Autoantibodies with Antilipoprotein Specificity and Hypolipoproteinemia in Patients with Cancer

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SUMMARY

Sera from 151 patients with a variety of cancers were screened for antibody-like activity against lipoproteins. Eighteen % of the sera exhibited activity against autologous and homologous high-density lipoproteins and 3% exhibited activity against autologous and homologous low-density lipoproteins. Antibody-like binding was proven by its restriction to the Fab fragment of IgG. The reactive part of the lipoprotein molecule was shown to be the apoprotein. Quantitation of the serum lipoproteins indicated that the high-density lipoprotein concentration in the sera of cancer patients was significantly lower (p < 0.01) when antibody was present. These observations suggest that autoimmune mechanisms may be responsible for the decreased high-density lipoprotein serum levels in some patients with cancer.

INTRODUCTION

A close relation between serum lipoproteins and cancer has already been implied by several authors (2-5, 15, 36, 45). Their studies indicate that patients with cancer exhibit disturbances of the synthesis and/or catabolism of lipoproteins leading to abnormal concentrations of serum lipoproteins and lipids.

Thus, Barclay et al. (2-5) have reported a significant decrease of HDL's and an increase of LDL's in cases of advanced cancer of the breast, correlating the degree of the alteration with the extent of the disease. The corresponding studies on cases of gynecological neoplasias (15) and of other forms of cancer (5, 36) likewise strengthened a significant decrease of the serum HDL fraction. It appears, therefore, that the histological type of cancer does not play a critical role in this decrease.

Serum lipoproteins are complexes of proteins and lipids differing in size and composition. Their concentration in plasma is known to be altered by changes in food intake, hormonal factors, and pathophysiological events (18). The cause of reported changes in serum lipoproteins in cancer patients, however, requires further clarification.

Riesen et al. (40) have recently described a decrease of the serum LDL levels in myeloma sera. This decrease was found to be closely associated with an autoantibody-like activity of the M-component against LDL. Furthermore, Noseda et al. (34) observed hypolipoproteinemia in sera of patients with seronegative rheumatoid arthritis and autoantibodies against lipoproteins. Additional evidence for a close relationship between autoantibody and hypolipoproteinemia was provided by turnover studies in such patients (34, 35).

The opposite phenomenon, i.e., autoantibodies associated with hyperlipidemia, was first noticed by Kayden and Franklin (26), and then later by Levin et al. (28), Lewis and Page (29), and Beaumont (7). These authors described myeloma sera, which behaved like autoantibodies against lipoproteins. Beaumont also detected autoantibodies with lipoprotein specificity in hyperlipidemic non-myeloma sera (8).

These findings suggest that autoimmunity may occasionally induce metabolic disorders of the serum lipoproteins, leading to either hypolipoproteinemia or hyperlipoproteinemia. The purpose of the present study was, therefore, to test whether autoimmune reactions might be responsible for the known decrease of the HDL concentration in sera of cancer patients.

PATIENTS AND METHODS

Patients. Sera from 151 patients with a variety of cancers were collected after a 12-hr fast and studied (see Table 1). Diagnosis and proof of cancer were provided by clinical and histological or cytological data. Information concerning local growth or metastatic spread of malignant tissue was judged on clinical and radiological and/or autopsy criteria. One-half of the cases of this study had local cancers and one-half had cancers with metastatic growth. In 97 of 151 patients the serum lipoprotein and lipid concentrations were determined. These patients were personally seen by one of the authors and were clinically described as of good overall nutritional status. In addition, serum protein concentrations were chosen to reflect the nutritional state of the patients. The mean value ± S.D. was 6.4 ± 0.8 (normal values are between 6.2 and 8.3) as estimated by the biuret method.

1 Supported by the Swiss National Foundation for Scientific Research.
2 The abbreviations used are: HDL, high-density lipoprotein (a-lipoprotein); LDL, low-density lipoprotein (β-lipoprotein); VLDL, very-low-density lipoprotein (pre-β-lipoprotein).

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Table 1
Screening of sera from cancer patients for binding activity against lipoproteins as determined by passive hemagglutination

<table>
<thead>
<tr>
<th>Tumor localization</th>
<th>No. of cases</th>
<th>Positive reaction with HDL</th>
<th>Positive reaction with LDL</th>
<th>( \text{No.} )</th>
<th>( \text{%} )</th>
<th>( \text{No.} )</th>
<th>( \text{%} )</th>
<th>( \text{No.} )</th>
<th>( \text{%} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urogenital</td>
<td>32</td>
<td>Weakly positive reactions*</td>
<td>Clear positive reactions*</td>
<td>6</td>
<td>19</td>
<td>4</td>
<td>12</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>30</td>
<td></td>
<td></td>
<td>7</td>
<td>23</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory tract</td>
<td>33</td>
<td></td>
<td></td>
<td>5</td>
<td>15</td>
<td>4</td>
<td>12</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>23</td>
<td></td>
<td></td>
<td>6</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Skin and mamma</td>
<td>16</td>
<td></td>
<td></td>
<td>1</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other localizations</td>
<td>17</td>
<td></td>
<td></td>
<td>2</td>
<td>12</td>
<td>1</td>
<td>6</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>151</td>
<td></td>
<td></td>
<td>27</td>
<td>18</td>
<td>9</td>
<td>6</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>( \sum )</td>
<td>36</td>
<td>(24%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* See Chart 1.

indicating that the concentration of the serum proteins was at the lower limit of the normal values. The albumin-globulin ratio was 0.87 ± 0.31, indicating a slight relative increase of globulins.

Sera of patients with cancer of the upper intestinal tract and of patients with recent diet or weight loss were not considered in the evaluation of the lipoprotein and lipid concentrations, in order to exclude food-induced disturbances of the lipoprotein levels. Icteric patients were excluded from the study.

Thirty-one patients were treated with cytostatic agents at the time that the blood was drawn. Two of these exhibited antibody activity. The lipoprotein levels could be determined only in 15 of these cases. Three patients with prostate neoplasm and 5 with breast cancer were treated with diethylstilbestrol and/or ethinyl estradiol, respectively, and were excluded from the evaluation of the lipoprotein concentration in view of the alterations that are known to follow hormone therapy.

Sera of 103 healthy blood donors, obtained after a 12-hr fast, were used for the determination of the mean values for normal lipoprotein and lipid concentrations. LDL of known Ag-specificity (genetic polymorphism) (11) was obtained from 6 donors.

Detection of Binding Activity against Lipoproteins. Binding activity against lipoproteins was detected by (a) passive hemagglutination of human red cells (0 Rh neg.) coated with HDL or LDL by using bisdiazotized benzidine as the coupling agent (7); (b) double diffusion in agarose; or (c) a radioimmunoassay, using bromacetyl cellulose conjugates of IgG (41) and \(^{125}\)I-labeled LDL and HDL. The labeling of LDL and HDL was performed by the iodine monochloride technique as described by McFarlane (32). Passive hemagglutination and gel diffusion methods were used for screening. The sera used in hemagglutination experiments were inactivated at 56° for 30 min. We set up 2 negative controls, (a) an inactivated normal human serum pool incubated with lipoprotein-coated red cells and (b) the inactivated sera of cancer patients incubated with uncoated red cells, and a positive control, rabbit anti-LDL or anti-HDL antisera (Behringwerke, Marburg/Lahn, Germany) that were preabsorbed with human red cells. A complement fixation test was performed by the microtechnique of Wassermann and Levine (44). Specificity against Ag factors was analyzed as described by Büttler and Brunner (12).

Isolation and Proteolytic Fragmentation of Immunoglobulins. IgG was isolated by ion-exchange chromatography on DEAE-Sephadex in 0.01 M Tris, pH 7.5. IgM was purified by repeated eluoglobulin precipitation at pH 5.8 and filtration through Sephadex G-200.

Papain cleavage of IgG was performed essentially according to the method of Porter (38) for 15 hr at 37°. The Fab and Fc fragments were separated by filtration through Sephadex G-100 and subsequently isolated by zone electrophoresis.

Isolation and Delipidation of Lipoproteins. Homologous, autologous, and heterologous lipoproteins were isolated by repeated preparative ultracentrifugation at different densities (19). LDL was delipidated with diethyl ether-ethanol by the method of Shore and Shore (42).

Lipoprotein and Lipid Assay. The radial immunodiffusion technique was used for quantitative determination of HDL (31, 36). Rabbit antisera against HDL were purchased from Behringwerke. The LDL + VLDL quantitation was done on immunodiffusion plates obtained from the same supplier. Considering the various difficulties in the quantitative determination of lipoproteins (see reviews in Refs. 17, and 22), the concentration of LDL + VLDL was alternatively calculated on the basis of the total lipid content of LDL and VLDL and the relative percentage of these fractions, determined by lipoprotein electrophoresis (33). The data reported in Chart 2 were obtained by the radial immunodiffusion method (36).

Since standard preparations of lipoproteins were not available, 96 sera from 20-year-old male adults were pooled and the HDL and LDL + VLDL contents were used as...
Coated red cells were incubated with sera of cancer patients. Titer was negative (−), weakly positive (±), or positive (+).

**RESULTS**

Demonstration of Binding Activity against Lipoproteins. The results of the screening of 151 sera of cancer patients for binding activity against lipoproteins are summarized in Table I. In 27 cases (18%) weakly positive reactions were detected with HDL (Chart 1). Clear positive hemagglutination titers between 1:16 and 1:256 were observed in 9 sera. Five sera gave positive reactions with LDL; 3 of these reacted with HDL as well, whereas 2 displayed anti-LDL activity only. In order to strengthen the autoimmune character of the reaction, autologous, homologous, and heterologous lipoproteins were assayed. In all positive cases a reaction with autologous and homologous lipoprotein occurred, whereas with rabbit or sheep HDL or LDL no reaction was detected. No precipitations were observed in the immunodiffusion technique in agarose. The sera exhibiting binding activity were not restricted to a distinct type of cancer but occurred within all tumor groups (Table 1). When the weakly positive reactions are disregarded, antilipoprotein activity seems to occur mainly in tumors of the urogenital and respiratory tracts. The binding activity was present in sera from patients with both metastatic and local tumors. Of the 31 cases treated with cytostatic agents, the sera of 2 patients exhibited antilipoprotein activity.

None of 200 sera from normal healthy blood donors screened for antilipoprotein specificity reacted with lipoproteins. Likewise, among 200 sera from various patients with a variety of diseases (excluding rheumatoid arthritis, multiple myeloma, or “benign” gammopathies) antilipoprotein activity could not be detected.

Immunochromatographic studies were carried out with the sera of 3 patients exhibiting different specificities. Serum E. S. reacted with HDL only, Serum G. M. reacted with both HDL and LDL, and Serum M. S. reacted with LDL only. Antilipoprotein activity was shown to be associated with the IgG class of immunoglobulins. The IgM of the patients did not react with lipoproteins. Moreover, after removal of the IgG fraction, the remaining immunoglobulins of the sera showed no reaction with lipoproteins, thus suggesting that the IgA did not exhibit antilipoprotein activity. In addition, the IgG-lipoprotein complexes studied did not bind complement.

Studies on the localization of the binding site on the immunoglobulin molecule were done after papain cleavage of the IgG molecule. Fab fragments inhibited the passive hemagglutination of lipoprotein-coated red cells, but Fc fragments did not. Moreover, the addition of an anti-light chain antiserum after incubation of Fab fragments with lipoprotein-coated red cells caused agglutination. No agglutination occurred when the same experiment was done substituting Fc fragment for Fab fragment and anti-γ for anti-light chain. These results indicate that the active site was located on the Fab fragment of IgG (Table 2).

After the lipid fraction was removed from the HDL molecule, the remaining protein moiety inhibited the agglutination of HDL-coated red cells to the same extent as did the native HDL molecule. Red cells sensitized with apoprotein-HDL were agglutinated by the sera that had reacted with HDL. This indicates that the antibody was directed towards the apoprotein moieties of the HDL molecules.

In the case of Serum G. M., which reacted with both HDL and LDL, the possibility of a reaction with LDL due to isoantibodies against Ag factors could be ruled out by the passive hemagglutination and its inhibition using the LDL’s of 6 different donors with known Ag specificity. The passive hemagglutination reaction was inhibited by all 6 LDL’s including the patients’ own. Cross-wise inhibition of the passive hemagglutination of LDL-coated red cells with LDL and HDL and of HDL-coated red cells with HDL and LDL in 2 cases that showed both anti-HDL and anti-LDL specificity indicated that these sera contain 2 different antibody populations with different specificities that do not cross-react with both lipoprotein classes.

Lipoprotein and Lipid Concentrations. The concentrations of the serum lipoproteins and lipids in 27 sera of cancer patients exhibiting binding activity against lipoproteins, in 70 sera of cancer patients without detectable antibody activity, and in 103 normal sera are illustrated in Chart 2. The mean values of the HDL (p < 0.01), the total lipid (p < 0.02), and the phospholipid (p < 0.05) concentrations in the

<table>
<thead>
<tr>
<th>Agglutination of lipoprotein-coated red cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients’ IgG</td>
</tr>
<tr>
<td>Patients’ IgG + Fab</td>
</tr>
<tr>
<td>Patients’ IgG + Fc</td>
</tr>
<tr>
<td>Fab + anti-light chain antiserum</td>
</tr>
<tr>
<td>Fc + anti-light chain antiserum</td>
</tr>
<tr>
<td>Fc + anti-γ antiserum</td>
</tr>
</tbody>
</table>

MARCH 1975
sera of cancer patients with binding activity were significantly lower than those found in the sera of cancer patients without binding activity. The mean concentrations of the triglycerides and of the total cholesterol, however, were not significantly different in either group of sera. Moreover, Chart 2 indicates that, in the sera of cancer patients without antibody activity, the average values of the HDL ($p < 0.002$) and of the phospholipid concentrations ($p < 0.002$) were also significantly lower than those determined in normal sera. The mean concentrations of the triglycerides ($p < 0.01$) and of the LDL + VLDL ($p < 0.05$), however, were increased in the sera of cancer patients without antibodies against lipoproteins when compared with normal sera, whereas the average value for the cholesterol concentration was not significantly altered within these 2 groups.

Diet, weight change, and age, factors that are known to influence the VLDL and the triglycerides very sensitively, do not seem to be responsible for the difference found, since these parameters were nearly the same within the 2 groups being compared.

The relationship between serum lipoprotein concentrations in cancer patients with hepatic metastases or in cancer patients free of hepatic metastases and the influence of antibody activity are shown in Table 3. The limited data (only some of the patients could be unequivocally associated with one of these groups) indicate that depressed HDL levels occur either when antibody is present or in patients without antibody but with hepatic metastases. One patient, however, exhibiting both anti-HDL activity and hepatic metastases, showed a depressed LDL value instead of HDL, the reasons for which are unknown.

Two of the 27 "antibody producers" and 13 of the 70 "nonantibody producers" received cytostatic agents. Those patients have been previously described in a publication by Nydegger and Bütler (36) that showed that cytostatic agents had no influence on the LDL levels.

**DISCUSSION**

The antibodies in sera of cancer patients described in this study were directed against the patients' own lipoproteins. In this sense they would fit the generally accepted concept of autoantibodies (27). The prevailing specificity was directed against HDL, but reaction with LDL occurred as well. The antigen-antibody character of the reaction is strengthened by its high specificity and by its restriction to the Fab fragment of the immunoglobulin molecule. The inhibition experiments with the delipidated HDL indicate that the apoprotein is the reactive part of the lipoprotein molecule. The binding activity could be demonstrated by the passive hemagglutination technique and by the absorption of iodinated lipoproteins into a bromoacetyl cellulose conjugate of the patients' IgG. In the immunodiffusion technique, however, no precipitation line was formed. The failure of the precipitin reaction may be explained by the low concentration of the antibody or by its low avidity or because it is a nonprecipitating antibody. The M-components described by Beaumont (8), which agglutinated LDL- and HDL-coated red cells in exceedingly high titers, precipitated LDL in agarose or agar only, whereas HDL was not precipitated.

As in the previously reported cases of multiple myeloma or seronegative rheumatoid arthritis (34, 35, 40), the autoantibodies described here were found to be associated with hyperlipidemia. This hyperlipidemia may be explained by the intravascular presence of antigen-antibody complexes, which are catabolized faster than the unbound lipoprotein. Indeed, turnover experiments done with iodinated LDL, in a case of seronegative rheumatoid arthritis and autoantibodies against LDL (34), indicate a reduced biological half-time of the LDL in the presence of the
corresponding autoantibodies, suggesting that the low serum lipoprotein levels are due to an increased phagocytosis of the immune complexes.

Hyperlipidemia associated with autoantibodies, as described by Beaumont (8) and by others (26, 28, 29), appears to have a different origin. The current concept is that a blockade of the lipolysis of the circulating lipoproteins is responsible for these hyperlipidemias (8). This blockade can be induced by antibodies that react with lipoprotein determinants and therefore may mask the sites of the enzyme attack. It may also be induced by antienzyme antibodies; Glueck et al. (20) showed that the lipoprotein lipase activity was impaired because of inactivation of heparin, which was bound to immunoglobulins. The physiological role of heparin in promoting lipoprotein lipase activity was thus inhibited. A similar mechanism was suggested by Albrink and Albrink (1) in studying hyperlipidemia in lymphoma-bearing hamsters. The observation that sera of cancer patients without autoantibodies against lipoproteins also exhibit significantly reduced HDL concentrations is of interest. The limited data available from this study suggest that hepatic metastases are responsible for the depressed HDL levels in these patients. However, the involvement of other disturbances, such as hormonal influence or inherited alterations of the HDL synthesis, should not be overlooked. Indeed, Barclay et al. (4) have reported a decrease in HDL level in sera of healthy relatives of patients suffering from cancer. The possibility that cytostatic agents cause low HDL levels can be excluded, because these agents do not seem to provoke alterations of the serum lipoprotein levels (36).

The decrease noted with the phospholipids may be a consequence of the decreased levels of HDL, which transports the phospholipids to a major extent.

The reported hypolipidemia is in contradiction to the antilipoprotein activity of human M-components associated with hyperlipidemia described by Lewis and Page (29) and extensively studied by Beaumont (8), who observed antilipoprotein activity also in hyperlipidemic nonmyeloma sera. The autoantibodies described by Beaumont cross-reacted with both LDL and HDL, a fact that is observed neither with conventionally induced antibodies in heterologous systems to either HDL or LDL nor with the autoantibodies described in this paper. Furthermore, Beaumont and Baudet (9) were able to show that lysolecithin inhibits the reaction of the autoantibody with lipoprotein, indicating that the reactive haptenic group is a phospholipid, whereas the autoantibodies described here are directed against the protein moiety of the lipoprotein.

Immune reactions of both cellular and humoral immunity have been shown to occur within a large variety of neoplasms in humans (24). The biological significance of the autoantibodies reported in this study is not yet understood. The possibility that these autoantibodies are so-called blocking antibodies that enhance tumor growth should be considered (23). Such an enhancement may be due to antibodies that have no cytotoxic effect, such as non-complement-fixing antibodies, or to antibodies unable to activate complement, or to both (14). The results of the complement-fixation tests indicate that the autoantibodies against lipoproteins in sera of cancer patients do not activate complement. Failure to fix complement has also been reported for isoantibodies against LDL (13). According to the present knowledge, one would expect a rather higher incidence of tumor-specific antibodies in patients with metastatic tumors. Antilipoprotein activity, however, occurs in both groups of tumors, metastatic or local. The fact that tissue proteins can exchange with serum proteins and the possibility of cross-reactions with tissue components (tumoral tissue has been shown to contain lipids apparently associated with cancer (25, 43)) do not completely rule out a tumor-associated specificity.

On the other hand, the possibility exists that the tumor-dependent tissue decomposition could lead to the generation of autoantibodies against lipoproteins or degradation of lipoproteins. The fact that antilipoprotein activity occurs in association

<table>
<thead>
<tr>
<th>Patients with antibody to HDL</th>
<th>Serum levels of HDL (%) of standard</th>
<th>Serum levels of LDL + VLDL (%) of standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>105</td>
<td>95</td>
</tr>
<tr>
<td>9</td>
<td>79 ± 24*</td>
<td>123 ± 42</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients without antibody to HDL or LDL</th>
<th>Serum levels of HDL (%) of standard</th>
<th>Serum levels of LDL + VLDL (%) of standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>80 ± 25</td>
<td>128 ± 30</td>
</tr>
<tr>
<td>12</td>
<td>107 ± 35</td>
<td>126 ± 47</td>
</tr>
</tbody>
</table>

* Mean ± S.D.
with several types of diseases such as paraproteinemia (40),
rheumatoid arthritis (34, 35), and various forms of cancer
(this report) speaks against a tumor-directed specificity.
Anti-IgG specificity (rheumatoid factors) appears as well in
similar origin.
protein autoantibodies and rheumatoid factors might be of a
similar origin.

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