for women who resided in northern Sardinia but 129 for those living in southern Sardinia. Antilatent HHV-8 antibodies were found in only three women (95% CI = 0.0%–6.3%); all of these individuals were from northern Sardinia (Table 1).

Our results confirm the association between seroprevalence of HHV-8 and incidence rates of KS in different regions of Italy as reported by Whitney et al. (4). The results also highlight the possibility that substantial variations exist between neighboring areas. However, HHV-8 seroprevalence rates must be interpreted with caution on account of limitations of assay specificity for different HHV-8 antigens (7) and the predominance of selected population groups such as blood donors (4).

**Diego Serraino**

**Marco Songini**

**Gianfranco Bottazz**

**Paolo De Paoli**

**Rosa Tedeschi**

**Silvia Franceschi**

**References**


**No Association Between Human Herpesvirus Type 8 Infection and Multiple Myeloma**

Human herpesvirus type 8 (HHV-8) is a human herpesvirus that is associated with Kaposi’s sarcoma (KS), Castemans disease, and a rare form of body cavity lymphoma (1,2). Recently, Retting et al. (3) have also demonstrated the presence of HHV-8 in cultured bone marrow stromal dendritic cells from 15 of 15 samples obtained from patients with multiple myeloma and in two of eight samples from patients with monoclonal gammopathy of undetermined significance (MGUS). However, the virus was not found not in malignant plasma cells. Therefore, the researchers believed that the virus might cause the bone marrow cancer by infecting nonmalignant cells, possibly through alteration in the bone marrow microenvironment and production of viral interleukin 6 (3). Since then, other investigators have evaluated the possible link between HHV-8 and multiple myeloma through either serologic assays or polymerase chain reaction (PCR)-based experimental designs. None of these investigators could confirm this association, but one group (4) did detect HHV-8 in 18 of 20 acetonate-fixed and paraffin-embedded bone marrow biopsy samples tested.

We have demonstrated (5) the presence of HHV-8 by PCR in biologic samples of human immunodeficiency virus-positive and -negative individuals in western Sicily, an area with one of the highest incidence rates of classical KS in developed countries, suggesting that HHV-8 is widespread in the general population (5). Therefore, to establish the possible association between HHV-8 and plasma cell dyscrasias, we used a nested PCR to amplify the HHV-8 KS330 sequence (a 233-base-pair herpesvirus-like DNA sequence). We extracted DNA from peripheral blood mononuclear cells (PBMCs), bone marrow aspirates, and bone marrow stromal cells isolated from 20 patients with multiple myeloma and two patients with MGUS as described (5). PBMCs and bone marrow mononuclear cells were separated by Ficoll–Hypaque density sedimentation from EDTA-treated blood samples and fresh bone marrow aspirates. Bone marrow mononuclear cells were used to establish long-term bone marrow stromal cell cultures as described (3). An immunofluorescence assay, using body-cavity-based lymphoma-1 cells, that detects antibodies against latent and lytic antigens of HHV-8 was also performed to investigate the presence of antibodies to HHV-8 in patients with multiple myeloma and MGUS.

Table 1 shows that none of the 22 patients had HHV-8 DNA sequences in PBMCs, in bone marrow aspirates, or in dendritic stromal cells. Antibodies to HHV-8 antigens were detected in four of 22 patients. This seroprevalence rate is similar to that found in our earlier stud-

**Table 1. Detection of human herpesvirus type 8 (HHV-8) DNA by polymerase chain reaction (PCR) and serologic response (as measured by an immunofluorescence assay [IFA]) to HHV-8 antigen(s) of 20 patients with multiple myeloma and two patients with gammopathy of undetermined significance (eight females and 14 males; age range, 50–75 years).**

<table>
<thead>
<tr>
<th>Test</th>
<th>PCR</th>
<th>IFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biologic sample</td>
<td>No. positive/No. tested</td>
<td>No. positive/No. tested</td>
</tr>
<tr>
<td>Peripheral blood mononuclear cells</td>
<td>0/22</td>
<td>—</td>
</tr>
<tr>
<td>Bone marrow aspirates</td>
<td>0/22</td>
<td>—</td>
</tr>
<tr>
<td>Bone marrow stromal dendritic cells</td>
<td>0/22</td>
<td>—</td>
</tr>
<tr>
<td>Serum</td>
<td>—</td>
<td>4/22</td>
</tr>
</tbody>
</table>
Re: When and to What End Do Pathologists Agree?

In a recent editorial discussing diagnostic precision in breast cancer, Page et al. (1) present an upbeat view of the troublesome area of precision in the diagnosis of ductal proliferative lesions. Unfortunately, their view is not supported by the literature or by the experience of other pathologists. Their editorial reports that the precision study by Schnitt et al. (2) showed that evaluation of ductal proliferative lesions resulted in a “greater than 90% agreement when the several pathologists involved used agreed-upon criteria” (1). However, the article by Schnitt et al. documented disagreement at the benign-malignant threshold in 33% of the cases, demonstrating that, although non-necrotizing ductal carcinoma in situ (DCIS) is an appealing theoretic step in the development of some cases of invasive carcinoma, this step remains refractory to histopathologic definition that would result in satisfactory diagnostic precision.

Further evidence that this subtype of DCIS is a failed diagnostic category is provided by the findings in a study of diagnostic precision conducted by Rosai (3) and by the findings in a study by Wells et al. (4) that prompted the editorial by Page et al. In the Rosai study (3), there was disagreement at the benign-malignant threshold in 40% of the proliferative ductal cases, and in the study by Wells et al. (4), “critical disagreements occurred primarily in the differentiation between diagnoses of benign with atypia and noninvasive malignant.” More important, pathologists have found that the diagnosis of non-necrotizing DCIS fails in daily practice. For example, a breast consultant at the Armed Forces Institute of Pathology (5), who was also a co-author of the article by Schnitt et al. cited by Page et al. noted, “...interobserver variability in separating AIDH [atypical intraductal hyperplasia] from DCIS remains notoriously high among pathologists.” Page et al. seek to avoid the problems with precision by advocating “central review,” but the studies by Schnitt et al. (2) and Rosai (3) document low precision among the very subspecialty pathologists who would be performing central review. Central review structures the diagnostic process by defining which pathologist is correct; however, the central review is a political solution to the inherent low precision of non-necrotizing DCIS, and it does not address the underlying defects in the diagnostic category.

When theories of cancer development are used to declare a portion of a morphologic continuum to be a diagnostic category, pathologists are often faced with a lack of distinctive features, leading to poor diagnostic precision. Without precision, we lack one of the basic tools required for improving diagnostic accuracy. Unfortunately, diagnostic categories can often develop a political momentum that makes them difficult to modify or replace, even when they have deficiencies that compromise their clinical or scientific value. With 23 statistical editors and a neutral position on the issue, a publication like the Journal of the National Cancer Institute would appear to be well positioned to sponsor an evidence-based investigation of the validity of non-necrotizing DCIS as a malignant diagnostic category that is distinct from benign atypical hyperplasia. A good starting point for the evaluation would be: What do the studies by Schnitt et al., Rosai, and Wells et al. say about precision in the diagnostic setting? Would an objective reader conclude that these studies support DCIS as a valid diagnostic category, or do they provide objective evidence that this experiment in labeling many cytologically low-grade intraductal proliferations as “carcinoma” has been a failure?

Elliott Foucar

References