</td>
<td>Neg</td>
<td>90%</td>
</tr>
<tr>
<td>6</td>
<td>V+R</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Neg</td>
<td>Neg</td>
<td>90%</td>
</tr>
<tr>
<td>7</td>
<td>V+R</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Neg</td>
<td>Neg</td>
<td>90%</td>
</tr>
<tr>
<td>8</td>
<td>V+R</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
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<td>Neg</td>
<td>70%</td>
</tr>
<tr>
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<td>V</td>
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<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
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<td>90%</td>
</tr>
<tr>
<td>10</td>
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<td>Pos</td>
<td>Pos</td>
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<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Neg</td>
<td>80%</td>
</tr>
<tr>
<td>11</td>
<td>V</td>
<td>Pos</td>
<td>NP</td>
<td>Pos</td>
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<td>V</td>
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<td>NP</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>NP</td>
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<td>90%</td>
</tr>
<tr>
<td>14</td>
<td>V</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Neg</td>
<td>80%</td>
</tr>
<tr>
<td>15</td>
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<td>NP</td>
<td>90%</td>
</tr>
<tr>
<td>16</td>
<td>V</td>
<td>Pos</td>
<td>NP</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>NP</td>
<td>NP</td>
<td>90%</td>
</tr>
</tbody>
</table>

All cases were WHO subtype DLBCL. V, vitreous biopsy; R, chorioretinal biopsy; V+R, combined vitrectomy and chorioretinal biopsy; NP, not performed (due to limited tissue).

**FIGURE 1.** (A) A cytospin specimen of the vitrectomy specimen from patient 10 showing blasts with large nuclei and prominent nucleoli (MGG staining). (B) CD20-positive tumor cells with erythrocytes in the background (APAAP staining). (C) Neoplastic B cells demonstrating a large growth fraction (APAAP staining, Ki-67 antigen). (D) Histologic section of a stereotactic biopsy specimen of the corresponding cerebral lymphoma in patient 10, demonstrating the typical perivascular infiltration of the lymphoid blasts (MGG staining). Original magnification: (A, D) ×40; (B) ×60; (C) ×20.
information. In three of six PIOL cases in which oculocerebral lymphoma was known (patients 8, 9, and 10), identical clonal B-cell populations were demonstrated (Figs. 2A, 2B). Furthermore, in one patient, it was possible to demonstrate the identical B-cell clone in vitreous specimens taken from both eyes and in the cerebral biopsy (patient 9; Figs. 2B, 2C).

Results of the sequence analysis are summarized in Table 4. The lymphoma VH gene segments showed the highest homology to the germ-line genes of the VH4 and VH3 gene families. While the VH4-34 (also called HV-21 or DP63) gene of the VH4 gene family was used in four cases, the VH3-23 gene segment was used in two cases, the VH3-7 and the VH3-30 gene in one case each, respectively (Table 4). A high frequency of somatic mutation, ranging from 16 to 65 (average 38.57) was seen in PIOL. The mean mutation frequency was 14.5% (range, 6.5%-24.3%) of the VH genes.

The R-to-S ratio in FR1-3 was calculated for all in-frame IgH genes. This parameter indicates whether the corresponding B lymphocyte was selected for expression of a functional antibody. The R-to-S ratios for the FRs were determined as 1.3 (range, 0.2-2.3) for the IgH genes. According to this calculation, the ratios clearly indicate that the tumor cells or their precursors were selected for antibody expression, because selected B cells usually show RtoS ratios below 1.5 for the FRs.

**DISCUSSION**

The purpose of the present study was to investigate the differentiation stage of the neoplastic B-cells of PIOL, which develop in an environment that normally contains a very low number of lymphocytes and actively suppresses the proliferation of lymphocytes. To investigate, we performed IgH-PCR on tumor samples from 13 patients. All PIOLs of our series carried monoclone rearranged immunoglobulin heavy chain (IgH) genes. The DNA amplificates of eight cases could be sequenced and analyses demonstrated the introduction of numerous somatic mutations into the rearranged VH genes. These data suggest that PIOLs are derived from neoplastic B cells that have undergone a prolonged interaction in the microenvironment of the germinal center.

In the majority of PIOLs an intermediate to large number of mutations in the VH region, ranging from 16 to 65 (average, 37.38; 14.5%) were observed (Table 4). This average frequency significantly exceeds that of normal B cells (2%-3%) and that of most B-cell lymphomas (average, 7%). A similar high mutation frequency was reported for VH region genes in PCNSL, but differs from systemic DLBCL, the same histologic subtype as PIOL, which demonstrates variable mutation frequencies. The reasons for the differences between PIOL/PCNSL and systemic DLBCL remain unclear. The current findings of a high frequency of somatic mutations in the VH genes of PIOLs, together with the tumor cell phenotype (PAX5/BSAP, CD20+, BCL-6+/−, CD10−/−, MUM1/IRF4+/−) provide further evidence for the hypothesis that PIOLs are derived from mature B cells that have undergone a prolonged interaction in the microenvironment of the germinal center and are either at the late germinal center stage of differentiation or are early post-germinal-center B cells. This may explain the extensive loss of CD10 and the variable expression of BCL-6, both of which are normally expressed by germinal-center cells but not by post-germinal-center lymphocytes, as well as the positivity of MUM1/IRF4 (post-germinal-center marker) in PIOLs.

A limited germ line VH gene usage was seen in the development of PIOLs, with preferential expression of the VH3 and VH4 germ-line families. In particular, a biased inclusion of the VH4-34 gene segment by PIOLs became apparent. The VH4-34 gene is present in 4% to 7% of normal adult peripheral B cells in healthy adults and appears to be overexpressed in some autoimmune diseases and B-cell lymphomas. For example, the VH4-34 gene has been demonstrated to be mandatory for encoding the IgM proteins of cold agglutinin disease. In this case, the red blood cell I/A antigens bind to the FR1 of the immunoglobulin. This binding outside the CDRs is an indication of a B-cell superantigen. Preferential use of the VH4-34 gene has been reported in PCNSL, as well as in other lymphoma entities, such as high-grade mucosa-associated lymphoid tissue lymphoma, mantle cell lymphoma, and Burkitt lymphoma. Overrepresentation of the VH4-34 gene in peripheral DLBCL is controversial, however, with one study suggesting a biased presence of this gene, but the second not confirming the finding.

The relatively high usage frequency of the VH4-34 gene in PIOLs suggests a functional role of the Ig encoded by this gene in its development. Either of two mechanisms may underlie its
biased usage: an antigen-driven expansion or a superantigen expansion of VH4-34-encoded Ig, which may have autoreactive properties. The notion of an antigen-selected maturation of the tumor cells is supported by the R-to-S ratio's being >2.9 in the CDR regions and <1.5 in the FR3 region, which reflects counterselection of R mutations in the FRs and indicates that the tumor cells have been, if only temporarily, antigen selected for expression of a functional antibody. Evidence for such an antigen-selection process has been reported previously in PCNSL.

At present, the process of somatic hypermutation and antigen selection is believed to occur exclusively in germinal centers in peripheral lymphatic tissues (e.g., tonsil, mucosa-associated lymphatic tissue, and lymph nodes) only. Because intraocular and cerebral tissue is devoid of an organized germinal center structure, our data and others' findings imply that PIONs and PCNSLs are tumors that arise initially in an extraneural germinal center environment. Subsequent homing of the neoplastic B cells to the retina and/or to the central nervous system (CNS) may involve the development of a neurotropic cellular phenotype, or it may be a result of the influence of chemokine receptors and their ligands. In one of the examined cases (patient 9), there was evidence of intraclonal heterogeneity in the recurrent B-cell clone occurring in the contralateral eye, indicating that the mutation mechanism is possibly still active in the PIONs/PCNSLs in this patient (Fig. 2C). One may speculate that an antigen within the intraocular environment or in the CNS together with T cells and antigen-presenting cells supports ongoing mutations in these milieu. Although several viruses with the capacity to persist in cerebral and retinal tissue (e.g., polyomavirus and herpes viruses) have been thought to play a role in lymphomagenesis, an antigen has not been identified to date. Further research is necessary at the molecular level of PIONs/PCNSLs to understand their pathogenesis, possibly with the purpose of designing therapeutics that exploit the apparent immunoglobulin gene usage, perhaps in the form of engineered anti-idiotypic antibodies or other compounds that specifically target autoantibody-producing B cells.

Finally, in oculocerebral lymphoma, it is assumed on the basis of clinical, morphologic, and immunohistochemical findings that the cerebral and ocular infiltrations represent the same tumor. Recently, our group provided molecular biological evidence for the first time in the literature that the lymphomatous manifestations in oculocerebral lymphoma consist of the identical neoplastic B-cell population and that they derive from the same tumor precursor cell. In this study, we were able to demonstrate that the ocular and cerebral lymphomatous manifestations were derived from the same neoplastic clones in two additional oculocerebral cases of lymphoma (Fig. 2). These results underline the close relationship between PION and PCNSL.

In summary, the present study demonstrates that most PIONs, similar to cerebral counterparts, are derived from mature B cells that have undergone the germinal center reaction.
This detailed characterization of the molecular phenotype of P10L could provide further insight into their development, possibly having an influence on their future treatment strategies.

References


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