Virchows Archiv A Pathol Anat (1991) 419:69–75

Virchows Archiv A
Pathological Anatomy and Histopathology

Case report

Focal fatty change of the liver

A review and a case associated with continuous ambulatory peritoneal dialysis

Anni Grove [1], Bente Vyberg [2], and Mogens Vyberg [1]

[1]Institute of Pathology and [2]Department of Medicine C, Aalborg Hospital, DK-9100 Aalborg, Denmark

Received October 22, 1990 / Accepted January 28, 1991

Summary. Focal fatty change (FFC) of a liver with unequivocal normal architecture is rare. A review of the literature revealed 39 histologically well-documented cases. Well-known steatogenic conditions were present in most of these cases. Focal ischaemia or a varying rate of mobilization of fat in the liver have been suggested as a cause of the focality of the lesions. FFC occurring in a diabetic patient on continuous ambulatory peritoneal dialysis (CAPD) is presented. The FFC in this and in ten previously reported cases associated with CAPD and intraperitoneal insulin therapy had a unique subcapsular distribution, which may suggest a specific pathogenetic mechanism involving insulin. The clinical significance of FFC in the differential diagnosis from other fatty lesions of the liver is summarized.

Key words: Liver – Focal fatty change – Continuous ambulatory peritoneal dialysis

Introduction

Fatty change of the liver is an extremely common lesion, generally found as a diffuse process involving the entire organ. Radiological imaging procedures have revealed an occasionally non-uniform (focal) distribution of the change (Gale et al. 1983; Halvorsen et al. 1982; Livraghi et al. 1984; Tang-Barton et al. 1985). In most cases, histological examination has not been carried out and the morphological basis for this is uncertain. Where histological examination has been performed non-uniform fatty change has generally accompanied architectural changes such as cirrhosis (Bashist et al. 1982; Mulhern et al. 1979) and focal nodular hyperplasia (Shojania and Hoog 1975).

Focal fatty change (FFC) has a more restricted morphological meaning – it describes one or more circumscribed portions of the liver showing pronounced steatosis, unequivocal normal liver architecture and no or minimal steatosis in the rest of the parenchyma. It appears to be rare and the literature contains only 39 cases with histologically well-documented FFC (Amoyal et al. 1989; Baker and Silverman 1985; Brawer et al. 1980; Clain et al. 1984; Flournoy et al. 1984; Hartshone et al. 1985; Pardes et al. 1982; Rampal et al. 1986; Sawada et al. 1983; Simon 1934; Wanless et al. 1989; Yates and Streight 1986; Yoshikawa et al. 1987).

We present another case of hepatic FFC occurring in a patient with insulin-dependent diabetes mellitus (IDDM) on continuous ambulatory peritoneal dialysis (CAPD). To our knowledge, Wanless et al. (1989) provide the sole previous report of this association.

Offprint requests to: A. Grove

Case report

The patient was a 55-year-old man with a 35-year history of IDDM, which for several years had been complicated by retinopathy, severe generalized atherosclerosis and nephropathy. From the occurrence of terminal uraemia in 1985, until his death 4.5 years later, he was successfully treated by CAPD with intraperitoneal insulin therapy. The dialysis was uncomplicated with no symptoms or signs of peritonitis and the diabetes was well regulated. The patient had never had symptoms or signs of liver disease, was not obese and had no history of alcohol abuse. Laboratory tests of liver function and serum cholesterol were normal.

The patient was last admitted to a hospital in July 1989 because of incipient gangrene of the right foot, and died with signs of congestive heart failure.

Results

Macroscopical examination disclosed a liver of normal size and with a smooth surface, without signs of acute inflammation or fibrosis. On the postero-inferior surface of the right liver lobe, a 10×8 cm sharply delineated homogeneous subcapsular area of bright yellow tissue was found, 4–6 mm in thickness (Fig. 1a). The anterior

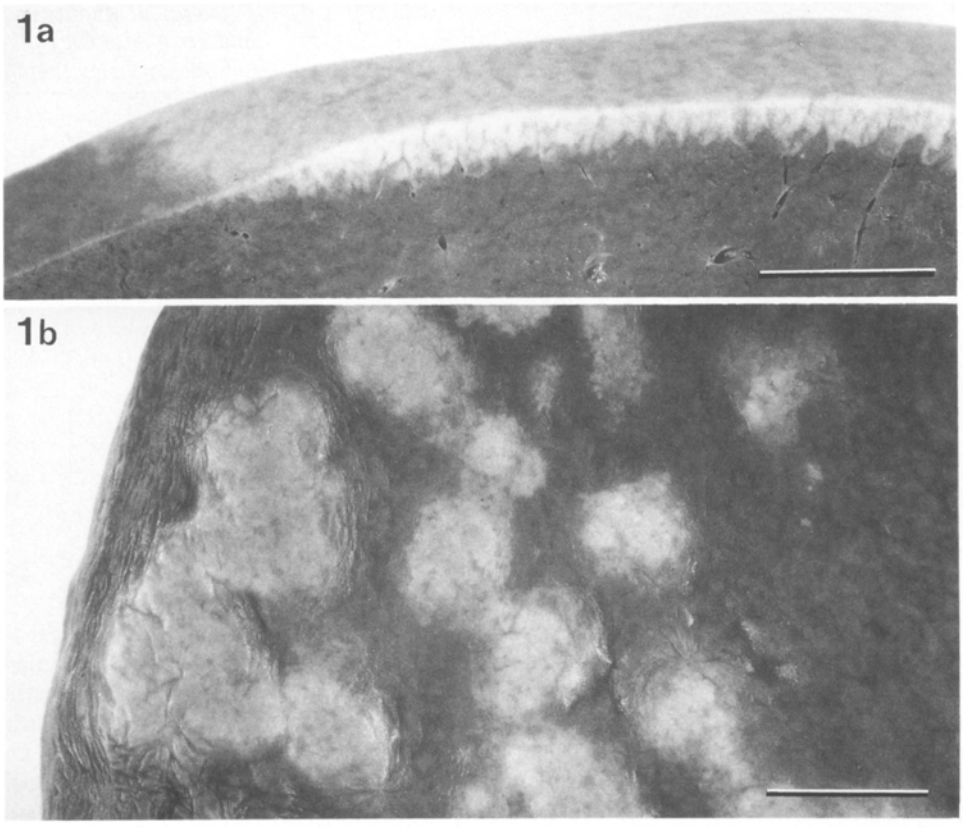

Fig. 1. a Postero-inferior part of the right liver lobe showing the smooth capsule and the focal fatty change (FFC) appearing as a thin subcapsular zone on the cut section. *Bar* = 1 cm. **b** Surface of the left liver lobe with several, partly confluent slightly elevated, light nodules. *Bar* = 1 cm

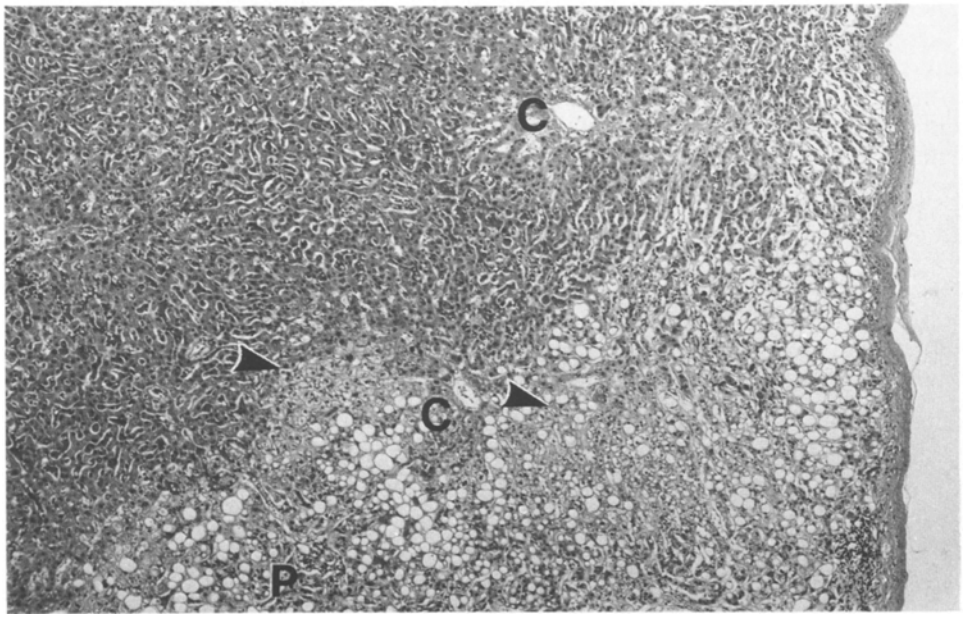

Fig. 2. Microscopic view of FFC showing irregular, macrovesicular steatosis in the subcapsular liver parenchyma. Adjacent groups of liver cells with glycogen accumulation (*arrows*). No fatty change in the parenchyma outside the lesion. Two central veins (*C*) and a portal tract (*P*) are readily seen. Haematoxylin and eosin, ×40

surface of the left liver lobe showed a 10-cm area with multiple, partly confluent 0.5–2.5 cm slightly elevated, yellow nodules up to 5 mm in thickness (Fig. 1b). The rest of the liver showed a moderate nutmeg pattern without focal changes. No lesions similar to those in the liver were seen elsewhere in the abdominal organs or peritoneum.

On microscopy the overall appearance of the liver was of normal architecture with chronic congestion; there was no steatosis, glycogen-filled nuclei, inflammation or fibrosis. Sections from lesions in both lobes disclosed a subcapsular rim of liver parenchyma with severe macrovesicular fatty change in an irregular distribution, with a scalloped margin. This showed no definite topographical relation to the microvasculature of the lobules (Fig. 2). Adjacent groups of hepatocytes contained large

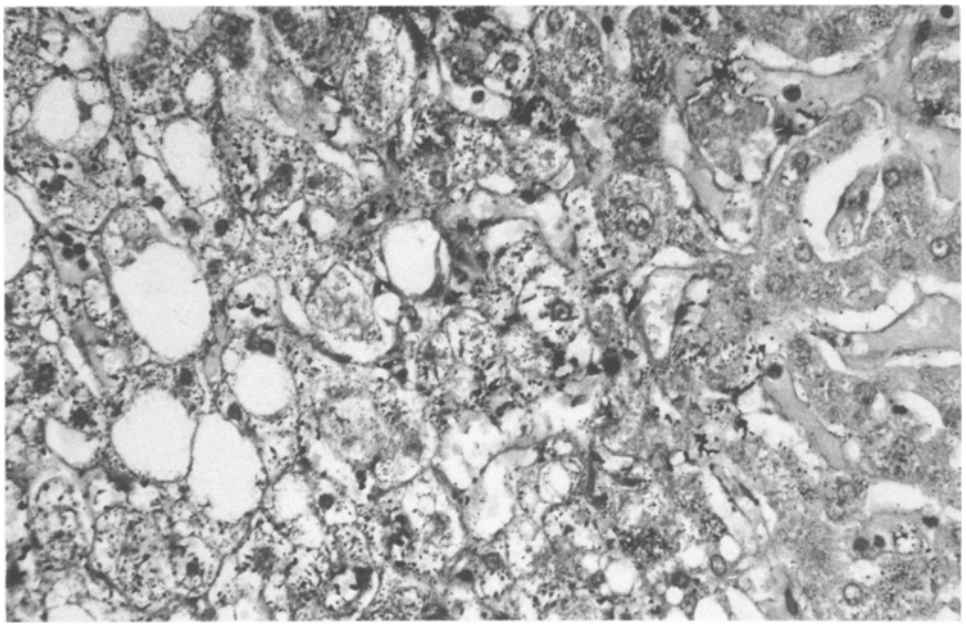

Fig. 3 High-power view of liver cells with large fatty vesicles, intermingled with cells showing glycogen accumulation. Periodic acid Schiff, ×250

amounts of cytoplasmic glycogen (Fig. 3). In the fatty lesions a slight focal lymphocytic infiltration and slight pericellular fibrosis was found. There were no Mallory bodies, and only a single focus of liver cell necrosis was seen with infiltration of neutrophilic granulocytes. The lesions were covered by a Glisson's capsule of normal thickness with slight lymphocytic infiltration.

Discussion

The aetiology and pathogenesis of FFC is unknown, and the pathogenesis of diffuse fatty change cannot explain the peculiar distribution of steatosis in FFC.

In order to investigate the mechanisms inducing FFC we reviewed the clinico-pathological findings in 39 previously reported cases. Only histologically well-documented cases are considered and we recognize that some cases of FFC, mainly reported in alcoholics, may have been excluded (Gale et al. 1983; Halvorsen et al. 1982; Livraghi et al. 1984; Tang-Barton et al. 1985)

The findings reported in the literature and in the present case are summarized in Table 1. The clinical histories indicate that FFC is associated with conditions associated with diffuse fatty change: alcoholic liver disease, congestive heart failure, diabetes mellitus, obesity, emaciation, and febrile conditions. Corticosteroids, well-known steatogenic drugs (Steinberg et al. 1952) were given in 8 cases (nos. 4, 7–10, 24, 28–29). No other drug exhibited in the reviewed cases or in our own case could reasonably be suspected of causing fatty change. Diabetes mellitus was present in 17 patients, and was insulin dependent in nearly all of them. In a few patients, no obvious predisposing steatogenic condition was revealed.

Brawer et al. (1980) and other authors suggest focal tissue hypoxia is involved in the pathogenesis of FFC. Lesions are often close to the liver surface, at the periphery of the portal and hepatic arterial circulation. Resembling hepatic infarctions, the subcapsular fatty lesions are wedge-shaped with the broad base at the surface. They occur almost exclusively in livers with chronic congestion. In 3 patients reported by Pardes et al. (1982), blunt liver trauma seems to have resulted in FFC (case 15).

In 6 patients, including a young child (case 6), a single nodule of fatty change was located along the falciform ligament, which delineates the "watershed" of the right and left hepatic artery, an area of potential hypoxia. Insufficient vascular supply due to a congenital anomaly may have resulted in FFC (Brawer et al. 1980).

Radiological imaging procedures with administration of intravenous contrast medium in cases of non-uniform fatty change have revealed that the fatty lesions are less well perfused than the unaffected regions of the liver (Tang-Barton et al. 1985). While this may be a result of compression of the vessels by the enlarged hepatocytes rather than the cause of the fatty change, it may influence the mobilization of deposited hepatic fat. The rapid reversibility of non-uniform fatty change, especially in alcoholics, suggests that it represents a phase in the dynamics of hepatic fat deposition and mobilization (Bashist et al. 1982).

In the present case, as in those reported by Wanless et al. (1989), the FFC was restricted to a very thin subcapsular rim. Although local hypoxia in the subcapsular liver parenchyma cannot be excluded, the pathogenetic mechanism is more likely to be associated with peritoneal dialysis.

It is well known that glucose from dialysis solutions, in particular from hypertonic ones, diffuses through the serosal lining of the abdominal cavity – including the liver surface (Khanna et al. 1981). Increased absorption into hepatocytes occurs especially in the subcapsular area, a process which is apparently insulin independent (Van Theil et al. 1987). As soon as the glucose is within the hepatocytes, it is converted to glucose-6-phosphate

Table 1. Clinico-pathological findings in 40 patients with focal fatty change of the liver

Case no.	Reference	Sex	Age (years)	Primary diagnosis Clinical presentation	Other diagnoses	Number of fatty lesions	Size of fatty lesions	Location of fatty lesions	Comments on the microscopic appearance of the fatty lesions
1	Amoyal	F	?	Obesity	None	Numerous	1–2 cm	Throughout both liver lobes	Macrovacuolar steatosis of irregular distribution
2	Baker	F	53	Diffuse lymphadenopathy and fever		Numerous	Not specified	Diffuse	
3	Brawer	F	51	Adenocarcinoma of the breast, widely metastatic	Multiple pulmonary emboli, generalized atherosclerosis, congestive heart failure, obesity	Several	Up to 0.9 cm	Surface and within the right lobe	Macrovacuolar steatosis, some centrolobular sparing, lesions bordered by central veins
4	Brawer	F	21	Bilateral chronic pyelonephritis, renal transplant	Iatrogenic Cushing's syndrome, staphyloccal septicaemia, pneumonia, congestive heart failure, emaciation	Several	Up to 0.4 cm	Throughout the liver, primarily subcapsular	Macrovacuolar steatosis, most lesions bordered by central veins
5	Brawer	F	45	Adenocarcinoma of the breast, widely metastatic	Emaciation	Several	Up to 1.5 cm	Throughout the liver, primarily subcapsular	Macrovacuolar steatosis, lesions bordered by central veins, some centrolobular sparing, centrolobular congestion
6	Brawer	M	26mo	Perforated vermiform appendix, generalized peritonitis		One	Not specified	Adjacent to the falciform ligament, subcapsular	Microvacuolar steatosis, lesion bordered by central veins, some centrolobular sparing
7	Brawer	F	60	Bypass graft for superficial femoral artery occlusion	Idiopathic trombocytopenic purpura, iatrogenic Cushing's syndrome, fungal and bacterial bronchopneumonia, hepatitis, obesity	Several	Up to 2.0 cm	Throughout the liver, largest lesion deep within the left lobe	Macrovacuolar steatosis
8	Brawer	F	75	Astrocytoma, grade III	Cholecystectomy and choledochojejunostomy (20 years earlier), total parenteral nutrition (9 days), urinary tract infection, *E. coli* septicaemia, obesity	One	0.4 cm	Deep within parenchyma, site unspecified	Macrovacuolar steatosis
9	Brawer	F	79	Cerebral infarction, myocardial infarction	Congestive heart failure, obesity	One	0.8 cm	Near the hilum, subcapsular	Macrovacuolar steatosis
10	Brawer	F	50	Squamous carcinoma of uterine cervix	Multiple sclerosis, congestive heart failure, seizures, obesity	One	1.2 cm	Anterior edge of liver, subcapsular	Macrovacuolar steatosis, extensive fibrosis, some periportal sparing
11	Brawer	F	46	Ruptured berry aneurysm with massive cerebral haemorrhage	Hypertension	Multiple	0.5 cm	Throughout the liver	Macrovacuolar steatosis
12	Clain	F	34	IDDM for 31 years	Cholecystectomy (8 years earlier)	Multiple	Up to 9 cm	Both lobes, the largest in the right lobe, wedge-shaped with base subcapsular	Macrovacuolar steatosis

Table 1 (continued)

Case no.	Reference	Sex	Age (years)	Primary diagnosis Clinical presentation	Other diagnoses	Number of fatty lesions	Size of fatty lesions	Location of fatty lesions	Comments on the microscopic appearance of the fatty lesions
13	Flournoy	F	67	Subtotal gastrectomy with Billroth II anastomosis for stage I adenocarcinoma of the stomach 13 months earlier, mild elevation of liver-associated serum enzymes	IDDM	Multiple	Not specified	Both lobes	
14	Hartshone	F	50	Multiple myeloma	DM, obesity	One	Not specified	Between right and left lobe	Increased fibrosis in the portal triads
15	Pardes	F	19	Pain in the right hypochondrium and fever		One	Large but not specified	Posterosuperior aspect of right	Areas of necrosis with leucocyte infiltration, and background blood clot
16	Rampal	F	65	Pain in the right hypochondrium	Previous alcohol abuse	One	4 cm	Right lobe	No pathological features besides the FFC
17	Rampal	F	61	Operated for breast cancer		Two	1–5 cm	Right lobe	No pathological features besides the FFC
18	Rampal	F	54	Pain related to the biliary tract	NIDDM for 8 years	One	11 cm	Right lobe	No pathological features besides the FFC
19	Rampal	M	40	Operated for a rectal cancer		One	4 cm	Right lobe	No pathological features besides the FFC
20	Rampal	M	34	Alcoholism		One	8 cm	Left lobe	No pathological features besides the FFC
21	Rampal	F	69	Diarrhoea after partial duodeno-pancreaectomy	Previous partial resection of the thyroid gland	Two	1.2–3.5 cm	Right lobe	No pathological features besides the FFC
22	Sawada	F	29	DM		One	Not specified	Right lobe	
23	Simon	F	70	Adenocarcinoma of the gallbladder with metastases to the liver and other organs		One	2 cm	Left lobe subcapsular	Macrovacuolar steatosis, at the periphery occasional lymphocytes and monocytes, large arteries, thin-walled veins and capillaries
24–33	Wanless	Fx2 Mx8	26, 73 28–73	Renal failure-CAPD, and IDDM	See ref.		Lesions involving 5 to 80% of the surface area	Thin subcapsular rim 0.05–12 mm in thickness	Mallory bodies in 2 cases, in 1 with neutrophilic inflammation and fibrosis
34	Yates	F	45	Right upper quadrant abdominal pain	Mild obesity	Multiple	Small	Throughout the liver	Steatosis with a predominantly centrilobular distribution, marked haemosiderosis
35–39	Yoshikawa	F	47–57	Cholelithiasis (3 cases), or colon cancer (1 case), or both (1 case)	DM (1 case)	One in 4 cases, two in 1 case	Small	Adjacent to the falciform ligament, on the medial side in 4 cases, on both sides in 1 case	
40	Grove	M	55	Uraemia treated with CAPD	IDDM, generalized atherosclerosis, arterial hypertension	Multiple	0.5–10 cm	The largest one in the right lobe, all the rest in the left lobe, all lesions were subcapsular	Macrovesicular steatosis of irregular distribution, slight pericellular fibrosis and lymphocytic infiltration, increased glycogen in adjacent hepatocytes

and the reaction rate of this enzymatic process is only dependent on the intracellular substrate concentration. Thus, if the load of glucose is unphysiologically high, a "glucose sink" develops in hepatocytes (Van Theil et al. 1987). The insulin added to the peritoneal dialysis solutions also diffuses through the hepatic capsule (Zingg et al. 1982). As with the glucose, the insulin concentration will be highest in the subcapsular hepatocytes and decrease as the insulin is diluted by blood from terminal portal tracts. Insulin facilitates glycogen synthesis. The high glucose load in conjunction with the insulin may result in glycogen accumulation prior to the development of steatosis (as seen in the present case).

Based upon the observations of Wanless et al. (1989) the high insulin concentration rather than the glucose load is the most important steatogenic factor. By inhibiting the oxidation of free fatty acids and stimulating the synthesis of triglycerides, the high insulin concentration in the subcapsular hepatocytes results in localized steatosis. A sole steatogenic role for the glucose in the dialysate (Dianeal; Baxter Allerød Denmark) might be explored by using an osmotic agent other than glucose.

Other factors, including the duration of CAPD, regulation of the diabetes mellitus, obesity, the hypertonicity of the dialysis solutions as well as local factors such as peritonitis involving the liver, may influence the degree of steatosis. The abdominal anatomy and the influence of gravitational forces may explain the particular location of the FFC associated with CAPD.

The major clinical importance of FFC lies in its differential diagnosis from other focal liver lesions. These include primary and secondary neoplasms, hamartomatous lesions, haematomas and abscesses. The differential diagnosis may not be possible by any diagnostic technique short of liver biopsy.

Histologically, FFC should be distinguished from a number of other fatty liver lesions. Fatty change may occur in liver cells in cirrhotic nodules (Bashist et al. 1982; Mulhern et al. 1979), and in focal nodular hyperplasia (Shojania and Hoog 1975), conditions associated with abnormal blood vessels and local ischaemia, suggesting anoxia as a steatogenic factor in these cases. Moreover, fatty change may occur in hepatocellular adenoma (Edmondson 1976) and carcinoma (Patrick and McGee 1988), possibly as a consequence of anoxia or an aberrant metabolism.

Liver lipomas are extremely rare tumours composed entirely of mature adipocytes, with no intervening hepatocytes or portal areas (Ishak 1976; Roberts et al. 1986). The more common pseudo-lipomas, also called coelomic fat ectopias, are always found on the surface of the liver (Karhunen 1985) outside the liver capsule.

Some of the most common stromal fatty liver lesions are the hamartomatous malformations which, in addition to a varying proportion of adipose tissue, contain other elements giving rise to names like angiolipoma, angiomyo(myelo)lipoma or myelolipoma (Goodman and Ishak 1984; Roberts et al. 1986; Rubin et al. 1984).

In the interpretation of needle biopsies of the liver the pathologists should always be aware of the problem of sampling errors. If there is massive steatosis associated with little or no biochemical disturbance or clinical symptoms, the possibility of FFC should be considered.

References

Amoyal P, Bauret P, Bories P, Michel H (1989) Diffuse multinodular hepatic steatosis of metastatic appearance. A case description. Endoscopy 21:193–194

Baker ME, Silverman PM (1985) Nodular focal fatty infiltration of the liver: CT appearance. AJR 145:79–80

Bashist B, Hecht HL, Harley WD (1982) Computed tomographic demonstration of rapid changes in fatty infiltration of the liver. Radiology 142:691–692

Brawer MK, Austin GE, Lewin KJ (1980) Focal fatty change of the liver, a hitherto poorly described entity. Gastroenterology 78:247–252

Clain JE, Stephens DH, Charboneau WJ (1984) Ultrasonography and computed tomography in focal fatty liver. Report of two cases with special emphasis on changing appearances over time. Gastroenterology 87:948–952

Edmonson HA (1976) Benign epithelial tumors and tumorlike lesions of the liver. In: Okuda K, Peters RL (eds) Hepatocellular carcinoma. Wiley, New York, pp 309–330

Flournoy JG, Potter JL, Sullivan BM, Gerza CB, Ramzy I (1984) Case report. CT appearance of multifocal hepatic steatosis. J Comput Assist Tomogr 8:1192–1194

Gale EM, Gerzof SG, Robbins AH (1983) Portal architecture: a differential guide to fatty infiltration of the liver on computed tomography. Gastrointest Radiol 8:231–236

Goodman ZD, Ishak KG (1984) Angiomyolipomas of the liver. Am J Surg Pathol 8:745–750

Halvorsen RA, Korobkin M, Ram PC, Thompson WM (1982) CT appearance of focal fatty infiltration of the liver. Am J Radiol 139:277–281

Hartshone MF, Crooks LA, Bennett W, Ramirez H, Bunker SR, Cawthon MA, Karl RD, Bauman JM (1985) A false-negative xenon-133 study in focal fatty infiltration of the liver. Clin Nucl Med 10:43–48

Ishak KG (1976) Mesenchymal tumours of the liver. In: Okuda K, Peters RL (eds) Hepatocellular carcinoma. Wiley, New York, pp 247–307

Karhunen PJ (1985) Hepatic pseudolipoma. J Clin Pathol 38:877–879

Khanna R, Oreopoulos DG, Dombros N, Vas S, Williams P, Meema HE, Husdan H, Ogilvie R, Zellerman G, Roncari DAK, Clayton S, Izatt S (1981) Continuous ambulatory peritoneal dialysis (CAPD) after three years: still a promising treatment. Perit Dial Bull 1:24–34

Livraghi T, Mattoni C, Sangalli G, Vettori C (1984) Focal fatty liver change by sonography. Diagn Imaging Clin Med 53:226–230

Mulhern CB, Arger PH, Coleman BG, Stein GN (1979) Nonuniform attenuation in computed tomography study of the cirrhotic liver. Radiology 132:399–402

Pardes JG, Haaga JR, Borkowski G (1982) Focal hepatic fatty metamorphosis secondary to trauma. J Comput Assist Tomogr 6:769–771

Patrick RS, McGee JO'D (1988) Biopsy pathology of the liver. Chapman and Hall, Cambridge, p 340

Rampal P, Desmorat H, Bruneton JN, Saint-Paul MC, Rampal A, Mouiel J, Serres JJ (1986) Stéatose hépatique irrégulière. Étude clinique et iconographique de 6 cas. Gastroenterol Clin Biol 10:43–48

Roberts JL, Fishman EK, Hartman DS, Sanders R, Goodman Z, Siegelman RL (1986) Lipomatous tumours of the liver: evaluation with CT and US. Radiology 158:613–617

Rubin E, Russinovich NAE, Luna RF, Tishler JMA, Wilkerson JA (1984) Myelolipoma of the liver. Cancer 54:2043–2046

Sawada S, Kawa S, Murata T, Tanaka Y, Koishi T, Fukagae N

(1983) Localized fatty infiltration of the liver. CT demonstration of its disappearance on treatment. Acta Radiol Diagn 24:359–361

Shojania NG, Hoog GR (1975) Isolated liver nodules. Gastroenterology 69:28–34

Simon MA (1934) Focal fat infiltration in the liver. Am J Pathol 10:799–803

Steinberg H, Webb WM, Rafsky HA (1952) Hepatomegaly with fatty infiltration secondary to cortisone therapy: case report. Gastroenterology 21:304–309

Tang-Barton P, Vas W, Weissman J, Salimi Z, Patel R, Morris L (1985) Focal fatty liver lesions in alcoholic liver disease: a broadened spectrum of CT appearances. Gastrointest Radiol 10:133–137

Van Theil DH, Stone BG, Schade RR (1987) The liver and its effect on endocrine function in health and diseases. In: Schiff L, Schiff ER (eds) Diseases of the liver. Lippincott, Philadelphia, pp 131–140

Wanless IR, Bargman JM, Oreopoulos DG, Vas SI (1989) Subcapsular steatonecrosis in response to peritoneal insulin delivery: a clue to the pathogenesis of steatonecrosis in obesity. Mod Pathol 2:69–74

Yates CK, Streight RA (1986) Focal fatty infiltration of the liver simulating metastatic disease. Radiology 159:83–84

Yoshikawa J, Matsui O, Takashima T, Sugiura H, Katayama K, Nishida Y, Tsuji M (1987) Focal fatty change of the liver adjacent to the falciform ligament: CT and sonographic findings in five surgically confirmed cases. Am J Radiol 149:491–494

Zingg W, Shirriff JM, Leibel BS (1982) Experimental routes of insulin administration. Perit Dial Bull 2 [Suppl 2]:24–27