Short Communication

Interpretation of Zonal Lesions by Different Concepts of the Hepatic Lobule

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Abstract: Zonal lesions in the hepatic lobules observed in drug-treated rats, dogs, and monkeys or spontaneously diseased monkeys were considered in reference to the different concepts of the hepatic lobule in order to understand the significance of zonal lesions of the liver correctly. Lesions due to congestion appeared at the periphery of the portal lobule of Mall’s concept. Incipient changes due to severe anemia occurred in a triangular shape at the center of the classical lobule where the apices of primary lobules become confluent as proposed by Matsumoto and Kawakami. Drug-induced centrilobular necrosis appeared evenly around the central venules showing clear contrast with the change observed in anemia. Periportal necrosis was located along the portal tract at the periphery of the classical lobule. None of these lesions match the zones of the acinar concept proposed by Rappaport. The concept of the hepatic lobule is essential to understand zonal lesions correctly. (J Toxicol Pathol 2001; 14: 163–167)

Key words: liver, hepatic lobule, zonal necrosis, congestion, anemia

Zonal lesions of the liver are often found in histopathological examination in toxicity studies. The location or shape of zonal lesions varies from case to case. Understanding of the zonal lesions in relation to the basic architecture of the hepatic lobule is the basis in understanding the significance of the distribution or location of zonal lesions and clarifying its pathogenesis. What then is the basic architecture of the hepatic lobule? The functional unit of the hepatic lobule has been studied for more than a century. As pointed out by McCuskey¹, functional unit is an indefinite term since the meaning is dependent on the definition of the minimal amount of tissue required to perform the function of the liver. The hepatic lobule has mostly been defined on the basis of the hepatic microvascular system by many investigators. McCusky¹ introduced the historical views and the details of various concepts of the hepatic lobule in his textbook. Major concepts are briefly quoted here. According to McCusky¹, the classical hepatic lobule described by Kiernan (1883) is a polygonal structure bounded at its periphery by terminal branches of portal veins and hepatic arteries, having a central venule as its axis. The concept of the portal lobule proposed by Mall² is a hexagonal unit circumscribed by the line connecting the neighboring central venules with the portal tract as its axis. Rappaport³,⁴ proposed an acinar concept by a modification of the portal lobule by Mall². The hepatic acinus is a unit having a portal tract and hepatic artery as its axis. The acinus circumscribed by an imaginary line connecting the neighboring central venules with the center of Glisson’s sheath. The acinus consists of three zones having different levels of oxygenation and metabolic function. The acinar concept has been widely accepted and appeared often in various textbooks, however, inconsistencies have been identified by three-dimensional studies with the reconstruction method⁵,⁶ or the microvascular corrosion casting/scanning electron microscope method⁷,⁸. Matsumoto and Kawakami⁵,⁶ proposed the concept of primary lobule based on detailed three-dimensional reconstructions of human livers. According to their concept, six to eight primary lobules make up one classical lobule (secondary lobule). Each primary lobule supplied by the terminal branches of portal venules and hepatic arterioles is shaped like a cone having its apex at the center surrounding the central venule.

In order to understand the meaning of difference in location or shape of zonal lesions in relation to microcirculation or lobular architecture, hepatic changes following severe anemia in rats and monkeys, congestion in dogs and monkeys, and drug-induced zonal necrosis in rats and monkeys were considered referring to the concepts of Mall², Rappaport³,⁴ or Matsumoto and Kawakami⁵,⁶.

Figure 1-a is a congestive liver from a dog treated with a high dose of Ca++-antagonist for 4 weeks. The names of the drugs are not mentioned here since treatment per se has no important meaning in this report because our purpose is to
discuss about the relationship between zonal lesions and lobular structure. Severe atrophy is seen in the zone connecting central venules, and severe fatty degeneration occupies the remaining zone. These changes are typical of congestive fatty liver. In Fig. 1-b, the periphery or edge of the portal lobules (Mall’s concept) and the zone 3 of the acinar concept by Rappaport are drawn on the same photo as shown in Fig. 1-a. Atrophy is seen at the portal lobule boundary. G: Glisson’s sheath. C: Central venule. HE × 25. c. Chronic congestion of a rhesus monkey liver. Dilation of sinusoid is extensive and most conspicuous at the portal lobule boundary. Masson trichrome staining × 25. d. Congestive necrosis found in a rhesus monkey. The necrotic area is extended in the congestive zone. The survival areas show an elliptic shape with the portal triad at its axis. Notice that there are no indentions abutting to the triad or any patterns corresponding to the zone 3 of the acinar concept by Rappaport. Masson trichrome staining × 25.

Figure 1-c shows slight and chronic congestion of the liver from an untreated-rhesus monkey. The cause of congestion was not known. Dilation of sinusoid is seen all over the lobules, but it is conspicuous in the boundary area of the portal lobule(congestive zone). No patterns indicative of the acinar zone are seen here again. Figure 1-d shows severe zonal necrosis observed in a debilitated rhesus monkey, although the etiology was not known. The zonal necrosis extends apparently along the congestive zone. Absence of inflammatory cells is a characteristic of congestive necrosis. The surviving areas extending along both sides of the portal tracts show an elliptic shape. It is hard to find any zoning patterns of the acinar concept in the necrotic area nor the remaining area. In the remaining area, the convex triangular area mentioned in the congestive liver of Fig. 1-a is not apparent in this case. The difference is thought to be derived from the difference in duration when the congestion continued.

Figure 2-a is the liver from a rat with severe anemia (Hb...
Fig. 2.  

a. Slight necrosis at the center of lobule found in an anemic rat treated with a drug for 2 weeks. The necrotic cells distribute irregularly around the central venules. HE $\times$ 25.  
b. Tracing of the zone 3 by Rappaport’s concept (purplish red color) and the primary lobules (solid line) proposed by Matsumoto and Kawakami on the same picture as shown in Fig. 2-a. Necrotic cells are seen at the area corresponding to the apex of primary lobules. G: Glisson’s sheath, C: Central venule. HE $\times$ 25.  
c. Higher magnification of Fig. 2-a. Necrotic cells are localized at the apex of the primary lobules and the pattern of primary lobule has become visible. HE $\times$ 50.  
d. A star-shaped cetrilobular necrosis observed in a malarial cynomolgus monkey. Extramedullary hematopoietic foci are seen in the Glisson’s sheaths. Masson trichrome staining $\times$ 25.  
e. Tracing of the zone 3 (purplish red color) by Rappaport’s concept and the primary lobules (solid line) proposed by Matsumoto and Kawakami on the same picture as shown in Fig. 2-d. The area of necrotic cell distribution apparently corresponds to the apices of primary lobules but not to the zone 3. G: Glisson’s sheath, C: Central venule. Masson trichrome staining $\times$ 25.  
f. The triangle-shaped focal necrosis is observed in the same malarial monkey as shown in Fig. 2-d. Extramedullary hematopoiesis and lymphocyte infiltration are seen in the Glisson’s sheath. The necrotic triangle area at the central zone is estimated to correspond to the apex of a cone-shaped primary lobule. Masson trichrome staining $\times$ 25.
2.6 g/dL, Ht 7.1 %, RBC 161 × 10^4) induced by the administration of a drug for 2 weeks. The drawing of zone 3 of the acinar concept and the putative edge lines of the primary lobules of Matsumoto and Kawakami’s concept on the same photo as Fig. 2-a is shown in Fig. 2-b. Higher magnification of Fig. 2-a is shown in Fig. 2-c. In these photos, necrosis is seen around the central venules, but the necrotic cells distribute unevenly around the central venule. Fig. 2-d is from a monkey suffering from malaria (Hb 2.3 g/dL, Ht 8 %, RBC 107 × 10^4; schizonts were observed in erythrocytes), and the drawing of the acinar zone and the putative frame of the primary lobules are shown in Fig. 2-e. The necrotic area corresponds satisfactorily to the apices of cone-shaped primary lobules of both livers from the rat and monkey with anemia. The zone 3 of acinar concept does not match any one of necrotic areas. Thus, it was clearly demonstrated that the necrosis under severe anemia appeared in the circulatory periphery of the hepatic lobule where the apices of the primary lobule join.

The difference of microcirculation environment among the primary lobules under an anemic condition may influence the incidence of necrotic cells or severity of necrosis among the primary lobules. This is applicable especially to the anemic liver of malarial monkey. In the malarial liver, strong extramedullary hematopoiesis and lymphocyte infiltration were seen in the Glisson’s sheath, which possibly disturbed the blood flow of some portal and arterial branches resulting in uneven microcirculatory condition at the apex of primary lobules. Significantly uneven circulatory condition among primary lobules probably induced typical triangle-shaped necrosis in the area adjacent to the central venule as shown in Fig. 2-f.

These irregular necroses occurring at the central zone of lobules are apparently due to the disturbance of microcirculation and are different from a centrilobular necrosis induced by drugs (described later) morphologically and etiologically. Therefore, the expression of “necrosis at circulatory periphery”, for instance, might be appropriate to describe the characteristic distribution of necrotic cells in anemia, or the disturbance of microcirculation in order to make distinction from evenly distributed centrilobular necrosis induced by direct drug action to the liver.

As a representative of drug-induced centrilobular necroses found most often in the toxicity tests of drugs, the lesion of a CCl₄-treated monkey (1 week after a single S.C. injection of 1 ml/kg) is shown in Fig. 3-a. The necrosis appeared evenly around the central venules. The necrotic zone is found evenly around the central venules, which is strikingly different from the necroses in anemic liver shown in Figs. 2-a, c, d. The necrotic and fatty-degenerative zone shows a somewhat polygonal shape rather than a circle when observed carefully. Several slightly concaved regions are visible around the necrotic zones (arrows). This shape indicates that the necrosis occurred evenly at the apex of the primary lobules.

A type of periportal necrosis induced by a drug (4 week administration) in a rhesus monkey is shown in Fig. 3-b. The necrotic zone distributes along a putative portal tract at the periphery of the classical lobule. In this zonal necrosis, no patterns or indention corresponding to the zone 3 of Rappaport's concept is seen. Glisson’s sheath. C: Central venule. Masson trichrome staining × 25.
induced centrilobular necrosis was distributed evenly at the apices of the primary lobules, and drug-induced periportal necrosis appeared at the periphery of the classical lobule. None of these zonal lesions matched the acinar zones proposed by Rappaport. The concept of Rappaport has prevailed for a long time since it was adopted in most of the textbooks without suitable criticism. However, Matsumoto and Kawakami have clearly demonstrated that the primary lobule is a functional unit of hepatic lobule by a detailed three-dimensional reconstruction method. Their concept has recently been confirmed and supported by Ekataksin and Teutsch. The latter demonstrated that hepatocellular metabolic gradients also conformed to the functional-unit concept proposed by Matsumoto and Kawakami. McCunsky has concluded in a textbook that this concept is the most consistent with existing evidence. Taking the concept of the hepatic lobule into consideration, zonal necrosis which is found often in toxicologic pathology practice should be evaluated precisely and correctly.

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References