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Letter to Editor

Hepatocellular carcinoma and type 2 diabetes mellitus: cytokeratin 8/18 expression in hepatocellular carcinoma and glycogen-storing hepatocytes

Kunio Takegoshi[1], Eikichi Okada[2], Qin Su[3]

[1]Takegoshi Internal Medicine Clinic, Takaoka, Toyama 933-0014, Japan.
[2]Pathological Division of Takaoka City Hospital, Takaoka, Toyama 933-8550, Japan.
[3]Cell Marque, Sigma-Aldrich, Rocklin, CA 95677, USA.

Corresponding Author:
Dr. Kunio Takegoshi, Takegoshi Internal Medicine Clinic, 377-7 Nomura, Takaoka, Toyama 933-0014, Japan. E-mail: kunio@takegoshi.jp

Received: *04-07-2016*; **Accepted:** *08-07-2016*

Sir,

We have reported two patients with hepatocellular carcinoma (HCC) and type 2 diabetes mellitus (T2DM), who showed abundant glycogen in their liver parenchyma but a marked reduction of glycogen content in HCC.[1] It was suggested that the latter was associated with appearance of a Warburg type glycolysis[1] and discussed in some detail.[2]

Cytokeratins (CKs), the intermediate filament (IF) proteins of epithelia, are sub-divided into type I (CK9-20) and type II (CK1-8) and expressed as type I/II pairs in a cell differentiation manner. In adult liver, hepatocyte IF comprise only CK8/18.[3] CK8/18 expression in normal and diseased liver has been reported, including positive expression in alcoholic steatohepatitis (ASH) and/or non-alcoholic steatohepatitis (NASH) and HCC.[3]

We examined the expression of CK8/18 in the liver to investigate cytoskeletal alterations in hepatocytes, possibly related to changes in hepatocellular glycogen content during hepatocarcinogenesis. Our studies revealed that immunoreactivity for CK8/18 was reduced or frequently even negative in glycogen-rich hepatocytes of background liver [Figure 1b and d], but moderately positive in normal hepatocytes and glycogen-poor cells in HCC [Figure 1a, c, e and f]. Overexpression of CK8/18, as Malory Denk bodies, which are hallmark lesions in ASH and NASH,[3] was not detected [Figure 1b and d]. The results provide evidence for reduced to negative CK8/18 expression in glycogen-rich hepatocytes.

The mechanism of alteration of CK8/18 expression in glycogen-rich hepatocytes has not been elucidated. Su *et al*.[4] demonstrated that CK8/18 expression was reduced in excessively glycogen-storing (glycogenotic) clear hepatocytes, which also showed a relative reduction of cytoplasmic organelles as demonstrated by electron-microscopic studies. Given simple CK8/18 expression patterns, hepatocytes are sensitive to alterations of cytokeratin architecture.[3] Using hepatic cell culture systems, Mathew *et al*.[5] reported recently that CK8/18 is involved in the interplay between glucose utilization and insulin signaling. The authors demonstrated that insulin stimulates glucose uptake, glucose-6-phosphatase formation, lactate release, and glycogen formation in hepatocytes via the PI-3 kinase dependent signaling pathway, and that CK8/18 IF loss makes them more efficient glycogen producers.[5] This is in line with the notion that an insulinomimetic effect of oncogenic agents is responsible for the preneoplastic hepatocellular glycogenosis,[2] which is associated with a reduced or negative expression of CK 8/18 in glycogenotic clear cells appearing in chronic human and woodchuck hepadnaviral infection.[4] CK8/18 immunohistochemistry may allow distinct recognition of the glycogen-rich hepatocytes as shown in glycogenotic clear cells under various conditions.[4]

Access this article online	
Website: http://www.hrjournal.net/	Quick Response Code
DOI: 10.20517/2394-5079.2016.26	

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How to cite this article: Takegoshi K, Okada E, Su Q. Hepatocellular carcinoma and type 2 diabetes mellitus: cytokeratin 8/18 expression in hepatocellular carcinoma and glycogen-storing hepatocytes. Hepatoma Res 2016;2:229-30.

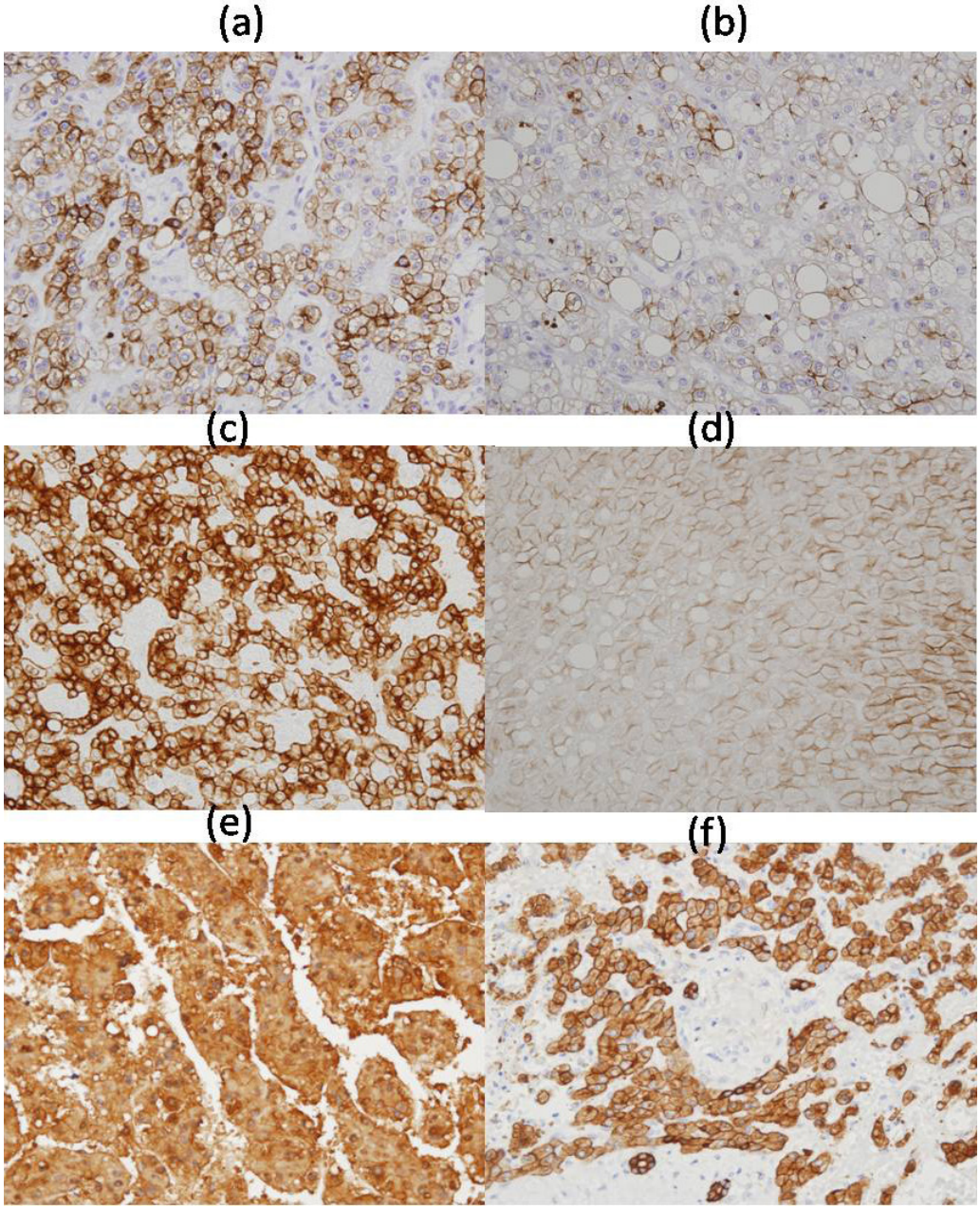

Figure 1: CK8/18 expression in hepatocellular carcinoma (a; case 1, c; case 2, e; control) and background liver (b; case1, d; case 2, f; control), demonstrated with mouse monoclonal antibodies B22.1/B23.1 (Cell Marque, USA) and visualized using the Envision method (Dako) (a-f, ×400). Control (a 79-year-old male, moderately differentiated adenocarcinoma in background of nearly normal liver)

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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