antiarrhythmic agent structurally close to propisomide (6–9).

The present method can be conveniently applied to the determination of the parent drug and its MND metabolite in plasma and urine samples from volunteers treated with 200 mg of propisomide (10). It is sensitive enough for routine applications in pharmacokinetic studies and drug monitoring. When we applied our method to the determination of the drug and its metabolite in whole blood and plasma, we found that the parent drug is preferentially distributed in plasma, whereas the metabolite is almost equally distributed between blood and plasma.

This HPLC method, like the gas-chromatographic assay, measures the total concentrations of propisomide in plasma. Because protein-binding of the drug in plasma reportedly (11) is concentration dependent within the range of therapeutic concentration, measurement of the concentration of the free drug may be important for achieving optimal therapeutic effect. Combining the HPLC method with use of equilibrium dialysis would provide determinations of total and free propisomide in plasma.

References

Paraproteinemia in Patients with Acquired Immunodeficiency Syndrome (AIDS) or Lymphadenopathy Syndrome (LAS)

Kirk Heriot, Allan E. Halquist,1 and Russell H. Tomar2

Eight of 15 patients with acquired immunodeficiency syndrome (AIDS) and six of nine patients with lymphadenopathy syndrome (LAS) had paraproteins in their sera. Twelve of these 14 were IgG kappa; the other two had no demonstrable light chains. The relationship of the paraprotein to the pathogenesis of AIDS is not clear, but we discuss its relation to derangements of B-cell immune regulation and function and to B-cell tumors in AIDS patients.

Acquired immune deficiency syndrome (AIDS) is characterized by opportunistic infections and such disorders as Kaposi’s sarcoma in certain high-risk groups. Within two years of diagnosis, the mortality rate is more than 60% (1–4). Another syndrome, which is known by several names—AIDS-related complex (ARC), pre-AIDS, or the lymphadenopathy syndrome (LAS)—is seen in the same risk groups and may be a precursor of AIDS.

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The wide variety of immune abnormalities reported in AIDS cases includes lymphopenia, increased polyclonal serum immunoglobulins, inverted T4/T8 lymphocyte ratios, markedly depressed cellular immunity, and depressed in vitro response of lymphocytes to antigen and mitogen stimulation (5–7). However, to our knowledge, paraproteins have not been reported.

In our investigations, we noticed that two of our first three patients with AIDS had IgG paraproteins. This led us to study the sera of our other patients. We found that most of the patients with AIDS and LAS also had such abnormalities.

Materials and Methods

Serum was sampled from 24 patients—15 with AIDS and nine with LAS—all from central New York and all treated at the State University Hospital. All AIDS patients fulfilled the criteria of the Centers for Disease Control for AIDS: the patient had a tumor or opportunistic infection fairly predictable of an underlying defect in cellular immunity without a primary immunodeficiency, a malignancy, or a history of immunosuppressive therapy. All patients with LAS had
lymph nodes larger than 1 cm in diameter with involvement of two or more regions (other than the inguinal nodes) for more than three months. Not all of these LAS patients had constitutional symptoms at the time of study. We subjected these sera to serum protein electrophoresis on agarose gels (Helena Laboratories, Beaumont, TX) and immunoelectrophoresis on agarose gels (Corning Medical, Corning, NY) with goat antiserum to gamma heavy chains, alpha heavy chains, mu heavy chains, kappa light chains, lambda light chains, and a mixture of IgG, IgA, and IgM including light chains (Meloy Laboratories, Springfield, VA). Gels were coded, then analyzed independently by each of us without knowledge of the patients' names or diagnoses until results for all of the gels were completed. At least two of us had to agree on the presence and type of paraprotein. Samples for which results were considered equivocal were reported as "indeterminate."

Results and Discussion

Table 1 summarizes our results. Overall, serum samples from eight of 15 AIDS patients and six of nine LAS patients had paraproteins. All of these were IgG and most had an accompanying kappa light chain. Figure 1 shows a representative serum protein electrophoregram from an AIDS patient; by immunoelectrophoresis this was shown to be an IgG-kappa paraprotein. Figure 2 shows representative immunoelectrophoretograms of sera from two LAS patients with IgG kappa monoclonal proteins. Several "positive" sera were treated with 2-mercaptoethanol before electrophoresis, but there was no change in their electrophoretic patterns.

We have identified a subset of AIDS and LAS patients whose serum contains IgG paraproteins. We emphasize that the serum protein electrophoresis gels must be carefully scrutinized, because the paraproteins may be difficult to distinguish in a background of generalized hypergammaglobulinemia. It is not clear whether these paraproteins are directed against a specific antigen or antigens but, if so, there are several possibilities. Kloster et al. (8) demonstrated lymphocytoxic antibodies in the sera of AIDS patients. Schupbach et al. (9) showed that AIDS and LAS patients form antibodies to human T-cell lymphotrophic virus (HTLV-III) antigens with molecular masses of 65, 60, 55, 41, and 24 kDa. Perhaps the paraproteins we have observed fall into one of these classes, i.e., against either lymphocytes or organisms, particularly HTLV III or the Lymphadenopathy-Associated Virus.

Paraproteinemias has been reported in other patients with primary immune deficiency states. Geha et al. (10) reported an IgG paraprotein in a patient with severe combined immunodeficiency syndrome; Dictor et al. (11) found an IgG lambda paraprotein in a three-year-old child with a combined immunodeficiency; and Bushell et al. (12) reported serum paraproteins and urinary Bence Jones proteins (IgG kappa in serum with kappa light chain in the urine) in a patient with type I dysgammaglobulinemia.

Several derangements of B-cell function have been described in AIDS. Patients with AIDS fail to respond to primary immunization in vivo: their B-cells demonstrate an increased spontaneous production of immunoglobulin in vitro (13) but fail to respond to the usual controls by T-cells. In addition, B-cell lymphomas, including primary B-cell lymphomas of the central nervous system, are frequently seen in AIDS and LAS patients (14, 15). Franco et al. (16) found plasmacytosis with some clustering of plasma cells in the bone marrow, and Israel et al. (17) reported a case of plasmacytoma in an AIDS patient. Recently, a monoclonal B-cell proliferation with IgG kappa on the membrane surface has been reported in an AIDS patient (18). There is no

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![Protein electrophoretogram of serum from a patient with AIDS](image)

This paraprotein later was shown to be IgG kappa by immunoelectrophoresis. A monoclonal band (indicated by the marker) is seen in the immunoglobulin region. Normal serum at left, for comparison.

![Immunoelectrophoretogram of serum from two patients (a and b) with LAS](image)

Thickened, distorted bands representing IgG-kappa paraprotein are seen with antisera specific for the gamma or kappa chain and with antiserum to a combination of IgG, IgA, and IgM (GAM). Pt = patient; NHS = normal human serum; aGAM = anti-IgG, -IgA, and -IgM, including kappa and lambda chains; aG = anti-IgG chain; aM = anti-mu chain; aκ = anti-kappa chain; aλ = anti-lambda chain.

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Table 1. Summary of Results

<table>
<thead>
<tr>
<th>Results of Immunoelectrophoresis</th>
<th>AIDS (15)*</th>
<th>LAS (9)</th>
<th>Total (24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No abnormality</td>
<td>4</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>IgG-kappa M proteins</td>
<td>8</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Igκ M protein</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>All M proteins</td>
<td>8</td>
<td>6</td>
<td>14</td>
</tr>
</tbody>
</table>

*Total number of patients in each group in parentheses.
mention of paraproteins in any of these cases. It is not clear if these B-cell abnormalities are primary in AIDS/LAS patients or are secondary to T-cell abnormalities and infections.

Whether as primary or secondary agents, these proteins possibly play a role in perpetuating the immune defects. We found it interesting that all of our patients expressing a light chain had a kappa paraprotein. Although our sample is too small to conclude that only kappa chains will be involved, the findings are highly suggestive that this is not a random event.

These observations may prove helpful in understanding the pathogenesis of AIDS and perhaps in the diagnosis of AIDS and LAS. Furthermore, paraprotein evaluation perhaps will be useful in monitoring the progress of the disease. We are currently evaluating these proteins in LAS patients in relation to the course of the disease. Their significance and meaning in the AIDS/LAS spectrum obviously requires more study.

References