The authors report a case of sarcoidosis associated with protein losing enteropathy. The diagnosis of intrathoracic stage I sarcoidosis was based on x-ray and biopsy of mediastinal lymph nodes. Enteric protein loss was suspected because of edema lasting for 2 yr, hypoproteinemina, decreased concentrations of serum immunoglobulins, and lymphopenia involving mainly T-cells and proved by \( ^{51} \text{CrCl}_2 \) test (21%/120 hr). Lymphography was consistent with granulomatous involvement of retroperitoneal lymph glands while small bowel biopsy showed blunt villi and dilated lacteals. All the pathological parameters normalized after 6 mo of prednisone treatment. In some cases of sarcoidosis, when abdominal lymph glands are involved, cellular and humoral immunologic derangements may be caused or potentiated by excessive enteric protein and lymphocyte loss.

Sarcoidosis is a systemic granulomatous disease which may invade many organs with special preference for lymph glands. Digestive symptoms of the disease are very rare as it spares the bowel. However, the involvement of lymph glands along the lymphatic drainage of the gut may not be so rare. From this point of view, it is curious that protein losing enteropathy caused, or at least associated with sarcoidosis, the combination observed in our patient, has not been described previously.

Case Report

A 32-yr-old nurse was admitted to Belgrade City Clinic Hospital in June 1978 for evaluation of ankle edema and low serum protein which had persisted for 2 yr. One week before admission she experienced pain and swelling of both knee and ankle joints associated with erythema of the overlying skin. She was treated with penicillin and aspirin. She had no other complaints. Since adulthood she had approximately two bowel movements per week which she regarded as normal in appearance and consistency. Four years earlier she had acute HBsAg-positive hepatitis. As a child she was vaccinated with Bacillus Calmette-Guerin (BCG).

On admission, physical findings were unremarkable except for moderate ankle and pretilial edema. The following laboratory studies were normal: sedimentation rate, complete blood counts, except for lymphopenia (900/mm\(^3\)); urinalyses; blood urea and glucose; serum creatinine; uric acid and electrolytes, except potassium (3.46 meq/liter); iron and total iron binding capacity; cholesterol; transaminases; bilirubin; alkaline phosphatase; prothrombin time; fibrinogen; and the components of complement (C\(_1\), C\(_4\), C\(_5\)). Tests for HBsAg, LE cells, ASTO, CRP, RF, VDRL, cryoglobulins, and Coombs and Paul-Bunnel tests were negative. Sabin-Feldman test was positive at a low titer (1:10) and did not change.

Albumin and gammaglobulin were decreased on two occasions while other protein fractions were normal (Table 1). All the three major immunoglobulins showed low serum concentrations as well, while on immunoelectrophoresis, no qualitative changes were observed.

An x-ray of the chest showed bilateral hilar lymph gland enlargement (Figure 1a). Spirography was normal while capillary blood gas analyses performed before and after exercise were consistent with deranged distribution of ventilation. Mediastinoscopy revealed enlarged succulent lymph glands which were biopsied, and typical sarcoid lesions were found (Figure 2). A Kveim test was not performed due to unavailability of the antigen preparation. Ophthalmologic findings and x-ray of the hands were normal.

Upper gastrointestinal x-ray series and esophagogastroduodenoscopy revealed no gross abnormalities. Biopsy of gastric fundus showed atrophic gastritis. Slight mucosal edema was observed on barium follow through the small intestine (Figure 3). Jejunal biopsy showed blunt, edema-
Figure 1. a. An x-ray of the chest showing bilateral hilar lymph gland enlargement (June 1978). b. Control x-ray of the chest (January 1979). Hilar lymph glands are no more prominent.

Figure 41. Zonal disintegration of basal membrane and detachment from lamina epithelialis were observed even in villi which appeared otherwise normal (Figure 40). Changes in villous villi and dilated lacteals (Figure 40).

Table 1. Serial Analysis of Serum Proteins, Immunoglobulins, Absolute Lymphocyte Counts and $^{51}$CrCl$_2$ Tests Results in Relation to Treatment in 1978/1979

<table>
<thead>
<tr>
<th></th>
<th>Normal values</th>
<th>June 21</th>
<th>30</th>
<th>5</th>
<th>13</th>
<th>23</th>
<th>July 22</th>
<th>13</th>
<th>21</th>
<th>August 3.5-8.0</th>
<th>3.5-5.5</th>
<th>0.7-12</th>
<th>90-450</th>
<th>60-200</th>
<th>500-1800</th>
<th>1500-3000</th>
<th>October 20</th>
<th>13</th>
<th>16</th>
<th>January 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total proteins (g/100 ml)</td>
<td></td>
<td>6.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.7</td>
<td></td>
<td></td>
<td></td>
<td>2.9</td>
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<td>1.00</td>
<td>1.44</td>
<td>0.97</td>
<td>0.75</td>
<td>0.76</td>
<td></td>
<td></td>
<td>7.8</td>
</tr>
<tr>
<td>Albumin (g/100 ml)</td>
<td></td>
<td>4.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.42</td>
<td></td>
<td></td>
<td>4.50</td>
<td>3.50</td>
<td>3.47</td>
<td>3.90</td>
<td>3.91</td>
<td>4.60</td>
<td>1.09</td>
<td></td>
<td></td>
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<tr>
<td>Gamma globulin (g/100 ml)</td>
<td></td>
<td>0.52</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.62</td>
<td></td>
<td></td>
<td>0.91</td>
<td>0.80</td>
<td>1.09</td>
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<td>IgA (mg/100 ml)</td>
<td></td>
<td>82</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>127</td>
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<td>134</td>
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<td>162</td>
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<tr>
<td>IgM (mg/100 ml)</td>
<td></td>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>72</td>
<td></td>
<td></td>
<td>97</td>
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<td>IgG (mg/100 ml)</td>
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<td>639</td>
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<td>795</td>
<td></td>
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<td>657</td>
<td>831</td>
<td>988</td>
<td></td>
<td></td>
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<td>Lymphocytes/mm$^3$</td>
<td></td>
<td>900</td>
<td>880</td>
<td>1084</td>
<td>966</td>
<td>760</td>
<td>1200</td>
<td>1248</td>
<td>1070</td>
<td>1120</td>
<td>2047</td>
<td>1265</td>
<td>1300</td>
<td>1300</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>$^{51}$CrCl$_2$ (%/120 hr)</td>
<td>&lt;1</td>
<td>210</td>
<td></td>
<td>15</td>
<td>10</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td>120</td>
<td>10</td>
<td>15</td>
<td>30</td>
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Treatment

Prednisone (mg/day)

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<th>25</th>
<th>16</th>
<th>15</th>
<th>10</th>
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</table>

Low fat diet

$^a$ Between 20-30 g fat/day.
Figure 2. a. Biopsy of mediastinal lymph node. Diffuse, multiple granulomata (HE × 32). b. Detail showing the structure of noncaseating granulomata with giant multinucleated cells (arrow) (HE × 200).

Figure 3. Barium follow-up: the small intestine showing a slight mucosal edema.

Serum carotene (26.5 μg/100 ml) and 5-g urinary xylose test (2 hr—9.0%, 5 hr—14.0%, normal more than 14.8% and 23.6%, respectively) were diminished. Stools and duodenal juice were repeatedly negative for ova and parasites.

On lymphography, lymphangiographic phase was normal. Visualized inguinal, iliac, and paraaortic glands were slightly enlarged with small defects consistent with granulomatous inflammation in bilateral iliac and left paraaortic glands (Figures 5 and 6a).

Treatment with prednisone (30 mg/day) was started at the beginning of July (Table 1). Very soon normalization of serum albumin, gammaglobulin, and immunoglobulins ensued while the lymphocyte count stayed low. However, prednisone dosage had to be diminished to 10 mg/day because of irritability and insomnia. In August, albumin, gammaglobulin, and IgG were again low. Prednisone dosage was augmented to 15 mg/day, and in September, some improvement of albumin and IgG was noted. The patient had no more ankle edema. The 51CrCl was almost normal (1.2%/120 hr). Prednisone was again diminished to 10 mg/day and a low fat, high protein diet instituted. In November, albumin, gammaglobulin, and IgG were normal, and a further rise of lymphocyte count was noted. The diet was gradually discontinued, and in January, a further rise of serum proteins was observed, and the number of lymphocytes was normalized.

Control x-ray of the chest (Figure 1b) showed diminution of hilar lymph glands. Films of the abdomen showed diminution of involved lymph glands and normalization of their structure (Figure 6b). Biopsy of the small intestine was essentially normal (Figure 4c and d). All the other previously pathological findings reverted to normal: serum carotene, potassium, d-xylose test, and analyses of capillary blood gases.

Cellular Immunity

Representation of immunocompetent peripheral blood cells was examined by the E, EA, EAC, and “active” E rosettes methods (Table 2). Total lymphocyte count and E rosettes were greatly diminished before the start of treatment, while EA and EAC rosettes were slightly reduced. During the treatment, all the investigated parameters increased.
Figure 4. a. Biopsy of jejunal mucosa (June 1978). Many blunt edematous and ballooned villi with normal enterocytes and dilated lacteals in lamina propria mainly just above lamina muscularis mucosae (two shown by arrows) (HE x 65). b. Detail showing villous tip of normal size but with zonal disintegration of basal membrane (arrow) and detachment from lamina epithelialis. (Reticulin x 250). c. Control biopsy of jejunal mucosa (January 1979). Normal appearance (HE x 80). d. Detail showing clearly delineated basal membrane at the tip of the villus (Reticulin x 200).
and completely normalized after 6 mo. "Active" E rosettes were investigated at the end of the observation period and were normal, as was the E/"A" E rosettes index.

The Mantoux test was performed twice, in June 1978, with Alt Tuberculin (1:10,000) and in January 1979, with 5 IU PPD injected subcutaneously in the forearm. It was positive on both occasions. The diameter of induration was 23 and 20 mm, respectively. In vitro generation of LIF (leucocyte inhibition factor) with PPD was investigated in January 1979. Migration inhibition index of peripheral leucocytes was within the limits of healthy persons with a positive skin test (Figure 7).

Table 2. Parameters of Cellular Immunity Before and During Treatment

<table>
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<tr>
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<th>9/20/78</th>
<th>11/14/78</th>
<th>1/16/79</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytes/mm³ (range)</td>
<td>1500-3000</td>
<td>760</td>
<td>1248</td>
<td>1220</td>
<td>2047</td>
</tr>
<tr>
<td>E rosettes/mm³ (x ± SD)</td>
<td>739 ± 131</td>
<td>228</td>
<td>324</td>
<td>422</td>
<td>594</td>
</tr>
<tr>
<td>EA rosettes/mm³ (x ± SD)</td>
<td>229 ± 86</td>
<td>106</td>
<td>125</td>
<td>234</td>
<td>267</td>
</tr>
<tr>
<td>EAU rosettes/mm³ (x ± SD)</td>
<td>212 ± 82</td>
<td>91</td>
<td>137</td>
<td>211</td>
<td>307</td>
</tr>
<tr>
<td>&quot;Active&quot; E rosettes/mm³ (x ± SD)</td>
<td>471 ± 165</td>
<td>np</td>
<td>np</td>
<td>np</td>
<td>348</td>
</tr>
<tr>
<td>Index E/&quot;A&quot; E rosettes</td>
<td>1.56 ± 0.21</td>
<td>np</td>
<td>np</td>
<td>np</td>
<td>1.70</td>
</tr>
</tbody>
</table>

np = not performed.

Discussion

Our patient had an unequivocal intrathoracic stage I sarcoidosis which was clinically silent, except for a short phase of arthralgia which prompted the hospitalization. The only manifestations of the disease state were edema and hypoproteinemia lasting for 2 yr.

As the small bowel biopsy appearance was consistent with a disorder of intestinal lymphatics causing protein losing enteropathy, it is possible that sarcoidosis of glands draining the small intestine or some unrelated disorder caused exudative enteropathy.

An extensive review of the disorders associated with protein losing enteropathy, to which we would add tuberculosis of mesenteric lymph glands, did not include sarcoidosis among the relevant disorders of intestinal lymphatics (Table 3). Clinical, laboratory, and x-ray examinations of the patient excluded practically all the listed diseases.

Although the definitive proof for mesenteric lymph gland involvement by sarcoidosis is lacking, the findings of lymphography support the systemic nature of the disease involving retroperitoneal lymph glands. Further proof consists of simultaneous response of hilar and abdominal lymph glands, small intestinal structure, and protein losing to corticosteroid treatment, although the treatment was assisted by a low fat, high protein diet when daily prednisone dosage was diminished.

According to autopsy, scintigraphic, and lymphographic studies in sarcoidosis patients, the involvement of intraabdominal lymph glands is not rare, and it is curious that cases with protein losing enteropathy have not been described previously. Overt edema is rarely encountered in sarcoidosis. In a rare patient it may be the result of inguinal lymph node involvement and stasis. However, it is possible that subclinical protein losing may also exist.

Abnormalities of humoral and cellular immunity are often encountered in patients with sarcoidosis. Our patient had hypogammaglobulinemia before the treatment. This is not characteristic for sarcoidosis although it has been described. Normal or elevated levels of gammaglobulins, especially IgG, are usually

Figure 5. Lymphography. Slightly enlarged inguinal, iliac, and paraaortic glands with small defects in bilateral iliac and left paraaortic glands.
encountered in sarcoidosis.\textsuperscript{9,13,14} Both increased production and loss may coexist in sarcoidosis, the last one being evident in our patient.

Decreased number of peripheral lymphocytes, with decreased T-cell compartment, as determined by E rosettes formation, and usually normal B-cell subpopulations bearing Fc receptors (EA rosettes) and C\(_3\_\) receptors (EAC rosettes) is characteristic for the majority of patients suffering from sarcoidosis.\textsuperscript{14,15} Our patient exhibited all these features. Impaired delayed skin sensitivity to various antigens including tuberculin is often encountered, but no correlation of total T-lymphocyte number and skin tests can be made.\textsuperscript{13} Our patient responded to tuberculin when the number of T-cells was low as well as when it was restored to normal values. Production of lymphokines by T-cells is normal in sarcoidosis.\textsuperscript{16} Generation of LIF in the presence of PPD was normal in our patient.

\begin{table}
\centering
\begin{tabular}{l}
\hline
\textbf{Table 3. Diseases with Disorders of Intestinal Lymphatics Associated with Protein-Losing Enteropathy}\textsuperscript{a} \\
\hline
\textbf{Intestinal lymphangiectasia} \\
\textbf{Retroperitoneal fibrosis} \\
\textbf{Whipple’s intestinal lymphostrophy} \\
\textbf{Fistula between thoracic duct and small intestine} \\
\textbf{Neoplasms involving mesenteric lymphatics} \\
\textbf{Lymphosarcoma} \\
\textbf{Hodgkin’s disease} \\
\textbf{Mycosis fungoides} \\
\textbf{Mesenchymoma of mesentery} \\
\textbf{Nonspecific granuloma involving the small bowel and mesentery} \\
\textbf{Congestive heart failure} \\
\textbf{Constrictive pericarditis} \\
\textbf{Intestinal septal defect} \\
\textbf{Tricuspid regurgitation} \\
\textbf{Familial cardiomyopathy} \\
\textbf{Myocarditis with generalized myopathy} \\
\textbf{Congenital pulmonic stenosis} \\
\textbf{Thrombosis of superior vena cava} \\
\hline
\end{tabular}
\end{table}
Quantitative lymphocyte depletion, resulting mainly from T-cell deficiency, is characteristic for sarcoidosis. The cause of this defect is unknown. Destruction or redistribution of T-cell in granulomas and effects of T-cell antibodies, as well as intestinal loss, must be taken into consideration, however. Normalization of total lymphocyte count, T-cell number, and proportional rise of B-cell subpopulations paralleled normalization of other parameters in our patients.

The association of sarcoidosis and enteric protein loss, as demonstrated in our case, may be an oddity or a process which may, to some extent, operate in this disease. This can be solved by systematic investigations using appropriate methods.

References