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Čedo KUTLEŠIĆ
Vuka KATIĆ
Ljubinka VELIČKOVIĆ
Katarina KATIĆ

INSTITUTE OF CLINICAL PATHOLOGY, SCHOOL OF MEDICINE NIŠ, SERBIA AND MONTENEGRO

Atypical adenomatous hyperplasia in liver cirrhosis

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ABSTRACT

The term adenomatous hyperplasia was originally coined by Edmondson for sizable and discrete parenchymal nodules that may follow acute or chronic liver injury. He considered adenomatous hyperplasia to represent a regenerative process with a limited growth potential. Adenomatous hyperplasia is divided into ordinary and atypical types. The ordinary type consists of hepatocytes like those surrounding regenerative nodules. This type seems to correspond to the adenomatous hyperplasia originally described by Edmondson. Atypical adenomatous hyperplasia nodules are clearly different from surrounding regenerative nodules. Cytological and structural patterns are characteristically heterogeneous within a given nodule. This lesion shows cytological changes such as small cell change with nuclear crowding, large cell change with nuclear atypia, increased cytoplasmic eosinophilia or basophilia, clusters of Mallory bodies, ground glass change and fatty change. All of these changes are known cytoplasmic and cellular expressions of hepatocellular carcinoma. These findings suggest that atypical adenomatous hyperplasia may represent an important group of lesions in neoplastic development and raise the question of whether it is peculiar form of low-grade hepatocellular carcinoma.

DEFINITION

The term adenomatous hyperplasia (AH) was originally advocated by Edmondson to denote "sizable nodules following liver injury, either acute or chronic" (1). According to this original concept, AH is a benign regenerative lesion. The histological feature of AH found in cirrhotic livers, however, varies depending on the reports, possibly comprising well-differentiated hepatocellular carcinoma (HCC) and absolutely benign large regenerative nodules (2). In view of such a confused definition of AH, we have attempted to describe and classify the nodular hyperplastic lesions and to clarify their pathology.

Address correspondence to:
Prof. Dr. Čedo Kutlešić Institute of Pathology, School of Medicine Niš, 18000 Niš, Bulevar Zorana Đinđića 81, Serbia and Montenegro

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HEPATIC STEM CELLS

The liver in an adult healthy body maintains a balance between cell gain and cell loss. In response to parenchymal cell loss, the hepatocytes are the cells that normally restore the liver mass, rapidly re-entering the cell cycle from the Go phase (3). Trough normally proliferatively quiescent, hepatocyte loss such as that caused by partial hepatectomy, uncomplicated by virus infection or inflammation, invokes a rapid regenerative response to restore liver mass. This restoration of moderate cell loss and "wear and tear" renewal is largely achieved by hepatocyte self-replication. Furthermore, hepatocyte transplants in animals have shown that a certain proportion of hepatocytes can undergo significant clonal expansion, suggesting that hepatocytes themselves are the functional stem cells of the liver. More severe liver injury can activate a potential stem cell compartment located within the intrahepatic billiary tree, giving rise to cords of bipontential so-called oval cells within the lobules that can differentiate into hepatocytes and biliary epithelial cells. A third population of stem cells with hepatic potential resides in the bone marrow; these hematopoietic stem cells can contribute to the albeit low renewal rate of hepatocytes, make a more significant contribution to regeneration, and even completely restore normal function. How these three stem cell populations integrate together to achieve a homeostatic balance is not known. (4).

CLASSIFICATION

AH was divided into "ordinary" and "atypical" types. (5). Ordinary type consists of hepatocytes like those of surrounding regenerative nodules. While they are generally monotonous, mild and focal heterogeneous changes may be present such as alternative hyperplastic and atrophic areas, fatty change, bile plugs or Mallory body formation. A majority of these heterogeneous changes may be due to circulatory or biliary disturbances within adenomatous hyperplasia nodules. The ordinary type may not have a neoplastic nature but represent a large-sized regenerative nodule in cirrhosis. In this sense, ordinary type seems to correspond to the adenomatous hyperplasia originally described by Edmondson (1). Wada et al (6) termed them large regenerative nodules. Atypical adenomatous hyperplasia nodules are clearly different from surrounding regenerative nodules.

HISTOPATHOLOGY OF ATYPICAL ADENOMATOUS HYPERPLASIA

Cytological and structural patterns are characteristically heterogeneous within a given nodule. Four types of structural patterns (normotrabecular, compact, pseudoglandular and scirrhous) may be present as areas or compartments, and these areas show a replacing or compressive growth pattern to each other, suggesting that metabolic activities and also growth potential are different in each. Previous reports disclosed that some of these areas showed iron-resistance in siderotic adenomatous-hyperplasia nodules, suggesting active cell proliferation (7). Furthermore, the atypical hepatocytes may infiltrate into the portal tracts, suggesting that the growth and proliferation potentials of these atypical hepatocytes are high, and that they have a capacity to actually infiltrate neighboring structures.

In addition to structural changes, atypical adenomatous hyperplasia shows cytological changes such as small cell change with nuclear crowding, large cell change with nuclear atypia, increased cytoplasmic eosinophilia or basophilia, clusters of Mallory bodies, ground-glass change and fatty change. All of these changes are known cytoplasmic or cellular expressions of hepatocellular carcinoma and these histological features may also suggest a preneoplastic change (8,9,10). These findings suggest that atypical adenomatous hyperplasia may represent an important group of lesions in neoplastic development, and raise the question of whether it is peculiar form of low-grade hepatocellular carcinoma (10). Grigioni et al. (11) reported that Ki67 antibody, which reacts with nuclei of proliferating cells, is detectable in hepatocellular carcinoma as well as in equivocal nodular lesions corresponding to

atypical adenomatous hyperplasia. They concluded that such equivocal lesions are in fact malignant. Further investigations, including enzymatic deviation, iron metabolism and expression of oncofetal antigens and other markers for preneoplasia are needed in experimental hepatocarcinogenesis (5).
It is unclear what proportion of atypical adenomatous hyperplasia nodules finally become malignant (12). It is also unknown whether ordinary adenomatous hyperplasia may eventually transform to an atypical one. All that may be said in the current state of knowledge is that nodular growth and cytological/structural atypia indicate an increased likelihood of malignant transformation.

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