THYMIC ABNORMALITIES AND THE CHRONICITY OF LIVER DISEASE

—Report of 10 Cases and Follow-up Study—

Kiyotaka Kamegaya, Masaharu Tsuchiya, and Ken Sambe

Department of Internal Medicine, School of Medicine, Keio University, Tokyo

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Repeated liver biopsy and laparoscopy as well as routine examination of transaminase level have added much to the progress of the diagnoses of the liver diseases. Liver biopsy, together with repeated liver function tests, have disclosed many of the masked liver impairments that occur without jaundice, hepatomegaly or symptoms at all. Most of these fall into the category of "chronic hepatitis."

Liver function tests reveal normal values in the majority of cases with "benign viral hepatitis" within 4 weeks of the onset of the symptoms without exacerbation. Some cases, on the other hand, show intermittent elevations or persistent low grade elevations of transaminase levels with or without hypergammaglobulinemia and/or abnormal serum colloidal reactions for over 6 months or more. Liver biopsies of many of these cases reveal the picture of chronic active hepatitis characterized by round cell infiltrations and fibrous widening of portal tracts, focal destruction of the limiting plate, mobilization of Kupffer cells and spotty necrosis of the liver parenchyma. Others show a histological picture of acute hepatitis with little fibrosis despite long clinical courses of over 6 to 12 months. This is differentiated from chronic hepatitis, being called persistent hepatitis.

In the early 1950s, Kunkel, Saint and their co-workers pointed out the frequent occurrence of hypergammaglobulinemia and chronic progressive hepatitis with a prominent plasma cell infiltration in young women under 30 years of age. Later, Bearn reported a high incidence of systemic manifestations as fever, polyarthralgia and amenorrhea in these cases. Furthermore, a positive
LE test and some systemic features of SLE often found in these cases led Mackay to his concept of “lupoid hepatitis” suggestive of the close relationship between this special type of hepatitis and SLE, namely “autoimmune disease.” Schaffner and Popper proposed histological findings of “piecemeal necrosis” as a morphological feature of chronic progressive liver disease based on a close correlation between this finding and the statistical data. “Piecemeal necrosis” includes round cell infiltration of portal tracts, destruction of the limiting plate, Kupffer cell mobilization and prominent plasma cells in the periportal area. They tried to correlate these findings with the immunological process. Direct evidence, however, is lacking. The mechanism of the self-perpetuation of hepatitis still remains a question to date. Klatskin claimed persistent viral infection as a cause of chronic hepatitis based on some similarity in histological findings between acute viral hepatitis and chronic hepatitis. Actually, Creutzfeldt and his colleagues reported 9 cases of viral hepatitis in the recipients of blood from the same donor who had had a history of hepatitis 17 years ago and was proved to have postnecrotic cirrhosis. This suggests a long term infection of hepatitis virus causing the cirrhosis and intermittent viremia. Approximately 25% of the cases of postnecrotic cirrhosis have been reported to have had a history of acute viral hepatitis. Direct evidence, however, of the virus itself causing hepatic cell damage with resultant formation of liver cirrhosis is still lacking. Several circulating “autoantibodies” have been discovered in cases of “lupoid hepatitis” and a portion of chronic hepatitis. A concomitance of hepatitis and autoimmune diseases such as Hashimoto’s thyroiditis and ulcerative colitis has been reported. This supports the concept of a participation of the autoimmune process in the persistence and progression of hepatitis. However, direct evidence of hepatocellular damage by autoantibody is not enough to explain this concept.

CASE RECORDS OF THYMIC ABNORMALITIES ASSOCIATED WITH HEPATITIS OR CIRRHOSIS AND INFLUENCE OF THYMECTOMY ON THE CLINICAL COURSE

The authors have reported a high incidence of thymic abnormalities in “autoimmune diseases.” Needle biopsies of the liver have been performed on these cases when hepatic abnormalities were discovered upon physical or laboratory examinations. Findings of chronic hepatitis or fatty liver have been obtained in all of these cases. Clinical course has been followed for several months to years after thymectomy in 7 cases. These 7 cases are briefly summarized here with special reference to serum gamma-globulin levels before and after thymectomy.
### Table 1

**THYMIC ABNORMALITIES AND HEPATIC CHANGES**

<table>
<thead>
<tr>
<th>Thymus</th>
<th>Liver</th>
<th>Laboratory Data</th>
<th>TRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>48y.a.</td>
<td>+ + + +</td>
<td>before</td>
<td>+ + + -</td>
</tr>
<tr>
<td>52y.a.</td>
<td>- + + + +</td>
<td>post 1mon 6mos</td>
<td>- - -</td>
</tr>
<tr>
<td>SLE</td>
<td>- + + - +</td>
<td>1 yr</td>
<td>- -</td>
</tr>
<tr>
<td>21y.a.</td>
<td>+ + + d</td>
<td>1.5yrs</td>
<td>-</td>
</tr>
<tr>
<td>SLE</td>
<td>- - + + +</td>
<td>2 y'rn</td>
<td>-</td>
</tr>
<tr>
<td>60y.a.</td>
<td>+ + d</td>
<td>3 y'rn</td>
<td>-</td>
</tr>
<tr>
<td>Hashimoto</td>
<td>+ + +</td>
<td>2 y'rn</td>
<td>-</td>
</tr>
<tr>
<td>56y.a.</td>
<td>+ + -</td>
<td>4yrs</td>
<td>-</td>
</tr>
<tr>
<td>Masaki</td>
<td>+ + d</td>
<td>4.5yrs</td>
<td>-</td>
</tr>
<tr>
<td>56y.a.</td>
<td>- + +</td>
<td>post 3mos</td>
<td>-</td>
</tr>
</tbody>
</table>

| histological findings | | |
|-----------------------|-------------|
| Thymus                | Liver       |
| parenchymal          | parenchymal |
| hyperplasia          | hyperplasia |
| lymphatic infiltration | fatty liver |
| angiofibromatosis    | angiofibromatosis |
| norm                         | norm            |
| abnormality | abnormality |
| medulla        | medulla       |
| cortex       | cortex        |
| subcapsular  | subcapsular   |
| post-mortem  | post-mortem   |

<table>
<thead>
<tr>
<th>Coombs' test</th>
<th>Erythrocyte count</th>
<th>Leukocyte count</th>
<th>TIBC</th>
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<td></td>
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f: focal  d: diffuse
(Table 1). All of these cases showed abnormally large thymic shadow on pneumomediastinography and were subjected to thymectomy via the suprasternal notch.

**Case 1.** A 48-year-old Japanese female fulfilling the five markers of an autoimmune process proposed by Mackay. LE test was negative in all 4 occasions. Pneumomediastinography revealed an abnormally large thymic shadow. Exirpated thymus showed cystic dilatation of the Hassall's corpuscles, marked hyperplasia of thymic epithelial reticulum cells and prominent eosinophils and many plasma cells (Photo 1). Simultaneously biopsied liver revealed round cell infiltration and fibrous widening of portal tracts, destruction of the limiting

![Graph](image-url)
THYMIC ABNORMALITIES AND LIVER DISEASE

plate, presence of numerous plasma cells, mobilization of Kupffer cells, and spotty necrosis—the features of piecemeal necrosis (Photo 2). The immunoglobulin level before thymectomy was elevated with IgG 3,321 (normal range 1,240±220 mg/dl), IgA 1,000 (280±70), IgM 611 (120±35). A gradual improvement of the immunoglobulin level, especially of IgM, has been observed after thymectomy as represented by the value of IgG (3,364), IgA (434) and IgM (210) in one and a half years after the operation. The gamma-globulin level decreased from 4.6 g/dl to 3.0 g/dl in one and a half years. Improvement of the serum colloidal reaction was also noted.

Case 2. A 58-year-old Japanese female with clinical and laboratory findings of SLE. Extirpated thymus showed lymph follicles with germinal centers (Photo 3) and epithelial hyperplasia. Atypical large cells with segmented and tortuous nuclei as seen in runt disease were scattered throughout the germinal center (Photo 4). The biopsy specimen of the liver showed portal fibrosis and round cell infiltration with focal destruction of the limiting plate. Spotty necrosis and mobilization of Kupffer cells were also noted as seen in chronic hepatitis (Photo 5). Lymphocyte aggregates were noted in the portal areas. The anti-nuclear-factor before thymectomy was 8×(+), which decreased to 4×(+) in 4 weeks after the operation. An improvement was noted in serum IgM level (Table 1). The simultaneously biopsied thyroid showed a picture of focal lymphoid thyroiditis (Photo 6).

Case 3. A 23-year-old Japanese female with the chief complaint of struma. Pneumomediastinography revealed a large thymic shadow. Thymectomy and simultaneous biopsies of the thyroid, cervical nodes and sternocleidomastoid muscle were performed. The thymus showed lymph follicles with germinal centers and hyperplasia of epithelial reticulum cells. Features of diffuse lymphoid thyroiditis were also noted. Needle biopsy of the liver revealed round cell infiltration of portal tracts, mobilization of Kupffer cells and a scattered spotty necrosis of hepatic cells.

Case 4. A 21-year-old Japanese female with features of SLE as represented by erythematous skin rash over the face, intermittent polyarthralgia and a positive LE test. Marked hyperplasia of epithelial reticulum cells was noted in the removed thymus. The liver showed round cell infiltration and fibrous widening of the portal tract, mobilization of Kupffer cells and scattered plasma cells. An improvement of immunoglobulin and serum colloid reaction was noted one and a half years after thymectomy.

Case 5. A 40-year-old Japanese female who was admitted to the hospital because of struma, abnormal colloidal reaction and elevated IgM. The
thyroid showed diffuse infiltration of lymphocytes and plasma cells with areas of lymph follicle formation as seen in chronic lymphoid thyroiditis (Photo 7). Lymph follicles with germinal centers were noted in the thymus (Photo 8). Needle biopsy specimen of the liver revealed round cell infiltration of the portal tracts and around central veins, mobilization of Kupffer cells and spotty necrosis (Photo 9). No remarkable fibrosis was noted. No improvement was found in the laboratory data in 3 months after thymectomy.

**Case 6.** A 56-year-old Japanese male who was admitted to the hospital because of an abnormal colloid reaction and hypercholesterolemia discovered on an annual physical check-up. The patient also was noted to have struma. The thymus showed marked hyperplasia of epithelial reticulum cells. The thyroid was that of a chronic lymphoid thyroiditis with a diffuse round cell infiltration and lymph follicle formation, degenerated follicles and islands of oxyphilic as well as pale cells.

The liver revealed diffuse fatty metamorphosis of a moderate degree. Marked improvement of serum gamma-globulin, immunoglobulin and colloidal reaction was the laboratory findings in 4 years after thymectomy (Table 1).

**Case 7.** A 56-year-old Japanese female presented with epigastric discomfort. Abnormal colloid reaction, hypergammaglobulinemia and hepatomegaly of a moderate degree were noted. Pneumomediastinography revealed a large thymic shadow. Extirpated thymus showed hyperplasia of epithelial reticulum cells and the biopsied liver showed round cell infiltration and a slight fibrosis of portal tracts as well as mobilization of Kupffer cells.

**Case 8.** A 55-year-old Japanese male who expired following massive hematemesis and melena approximately 1 year after laparoscopy and needle biopsy of the liver with a diagnosis of liver cirrhosis. At autopsy a postnecrotic type of the cirrhosis was noted (Photo 10). Hyperplasia of thymic epithelial reticulum cells, some forming a glandular arrangement, was also noted (Photo 11).

**Case 9.** A 72-year-old Japanese male with a dull pain in the substernal region. X-ray films of the chest disclosed an abnormal shadow in the mediastinum. Biopsy of this lesion revealed the thymoma (epithelial type, Photo 12) located in the anterior mediastinum. Simultaneous biopsy of the thyroid discovered the presence of a focal lymphoid thyroiditis. Anterior mediastinal lymph nodes showed many plasma cells. Laparoscopy and needle biopsy of the liver confirmed a postnecrotic type of liver cirrhosis.

**Case 10.** A 39-year-old female with myasthenia gravis. Pneumomediastinography revealed an abnormal shadow in the anterior mediastinum,
which was diagnosed as a thymoma with biopsy. The patient died of respiratory failure despite irradiation and medication. The anterior mediastinum at autopsy was filled with a thymoma (epithelial type, Photo 13) and the liver showed round-cell infiltration of portal tracts and mobilization of Kupffer cells as well as spotty necrosis (Photo 14).

COMMENT

Now, evidences has been accumulated to support the idea of some participation of the immunologic process in the perpetuation and progression of a chronic liver diseases. Since the epoch-making report of Miller on the “Immunological Function of the Thymus” in the new-born mice, the role of the thymus has become one of the major field in the study of immunity. The suppression of immunological competence has been noted especially when thymectomy was performed on the 1st day of life. The suppression of graft-versus-host reaction is marked even when the suppression of the production of the circulating antibody is minimal. Miller counted the number of immunocytes in the spleen several times for a period of 2 years after thymectomy performed on the mice of 2~3 weeks of age, and reported an apparent decrease in immunocytes from 9 months and beyond after thymectomy on. This may suggest an immunological suppression occurring some time after thymectomy even in grown-up animals. A remarkably high incidence of thymic abnormalities in cases of “autoimmune disease” has been observed. In a series studied by the Keio University group, formation of the lymph follicles with germinal centers has been noted in exirptated thymuses in 55.6% of 18 cases of chronic lymphoid thyroiditis, in 73.5% of 34 cases of myasthenia gravis, in 1 out of 3 cases of SLE and in 1 out of 2 cases of autoimmune hemolytic anemia by the end of August, 1970 (Table 2). Another finding of thymic abnormality, namely abnormally marked hyperplasia of thymic epithelial reticulum cells, has been observed in approximately 80% of the cases of “autoimmune diseases.” Generally, lymph follicle formation in the thymus is rarely observed. Okabe reported only 18 such cases (1.3%) in 1,356 consecutive autopsy cases. Observation of lymph follicles in the thymus of NZB-strain mice, in which an autoimmune process such as autoimmune hemolytic anemia and positive Coombs reaction are frequently found, as well as in some cases of SLE, has drawn attention to the correlation of thymic abnormalities with the development of “autoimmune disease.” Thymic lymph follicles have been recognized in remarkably high incidence in “autoimmune disorders” including myasthenia gravis in which it is approximately 74% in the authors’
Castleman also reported it to be between 60%–70%.

Interestingly enough, runt animals, that are produced by inoculating newborn animals with intact adult lymphoid cells from a different strain, show foci of necrosis and cellular infiltration in the liver. Mackay interpreted these lesions as being due to an immunologic reaction between the injected lymphoid cells and the liver tissue. It might be surmised that a portion of human hepatitis could similarly be caused by immunologically competent cells directed against the individual's own liver.

Recently, cases of thymic abnormalities and chronic liver disease have been accumulated at the Keio University Hospital. The authors experienced 2 cases of liver cirrhosis (both postnecrotic), one (72-year-old male) with a thymoma and the other (55-year-old male) with a marked hyperplasia of thymic epithelial cells, which has already been presented in this paper. Corridan reported a case of a 34-year-old male with liver cirrhosis, splenomegaly and thymic abnormalities represented by lymph follicle formation with germinal centers as well as hyperplasia of thymic epithelial cells. Coexistence of liver cirrhosis and chronic lymphoid thyroiditis, one of the autoimmune diseases, has been reported. McConkey described 3 cases of chronic lymphoid thyroiditis (57-year-old female, 52-year-old female and 63-year-old female) with liver cirrhosis. If the immunological process plays a part in the development of chronic liver disease, the following might be postulated: 1) Impaired and degenerated liver tissue first caused by virus or other agents acquires antigenicity as a result of diverted antibody-forming system in the host. 2) A non-specific antigen-antibody-complex injures slightly impaired liver cells. 3) Abnormal antibody-producing-system in the host, namely abnormally high antibody-forming activity may produce lesions with or without specificity to the organs causing hepatitis, thyroiditis, SLE and allied disorders.
At the present absolute criteria for the diagnosis of autoimmune disease seems to be lacking with the exception of acquired hemolytic anemia. However, Mackay has proposed certain markers as evidence for an autoimmune process. These markers are: 1) pronounced hypergammaglobulinemia, over 2 g per 100 ml; 2) circulating autoantibodies; 3) dense plasma cell and lymphocytic invasion of affected tissues; 4) responsiveness to cortisone and its derivatives; and 5) association of the lesion under consideration with other lesions caused by autoimmunity. He claims the lupoid type of chronic hepatitis fulfills the above criteria. Cohen et al, using the fluorescein-labeled antibody technique, showed that cells containing gamma-globulin were present in the hepatic sinusoids and fibrous tracts. Even if intrahepatic gamma-globulin formation might indicate the formation in situ of antibodies to components of liver cells, it cannot be stated with certainty that the hypergammaglobulinemia and the associated lymphoid invasion of the liver is the actual cause of the persisting disease of the liver; it could be the result of liver damage from the causes.

**SUMMARY**

The present series include one case of chronic active hepatitis fulfilling the 5 markers for an autoimmune process, 2 cases of SLE, 3 cases of lymphoid thyroiditis and a case of hepatomegaly. Pneumomediastinography showed abnormally large thymic shadow and histological examinations revealed lymph follicle formation and/or marked hyperplasia of epithelial reticulum cells in all cases. The liver showed features of hepatitis ranging from non-specific reactive hepatitis to chronic active hepatitis. The presence of gamma-globulin in some cases was demonstrated in the germinal centers of the thymus with a fluorescein-labeled antibody technique. A long-term follow up study has disclosed an improvement of the serum gamma-globulin level, the colloidal reaction and the latex fixation test and so forth. (A case of liver cirrhosis with hyperplasia of thymic epithelial reticulum cells and two cases of thymoma with liver cirrhosis and/or fibrosis were also recorded.)

These findings would support the possibilities of a participation of thymic abnormalities or immunological processes in the development of some chronic hepatitis or cirrhosis.
REFERENCES


EXPLANATION OF PLATES

Photo 1. Case 1. a 48-year-old female. Extirpated thymus showing cystically dilated Hassall's corpuscles (H) and hyperplasia of epithelial reticulum cells. H. & E.

Photo 2. Case 1. a 48-year-old female. Liver biopsy specimen showing "piecemeal necrosis." Destruction of limiting plate and presence of many plasma cells. Methylgreen-pyronin.

Photo 3. Case 2. a 58-year-old female. Surgical specimen of the thymus showing a lymph follicle (G) and hyperplasia of epithelial reticulum cells. H. & E.

Photo 4. Case 2. a 58-year-old female. High power view of the germinal center (G) of Photo 3. Some cell showing pleomorphism, segmented and tortuous nuclei and mitotic figures. H. & E.

Photo 5. Case 2. a 58-year-old female. Biopsy specimen of the liver showing round cell infiltration of portal tract with lymphocyte aggregate (L), focal destruction of limiting plate and mobilization of Kupffer cells. H. & E.

Photo 6. Case 2. a 58-year-old female. Biopsy specimen of the thyroid showing focal round cell infiltration. H. & E.

Photo 7. Case 5. a 40-year-old female. Biopsy specimen of the thyroid showing a picture of lymphoid thyroiditis. Lymph follicle with germinal center (G) is noted. H. & E.

Photo 8. Case 5. a 40-year-old female. Surgically removed thymus showing a lymph follicle with germinal center (G). H: Hassall's corpuscle. H. & E.

Photo 9. Case 5. Needle biopsy of the liver showing round cell infiltration of portal tract and mobilization of Kupffer cells. H. & E.

Photo 10. Case 8. a 55-year-old male. Autopsy specimen showing postnecrotic type of liver cirrhosis. H. & E.

Photo 11. Case 8. a 55-year-old male. Surgical specimen of the thymus showing hyperplasia of epithelial reticulum cells with areas of glandular arrangement. H. & E.

Photo 12. Case 9. a 72-year-old male. Surgical specimen showing a picture of thymoma. H. & E.

Photo 13. Case 9. a 72-year-old male. Autopsy specimen showing a feature of thymoma. H. & E.

Photo 14. Case 10. a 39-year-old female. Autopsy specimen of the liver showing round cell infiltration and fibrosis of portal tract. Spotty necrosis and mobilization of Kupffer cells are also noted. H. & E.