Case Report

Dysplastic Nodules and Small Primary Carcinoma of the Liver: A Study Detecting the early Morphological Changes during Hepatocarcinogenesis

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Objective: *Detect the early histological changes relating to human hepatocarcinogenesis in three nodular hepatocellular lesions*
Material and Method: *Three cases of dysplastic nodules and one of small hepatocellular carcinoma were obtained from the authors' surgical-pathology file during 2000-2005 for a histopathological study in relevance to the early changes during hepatocarcinogenesis by employing hematoxylin and eosin stain, as well as some immunohistochemical staining.*
Results: *One nodular hepatocellular lesion, diagnosed as a complex lesion of focal nodular hyperplasia contained a microscopic focus (1.5 mm in diameter) of combined hepatocellular and cholangiocarcinoma.*
Conclusion: *The small dysplastic hepatocytes subjected to neoplastic transformation combined hepatocellular and cholangiocarcinoma and are the precursorial cells of hepatocellular carcinoma. Chronic viral hepatitis B or C, aflatoxin B_1 and nitrosamine(s), as well as some nodular hepatocellular lesions share distinct roles in the complex process of hepatocarcinogenesis pertaining to this Southeast Asian country.*

Keywords: *Liver cell dysplasia, Small dysplastic hepatocyte, Nodular hepatocellular lesion, Hepatocellular carcinoma, Combined hepatocellular and cholangiocarcinoma*

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Based on the recommendation of the International Working Party, the nodular hepatocellular lesions include diffuse nodular hyperplasia (nodular regenerative hyperplasia), dysplastic focus (less than 1 mm in diameter) or nodule (1-10 mm in diameter), classified as low-grade dysplasia due to minimal nuclear atypia with normal or slightly increased nuclear-cytoplasmic (N/C) ratios of the hepatocytes, high-grade dysplasia owing to high N/C ratios, small hepatocellular adenoma, and hepatocellular carcinoma (HCC) of less than 2 cm in diameter, as well as some others[1].

The small dysplastic hepatocyte (SDH) with a high N/C ratio, firstly described by Watanabe et al[2], is a leading candidate for the cell precursor of HCC[1-6]. Alternatively, Hsia et al mentioned the oval cell population located in close proximity to HCC or alpha - fetoprotein-positive nodule as the origin of HCC[7]. The large dysplastic cells described by Anthony et al are no longer considered as the cell precursors of the tumor and may represent a degenerative nature similar to the large hepatocytes in lasiocarpine-induced hepatitis occurring in rats[5,6,8,9].

The present study attempted to detect the early histological changes relating to human hepatocarcinogenesis in three nodular hepatocellular lesions with liver cell dysplasia and one lesion with small hepatocellular carcinoma. These lesions were obtained by surgery, from the patients having chronic viral hepatitis with abnormal computerized-tomographic study.

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One of the three nodular hepatocellular lesions with dysplasia, is described as a complex lesion of focal nodular hyperplasia. In this microscopic lesion that combined hepatocellular and cholangiocarcinoma, the authors observed SDHs in its central part (HCC-CGC)[10]. The roles of SDHs and oval cells in human hepatocarcinogeneses of HCC and HCC-CGC are discussed in relation to chronic viral hepatitis, aflatoxin B_1nitrosamine exposures, and some certain nodular hepatocellular lesions.

Material and Method

A retrospective search, from the authors' surgical pathology file dating between 2000 and 2005 for surgically resected liver specimens diagnosed as dysplastic nodules and small HCC or HCC-CGC was done. The paraffin blocks of selected cases were retrieved for resectioning and staining. Hematoxylin and eosin (H and E), reticulin, and immunohistochemical agents were used to detect BCL-2 protein (detecting protein protecting cells from apoptotic cell death due to withdrawal of the growth stimulating factors, Dako), cyclin D_1 (detecting elevations of the cyclins in the G 1-phase thereby allowing the cells to proceed to S phase, G 2-phase and mitotic phase, Dako), proliferative cell nuclear antigen and Ki 63 (detecting cyclin productions during G1- and G2- phases, Dako), glutathione S transferase-pi (detecting oncofetal expression, Immunotech), cytokeratin 7 (identifying the bile-duct cell, Dako), alpha - fetoprotein (identifying the fetal hepatocytes and HCC cells, Dako), and p53 protein (the product of tumor suppressor gene indicating the mutation of p53 gene, Dako)[11].

The N/C ratio imply the ratio of the nuclear volume by cytoplasmic volume[12], the nuclear area by cytoplasmic area[2], or the nuclear diameter by length of cytoplasmic zone as used by Chen et al[13] with normal value of 33%. The authors employed the method of Chen et al in detecting N/C ratio and reported in terms of nuclear-cytoplasmic linear proportion (N:C proportion) with normal value of 1:3 and values of more than 1:1 as high N:C proportions compatible with high-grade dysplasia seen in SDHs (Table 1).

Results

Four cases with nodular hepatocellular lesions met the authors' criteria. In case 1, the hepatectomized liver for liver transplantation was obtained from a 42-year-old female with severe portal hypertension secondary to hepatoportal sclerosis[14] and diffuse mono-acinar nodules (diffuse nodular hyperplasia) with low-grade dysplasia (Fig. 1A)[1]. In case 2, a male, 35 years of age, had a gray-white monoacinar nodule with low-grade dysplasia, 7 mm in largest diameter after formalin fixation (Fig. 1B), and chronic viral hepatitis B, fibrosis (F)-1, activity (A)-1 by METAVIR scoring system[1, 15]. In case 3, the patient was a 50-year-old female having a gray-white nodule of focal nodular hyperplasia, 1 cm in largest diameter, containing a microscopic focus of HCC-CGC (Fig. 1C). The microscopic diagnoses also included chronic viral hepatitis B, F-1, A-1. In case 4, an encapsulated small HCC of 1.2 cm in diameter was resected from a 45-year-old male (Fig. 1D) with the liver parenchyma of chronic viral hepatitis B, F-2, A-1. All of the patients were doing well up to the period for this report preparation.

The liver of case 1 microscopically revealed severe narrowing of the venules due to fibrosis in some portal tracts (Fig. 2A). Some non-fibrosed tracts were infiltrated by neutrophils due to an infectious process and contained several venules occasionally seen dilated with stagnation of blood flow as reflected by

Table 1. Nuclear and cellular diameters and nuclear-cytoplasmic linear proportions

Cell populations	Nuclear diameter (micrometers)	Cellular diameter (micrometers)	Nuclear-cytoplasmic proportions*
Regular hepatocyte - diploid	8-9	32-36	1:3
- polyploid	10-11	32-36	1:2.27-1:2.2
Small hepatocyte - diploid	6-8	18-32	1:3-1:2
Small dysplastic hepatocyte (SDH)			
- polyhedral shape	6-8	7-12	1:0.5-1:0.17
- oval shape	5-6**	8-10**	
Oval cell	6-10**	10-16**	

* nuclear - cytoplasmic proportion = nuclear diameter/cellular diameter - nuclear diameter
** Longitudinal diameter

the presence of red-blood-cell ghosts (Fig. 2B). The interlobular bile ducts were occasionally damaged (Fig. 2A) or dilated with bile sludge (Fig. 2B). These were the features of hepatoportal sclerosis and sclerosing cholangitis[14]. The abnormal portal tracts with venular narrowing were seen in the center of each of the monoacinar nodules of low-grade dysplasia. The liver trabeculae were one-to eight-cells-wide in the nodules.

The single monoacinar nodule of low-grade dysplasia in case 2 microscopically revealed a large thick-walled artery in the portal tract near the center of the lesion (Fig. 2C). The hepatocytes in the nodule were ranging from small to regular sizes with normal or slightly increased N:C proportions (Fig. 3A, Table 1) similar to those seen in chronic viral hepatitis. The binucleated cells were common. The liver trabeculae were one-to two-cells-wide. A slight pressure effect on the surrounding parenchyma was observed.

The lesion of focal nodular hyperplasia in case 3 consisted of central stellate fibrosis with a large thick-walled artery forming arterial spider-like malformation as well as fibrous septa with lymphocyte infiltration and bile-duct proliferation[1,16]. The septa encased nodules of parenchymal cells arranged in two-cell-wide trabeculae. The hepatocytes varied from small to regular sizes and had normal or slightly increased N:C proportions. These were interpreted as complex lesions of low-grade dysplastic nodules within focal nodular hyperplasia.

Inside the complex lesions mentioned above, three foci of SDHs, 0.3-0.5 mm in diameter, each with a hyperchromatic and slightly vesicular nucleus or solid nucleus were seen within two low-grade dysplastic

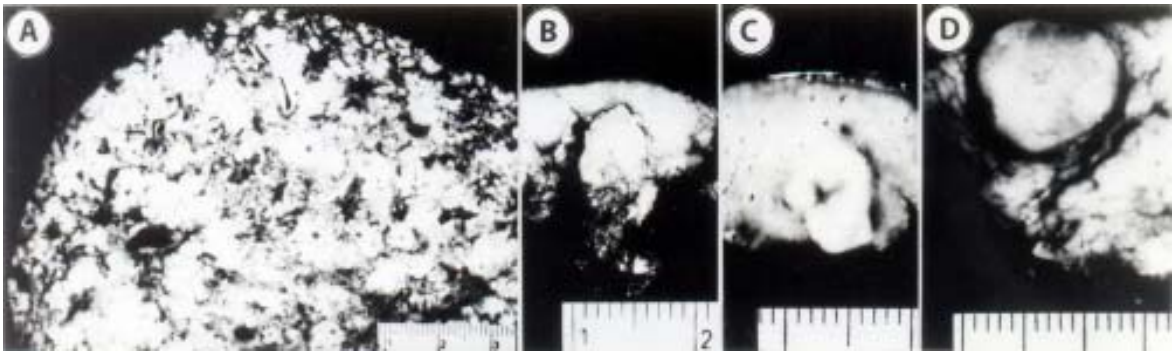

Fig. 1 Gross specimens of the cases 1-4:
A. The diffuse monoacinar nodules of low-grade dysplasia in case 1
B. The single monoacinar nodule of low-grade dysplasia in case 2
C. The complex lesion of focal nodular hyperplasia containing a microscopic lesion of HCC-CGC, case 3
D. The encapsulated small HCC in case 4

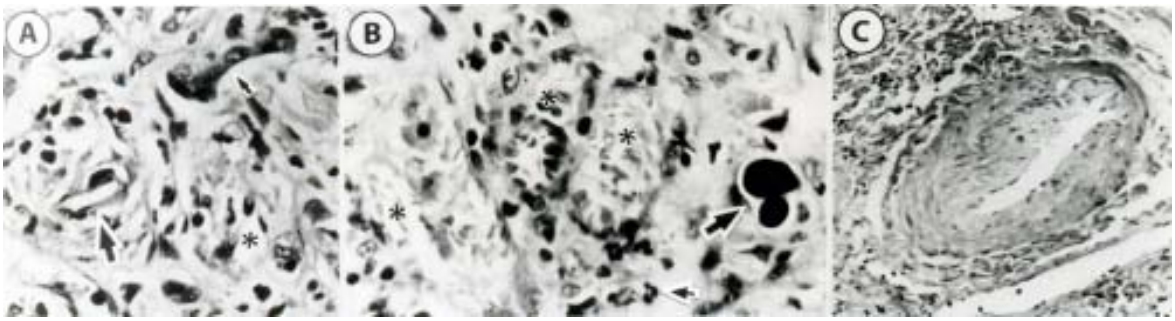

Fig. 2 A. The narrowed venules (arrow) in a fibrosed portal tract with prominent arteriole (asterisk) and damaged bile duct (small arrow) in case 1 (H & E; x 400)
B. Multiple venular channels in the portal tract (asterisks), a dilated duct with bile sludge (arrow), a neutrophil (small arrow) in case 1 (H & E; x 400)
C. The thick-walled artery in portal tract in case 2 (H & E; x 150)

nodules of 2 mm in diameter (Fig. 3B and C). These nodules were thereby interpreted as high-grade dysplastic nodules[1]. Tiny clusters up to 8 cells of shrunk SDHs undergoing apoptoses (large arrow) were seen with pale hematoxylin and eosin staining (Fig. 3C) and in various immunostaining (Fig. 4A C and D). The SDHs were arranged in trabecular pattern with two-to four-cell-wide trabeculae. Some oval SDHs could be seen (Fig. 3C).

A microscopic lesion of HCC-CGC of 1.5 mm in diameter inside another separated high-grade dysplastic nodule of 3 mm in diameter within the complex lesion of case 3 was observed. The tumor cells of HCC component were arranged in the sinusoidal pattern and trabecular pattern with two-to four-cells-thick trabeculae. The arrangement in acinar pattern and clear cell appearance in the HCC component could be seen (Fig. 5B). In the central part of the tumor, two cell clusters up to 50 mm in diameter consisting of SDHs and oval cells were seen (Fig. 4A). These oval cells were moderately positive to cytokeratin 7 (Fig. 4A). In the tumor periphery the oval cells strongly positive to cytokeratin 7 were seen blending with small HCC cells having a diameter less than 32 mm (Fig. 4B). Clusters of oval cells up to 20 in number could be seen with early canalization and with formation of tumor bile ducts (Fig. 5A). These oval cell lesions and tumor bile ducts were in direct contact with the regular HCC cells varying from 32 to 36 mm in diameter.

Due to BCL-2-protein production, the hepatocytes of small to regular sizes, SDHs, and oval cells (Table 2) were previously stimulated by the growth stimulating factors and protected from apoptosis. The very high proliferative rates of the SDHs were observed as shown by strong immunoreactivity for cyclin D1, high expression of proliferative cell nuclear antigen (Fig. 4C) and Ki63 (Table 2). A strong reaction to glutathione S transferase-pi staining indicated a

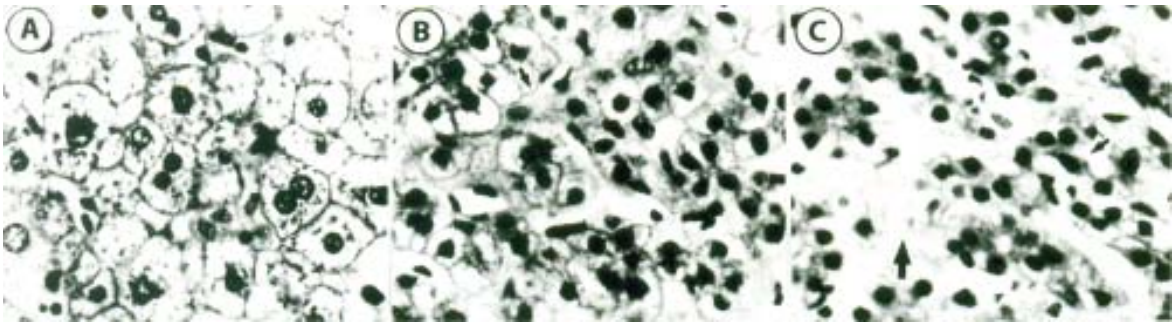

Fig. 3 A. The regular and small hepatocytes including binucleated cells in case 2 (H & E; x 400)
B. The small hepatocytes in the left upper quadrant, SDHs in the remaining area, the arrow indicates transitional zone in case 3 (H & E; x 400)
C. The polyhedral SDHs, an oval SDH (small arrow), apoptoses (large arrow) in case 3 (H & E; x 400)

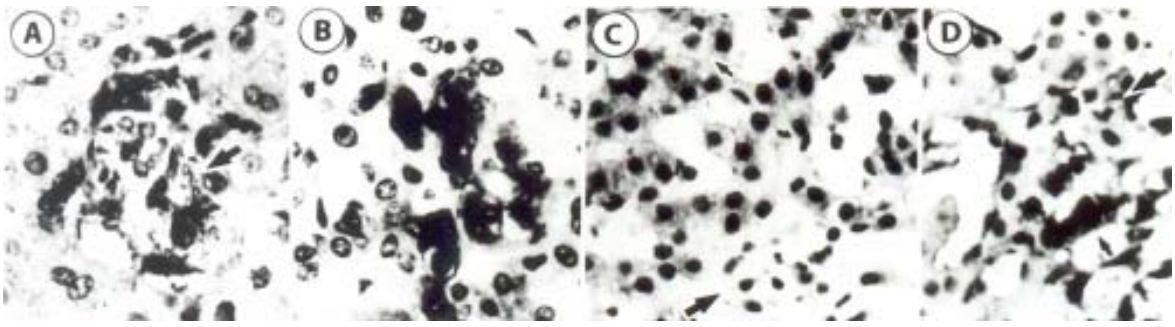

Fig. 4 A. The oval cells moderately positive to cytokeratin 7, apoptoses of the SDHs (arrow)
B. The oval CGC cells in the tumor periphery with strong positivity to cytokeratin 7
C. The SDHs are positive to proliferative cell nuclear antigen staining, a nonreactive cell (small arrow), apoptoses (large arrow)
D. The SDHs with a strong reaction to glutathione S transferase-pi (small arrow), apoptoses (large arrow). x 400

Table 2. Results of the immunohistochemical stainings

Cell compartments	BCL-2 protein	Cyclin D1 PCNA	Ki 63	GST-pi	CK 7	AFP	P53 protein
Bile-duct cell	–	–	–	–	+++*	–	–
Regular hepatocyte	+	+	±	–	–	–	–
Small hepatocyte	+	++	±	–	–	–	–
Small dysplastic hepatocyte	+	+++	+	+++	–	–	–
Oval cell	+	±	±	±	+++	±	–
HCC cells of small and regular sizes in the trabecular or acinar pattern	+	+	±	–	++	++	–
Polyploid HCC cell of large size	+	±	±	–	+++	+++	+
Tumor bile-duct cell	+	±	±	–	+++	–	–

Note:- PCNA – proliferative cell nuclear antigen, GST-pi – glutathione S transferase-pi, CK 7 – cytokeratin 7, AFP – alpha-fetoprotein
HCC cells, small (<32 mm in diameter), regular (32-36 mm in diam.), large (>36 mm in diam.)
* +++ strong phenotypic expression, ± weak expression
phenotypic expression in sporadic cells

distinct fetal expression of the SDHs (Fig. 4D). These cells may be in an undifferentiated state due to negative expression of neither cytokeratin 7 nor alpha-fetoprotein (Table 2). The tumor bile-duct cells were strongly positive to cytokeratin 7, whereas the HCC cells were sporadically positive to this immunostain (Fig. 5C).

Microscopic examination of the small HCC in case 4 revealed a thick fibrous capsule of 200 mm in thickness with condensed reticulin framework completely surrounding the tumor. The large polyploid HCC cells (larger than 36 mm in diameter) were arranged in the sinusoidal and trabecular patterns. The trabeculae between prominently dilated sinusoidal spaces were four-to six-cell-thick (Fig. 6A). Large HCC cells appeared with high N:C proportions averaging 1:0.5 (Fig. 6A) and sporadically revealed bipotential differentiation by the strong expressions of cytokeratin 7 (Fig. 6B) and alpha - fetoprotein (Fig. 6C). The expression of p53 protein was observed sporadically in some HCC cells (Table 2). Penetration of the diploid tumor cells through the capsule was observed. The proliferative rates of the HCC cells encased by the capsule were lower than or equal to the ones of the surrounding parenchymal cells as interpreted from cyclin productions (Table 2). No oncofetal expression by the tumors cells of HCC-CGC or HCC was observed in the cases 3 and 4.

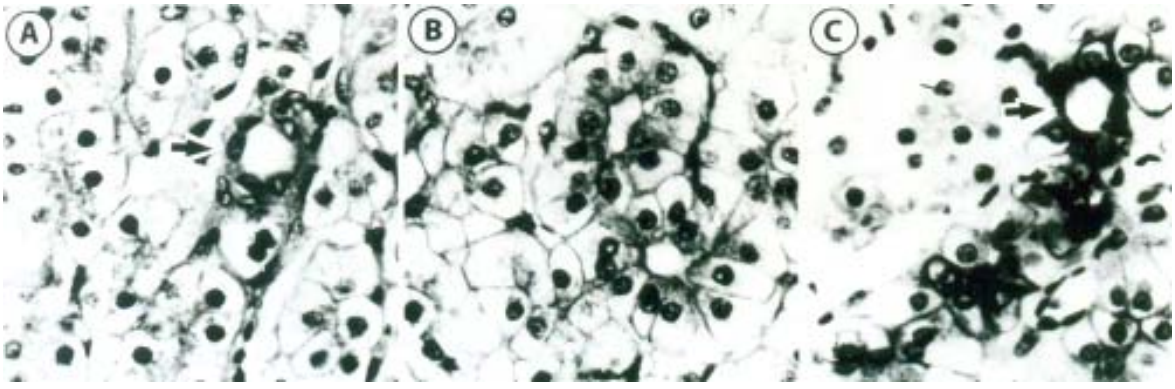

Fig. 5 A. A cluster of oval CGC cells forming a tumor bile duct (arrow) seen in direct contact with HCC cells
B. HCC with acinar pattern in the right half and trabecular pattern in the remaining. A and B. H & E staining
C. Cytokeratin 7-positive HCC cells in the trabeculae and the tumor bile-duct cells (arrow). x 400

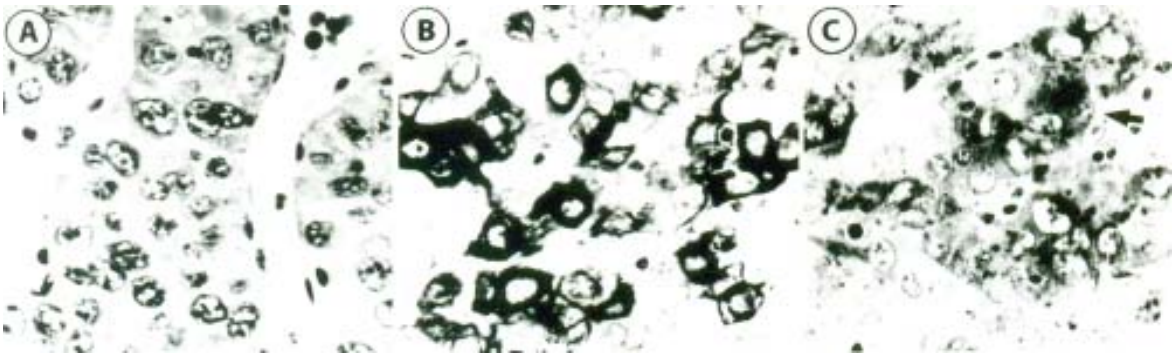

Fig. 6 A. The large polyploid HCC cells with high nuclear-cytoplasmic proportions, H and E staining
B. Strong positivity to cytokeratin 7 in sporadic HCC cells
C. Sporadic alpha-fetoprotein-positive HCC cells (arrow). x 400

Discussion

The formation of low-grade dysplastic nodules in cases 1-3 are related to abnormal vascular changes and considered as regenerative hyperplasia of the hepatocytes due to a response to actual arterial hyperperfusion in the presence of arterial malformation in the single monoacinar nodule of case 2 and focal nodular hyperplasia in case 3[1,16]. In the presence of reduced intraacinar portal-blood flow due to diffuse narrowing of the portal-tract venules secondary to an infectious process, relative arterial hyperperfusion appears to be the underlying mechanism of diffuse monoacinar nodules of low-grade dysplasia referred to as diffuse nodular hyperplasia in the case 1[1]. The hepatocyte hyperplasia in the zone of hyperperfusion may be secondary to higher oxygen supply from the increased arterial-blood flow comparing with the remaining parenchymal cells.

After acute or chronic submassive necrosis the source of regenerating hepatocytes is the stem cell compartment with the cells of polyhedral or oval shape, known as ductal hepatocytes[17], oval cells[7], hepatoblasts[12] or cholangiocytes[18] locating in or near the canal of Herring[17]. These cells multiply and differentiate to mature hepatocytes with normal or slightly increased N:C proportions. The SDHs although appearing similar in size to such stem cells, however, they are apparently not derived from the stem cell compartment since they are not in connection with the canal of Herring i.e. not located close to the portal tracts or septa in focal nodular hyperplasia. The origins of SDHs are here considered from the highly damaged and retrograded hepatocytes in survival after previous hepatotoxin exposures.

After variable periods of recovery, the SDHs may regenerate to small and regular hepatocytes under the condition of regenerative hyperplasia. The presence of shrunken SDHs in a tiny cluster (Fig. 3C) should represent apoptoses of the superfluous or overpopulated cells with a decrease in BCL-2 protein production. The actively regenerative nature of the SDHs with a strong fetal expression is similar to the physiologically growing nature of the hepatoblasts in the ductal plates during embryogenesis[12]. The gray-white color of the nodular hepatocellular lesions may be due to the color of overcrowded nuclei of the various small cells with scant cytoplasm.

Due to their bipotential differentiation, the malignant SDHs neoplastically induced by the chemical carcinogen(s) can multiply under stimulation further discussed and form clones of oval CGC cells and small polyhedral HCC cells (Fig. 4B). The oval CGC cells progress to acinar HCC cells and tumor bile ducts in HCC-CGC due to their strong cytokeratin 7 positivity. The small polyhedral HCC cells develop to trabecular cells with regular size of sole HCC and HCC component in HCC-CGC. The presence of oval cells not in connection with the canal of Herring and acinar pattern of the hepatocytes should be helpful in differentially diagnosing neoplasia from high-grade dysplasia because these SDHs of oval shape are not derived from the stem cell and they have a potentially neoplastic growth. The small cells of Watanabe et al[2] and oval cells described by Hsia et al[7] located in the periphery of HCC or alpha-fetoprotein-positive nodule are apparently small HCC cells (less than 32 mm in diameter) and oval CGC cells capable of maintaining their clonal cells as well as multiplying together with other larger HCC cells.

Possibly, in the early stage of malignancy the tumor cells in the small HCC-CGC in case 3 and small HCC in case 4 have low proliferative rates as reflected

by weak to mild reactions to cyclin D_1, proliferative cell nuclear antigen and Ki 63 staining (Table 2). This allows a slow tumor growth causing pressure effects and necroses of the surrounding parenchymal cells eventually replaced by a fibrous capsule with condensed reticulin frame work after several months referred to as small encapsulated HCC or HCC-CGC[1]. Because the fibrous capsule formation needs pressure necrosis of the surrounding parenchyma, the slow growth of the tumor has more chance of fibrous capsule formation than rapid growth. Following the penetration of the tumor cells through the capsule, a good supply of nutrients can bring to a rapidly proliferative nature, rapid tumor growth, leading to clinically poor prognoses of patients having HCC or HCC-CGC[5,10,19].

Continuous availability of the growth stimulating factors under chronic viral hepatitis[13] can stimulate the malignant SDH(s) in the high-grade-dysplastic focus or foci to multiply and form a nidus or nidi of either HCC or HCC-CGC, which is known to be associated with chronic viral hepatitis and cirrhosis due to hepatitis B virus (HBV) or hepatitis C virus (HCV) infection by the vertical transmissions or blood transfusions in the past in this country[20-31]. Without the regenerative stimulus, the malignant SDH(s) would remain dormant and not form any tumor. By detection of HBsAg and anti HCV in the HCC patients living in the central country region, the proportion of HCC associated with chronic HBV infection to HCC associated with chronic HCV infection is 6:1, while the cases of HCC associated with HBV-HCV co-infections contribute only 1 percent[24,28]. The detection of HBV in the non-tumor liver specimens of HCC patients in the same country region reveals 85 percent of HBV positivity and the remaining of 15 percent is likely due to HCV infection i.e. in the close proportion of 5.7:1[32].

The averaged annual incidence rates of HCC in the central and southern country regions of Thailand range from 9.7-10.7/10^5 in males[33]. Additional occurrence of liver fluke (*Opisthorchis viverrini*)-associated intrahepatic CGC raises the incidence rate of primary liver cancers up to 94.8/10^5 /year in the north-eastern country region[33]. Male preponderance in patients with HCC and HCC-CGC with male : female proportion up to 6.2:1 in similarity to the models in experimental animals due to sex-hormonal effects strongly suggests the role of naturally occurring aflatoxin B_1 in chemical hepatocarcinogenesis[20,25,34].

By the epidemiological investigations, aflatoxins in market food and foodstuffs are available in Thailand with the highest level of aflatoxin B_1 content in peanuts[35-38]. Hollstein et al observed a. the low frequency (7 percent) of the guanine to thymine transversion in codon 249 of the p53 gene in Thai HCC patients compared with 30-50 percent of the patient groups studied from Qidong (China) and South Africa, b. the lack of aflatoxin B_1-DNA adducts in the livers of Thai patients, and c. the low levels of aflatoxin B_1-albumin adducts in the peripheral blood of Thai patients, i.e. 15-20 folds lower than those in patient groups from Guangxi (China) and The Gambia, where the calculated individual intake of aflatoxins was estimated to be over 200 nanograms/kg of body weight/day[39]. In addition, rice is the dietary staple in Thailand and consumption of peanuts is infrequent in contrast to The Gambia. The estimated aflatoxin intake is between 5-45 nanograms/kg/day in Thai people[39]. These reflect the lower HCC rates (9.7-10.7/10^5/year) in Thai people than in those from China, The Gambia and South Africa with higher HCC rates up to 36-120/10^5/year in males, as well as a less distinct role of aflatoxin hepatocarcinogenesis in Thailand[33,39]. The p53 protein detectable by the immunostaining for the detection of the mutant p53 gene is only partially expressed as seen in the cases 3 and 4, and in patients from Japan and the USA[11, 40].

The daily intakes of nitrosamine precursors i.e. nitrate and nitrite in regular diets of Thai people in the central and northeastern regions are known[41]. These allow the formation of nitrosamines, potent carcinogens causing gastric adenocarcinoma, in the gastric acid environment[41,42]. In combination with liver fluke (*Opisthorchis viverrini*) infection, diethyl nitrosamine can effectively induce intrahepatic CGC in the experimental animals without sex preponderance and is likely the underlying mechanism for the high prevalence of intrahepatic CGC in the northeastern region[20,33,43]. Induction of nitric oxide synthetase by inflammatory cells due to fluke infection was alternatively proposed for the high prevalence of CGC in this same region[44].

The actions of the carcinogenic itrosamines cause DNA mutations most frequently by guanine to adenine transversion as reviewed by Fenoglio-Preiser et al[42]. The thymine to adenine transversion in codon 254 of p53 gene had been detected in one from 15 Thai HCC patients[39]. Apparently, the analyses for mutations seem to be inconclusive in indicating the assaulting carcinogen(s). From various information mentioned above, the aflatoxin B_1 in low blood levels and nitrosamine(s) appear to play synergistic roles in chemical hepatocarcinogeneses for HCC and HCC-CGC in

Thailand, where the hepatocarcinogenic role of various herbal medicines popularly used in Asian countries has never been recognized. The roles of HBV and HCV in viral hepatocarcinogenesis are considered unlikely due to random HBV-DNA insertions into the liver cell genomes and HCV-RNA cannot integrate into the genomes[4,19].

With the single monoacinar nodule or focal nodular hyperplasia, the arterial hyperperfusion mentioned prior may lead to an enhancement in metabolizing the aflatoxin B_1 to active aflatoxin B_1-5, 9 oxide as well as a selective increase in nitrosamine supply in the lesion[5, 16]. These offer a favorable occurrence of neoplastic or malignant induction to the degenerated hepatocytes. The proliferation of malignant SDH(s) leads to formation of a nidus or nidi of HCC or HCC-CGC in the high-grade dysplastic nodule (s) within some certain nodular hepatocellular lesions previously recognized and seen in cases 2 and 3[45]. This leads to a solitary or single liver mass.

Without any previous nodular hepatocellular lesion, the aflatoxin B_1 metabolite, and nitrosamine(s) in blood is uniformly distributed within the liver and capable of inducing malignant changes in multiple hepatocytes leading to multinodular and diffuse gross patterns of these tumors[4,5,19]. Impairment in DNA repair mechanisms may lead to a high risk for these tumors in the middle age group, 45-55 years of age[20,25]. The program of nation-wide vaccination against HBV has been launched since 1992 and expectedly may reduce the occurrences of primary liver tumors associated with chronic viral hepatitis B after a period of four to five decades in Thailand[31].

In conclusion, the aflatoxin B_1 in low blood levels and nitrosamine(s), in combination with regenerative hyperplasia due to chronic viral hepatitis B or C with or without some certain nodular hepatocellular lesions caused by arterial hyperperfusion, are responsible for the complex etiological process of HCC and its variant, HCC-CGC. The retrogrades and neoplastically transformed hepatocytes by some hepatotoxin(s) and changing to SDHs with bipotential differentiation are the precursorial cells of HCC and HCC-CGC. The malformed artery or arterial spider-like malformation in the nodular hepatocellular lesion could not be recognized in the single tumor as large as 1.2 cm in diameter of the case 4 due to the expansile tumor growth possibly pushing the abnormal structures into the fibrous capsule. The absence of small HCC cells and malignant oval cells in the small HCC in case 4 may indicate the inability of the tumor in keeping sustainable maintenance of such clonal cells. Nodular hepatocellular lesions under the items of dysplastic nodules and small HCC are rarely obtained as reflected by the presence of only four cases during the 6 year-period in Ramathibodi Hospital with 140 surgical hepatic resections (22 cases per year on average) for larger tumors and tumor-like conditions[46].

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ก้อนขนาดเล็กที่มีดิสเพลเซีย และมะเร็งปฐมภูมิขนาดเล็กในตับ: การวิเคราะห์ด้วยวิธีฮีสโตโลยี และด้วยการย้อมเชิงอิมมูโนวิทยา

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ก้อนขนาดเล็กในตับที่มีดิสเพลเซียสามราย และมะเร็งปฐมภูมิขนาดเล็กหนึ่งราย ถูกดึงออกมาจากฐานข้อมูลของหน่วยศัลยพยาธิ ช่วงปี พ.ศ. 2543 - พ.ศ.2548 เพื่อศึกษาทางด้านจุลพยาธิวิทยา ถึงการเปลี่ยนแปลงระยะต้นในการเกิดมะเร็งปฐมภูมิในตับ โดยการย้อมด้วยฮีมาทอกซิลินและอีโอซิน และย้อมด้วยวิธีอิมมูโนวิทยา ก้อนขนาดเล็ก 1 รายที่วินิจฉัยว่าเป็น focal nodular hyperplasia ที่มีมะเร็งของเซลล์ตับร่วมกับเซลล์ท่อน้ำดีขนาดเส้นผ่าศูนย์กลาง 1.5 มม ร่วมอยู่ด้วย เผยให้เห็นว่า small dysplastic hepatocytes เป็นเซลล์ต้นกำเนิดของมะเร็งปฐมภูมิของตับทั้งชนิดของเซลล์ตับอย่างเดียวและของเซลล์ตับร่วมกับเซลล์ท่อน้ำดี ตับอักเสบเรื้อรัง บี หรือ ซี สารแอฟลา-ทอกซิน บี$_1$ และไนโตรซามีน รวมทั้งก้อนในตับขนาดเล็กที่มีดิสเพลเซียอันเนื่องจาก arterial hyperperfusion ร่วมกันมีบทบาทอันซับซ้อน ในอันก่อให้เกิดมะเร็งปฐมภูมิของตับ สำหรับประเทศในเอเชียอาคเนย์นี้