THE EFFECTS OF LEUKEMIC INFILTRATES IN VARIOUS ORGANS IN CHRONIC LYMPHOCYTIC LEUKEMIA

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Abstract

Although the presence of leukemic infiltrate in isolated organs of patients with chronic lymphocytic leukemia has been reported, the effects of leukemic infiltration into various organs of such patients have never been comprehensively studied. To determine the effects of leukemic infiltration we reviewed the histologic sections of multiple organs in 47 cases of chronic lymphocytic leukemia at the University of Maryland Hospital. The leukemic infiltrates were seen in spleen (100 per cent), lymph nodes (100 per cent), liver (98 per cent), kidney (90 per cent), adrenal (71 per cent), heart (64 per cent), and pancreas (37 per cent). After exclusion of the known causes of fibrosis in these organs, the association of fibrosis with leukemic infiltration was as follows: liver (44 per cent), kidney (89 per cent), heart (44 per cent), pancreas (60 per cent), and adrenal (3 per cent). The heart showed endocardial,
myocardial, and epicardial infiltrates associated with fibrosis, with severe endocardial fibroelastosis in one case. The liver showed expansion of the portal tracts, bridging infiltration, bridging fibrosis, and cirrhosis with pseudolobule formation.

In patients whose livers showed bridging fibrosis or pseudolobule formation, the mean duration of chronic lymphocytic leukemia was 4.4 years, compared to 2.6 years in those showing no significant fibrosis, suggesting that the degree of infiltration and fibrosis was positively correlated with the duration of leukemia. The kidney showed interstitial and periglomerular fibrosis and tubular atrophy only in areas of leukemic infiltration, whereas no fibrosis or atrophy was observed in noninfiltrated areas. The renal lesions closely resembled the chronic inflammatory conditions of the kidney. In foci of leukemic infiltration the pancreas showed parenchymal destruction and fibrous scars, thereby resembling chronic pancreatitis. The adrenals showed replacement of medullary cells by dense leukemic infiltrates, and fibrosis was observed in one case. A strong association between fibrosis and the leukemic infiltration of chronic lymphocytic leukemia in various organs has been demonstrated. We therefore suggest that chronic lymphocytic leukemia may cause significant tissue destruction. Further studies are needed in this area.

Compared to other leukemias, chronic lymphocytic leukemia is a relatively benign disease of old age, and patients die of causes apparently unrelated to the leukemia. The most common complication and cause of leukemia related death is infection. Almost all the organs or areas of the body have been reported as having been infiltrated by leukemic cells in patients with chronic lymphocytic leukemia. Splenomegaly, hepatomegaly, and lymph node enlargement are frequently observed manifestations of leukemic infiltration. Many case reports regarding the presence of leukemic infiltration in single organs of patients with chronic lymphocytic leukemia have been reported in the literature, several with clinical correlates to the leukemic infiltration. However, a study encompassing the frequency and morphology of leukemic infiltration into various organs of such patients has not been reported, and the effects of lymphocytic infiltration in chronic lymphocytic leukemia have never been described. We therefore studied selected organs from patients with documented chronic lymphocytic leukemia.

MATERIALS AND METHODS

Forty-seven cases of chronic lymphocytic leukemia from the Department of Pathology of the University of Maryland Hospital were examined by light microscopy. These constituted all patients with chronic lymphocytic leukemia undergoing autopsy at the University of Maryland Hospital between 1950 and 1979. Initially we reviewed all the hematoxylin and eosin stained histologic sections of liver, kidney, spleen, lymph nodes, heart, pancreas, adrenal, thyroid, and prostate available from the autopsy files and assessed them for the presence of leukemic infiltrate. All observations regarding the sites, morphology, frequency, and extent of tissue infiltration, along with associated changes (i.e., tissue necrosis or fibrosis), were recorded.

In order to further assess the tissue responses to the leukemic infiltration, selected tissue sections were stained with Masson's trichrome stain for collagen, Verhoeff-van Gieson stain for elastic fibers, and Hortega's reticulum stain. Subsequently the hematoxylin and eosin and specially stained sections in all 47 cases of chronic lymphocytic leukemia were examined for consistent changes within each type of organ. The nature of the tissue response to leukemic infiltration in different organs was also compared. All information obtained as described, in addition to age and duration of the disease, was then tabulated and analyzed to discover statistically or morphologically significant manifestations of tissue involvement in leukemia. The frequency of infiltration by leukemic lymphocytes was calculated for each organ, as well as the frequency of fibrosis within each organ.

In examining the livers the most superficial 1 cm. of subcapsular parenchyma was excluded and only the deeper tissue was evaluated. The livers were evaluated with respect to the duration of the chronic lymphocytic leukemia as it compared with the extent and frequency of hepatic changes observed. In the kidneys the percentage of 50 glomeruli that showed both periglomerular leukemic infiltration and periglomerular fibrosis or glomerulosclerosis was calculated and compared to the same evaluation for 50 glomeruli on the same tissue section without associated leukemic infiltration. Ten kidneys from the autopsies of patients between the ages of 46 and 81 years were chosen as controls, and were similarly evaluated with respect to the glomerular changes. Whenever there was fibrosis of an organ due to a known cause (e.g., methotrexate, hepatitis, alcoholism, pancreatitis, pyelonephritis, vascular nephrosclerosis), that particular organ was excluded from the study.

RESULTS

Of the 47 patients with chronic lymphocytic leukemia reviewed, there were 35 males and 12 females, a male to female ratio of 2.9:1. The mean
TABLE 1. FREQUENCY OF LEUKEMIC INFILTRATION AND INCREASED FIBROSIS (TOTAL, 42 CASES)

<table>
<thead>
<tr>
<th>Organ</th>
<th>Percentage of Cases Showing Lymphocytic Infiltration</th>
<th>Percentage of Cases Showing Increased Fibrosis with Associated Lymphocytic Infiltration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>97.6</td>
<td>42.8</td>
</tr>
<tr>
<td>Kidney</td>
<td>90.4</td>
<td>80.9</td>
</tr>
<tr>
<td>Heart</td>
<td>64.1</td>
<td>28.2</td>
</tr>
<tr>
<td>Adrenal</td>
<td>70.7</td>
<td>2.4</td>
</tr>
<tr>
<td>Pancreas</td>
<td>36.5</td>
<td>21.9</td>
</tr>
</tbody>
</table>

Dense lymphocytic infiltrate in the liver showing "bridging" infiltrate, widened portal areas, and pseudolobulation. Some infiltrate can be seen in sinusoids. (Hematoxylin and eosin stain. × 150.)

and was only scant within the hepatic sinusoids. In most cases there was a several-fold increase in the size of the portal areas. The hepatic limiting plates were generally intact, but occasional foci of hepatocellular necrosis at the margins of the infiltrated portal areas could be seen. In 21 of the 42 livers (50 per cent) the leukemic infiltration was seen to bridge between adjacent portal areas and was accompanied by bridging of areas of hepatocellular necrosis (Fig. 1). Eighteen cases (43 per cent) showed bridging fibrosis and eight showed pseudolobule formation (Figs. 2, 3). All areas showing bridging fibrosis or pseudolobule formation were infiltrated by leukemic cells. There was marked bile duct proliferation in extreme cases. In patients whose livers showed bridging fibrosis or pseudolobule formation, the mean duration of chronic lymphocytic leukemia was 4.4 years, compared to 2.6 years in those showing no significant fibrosis.

The kidney was seen to be associated with leukemic infiltration in 90 per cent of the cases, and increased fibrosis was observed in 81 per cent. Infiltration of the kidney by leukemic lymphocytes occurred in discrete foci within the interstitium of the cortex, particularly the subcapsular cortex and along the vasa recta at the corticomedullary junction. Foci of leukemic infiltration were consistently associated with local fibrosis, whereas the parenchyma not infiltrated by leukemic cells did not show fibrotic changes (Fig. 4). Interstitial renal leukemic infiltration was accompanied by tubular atrophy and interstitial fibrosis. Periglomerular leukemic infiltration was significantly associated with periglomerular fibrosis or glomerulosclerosis (Fig. 5). Eighty-five per cent of the

The mean duration of the chronic lymphocytic leukemia from the time of diagnosis was 3.3 years, with a range of 3 months to 10 years.

The leukemic infiltrate within every organ consisted of small cells with hyperchromatic nuclei and scanty cytoplasm, histologically resembling mature lymphocytes. The most frequent finding in all the parenchymal organs showing leukemic infiltration was a disproportionate increase in fibrosis, most marked in areas associated with the leukemic lymphocytes (Table 1). Increased fibrosis was not generally observed in parenchyma not associated with leukemic infiltration.

Infiltration of the liver by leukemic cells was seen in 98 per cent of the cases, and increased fibrosis was observed in 43 per cent. In the liver the leukemic infiltration was most often seen in the portal tracts
glomeruli with periglomerular leukemic infiltration exhibited the foregoing fibrotic changes. In patients with chronic lymphocytic leukemia and control subjects, only 9 per cent of the glomeruli that were not associated with nearby leukemic infiltration exhibited increased fibrosis. In four cases the renal leukemic infiltration also occurred in more diffuse though well defined areas, without evidence of chronic inflammation elsewhere in the kidney. These larger areas of leukemic infiltration were associated with equally large areas of tubular atrophy, interstitial fibrosis, periglomerular fibrosis, and glomeruloscle-
rosis. In one section there was a dense focus of leukemic infiltration within the kidney capsule associated with a focal fibrotic thickening of the capsule. This thickened capsular segment was continuous with normal noninfiltrated capsule on either side.

Of the 25 cases in which leukemic infiltration was observed within the heart (64 per cent), 14 showed the infiltrate within the epicardium, 18 within the myocardium, and 12 within the endocardium (Fig. 6). In the endocardium and epicardium the leukemic
infiltration occurred both focally and diffusely in equal proportion; in the myocardium the leukemic infiltration was predominantly diffuse. Myocardial interstitial fibrosis was observed in five (28 per cent) of the cases showing myocardial leukemic infiltration. In one case endocardial and myocardial leukemic infiltration was accompanied by severe endocardial fibroelastosis and myocardial fibrosis.

In the adrenals leukemic infiltration was observed almost exclusively within the medulla (mild cortical leukemic infiltration was observed in two cases). The leukemic infiltration was associated with
Leukemic infiltration into the spleen and lymph nodes was characterized by destruction of the normal architecture. In both organs the parenchyma consisted of a dense diffuse array of small lymphocytes with absence of lymphoid follicles. Fibrosis was not observed in spleen and lymph nodes.

**DISCUSSION**

The histopathologic effects of leukemic infiltrates in various organs of patients with chronic lymphocytic leukemia is not well documented. Many case reports describe the presence of leukemic infiltrates within isolated organs of such patients, but the lymphocytic infiltrate seen in chronic lymphocytic leukemia has never been demonstrated to cause fibrosis of the involved tissues. We therefore undertook this investigation to correlate tissue destruction and fibrosis with leukemic infiltration, and we found a significant positive correlation. Our review of 47 cases of chronic lymphocytic leukemia has shown that leukemic infiltration has been associated with cirrhosis of the liver and fibrosis of the heart, kidney, pancreas, and adrenal.

The liver was the site of leukemic infiltration in 98 per cent of the cases of chronic lymphocytic leukemia reviewed, and 43 per cent showed increased fibrosis. Hepatic leukemic infiltration in chronic lymphocytic leukemia has been described as causing a several-fold enlargement of the portal areas with little infiltration into the hepatic sinusoids. Morphologically the least severe form of liver damage due to leukemic infiltration appears to be an expansion of the portal tracts, whereas the most severe form was associated with cirrhosis. It was found that the livers of patients in whom leukemia was of longer duration exhibited more pronounced fibrosis than in those of shorter duration. It was also observed that the formation of fibrous septa between adjacent portal areas was accompanied by the formation of bridges of leukemic infiltration between these areas. Thus, signs of long standing hepatic involvement with the leukemia include bridging infiltration, bridging hepatocellular necrosis, and bridging fibrosis. The sequel to hepatic bridging fibrosis appears to be the formation of pseudolobules, seen in 19 per cent of the cases reviewed. Chronic lymphocytic leukemia has never been reported as a cause of cirrhosis, although in our cases it was related to cirrhosis independent of alcoholism, malnutrition, or cirrhotogenic therapy. In addition, a suggestion of the possible association between lymphoproliferative disorders and cirrhosis has been reported. Infiltration of the renal parenchyma with small...
lymphocytes has been reported to occur in 64 per cent of the patients with chronic lymphocytic leukemia, but we have observed renal leukemic infiltration in 90 per cent of these patients. Leukemic infiltration in the kidney has been described as primarily involving the renal cortex and corticomedullary junction, and in association with both glomerular lesions and tubular atrophy.\(^1\) Such findings are in accordance with our observations. In addition, we found that in 80 per cent of the kidneys showing infiltration the leukemic infiltration was accompanied by fibrosis. These fibrotic lesions were believed not to be secondary to vascular or inflammatory conditions; fibrosis was observed almost exclusively in foci of leukemic infiltration and renal inflammation was not evident. For these reasons, most important of which is the lack of fibrosis in noninfiltrated areas, we believe that the leukemic lymphocytes induced the observed changes.

In many respects the morphology and effects of renal leukemic infiltration closely resembled those in chronic interstitial nephritis. Some glomeruli, which were only partially surrounded by infiltrate, exhibited early periglomerular fibrosis only in the areas associated with leukemic infiltration, whereas normal Bowman capsules were observed in the remaining "nonleukemic infiltration" portions (Fig. 5). Such examples best illustrate the earliest manifestations of glomerular damage due to leukemic infiltration as well as the capacity of lymphocytes to induce fibrosis of tissue in contact with leukemic cells. Since 85 per cent of the glomeruli associated with leukemic infiltration showed fibrosis, we believe that clinically evident renal failure could result from renal involvement with the leukemia. In addition, indications of an association between the nephrotic syndrome and renal involvement in chronic lymphocytic leukemia have been reported.\(^4\),\(^13\) Also noteworthy was our observation that infiltrated segments of the kidney capsule exhibited increased fibrosis and thickening, whereas adjacent noninfiltrated capsular segments showed no such thickening.

Infiltration of the heart with small lymphocytes in chronic lymphocytic leukemia was reported in a case of mitral insufficiency due to mitral valve fibrosis.\(^14\) In this patient the mitral valve leaflets and annulus, as well as the left atrium and left ventricle, revealed foci of fibrosis associated with foci of dense leukemic infiltration. In contrast, fibrosis was not observed in the noninfiltrated areas of the heart. Also described in the literature are cases of fibrotic epicardial thickening and endocardial fibroelastosis associated with leukemic infiltration in chronic lymphocytic leukemia.\(^15\),\(^16\) We observed areas of epicardial leukemic infiltration associated with fibrosis in five cases of chronic lymphocytic leukemia. In the case of endocardial fibroelastosis it was postulated that the fibroelastosis observed represented a proliferative response by the endocardial and subendocardial fibroblasts and smooth muscle cells to the presence of leukemic infiltration.\(^16\)

The adrenal medulla was the site of leukemic infiltration in 71 per cent of the cases. In most of these adrenals the only apparent alteration of the tissue morphology was the destruction and replacement of the medullary cells by leukemic lymphocytes. Only in one case was the leukemic infiltration accompanied by fibrosis. We speculate that this general lack of fibrosis in the adrenal medulla may have resulted from the relative sparsity of fibroblasts within that site in addition to other unknown factors.

The apparent capacity of the leukemic lymphocytes to induce fibrosis was also exemplified in the pancreas.

Prostatic leukemic infiltration in patients with chronic lymphocytic leukemia has been described many times in association with benign prostatic hyperplasia and urinary obstruction.\(^2\),\(^5\),\(^6\) Clinically significant leukemic infiltration in chronic lymphocytic leukemia has also been reported in the gingiva and palate, as well as in the iris in a case of glaucoma secondary to leukemic infiltration.\(^17\)–\(^20\) In each of these instances the leukemic infiltration presented as soft painless masses consisting of small lymphocytes. Following antileukemic therapy the oral masses were reduced in size, and in the latter case the glaucoma improved. It is not known what effects the antileukemic therapy had on the histologic changes in these cases.

Chronic mononuclear infiltrates are frequently seen in diverse conditions involving chronic inflammation. In chronic inflammation the white cell population is predominantly mononuclear and mostly lymphocytic. From a morphologic viewpoint the chronic reaction is characterized by a proliferative fibroblastic response. Therefore, chronic inflammatory reactions are often followed by considerable scarring with resultant deformities, e.g., permanent fibrous replacement of parenchymal elements, such as liver cells or kidney nephrons.\(^21\) Thus, such reactions can result in organ debilitation and persistent scars. Nevertheless the mechanism by which scarring and fibrosis proceed in chronic inflammation remains obscure.

Recently the first described lymphoid cell derived activity capable of enhancing collagen accumulation was reported.\(^22\) The authors speculated that this fibroblast stimulating activity had important implications in the development of fibrosis consequent to chronic inflammation.\(^22\) The latter hypothesis has also been proposed by other investigators who have demonstrated the capacity of lymphocytes or lymphocyte derived factors to induce the proliferation of connective tissue cells.\(^23\),\(^24\) It has also been shown that antisera prepared from lymphocyte fractions has a suppressive effect on the occurrence of experimental liver fibrosis.\(^25\)

In chronic lymphocytic leukemia the morphologic picture of leukemic tissue infiltration is strikingly similar to that of chronic inflammation. More important, the consequences of leukemic infiltration into parenchymal organs resemble in many respects those
seen in chronic inflammation. We observed significant and substantial examples of parenchymal leukemic infiltration with tissue destruction and fibrosis in a wide variety of organs and cases. The progression from tissue infiltration to fibrosis was exemplified by the liver and kidney in a manner similar to chronic hepatitis and chronic nephritis, by the pancreas in a manner similar to chronic pancreatitis, and by the adrenal and heart. We therefore conclude that the lymphocytic cells of chronic lymphocytic leukemia infiltrate various parenchymal organs and induce fibrosis in a manner similar to chronic inflammation. If these complications are prevented, life expectancy in chronic lymphocytic leukemia may possibly be increased even further. It is hoped that this report will stimulate further research in this field.

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REFERENCES