Fibrolamellar Hepatocellular Carcinoma in a Thai Man Who Presented with Hypoglycemia : Case Report and Review of Literature

PISIT TANGKIJVANICH, M.D.*, DUANGPORN THONG-NGAM, M.D.**,
PINIT KULLAVANIJAYA, M.B.Ch.B., F.R.C.P.**, PONGSEPEERA SUWANGOOL M.D.***

Abstract

We present a case of fibrolamellar hepatocellular carcinoma (FLHCC) in a 22 year old Thai man whose presenting symptom was hypoglycemic coma with right hemiparesis. The serum marker for hepatitis B virus (HBsAg) was positive and serum AFP was very high (over 100,000 IU/ml). The abdominal ultrasonography revealed a solitary heterogenic mass, size 5.5x6.5 cm in the right lobe. Chest X-ray showed multiple lung metastases. Ultrasound-guided needle liver biopsy was performed and typical histologic features of FLHCC in non-cirrhotic liver were diagnosed. The patient's comatose state and neurological deficits recovered rapidly after glucose administration. Unfortunately, the tumor mass could not be resected on account of far-advanced stage with metastases. Here, we also review of the literature concerning FLHCC in many aspects.

Key word : Fibrolamellar Hepatocellular Carcinoma, Hypoglycemia

TANGKIJVANICH P, et al
J Med Assoc Thai 2000; 83: 809-816

Fibrolamellar hepatocellular carcinoma (FLHCC) is one of the most important subtypes of hepatocellular carcinoma (HCC) which is distinct from ordinary HCC in many aspects[1]. Most cases of FLHCC occur in young adults without underlying chronic liver disease and the serum markers such as HBSAg, Anti HCV and alpha-fetoprotein (AFP) are usually negative except for rare cases. Moreover, compared with the more common HCC, FLHCC has relatively higher survival rates, higher resectability rate and more favorable prognosis after hepatic resection[2,3]. The pathological fea-

* Department of Biochemistry,
** Gastroenterology Unit, Department of Medicine,
*** Department of Pathology, Faculty of Medicine, Chulalongkorn University Hospital, Bangkok 10330, Thailand.

tures of FLHCC are unique and allow its identification and separation from other forms of HCC in that FLHCC contains large polygonal eosinophilic cells and diffuse fibrous stroma arranged in a lamellar pattern[4] which leads to the term "fibrolamellar".

Since Hugh Edmondson's initial discription in 1956[5], there have been less than 200 cases of FLHCC reported in the medical literature and most of them have been found to occur exclusively in Western countries and are relatively rare in Oriental countries where paradoxically, there are higher incidences of ordinary HCC associated with chronic hepatitis B and C. In Japan, approximately 18,000 people die of ordinary HCC annually, while only nine cases of FLHCC have been reported in the Japanese literature[6]. In Thailand where HCC are the most common tumors occuring in males, there were only a few cases of FLHCC have been reported previously. This is an interesting case of FLHCC in a young Thai man who had an unusual presentation of tumor-induced hypoglycemia.

CASE REPORT

A 22-year old Thai man was admitted to Chulalongkorn University Hospital in a semiconscious-state for 12 hours on 1 May 1996. The patient had been in good health until April 1996, 1 month prior to admission, when he developed progressive pain of the right upper abdomen and sought medical treatment from a local hospital. Five days before this admission, he was sent to another local hospital in a comatose state. His condition improved after intravenous glucose infusion and he went back to work a few days later. He had no history of serious illness, operations, illicit drug usage or blood transfusion. There was no personal or family history of hepatocellular carcinoma or other liver diseases.

On admission, the patient's height was 160 cm and his weight was 45 kg. The body temperature was 37°C and blood pressure was 110/70 mmHg. He was unconscious, but responded to painful stimuli with right hemiparesis grade 0. The bulbar conjunctiva showed neither icterus nor anemia. The liver was palpable 7 cm below the right costal margin with hard consistency and nodular surface. The spleen was not enlarged and intraperitoneal fluid was not detected. There were no other remarkable findings.

Hematological values were as follows : hematocrit 47.5 per cent, hemoglobin 15.5 g/dl white blood count 8,780/mm^3 with 75 per cent neutrophils, 25 per cent lymphocytes, and platelet count 150,000/mm^3. Blood chemistry studies revealed a mildly abnormal liver function test, alanine aminotransferase was 54 IU, alkaline phosphatase was 408 IU (normal < 279). The serum total bilirubin was 1.18 mg/dl and serum albumin was normal (4.2 g/dl). Plasma glucose was 31 mg/dl. Anti HCV was negative but HBsAg was positive and the level of AFP was very high (more than 100,000 IU/ml).

Chest X-ray revealed bilateral multiple nodular infiltrations varying in size from 0.5 cm to 1.5 cm. Abdominal ultrasonographic examination showed hepatomegaly with a well defined, mixed echogenicity, 5.5 cm x 6.5 cm. diameter mass located in the right lobe of the liver. Computerized tomography (CT scan) of the brain was done which showed generalized brain edema without intracranial focal lesion. Ultrasound-guided needle liver biopsy (Menghini type) of the hepatic mass and brochoscopic biopsy of lung masses were performed without complications. The two hallmark histologic features of FLHCC consisiting of large polygonal neoplastic hepatocytes with abundant eosinophilic cytoplasm, and lamellar bands of dense connective tissue lying between nests and cords of the neoplastic hepatocytes were present from these tissue specimens but histologic features of liver cirrhosis were not identified (Fig. 1-4).

The patient's comatose condition and right hemiparesis, presumably from hypoglycemia, rapidly improved after intravenous glucose infusion and the patient fully recovered within a few days after treatment. After medical discussion, we decided to treat the underlying hepatic tumor with symptomatic and supportive care due to the fact that the tumor was in an advanced stage with lung metastases. The patient was discharged from the hospital 10 days after the admission and he died one month later from a recurrent attack of hypoglycemia.

DISCUSSION

Being regarded as one of the most important variants of hepatocellular carcinoma (HCC), FLHCC is found to have many exclusive characters which differ from ordinary HCC[2-5,7,8]. It is common among younger patients aged between

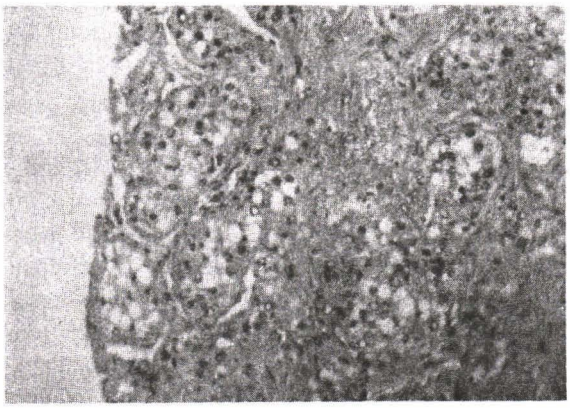

Fig. 1. FLHCC showing collagen fibers separating groups of malignant hepatocytes Mild fatty change is also seen. (H & E x 100)

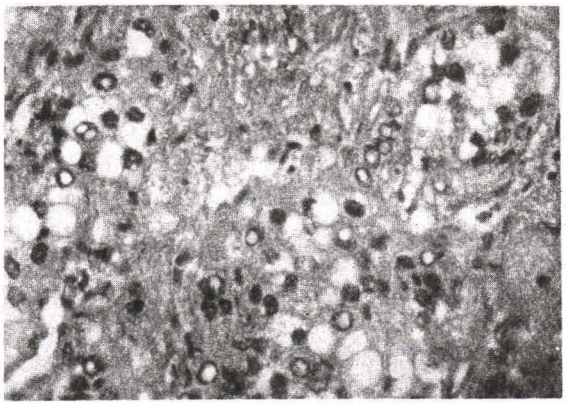

Fig. 3. FLHCC showing large cells with eosinophilic cytoplasm. Fatty change is also present. (H&E x 400)

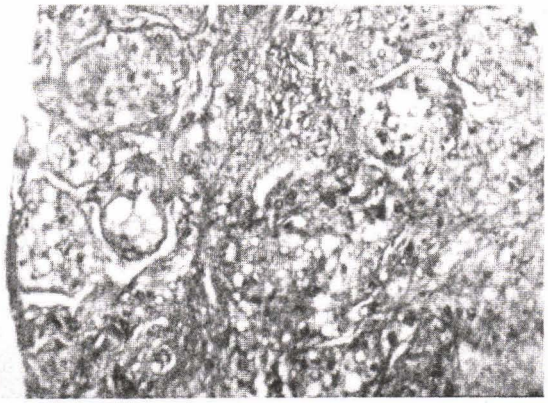

Fig. 2. FLHCC showing collagens fibers seperating groups of malignant hepatocytes. (Masson' trichrome x 100)

Fig. 4. FLHCC showing immunoreactive staining in tumor cells for AFP (arrows). (Immunoperoxidase x 400)

20-40 years who have no underlying liver disease, and is detected with similar frequency among members of both sexes. It is unrelated to infection of hepatitis B, C or alcoholic drinking and the AFP level is almost always normal. The case we present here is distinct from typical cases of FLHCC in many aspects, for example, serum HBsAg was positive and a very high serum AFP was present. Moreover, the presenting symptoms of hypoglycemic coma and hemiparesis without intracranial lesions are unusual for FLHCC. This case may be the first one of such presentation reported in the literature. The mechanism of tumor-induced hypoglycemia in ordinary HCC is believed to be the effect of insulin-like growth factor-II. Hypoglycemia is more common with large tumors and has been divided into type A, which occurs in patients with fast growing tumors at a preterminal stage. The other type, type B, appears quickly after fasting and is very difficult to control but not related to a terminal event[9].

The first reported case of FLHCC by Hugh Edmondson[5] was in 1956 in a 14 year old girl who presented with a liver mass. Atypical histologic features from surgical resection were, the stroma was profuse, and the tumor cells bore strik-

ing similarities to normal hepatocytes. In this case, there was no recurrence within 5 years. Many reports started to come in thereafter under various pathological names given as hepatocellular carcinoma with laminar fibrosis, hepatocellular carcinoma with polygonal cell type and fibrous stroma, oncocytic hepatocellular tumor, eosinophilic hepatocellular carcinoma with lamellar fibrosis[4,7,10,11], all of which at present widely accept the same name as fibrolamellar hepatcellular carcinoma.

While occasional presence of a central stellate scar appears to bear resemblance to focal nodular hyperplasia (FNH), pathological inspection usually reveals masses that have well a circumscribed border with fibrous band spreading across the surface of the tumor[12]. FLHCC usually occurs as a firm, large, tan-white and without encapsulated mass in a background of non-cirrhotic liver. The majority of cases are single but multiple masses with small satellite lesions may also be seen. From typical histopathologic features, two hallmark characters are usually identified[4]. The first is the parenchymal cells have the appearance of polygonal, with deep eosinophilic cytoplasm within the vesicular nucleus. The deep eosinophilic cytoplasm is due to numerous mitochondria. Mitotic activity of the hepatocytes is seldom found. The second feature is the fibrous bands of dense connective tissue lying in lamellar fashion between nests and cords of the tumor cells. The lamellae fibrosis is usually present throughout the entire mass without uniform patterns. Pathologically, FLHCC should be distinguished from sclerosing HCC and metastatic carcinoma to the liver since both lesions exhibit a prominent fibrous stroma. But a desmoplastic lesion in sclerosing HCC and metastatic carcinoma lacks multilaminated arrangement as that frequently seen in FLHCC.

Since clinical studies and reports of FLHCC became recognized and accepted in 1980 when Craig et al[4] and Berman et al[8] differentiated it from ordinary HCC, only 100 plus cases have been reported to date, most of which are from Western countries[13,14]. The common clinical presentations are palpable abdominal mass (predominantly located in the left lobe), abdominal pain, weight loss and cachexia. The duration of symptoms varies from 1 to 40 months[3,15]. In some cases, at the time of tumor detection, the tumors have already metastasised, more often than not, to the regional lymph nodes, peritoneal cavity, lung and spleen.

From various reports of FLHCC, no correlation with the level of serum AFP is found (Table 2). However, it is very common for ordinary HCC to have an elevation of serum AFP, which frequently serves as an important tumor marker for clinical diagnosis particularly when the level is over 500 ng/ml. Up to now no specific serum marker for FLHCC has been established. Elevation of serum neurotensin and vitamin B12 binding protein have been detected in patients with FLHCC in some reports[17,18] but these could still be elevated in non-fibrolamellar hepatocellular carcinoma and, thus, such assays lack specificity and have not been adopted on a wide scale. On the other hand,

Table 1. Summary of clinical features of 35 cases reported form USA[16].

Symptoms	Percentages	%	Signs	Percentages	%
Abdominal pain	25	71	Abdominal mass	16	
Nausea / vomiting	7	20	Nontender	12	34
Wt. loss	6	17	Tender	4	11
Fever	4	11	Hepatomegaly	9	
Fatigue	4	11	Nontender	8	23
Diarrhea	3	9	Tender	1	3
Chest pain	2	6	Normal physical exam	3	9
Pruritus	2	6	Peripheral edema	3	9
Abdominal distension	2	6	Gynecomastia	3	9
Dyspepsia	2	6	Ascites	2	6
Hematochezia	2	6	Hepatosplenomegaly	1	3
			Adenopathy	1	3
			Hepatic bruit	1	3

continuous monitoring the level of neurotensin may have a role in following cases of recurrences after hepatic resection(19).

The imaging studies of FLHCC often provide some diagnostic clues. Such appearances, however, are not exclusive to FLHCC and must be dis-

Table 2. Reports on the relationship of FLHCC to cirrhosis, hepatitis B and AFP.

	No. of cases	Increase AFP	HBsAg(+)	Liver cirrhosis
Berman et al (8)	12	-	-	1/12
Craig et al (4)	23	0/4	1/4	2/20
Stromeyer et al (20)	3	-	0/3	0/3
Slavutin (10)	1	0/1	0/1	-
Albuberk (21)	1	0/1	0/1	0/1
Wong et al (22)	1	0/1	1/1	-
Paradnas et al (18)	7	1/7	-	0/7
Chuong et al (23)	1	0/1	0/1	0/1
Farhi et al (15)	10	-	-	0/8
Lack et al (24)	5	1/5	-	-
Wetzel et al (25)	2	1/2	-	0/2
Bulthun & Pollock (11)	1	0/1	0/1	0/1
An et al (26)	1	0/1	0/1	0/1
Lefkowitch et al (27)	1	0/1	0/1	0/1
Vecchio et al (28)	1	1/1	0/1	0/1
Albaugh et al (29)	1	0/1	0/1	-
Soreide et al (30)	9	1/9	0/9	0/9
Titelbaum et al (31)	2	0/2	0/2	0/2
Davidson et al (14)	25	0/1	1/25	-
Ringe et al (19)	20	0/18	-	0/20
SAAB et al (16)	3	1/3	0/3	0/1
Japanese reports (6)	9	1/9	1/9	1/9
This report	1	1/1	1/1	0/9
Total	140	7/72 (9.7%)	5/65 (7.7%)	4/102 (3.9%)

Remark : - = data not available

Table 3. Results of surgical therapy of FLHCC.

	Case No.	Hepatic resection	OLT*	Outcome
Craig (4)	23	11	0	Overall mean survival 32 months
Berman (8)	12	12	0	Mean survival 68 months 2 year survival rate 82%
Soreide (30)	9	0	9	With resection : 5 yr survival rate 56% Without resection : no 5 yr survival
Lack (24)	5	3	0	Overall mean survival 28.5 months 4/5 dead from metastasis
Ringe (19)	20	14	6	With resection : median survival 44 months, with OLT : median survival 28.5 months
Starzl (36)	14	8	6	With resection : all alive at 11 months With OLT :2/4 alive at more than 24 months
Iwatsuku (37)	22	12	10	With resection : 5 yr survival 64.8% With OLT : 5 yr survival 37%
Ismail (38)	6	0	6	Median survival 18.5 months
Yokoyama (39)	9	0	9	1 year survival 89%, 5 year survival 46%

OLT* = Orthotopic liver transplantation

tinguished from focal nodular hyperplasia (FNH) or, sometimes with more difficulty, from hepatocellular carcinoma. The radiographic appearances of FLHCC are as follows:[22,31-33].

99m Tc Sulfur Colloid scan - present in the form of cold masses.

Ultrasonography - variable echogenic mass is detected, with or without calcification.

CT scan - In non-contrast study, seen in the form of a well-demarcated hypodensed mass with central scar and central punctate calcification.

Arteriography - it appears to be an encapsulated hypervascular mass, portal vein thrombosis can also be seen.

MRI - in T1 it appears as an iso-hypointensified mass with central low signal, while in T2 it appears as an heterogeneous high signal and central area of lower signal intensity (central scar).

The study of radiographic appearances by Soyer P et al[34]conducted in 10 cases of FLHCC patients revealed that 6 out of 10 cases (60%) had single masses; 7 out of 10 (70%) were well delineated; 8 out of 10 (80%) were hypervascular masses, with CT scan being the most accurate technique in the diagnosis and staging processes. In contrast, MRI is more useful in separating the central scar in FLHCC from FNH.

The mainstay of therapy for FLHCC is surgical resection. Although the natural history of FLHCC is not well known, the comparison of the results of surgical therapy which are hepatic resection and liver transplantation have shown higher success rates and improved 5-year survival rate over that of ordinary HCC (Table 3). Moreover, prolonged survival for some patients with advanced stage with metastatic disease have been reported [35]. These data support that FLHCC has a less aggressive nature with a more favorable prognosis if treated with potentially curative hepatic resection.

(Received for publication on August 17, 1998)

REFERENCES

1. LaBrecque DR. Neoplasia of the liver in Textbook of liver and biliary diseases. Edited by Kaplowitz N. Williams & Wilkins Company 2nd edition 1996: 391-438.
2. Wood WJ, Rawlings M, Evans H, Lim CNH. Hepatocellular carcinoma: importance of histologic classification as a prognostic factor. Am J Surg 1988;155:663-6.
3. Nagorney DM, Adson MA, Weiland LH, Knight CD Jr, Smalley SR, Zinsmeister AR. Fibrolamellar hepatoma. Am J Surg 1985;149:113-9.
4. Craig JR, Peters RL, Edmondson HA, Omata M. Fibrolamellar carcinoma of the liver : a tumor of adolescents and young adults with distinctive clinicopathologic features. Cancer 1980; 46: 372-9.
5. Edmonson HA. Differential diagnosis of tumors and tumor-like lesion of the liver in infancy and childhood. Arch Dis Child 1956; 91: 168-86.
6. Hoshino H, Katada N, Nishimura D, et al. Case report: Fibrolamellar hepatocellular carcinoma in a Japanese woman : A case report and review of Japanese cases. J Gastroenterol Hepatol 1996; 11: 551-5.
7. Peters RL. Pathology of hepatocellular carcinoma. In Hepatocellular carcinoma K Okuda, R Peters (eds). New York, John Wiley & Sons. 1976: 107-66.
8. Berman MM, Libbey NP, Foster JH. Hepatocellular carcinoma: polygonal cell type with fibrous stroma- an atypical varient with a favorable prognosis. Cancer 1980; 46: 1448-55.
9. Shapiro ET, Bell GI, Polonsky KS, Rubenstein AH, Kew MC, Tager HS. Tumor hypoglycemia:a relationship to high molecular weight insulin-like growth factor II. J Clin Invest 1990; 85: 1672-9.
10. Slavutin LJ, Diamond N. Case report Hepatocellular carcinoma with lamellar fibrosis : An important histological variant. Pathology 1981; 13: 775-81.
11. Baithun SI, Pollock DI. Oncocytic hepatocellular carcinoma. Histopathology 1983; 7: 107-12.
12. Hodgson HJF. Fibrolamellar cancer of the liver. Hepatology 1987; 5: 241-7.
13. Eckstein RP, Bambach CP, Steil D, Roche J, Goodman BN. Fibrolamellar carcinoma as a cause of bile duct obstruction. Pathology 1988; 20: 326-31.
14. Davision FD, Fagan EA, Portmann B, Williams R. HBV-DNA Sequences in tumor and nontumor tissue in a patient with the fibrolamellar variant of hepatocelluar carcinoma. Hepatology 1990; 12: 676-9.

15. Farhi DC, Shikes RH, Murari PJ, et al. Hepatocellular carcinoma in young people. Cancer 1983; 52:1516-25.
16. Saab S, Yao F. Fibrolamallar hepatocellular carcinoma, case reports and a review of the literature. Dig Dis Sci 1996; 41: 1981-5.
17. Collier NA, Bloom SR, Hodgson HJF, et al. Neurotensin secretion by fibrolamelar carcinoma of the liver. Lancet 1984; 1: 538-40.
18. Paradinus FJ, Melia WM, Wilkinson ML, et al. High serum vit B12 binding capacity as a marker of the fibrolamella variant of hepatocellular carcinoma. Br Med J 1982; 285: 840-2.
19. Ringe B, Wittekind C, Weimann A, et al. Results of hepatic resection and liver transplanation for fibrolamellar carcinoma. Surg Gynecol Obstet 1986; 175: 290-305.
20. Stromeyer FW, Ishak KG, Gerber MA, Mathew T. Ground-glass cell in hepatocellular carcinoma. Am J Clin Pathol 1980; 74: 254-8.
21. Albukerk J. Hepatocellular carcinoma in young adults. NY State J Med 1981; 81: 1341-4.
22. Wong LK, Link DP, Frey CF, et al. Fibrolamellar hepatocarcinoma: radiology, management and pathology. Am J Radiol 1982; 139: 172-5.
23. Chuong JJH, Livstone EM, Barwick KW. The histopathologic and clinical indicators of prognosis in hepatoma. J Clin Gastroenterol 1982; 4: 547-52.
24. Lack EE, Neave C, Vawter G. Hepatocellular carcinoma. Review of 32 cases in childhood and adolescence. Cancer 1983; 52: 1510-5.
25. Wetzel WJ, Costin JL, Petrino RL. Fibrolamellar carcinoma : A distinctive clinical and morphologic variant of hepatoma. South Med J 1983; 76: 796-8.
26. An T, Ghatak N, Kaastner R, et al. Hyaline globules and intracellular lumina in a hepatocellular carcinoma. Am J Clin Pathol 1983; 79: 392-6.
27. Lefkowitch JH, Muschel R, Price JB, et al. Copper and copper binding protein in fibrolamellar liver cell carcinoma. Cancer 1983; 51: 97-100.
28. Vecchio FM, Fabiano A, Ghirlamda G, et al. Fibrolamella carcinoma of the liver : the malignant counterpart of local nodular hyperplasia with oncocytic changes. Am J Clin Pathol 1984; 81: 521-6.
29. Albaugh JS, Keeffe EB, Krippaehne WW. Recurrent obstructive jaundice causes by fibrolamellar hepatocellular carcinoma. Dig Dis Sci 1984; 29: 762-7.
30. Soreide O, Czerniak A, Badpiece H, et al. Characteristics of fibrolamellar hepatocellular carcinoma. A study of nine cases and a review of the literature. Am J Surg 1986; 151: 518-23.
31. Titelbaum DS, Hatabu H, Schiebler ML, et al. Fibrolamellar hepatocellular carcinoma : MR appearance. J Comput Assist Tomogr 1988; 12: 588-91.
32. Friedman AC, Lichtenstein JE, Goodman Z, et al. Fibrolamellar hepatocellular carcinoma. Radiology 1985 ; 157 : 583-7.
33. Titelbaum DS, Barke DR, Méranze SG, et al. Fibrolamellar hepatocellular carcinoma : pitfalls in nonoperative diagnosis. Radiology1988; 167: 25-30.
34. Soyer P, Roche A, Levesque M, et al. CT scan of fibrolamellar hepatocellular carcinoma. J Comput Assist Tomogr 1991; 15: 533-8.
35. Rosen CB, Nargoney DM. Fibrolamellar and less aggressive hepatocellular carcinoma. In : Terblanch J. ed. Hepatobiliary Malignancy. Boston: Little Brown & Company. 1994: 203-14.
36 Starzl TE, Iwatsuki S, Shaw BW, et al. Treatment of fibrolamellar hepatoma with partial or total hepatectomy and transplantation of the liver. Surg Gynecol Obster 1986; 162: 145-8.
37. Iwatsuki S, Starzl TE, Sheahan DG, et al. Hepatic resection versus liver transplantation for hepatocellular carcinoma. Ann Surg 199; 214: 221-9.
38. Ismail T, Angrisani L, Gunson BK, et al. Primary hepatic malignacy: The role of liver transplantation. Br J Surg 1990; 77: 983-7.
39. Yokoyama I, Todo S, Iwatsuki I, et al. Liver transplantation in the treatment of primary liver cancer. Hepatogastroenterology 1990; 37: 188-93.

ไฟโบรลาเมลลา เฮปาโตเซลลูลา คาร์สิโนมา ในผู้ป่วยชายไทยที่มีภาวะน้ำตาลในเลือดต่ำ : รายงานผู้ป่วยและทบทวนวรรณกรรม

พิสิฐ ตั้งกิจวานิชย์, พ.บ., ดวงพร ทองงาม, พ.บ.**,*
*พินิจ กุลละวณิชย์, พ.บ.**, พงษ์พีระ สุวรรณกูล, พ.บ.****

รายงานผู้ป่วยชายไทยอายุ 22 ปี ที่มีระดับน้ำตาลต่ำในเลือดร่วมกับอาการหมดสติและแขนขาข้างซ้ายอ่อนแรง ซึ่งอาการเหล่านี้ดีขึ้นจนเป็นปกติหลังการรักษาด้วยการฉีดกลูโคสเข้าเส้นเลือด ตรวจพบว่าผู้ป่วยมีก้อนในตับขนาด 5.5X6.5 ซม.จากอุลตร้าซาวด์ ตรวจเลือดพบว่า HBsAg ให้ผลบวกและ AFP ในเลือดมีระดับสูงมากกว่า 100,000 IU/ml ผลทางพยาธิของก้อนที่ตับจากการทำ liver biopsy เข้าได้กับลักษณะของ fibrolamellar hepatocellular carcinoma (FLHCC) และไม่พบว่ามีตับแข็งร่วมด้วย นอกจากนี้คณะผู้รายงานยังได้ทบทวนวรรณกรรมที่เกี่ยวข้องกับ FLHCC ในหลาย ๆ ด้าน

คำสำคัญ : ไฟโบรลาเมลลา เฮปาโตเซลลูลา คาร์สิโนมา, ภาวะน้ำตาลในเลือดต่ำ

พิสิฐ ตั้งกิจวานิชย์ และคณะ
จดหมายเหตุทางแพทย์ ฯ 2543; 83: 809–816

* ภาควิชาชีวเคมี,
** หน่วยทางเดินอาหาร, ภาควิชาอายุรศาสตร์,
*** ภาควิชาพยาธิวิทยา, คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย, กรุงเทพ 10330