So-Called Subacute Hepatitis Accompanied by Chronic Non-Suppurative Destructive Cholangitis

Report of a Case

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While chronic non-suppurative destructive cholangitis in the interlobular and septal bile ducts has been considered a characteristic histological finding in the early stage of primary biliary cirrhosis,[1),2)] certain chronic liver diseases other than primary biliary cirrhosis have been found to be accompanied by similar ductal lesions, although in rare instances.[2)-4)]

This report deals with our clinical experience obtained from a case with the so-called subacute hepatitis in which the sero-immunological abnormality and the typical histological manifestations characteristic of chronic non-suppurative destuctive cholangitis were observed.

CASE REPORT

The patient was a 52-year-old housewife who was hospitalized in our clinic on May 13, 1971, because of severe jaundice. Despite being normally healthy, she began to complain of general fatigue and anorexia from mid-March, 1971, followed by recognizing that her skin was becoming yellow. On March 20 of the same year, she was diagnosed as having acute hepatitis by a neighboring physician, and the jaundice gradually intensified in spite of hospital treatment. She had no history of blood transfusion, and she had not used any drug habitually. Her menstruation had ceased three years earlier.

At the time of admission, her illness was characterized by severe skin jaundice, without manifestation of exanthema, subcutaneous bleeding or vascular spider. No auscultatory abnormalities were noted on her heart or lung. The abdomen was flat, without venous dilatation. The liver was palpable three fingerbreadths below the right costal margin in the right mid-clavicular line, and was slightly firm, with a smooth surface, and

without tenderness. Neither the spleen or either kidney was palpable. Body temperature was 36.6°C.

Laboratory data at the time of admission revealed: Hemoglobin, 9.8 g/dl; red blood cells, 3,340,000 per cu. mm; white blood cells, 4,400 per cu. mm with a differential blood count of neutrophil 74%, eosinophil 7.0%, lymphocyte 1.8% and monocyte 1%; serum bilirubin, 25.9 mg/dl (direct bilirubin, 14.0 mg/dl); S-GPT, 38 units (normal, 10 units); serum alkaline phosphatase, 4.4 Bodansky units; serum lactic dehydrogenase, 64 units (normal 34 units);the serum cholesterol, leucine aminopeptidase, amylase, urea, ammonia and alpha ketoglutaric acid were at almost normal levels. Other values obtained included: serum total protein, 6.6 g/dl; serum albumin, 2.4 g/dl; serum gamma globulin, 3.1 g/dl; serum immunoglobulin G, 246 units (normal 100 units); serum immunoglobulin A, 340 units; serum immunoglobulin M, 250 units; C-reactive protein, positive; rheumatoid factor, positive; anti-liver antibody, positive; the antinuclear factor, mitochondrial antibody, smooth muscle antibody, lupus erythematous cell, and hepatitis B antigen were all negative. No hemorrhagic or hemolytic tendency was noted. X-ray films of the chest and alimentary tract were not contributory.

Hospital course: In view of the above data from various examinations and the clinical course until her admission to our hospital, the diagnosis of acute viral hepatitis was made provisionally. Despite the later normalization of SGPT levels, the jaundice persisted. In addition, the presence of a hemangioma was suspected in the left lobe of the liver as a result of a hepatic arteriography, and an exploratory laparotomy was performed on June 18, 1971. At the time of the laparotomy, an engorged vascular network, suggestive of hemangioma, was observed on part of the surface of the left lobe of the liver, whereas the cut surface of the resected liver did not exhibit any hemangioma. There was no obstructive mechanism acting in the extrahepatic biliary system, and the flow of bile was favorable. Postoperatively, serum total bilirubin levels fell slightly with a remarkable reduction of the serum albumin and cholesterol contents. The patient became comatose following suddenly intensified jaundice on July 3, and died on July 8, 1971.

Histological findings from the liver: submassive liver cell necrosis and collapse of the supporting reticulum fibers were noted from central vein areas to portal areas, and portal areas were fibrous and extended, and were connected to each other. (Figs. 1, 2, and 3) The so-called "bridging" due to a proliferation of connective tissues was seen between the portal area and the zone of the pericentral necrosis. (Fig. 4) In the portal area there was a

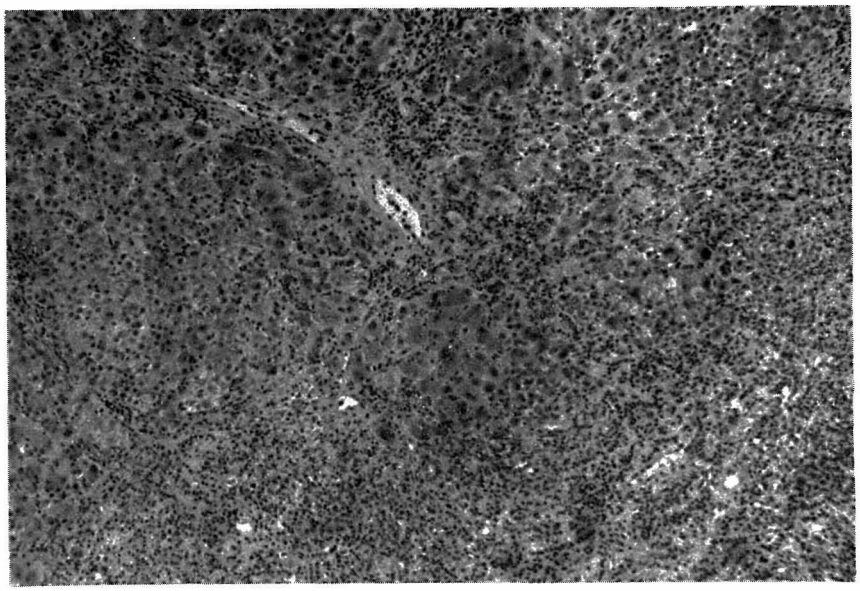

Fig. 1. Submassive loss of parenchymal cells from the central vein area to the portal area. Hematoxylin and eosin stain; ×150.

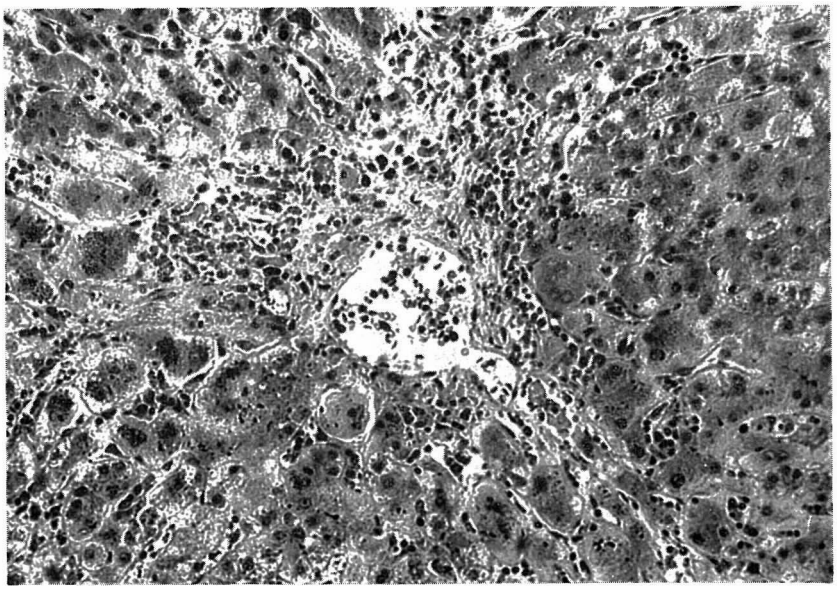

Fig. 2. The absence of parenchymal cells and the presence of a mononuclear inflammatory reaction around the central vein. Hematoxylin and eosin stain; ×360.

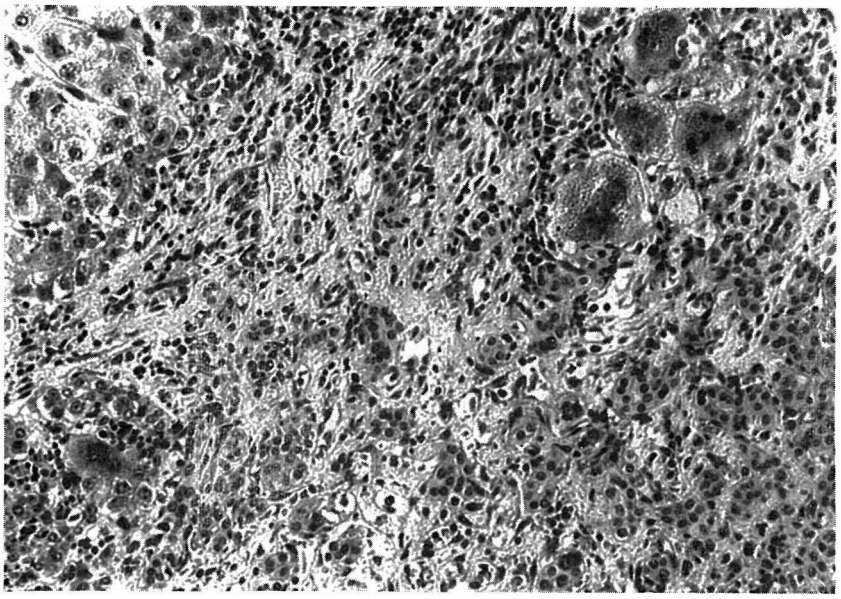

Fig. 3. Small island of multinucleated giant liver cells surrounded by a large zone of necrosis and stromal collapse. Hematoxylin and eosin stain; × 360.

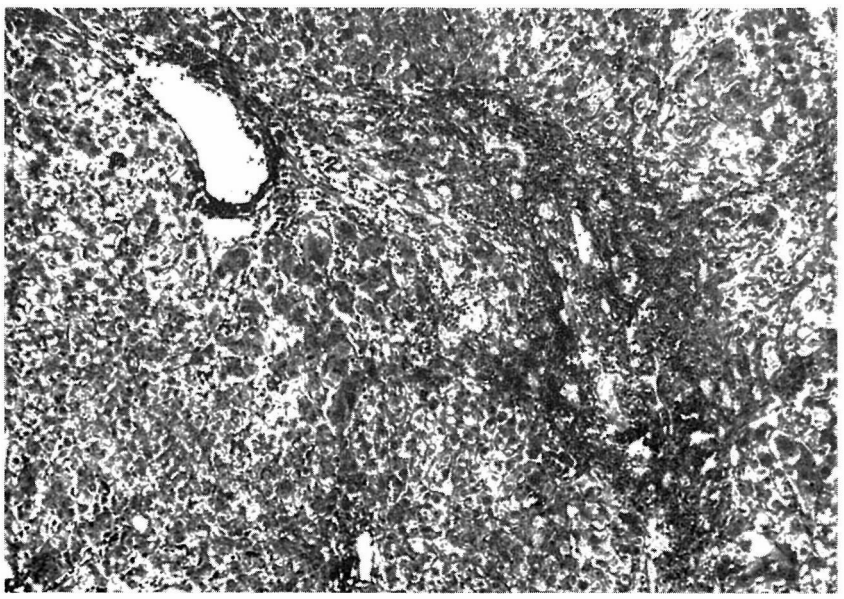

Fig. 4. The zone of necrosis bridging central and portal areas. Azan's stain; × 150.

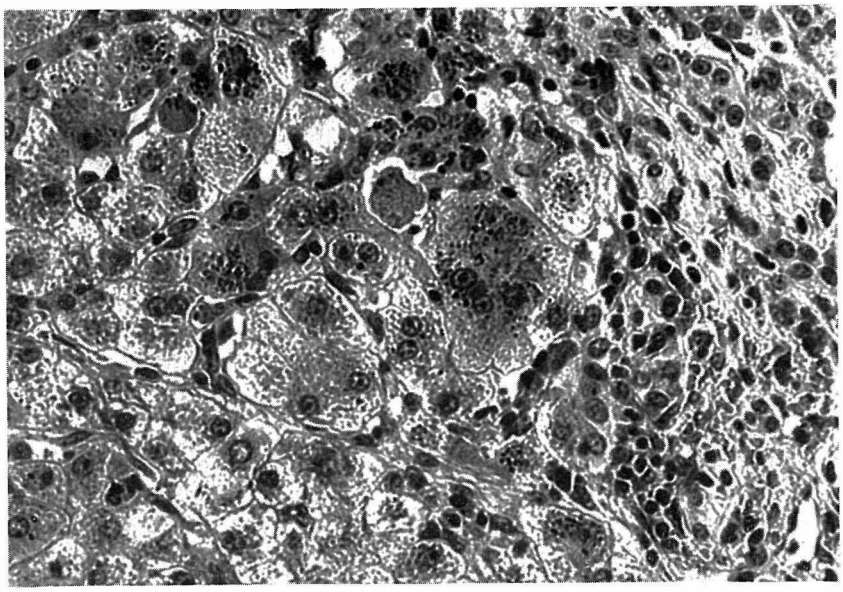

Fig. 5. The peripheral unicellular degeneration and an intense mononuclear reaction in portal area. Multinucleated giant cells and Councilman-like body are seen. Hematoxylin and eosin stain; ×720.

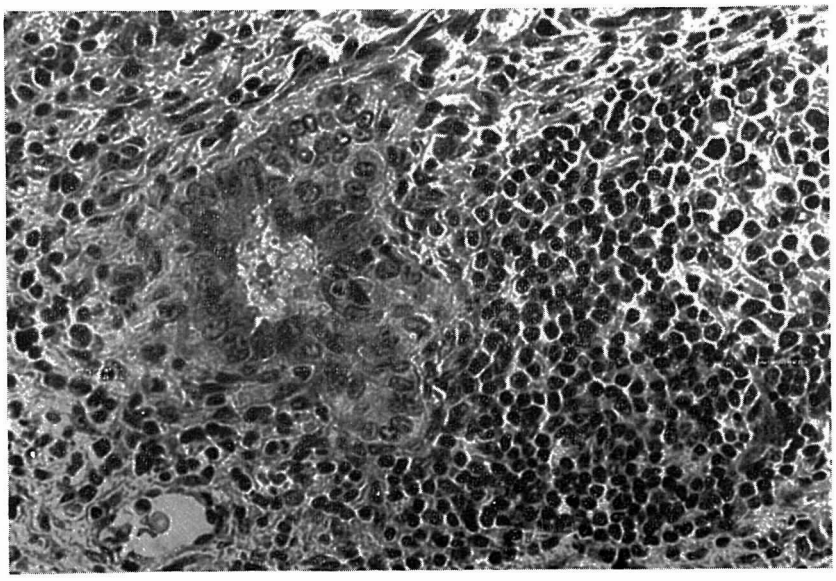

Fig. 6. Epithelial lining of bile duct is irregularly infolded and partly infiltrated by inflammatory cells. Hematoxylin and eosin stain; ×720.

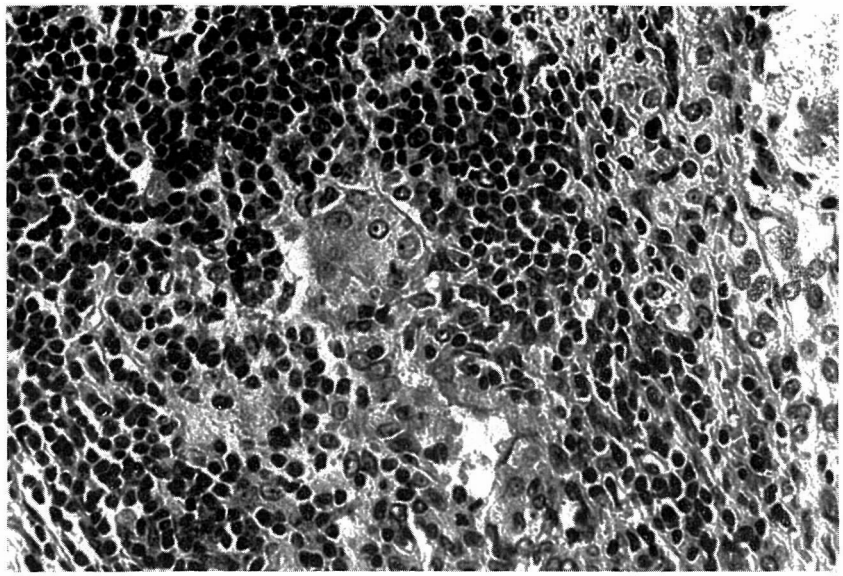

Fig. 7. A necrotic duct is surrounded by inflammatory cells. Hematoxylin and eosin stain; ×720.

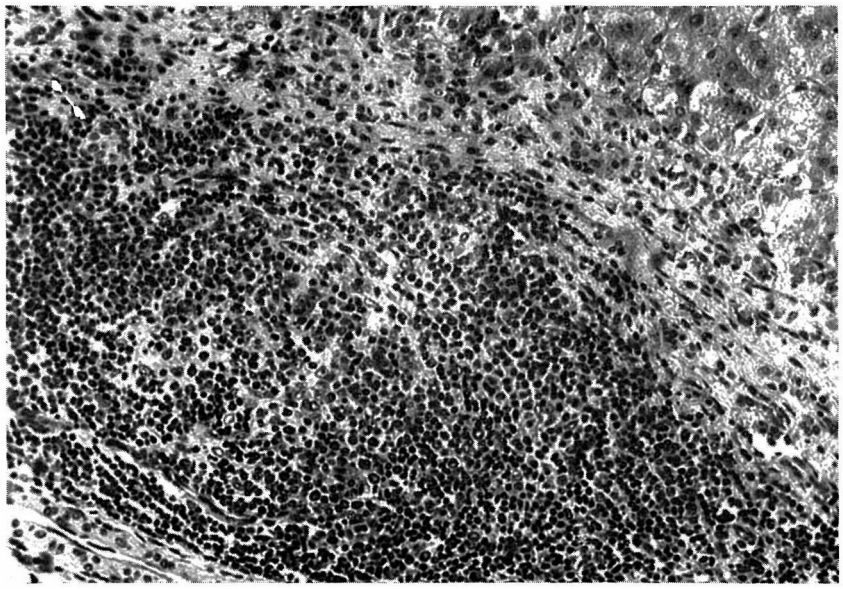

Fig. 8. A lymphoid follicle, containing a germinal center, is seen in a portal triad. Hematoxylin and eosin stain; ×360.

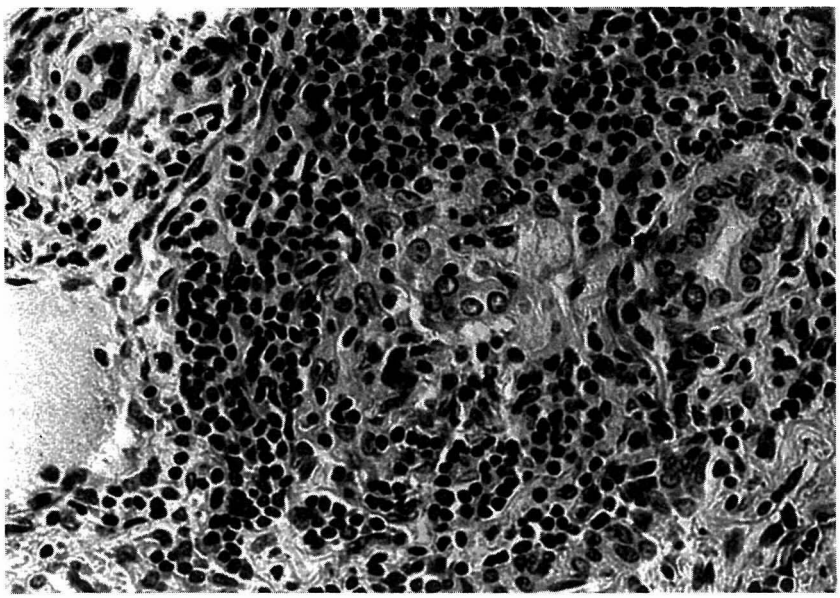

Fig. 9. A destructed interlobular bile duct is surrounded by epitheloid macrophage and lymphoid cells, forming a periductal granuloma Hematoxylin and eosin stain; ×720.

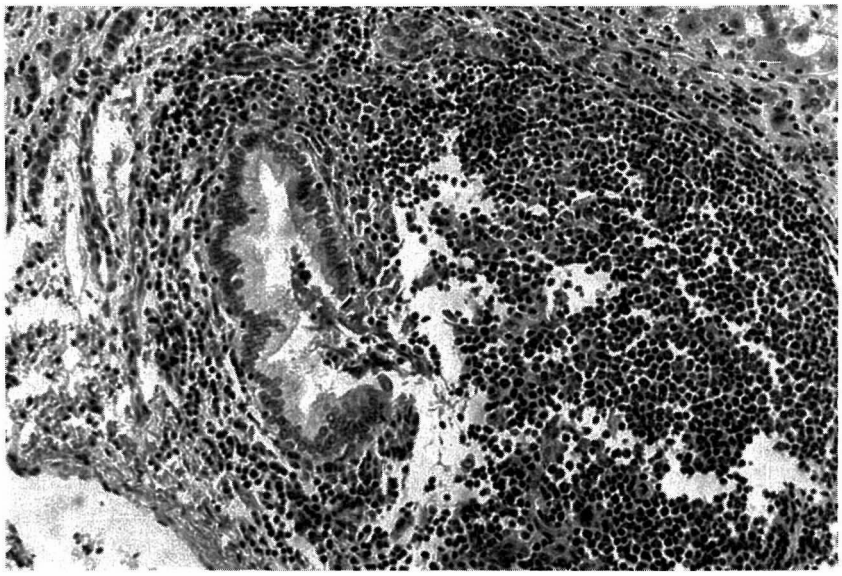

Fig. 10. A relatively large duct of more than 100 micron in inside diameter is also destructed and surrounded by many mononuclear cells. Hematoxylin and eosin stain; ×360.

remarkable infiltration of mononuclear cells and proliferation of bile ducts and bile ductules, and the parts of the remaining liver parenchymya looked like islands in a broad defect of the liver parenchyma. (Fig. 3) Liver cells were remarkably unequal in size, and there was an abundance of eosinophilic cells, Councilman-like body, multinucleated giant cells and balloon cells, especially in the periportal area. (Fig. 5) In addition to these, there was a deposition of bile pigments in the liver cells, a bile stasis in bile canaliculi, and a swelling of the Kupffer cells. On the other hand, in some of the interlobular bile ducts of the small to moderate size there was a degeneration or proliferation of the epithelium, and parts of the bile ducts were destructed, and embraced by infiltration of lymphocytes and plasma cells. (Figs. 6 and 7) Highly infiltrated area exhibited a lymphatic follicle-like aspect, and a germinal center was occasionally seen. (Fig. 7) Collected epitheloid macrophages and lymphoid cells were observed around some of the destructed bile ducts, forming periductal granuloma. (Fig. 9) In addition, similarly destucted ductal lesions were also seen in the relatively large bile ducts of more than 100 micron in inside diameter. (Fig. 10)

DISCUSSION

In summarizing this case, the patient was diagnosed as suffering from acute viral hepatitis in its early stage, gradually lost her liver function together with a progression of jaundice, and died in a coma about 4 months after the onset of her illness. Histologically the co-existence of findings coincidental to those of subacute hepatic necrosis[5)-7)] and typical chronic non-suppurative destructive cholangitis characteristic of the early stage of primary biliary cirrhosis was confirmed.

When studied from a clinical aspect, the present case was poor in its characteristic clinical manifestations of primary biliary cirrhosis, namely, the case lacked itching which precede the insidious onset of jaundice, xanthoma, highly elevated serum alkaline phosphatase and cholesterol values, positive finding for mitochondrial antibody and relatively benign and long clinical course. When studied by excluding the findings of chronic non-suppurative destructive cholangitis, the present case was clinically as well as histologically accorded with the subacute hepatitis described by Tesdale.[7)] Accordingly, the present case should be considered primarily to be subacute hepatitis with the ductal lesions rather than the generally accepted primary biliary cirrhosis itself or a co-existence of primary biliary cirrhosis and subacute hepatitis.

The combination of chronic progressive liver disease accompanied by sero-immunological abnormality, called active chronic (chronic aggressive)

hepatitis, with chronic non-suppurative destructive cholangitis or similar ductal lesions has been reported clinically, although it is rare.[2)-4)] In addition, even in typical primary biliary cirrhosis, piece meal necrosis has been noted, even in a mild degree, simultaneously with the development of characteristic ductal lesions.[8),9)] Therefore, it may be postulated that certain chronic hepatitis and primary biliary cirrhosis may histologically overlap. While tissue antibodies such as antinuclear factor, smooth muscle antibody and mitochodrial antibody have been found in high levels and for prolonged period of times in either active chronic hepatitis or primary biliary cirrhosis, Doniach et al.[10)] advocated the presence of an immunological overlap between both disorders. They gave the following explanation: there may be a certain common action mechanism, perhaps due to autoimmunity, in the development of both diseases, and this may interfere with both the liver cells and bile ducts, and depending upon which of these structures is affected, the disease may progress as active chronic hepatitis or primary biliary cirrhosis. And they pointed out the possibility of developing a primary biliary cirrhosis of "low grade non-progressive form". Although the thought from Doniach et al. can not be applied to our present case without question because there is a slightly different nuance between subacute hepatitis and active chronic hepatitis from the etiological or clinical and histopathological viewpoints,[7),11)-18)] their thought is a very interesting assumption for studying the etiology of primary biliary cirrhosis.

In any event, it may be interesting to see whether or not a clinical picture characteristic of primary biliary cirrhosis will be produced from the ductal lesions by some etiological factors in the future as seen in the relevent current clinical report and the report of our present case. If such a case is observed, it will be highly suggestive in the study of the etiology of primary biliary cirrhosis and its relationship to other hepatic disorders.

SUMMARY

This report deals with the clinical course of a 52-year-old postmenopausal woman who was diagnosed clinically as subacute hepatitis, but histologically exhibited the co-existence of subacute hepatic necrosis and chronic non-suppurative destructive cholangitis characteristic of the early stage of primaty biliary cirrhosis. This case suggested the possibility of a histological overlap between primary biliary cirrhosis and certain types of hepatitis.

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