Antibodies to Herpes Group Viruses in Patients with Nasopharyngeal and Other Head and Neck Cancers

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Summary

Elevated Epstein-Barr virus antibody titers were found in cases of nasopharyngeal carcinoma in all racial and ethnic groups tested. Titers were highest in patients with active, advanced disease. Antibody titers to other herpesviruses were not increased above controls. Elevated EBV titers were found also in patients with epidermoid cancer of the nasal cavity and hypopharynx.

Introduction

The EBV has been found to be closely associated with Burkitt's lymphoma and NPC. The relationship of EBV to a 3rd cancer, Hodgkin's disease, is less clear-cut. EBV DNA has been demonstrated in every biopsy of Burkitt's lymphoma and NPC (17, 22), and in lymphoid cell lines derived from such tumors (4, 21).

The serological association between EBV and NPC, first established by Old et al. (18), has been strengthened by Henle et al. (12) and others (3, 5, 7, 15, 16) through use of the indirect immunofluorescence test. Virtually 100% of NPC patients have detectable antibody to EBV capsid antigen in high titer (≥1:160). There is no apparent difference in NPC, either in frequency of positive titers or height of such titers, between Chinese cases and other racial groups. Recently, Burkitt's lymphoma and nasopharyngeal patients have also been shown to possess antibody to EBV-induced early antigens (9, 10). In Chinese patients with nasopharyngeal cancer, the early antigens detected are of the anti-D type whereas, in Burkitt's lymphoma, the anti-R type of early antigens prevails (13). The height of titers of both viral capsid antigen and anti-D in NPC is related to the initial stage and activity of disease, decreasing in long-term survivors.

This study has been conducted to relate these previous studies on EBV to nasopharyngeal patients in several racial groups and to follow up a suggestion by Feorino et al. (5) that herpes simplex type 1 and varicella titers are also elevated in NPC patients.

Materials and Methods

All patients were selected from the files of the University of Southern California Cancer Surveillance Program or the California Tumor Registry. For confirmation of diagnosis in all cases, histopathological specimens were reviewed. Patients with NPC were staged according to the Queen Elizabeth Hospital scheme of classification (14). For comparison, cases of NPC were divided into 2 groups; those referred to as active were studied prior to or within 3 months of therapy, and those referred to as inactive were persons without evidence of disease 3 or more years after diagnosis.

Controls were selected from among persons attending the same clinic or hospital as the patient. They were matched free of cancer, within 5 years of the patient's age, and of the same sex, race, and socioeconomic status. A maximum of 4 controls was selected for each case.

All serum samples were stored at −20° prior to testing. Immunofluorescent tests for EBV antigens were performed according to methods previously described (8, 13). Complement fixation tests for varicella, herpes simplex 1, and CMV were performed according to methods described by Sever (20).

Results

There was a significant (p = < 0.001) increase in the geometric mean titer of antibody to EBV in cases of NPC (182.9), compared with matched controls (58.4), as shown in Table 1. The titers to EBV early antigen were also increased in NPC cases; both the anti-D and anti-R components were elevated above control values. There was no significant difference in antibody titers to CMV, herpes simplex, or varicella between NPC cases and controls.

There was considerable variation in the geometric mean titer to the EBV antigens among the different racial and ethnic groups; highest viral capsid antigen titers observed were among Mexican-Americans (253.9) and Negroes (242.5); the highest early antigen titers were among Chinese (31.7) and Negroes (30.3). Lowest mean titers to both viral capsid antigens (168.1) and early antigens (15.6) were observed among the white nasopharyngeal cases.

The most important determinants of the height of the
antibody titer to EBV antigens were race, stage at diagnosis, and the activity or inactivity of the disease when the specimen was collected (Table 2). Active cases of NPC had very high viral capsid antigen and early antigen titers, most of the early antigen response being anti-D. By the time the patient had been in remission for 3 or more years, the antibody response to EBV antigens had declined, although the levels of viral capsid antigens and early antigens still exceeded those of the control population (Table 1). There was a marked difference in mean viral capsid antigen and early antigen titers among the Caucasian patients with active disease, compared with the non-Caucasian (Chinese, other Oriental, Negro, Mexican-American) active cases. There was no obvious explanation for this difference; the only other major determinant of antibody titer, stage of disease, did not appear to be responsible for this difference. Of the 17 Caucasian cases, 7 (41%) were stage III to V, and of the 23 non-Caucasian cases, 7 (30%) were stage III to V.

Antibody titers to the other herpesviruses did not vary significantly with respect to activity or stage of the disease.

During the course of this study, 12 patients with other cancers of the head and neck were also studied (Table 3). The 4 patients with nonepidermoid cancers of the nasopharynx included 2 mixed tumors, 1 reticulum cell sarcoma, and 1 rhabdomyosarcoma. The mean antibody titers to all 4 herpesviruses were similar to those of the controls (Table 1). In contrast, the mean antibody titers to EBV of the 8 Caucasian patients with epidermoid tumors of the nasopharynx and nasal cavity were elevated to levels comparable to those of the Caucasian NPC patients. There was an insufficient number of these cases to make a comparison by race, activity, and stage of disease with the data on nasopharyngeal cases given in Table 2.

Discussion

The titer of antibody to EBV antigens depended on the stage and activity of disease. Henle and Henle (8) clearly demonstrated that, in untreated cases, the titer was directly related to the total tumor burden. It was also apparent from their results and ours that the mean titer of antibodies to the D (diffuse) component of the early antigen complex in-

Table 1

<table>
<thead>
<tr>
<th>Racial group</th>
<th>No. of cases</th>
<th>VCA*</th>
<th>EA</th>
<th>Anti-D</th>
<th>Anti-R</th>
<th>CMV</th>
<th>Herpes simplex</th>
<th>Vari- cella</th>
</tr>
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<tbody>
<tr>
<td>Chinese</td>
<td>6</td>
<td>179.5</td>
<td>31.7</td>
<td>39.9</td>
<td>14.1</td>
<td>7.1</td>
<td>11.3</td>
<td>4.4</td>
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<tr>
<td>Negro</td>
<td>5</td>
<td>242.5</td>
<td>30.3</td>
<td>56.5</td>
<td>NT</td>
<td>15.9</td>
<td>18.3</td>
<td>4.5</td>
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<tr>
<td>Caucasian</td>
<td>14</td>
<td>168.1</td>
<td>15.6</td>
<td>8.5</td>
<td>10.7</td>
<td>6.5</td>
<td>15.9</td>
<td>5.6</td>
</tr>
<tr>
<td>Oriental non-Chinese</td>
<td>3</td>
<td>126.9</td>
<td>19.9</td>
<td>19.9</td>
<td>5.0</td>
<td>6.3</td>
<td>12.6</td>
<td>5.0</td>
</tr>
<tr>
<td>Mexican-American</td>
<td>3</td>
<td>253.9</td>
<td>18.1</td>
<td>5.0</td>
<td>5.5</td>
<td>10.2</td>
<td>12.0</td>
<td>4.5</td>
</tr>
<tr>
<td>All NPC cases</td>
<td>31</td>
<td>182.9</td>
<td>20.5</td>
<td>14.3</td>
<td>9.9</td>
<td>7.3</td>
<td>15.9</td>
<td>5.3</td>
</tr>
<tr>
<td>Matched controls</td>
<td>31</td>
<td>58.4</td>
<td>5.8</td>
<td>5.0</td>
<td>5.5</td>
<td>10.2</td>
<td>12.0</td>
<td>4.5</td>
</tr>
</tbody>
</table>

* VCA, viral capsid antigen; EA, early antigen; NT, not tested.

Table 2

<table>
<thead>
<tr>
<th>NPC cases</th>
<th>No. of cases</th>
<th>VCA*</th>
<th>EA</th>
<th>Anti-D</th>
<th>Anti-R</th>
<th>CMV</th>
<th>Herpes simplex</th>
<th>Vari- cella</th>
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<tbody>
<tr>
<td>Active</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>8</td>
<td>319.9</td>
<td>17.6</td>
<td>7.0</td>
<td>14.2</td>
<td>11.3</td>
<td>13.4</td>
<td>5.1</td>
</tr>
<tr>
<td>Non-Caucasian</td>
<td>15</td>
<td>442.2</td>
<td>83.7</td>
<td>76.3</td>
<td>8.4</td>
<td>8.5</td>
<td>17.5</td>
<td>5.2</td>
</tr>
<tr>
<td>Inactive</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>9</td>
<td>137.0</td>
<td>14.6</td>
<td>9.2</td>
<td>9.9</td>
<td>5.8</td>
<td>15.9</td>
<td>5.5</td>
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<tr>
<td>Non-Caucasian</td>
<td>8</td>
<td>123.3</td>
<td>14.8</td>
<td>10.5</td>
<td>9.9</td>
<td>6.7</td>
<td>14.6</td>
<td>5.6</td>
</tr>
<tr>
<td>Stage at diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I–II</td>
<td>18</td>
<td>137.1</td>
<td>13.1</td>
<td>9.1</td>
<td>8.7</td>
<td>8.3</td>
<td>14.2</td>
<td>5.6</td>
</tr>
<tr>
<td>III–V</td>
<td>22</td>
<td>377.4</td>
<td>52.0</td>
<td>33.9</td>
<td>14.6</td>
<td>7.0</td>
<td>16.5</td>
<td>5.2</td>
</tr>
</tbody>
</table>

* VCA, viral capsid antigen; EA, early antigen.
increased with the progression of the disease.

The mean titer of antibody to the viral capsid antigen, early antigen, and the D component of the early antigen were also higher in active cases. These titers gradually diminished toward control values in patients whose disease became quiescent for 3 or more years, and there was no longer a measurable difference in the titer to the D and R (restricted) components.

A notable exception to the above pattern occurred among the Caucasian nasopharyngeal patients with active disease; namely, the viral capsid antigen was elevated to levels similar to those observed in the non-Caucasian cases, but the early antigen titer was much lower and there was a higher titer to the R than to the D component of the early antigen system. There was no apparent explanation for this difference in response. It has been suggested that the height of the D component is related to the extent of lymph node involvement (11). It is possible that there is a difference in the manner in which Caucasian patients respond to tumor invasion that might account for a reduced or altered antibody response.

A major difference between our results and those reported earlier (3, 5, 7, 12, 15, 16) was that, although cancers arising in the nasopharynx other than NPC did not have elevated EBV titers, epidermoid carcinomas arising in the hypopharynx and nasal cavity did have elevated EBV titers that were equivalent to those observed among the comparable Caucasian nasopharyngeal cases. We have no explanation for this observation; however, the number of cases was quite small, and this finding should not be considered conclusive. We have also failed to confirm the observation (5) that antibody titers to other herpesviruses are elevated in NPC cases.

The nature of the relationship between EBV and NPC has been the subject of considerable debate concerning the passenger versus etiological role of the virus. A critical feature has been the failure of other authors to find elevated EBV antibody titers in cancers of the head and neck of types other than NPC. Certain epidemiological information certainly supports the possible passenger role of the virus. Recently, several workers (1, 2, 6, 19) isolated an ether-resistant transforming agent from throat washings of patients with infectious mononucleosis and from healthy subjects. This agent is more likely nonenveloped EBV (6, 19). It has been suggested that lymphoid cells in the nasopharynx constitute a target site for replication and persistence of the EBV (6). If carcinomas developing at this site infiltrate and stimulate the proliferation of this lymphoid tissue, an increase in EBV and its antibodies would be anticipated, even though the EBV antibodies in carcinomas arising in other areas of the head and neck could be related to both the presence of the EBV-containing lymphoid tissue in these other sites and the response of this lymphoid tissue to growth of the tumor.

At present, our studies are too limited to provide sufficient data to resolve the role of EBV in NPC and other tumors of the head and neck. Further studies are in progress.

References

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