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Complete Giant-Liver Cell Transformation with an Unusual Good Clinical and Histological Course (Case Report)

by

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A form of hepatitis occurring in the neonatal period and clinically simulating biliary atresia was first described by Craig and Landing in 1952. The characteristic histopathologic feature of the disease at biopsy and autopsy was the presence of multinucleated giant liver cells replacing most of the parenchyma. The general architecture of the liver lobule however was preserved, the portal triads and central veins were in their usual places. Because of these characteristic giant cells, the disease is called giant cell hepatitis, giant liver cell transformation, sometimes also neonatal hepatitis, because it was thought to occur only in neonates.

This last name is actually a misnomer, since it may also occur in a child up to 1 year of age. It should be emphasized that it is the number and the nature of these cells that distinguish this lesion from the viral hepatitis of postnatal life, including cases occurring in children between birth and 14 years of age (Popper and Volk, 1949; Williams and Gaber, 1949).

A study of a number of cases belonging to this category by Smetana and Johnson (1955) confirmed the gross and histologic features described by Craig and Landing (1952) and added other histopathologic features with regard to the proper interpretation of this condition. They concluded that hepatic giant cells are specific elements, and distinguished the incomplete or partial giant cell transformation from the complete form. Since giant liver cells do not divide into regular hepatic elements, but occupy the entire width ordinarily

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Fig 1 : *PA No. 683056, H & E stain, X 125. Complete giant liver cell transformation. Liver lobules are taken up by multinucleated giant liver cells, occupying the entire width of the cellular columns.*

taken up by the liver cell collumns, bile canaliculi cannot be formed. Therefore, no communication exists between the bile-secreting liver giant cells and the biliary passages. The accumulated bile is retained within the giant cells, causing damage, degeneration and eventually necrosis. Follow up studies by Smetana (1963) revealed that the final effect of the complete giant cell transformation of the neonatal liver is one of post-necrotic collapse and diffuse fibrosis, without regenerative pseudolobules, perhaps due to the inability of these giant liver cells to reproduce. Death occurs in hepatic insufficiency with persisting extreme jaundice and signs pointing toward biliary atresia. The incomplete form however is not necessarily fatal, since gradual substitution of the giant cells by regular elements can take place so that near normal condition may be obtained.

There is still no unanimity regarding the etiology of this disorder. Some etiologic factors have been thought to be responsible for this phenomenon, e.g. virus (Stokes et al. 1951, 1954), intrahepatic biliary atresia (Smetana and Johnson, 1955; Smetana, 1963), isoimmune reaction due to blood incompatibility (Zeitthofer and Speiser, 1950; Reiffenstuhl, 1953; Gellis et al. 1954; Ehrlich and Ratner, 1955; Krainin and Lapan, 1956; Stempfel et al. 1956; Bain et al. 1957), autosomal recessive inborn error of metabolism (Hsia et al., 1958). Giant cell formation has been noted (but not in all) in infections due to Coxsackie B virus, cytomegalo-virus, toxoplasma, and viruses of herpes simplex, herpes zoster, varicella, variola, vaccinia and rubella. It may be said that in earliest infancy hepatocellular injury of almost any cause may be associated with a tendency on the part of the parenchymal cells toward duplication and multiplication of the nuclei and cytoplasmic changes, including swelling and perhaps actual growth leading to the appearance of syncytial giant structures, probably a regenerative response. Usually these changes are relatively slight and will not confuse the diagnosis (Zuelzer, 1963).

The association of neonatal hepatitis and biliary atresia with the trisomy 17-18 syndrome adds to the complexity of an area that has plagued numerous clinicians and pathologists. Alpers et al. (1969) speculate that the best explanation would be a virus infection producing both the chromosome changes and the liver-biliary-tree findings.

This case is reported to show that the typical complete giant liver cell transformation as described by Smetana (1963) is not always fatal, but may have a good clinical and histologic course.

Case Report

R, an Indonesian girl was born on November 27, 1967 and admitted to

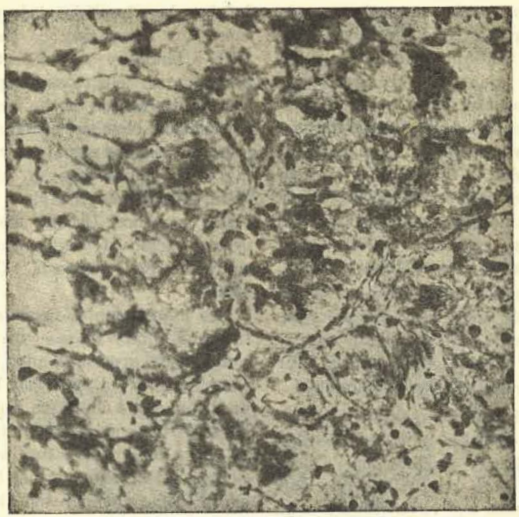

Fig. 2 : *PA No. 683056, Reticulum stain, X 250. Condensation of reticulum fibers about giant cells.*

the Department of Child Health on Febuary 13, 1970, because of subcutaneous bleeding, anemia and fever. Fever started 6 days prior to the admission with cough, common cold and followed by anorexia, general weakness and mild jaundice. Her parents noted that she often suffered from traumatic ecchymosis and cough during these 2 months period prior to the admission. On January 9, 1970, a pediatrician advised the parents to bring her to our Department for further examination, but her parents did not. She contracted this jaundice for the second time. The first episode was in infancy and recovered after surgical intervention at the age of seven months. On the fourth day of admission we knew from the pediatric surgeon and the pathologist that at that time she showed clinical features and laboratory findings of a classical obstructive jaundice. Ductal irrigation showed that the duct was patent and surgical biopsy of the liver performed concomitantly in one of the best privately managed Saint Carolus Hospital on June 19, 1968 revealed on gross examination a blackish green fresh liver specimen, which histologically showed the following features (fig. 1): The liver lobules were taken up by multinucleated giant liver cells, occupying the entire width of the cellular collumns radiating from the efferent vein to the periphery of the lobule. Giant liver cells contained up to 20 nuclei and tiny bile particles in cytoplasm. Bile canaliculi were not visualized. Reticulum stain revealed condensation of reticulum fibers about giant liver cells (fig. 2), presumably because of disintegration of cells. Sinusoids were narrowed, compressed by giant liver cells. Some Kupffer cells contained bile pigment. The portal areas were small and lightly infiltrated with lymphocytes and monocytes. The efferent veins were still in proper position. There was also marked perilobular fibrosis.

The mother did not suffer from jaundice during pregnancy and this child was delivered as a fullterm baby with a birthweight of 3800 grams.

Physical examination on the day of admission revealed a pale girl of satisfactory nutritional status, with low grade scleral icterus, suggilatae and ecchymoses on the corner of her left eye, arms and legs especially her elbows and knees, who looked moderately ill. Her height was 90 cm, weight 11.6 kg and her temperature 39.5 C. The lungs and heart were normal. The liver was enlarged for 2.5 cm below the costal margin, and not tender on palpation. There was a surgical scar along the paramedian line over the liver. The spleen was not palpable. The tuberculin test was negative. Laboratory examination on the day of admission revealed the following data: Hb 4.5 gm per 100

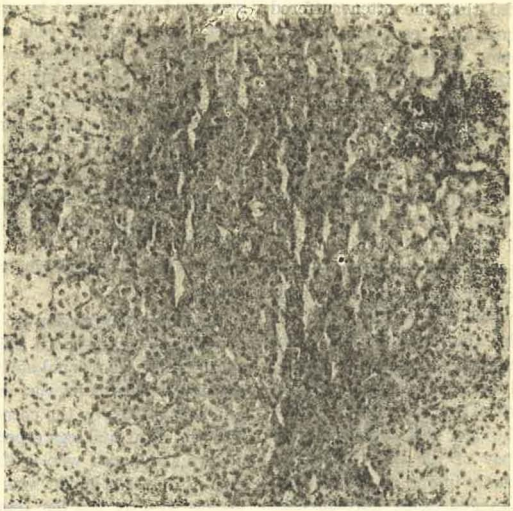

Fig 3 : *PA No. 710326, H & E stain, X 125. Postnecrotic scarring in an otherwise normal liver.*

ml of blood, leucocytes 30.600 per cubic mm, differential count showed a shift to the left, thrombocytes 320.000 per cubic mm, reticulocytes 17% and there were anisocytosis, poikilocytosis and fragmentocytes. Bleeding time was normal, but the clotting time (with a capillary tube) was 9 minutes. The bone marrow puncture showed a hypoplastic erythropoietic and hyperactive granulopoietic system. Liver function tests revealed: albumin 3.6 gm, globulin 2.8 gm per 100 ml of plasma, conjugated and total serum bilirubin levels of 1.9 and 3.1 mgm per 100 ml plasma, respectively. The alkaline phosphatase was 11.2 King-Armstrong units and the thymol turbidity test 2.4 Mc Lagan units. The reaction for bilirubin in urine and feces was negative. The plasma prothrombin time was not determined. Symptoms of shock appeared shortly after blood examination and hematomas increased in size after blood tapping. The shock could be overcome after vigorous treatment with intravenous fluid, blood transfusion and cortisone. The patient also got vitamin K and intravenous ampicillin. Jaundice disappeared after 5 days and the liver function tests on February 20, 1970 became normal again. The patient was discharged on February 22, 1970 and followed up in the outpatient department. Percutaneous needle biopsy of the liver, performed on March 18, 1970, showed surprisingly only postnecrotic scarring in an otherwise normal liver. (fig. 3 and 4). The plasma prothrombin time, SGOT, SGPT and LDH examined on April 22, 1970 were within normal limits.

Discussion

Although not carefully followed since birth, the histopathologic picture of the liver at the age of seven months clearly showed features of a complete giant liver cell transformation. According to the parents jaundice disappeared several months after the operation. It seemed that ductal irrigation in this case was useful in mobilizing bile from the liver. Although not conceivable from the pathologic point of view this bile flow might stimulate or enable the liver cells to regenerate. Thaler and Gellis (1968) stated that, if biliary flow is reestablished, the liver may recover completely even if extensive fibrosis is already present. Unknown factors related to host resistance and the virulence of the infecting organism apparently influence the course toward recovery and chronicity, and on occasion to postnecrotic collapse and diffuse fibrosis. The liver of the infant responds to injury with histologic changes, among which the formation of multinucleated giant cells is particularly prominent. Perhaps not all giant liver cells will undergo degeneration and necrosis as stated by Smetana (1963), because Mann and Magath (1922), Ashworth and

Fig. 4 : *PA No. 701326, Reticulum stain, X 250. Reticulum fibers about nodal liver cells.*

Reid (1947) considered the presence of giant cells as a manifestation of active amitotic regeneration. From this case it appears that the problem of giant liver cell transformation still remains a mistery though many hypotheses and explanations have been put foward by several authors.

The etiology of jaundice for the second time, accompanied with hemorrhagic diathesis, was not clear. Even without blood culture bacteriemia was very suggestive and in our opinion the clinical course which subsided very rapidly dit not seem to have any correlation with giant liver cell transformation.

The authors agree that at present the best explanation would be a viral infection producing both the chromosome changes and the liver-biliary-tree-findings.

Summary

A case of complete giant liver cell transformation in a 2¼-year-old Indonesian boy is reported. The etiology of jaundice appearing for the second time and associated with hemorrhagic diathesis was not clear, but bacteriemia was very suggestive. Familial occurrence of this disease or intrauterine infection could not be detected. The complete restoration of structure and function of the liver and the clinical course of this case suggest that giant liver cell transformation is not always a degenerative process, but sometimes may also regenerate. Viral infection is suggested to be the best explanation for its occurrence. The available literature is also reviewed.

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