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Case report

Nodular regenerative hyperplasia of the liver associated with metastases of pancreatic endocrine tumour: report of two autopsy cases

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Summary. Two autopsy cases with multiple hepatic metastases of pancreatic endocrine tumours and nodular regenerative hyperplasia of the liver (NRH) are reported. The tumour cells were positive for glucagon, insulin, gastrin and vasoactive intestinal polypeptide immunohistochemically and the serum gastrin was elevated in one case. In the other, tumour cells were positive for insulin. Controls failed to show NRH in the non-metastatic part of 35 autopsies of livers with multiple hepatic metastases. A combination of hepatotrophic hormonal factor(s) and disturbed hepatic circulation associated with hepatic metastases may be important in the development of NRH.

Key words: Nodular regenerative hyperplasia of the liver – Liver metastasis – Pancreatic endocrine tumour

Introduction

Nodular regenerative hyperplasia of the liver (NRH) is defined as diffuse nodules of hyperplastic hepatocytes without a fibrous rim within the liver (Nakanuma 1990; Ranstrom 1953; Steiner 1959; Stromeyer and Ishak 1981). NRH may be associated with a variety of conditions including collagen vascular diseases, haematological abnormalities, metabolic disease, and immunological disorders (De Sousa et al. 1991; Miyai and Bonin 1980; Moran et al. 1991; Nakanuma 1990; Nakanuma et al. 1984; Thung et al. 1982; Wanless et al. 1980). A number of patients with NRH present with portal hypertension (Harada et al. 1986; Stromeyer and Ishak 1981; Wanless 1990). The exact pathogenesis of NRH is controversial.

We have recently seen two autopsy cases of malignant endocrine tumour of the pancreas presenting with multiple metastases in the liver. The non-metastatic parenchyma of the liver showed diffuse fine nodularity, without a fibrous rim to the nodules, consistent with a diagnosis of NRH. We report these two cases with an emphasis on the morphological and immunohistochemical findings.

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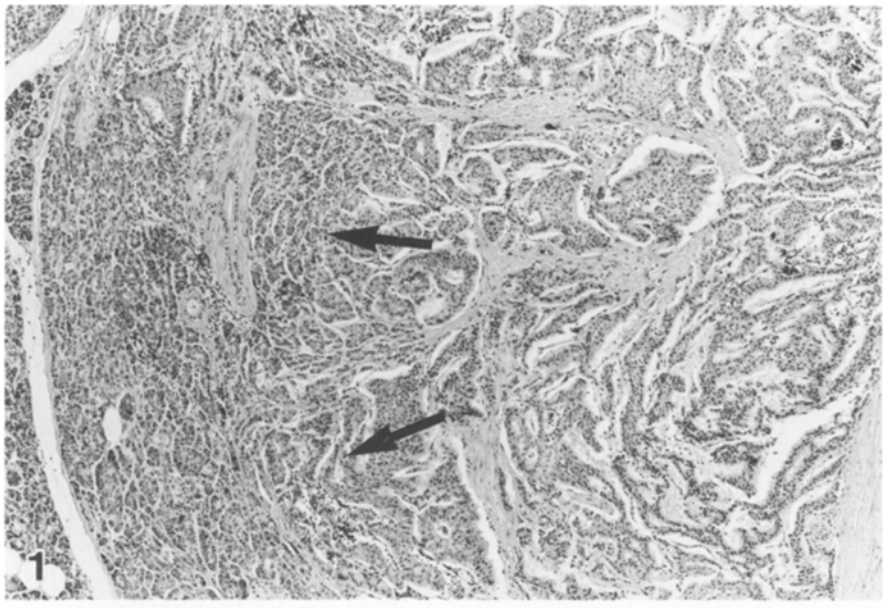
Materials and methods

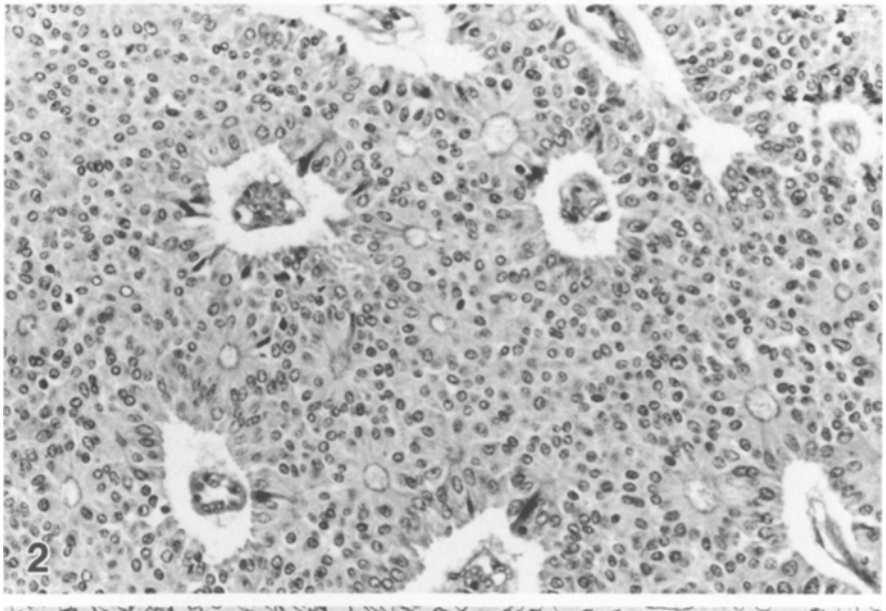
Metastatic liver nodules, non-neoplastic livers and primary pancreatic nodules from the two cases (vide infra) were fixed in 10% neutral formalin and embedded in paraffin. Serial sections (3 μm) were cut from each paraffin block, some of which were stained with haematoxylin and eosin, Gomori's reticulin, Mallory's azan, and aldehyde-fuchsin stains. The remaining sections were used for immunohistochemical staining by the avidin-biotin-peroxidase complex method (Hsu et al. 1981). Sources and optimal dilutions of primary antibodies used in this study are shown in Table 1. In brief, after blockage of endogeneous peroxidase activity, sections were incubated with the primary antibodies at 4° C overnight. These sections were then treated with biotinylated secondary antibodies for 40 min, followed by avidin complexed to biotinylated horseradish peroxidase (Vector, Burlingame, Calif.) for 30 min. Reaction products were visualized by immersion of the section in a 3,3′-diaminobenzidine tetrahydrochloride (DAB) (Sigma, St. Louis, Mo.) solution containing hydrogen peroxide. Sections were lightly counterstained with haematoxylin. No positive staining was obtained when hydrogen peroxide without DAB or DAB without hydrogen peroxide was applied, or when non-immune serum was used as the first layer.

Table 1. List of primary antibodies and their sources

Antisera against	Animal source	Dilution	Source of antibodies (Laboratory)
Chromogranin A	Mouse	1:200	BMB (Mannheim, FRG)
Insulin	Guinea pig	1:150	Dako (Santa Barbara, Calif., USA)
Glucagon	Rabbit	1:200	Dako
Pancreatic polypeptide	Rabbit	1:600	Dako
Serotonin	Mouse	1:10	Dako
Gastrin	Rabbit	1:300	Dako
VIP	Rabbit	1:400	CRB (Cambridge, UK)

VIP, Vasoactive intestinal polypeptide; BMB, Boehringer Mannheim Biochemica; CRB, Cambridge Research Biochemicals





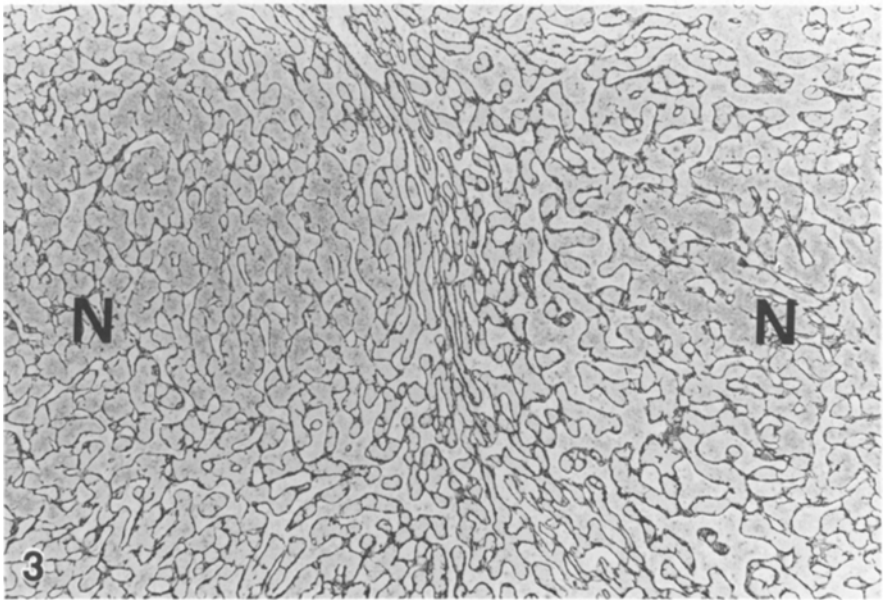


Fig. 1. Pancreatic tumour showing a ribbon-like or trabecular pattern and invading the pancreatic parenchyma (*arrows*). Case 1. H&E, ×65

Fig. 2. Pancreatic tumour showing a tubular pattern and rosette-like formation. Case 2. H&E, ×200

Fig. 3. Hyperplastic hepatocellular nodules (*N*) without a fibrous rim are seen. The hepatocytes between these nodules are atrophic. Case 1. Gomori's reticulin, ×170

Case reports

Case 1

A 54-year-old Japanese male noticed an abdominal mass in October 1981 and was admitted to hospital in July 1982. A diagnosis of metastatic malignant carcinoid tumour of the liver was made by several imaging modalities and needle liver biopsy. There were no clinical or imaging findings suggestive of pancreatic islet tumour. Interferon-beta and Adriamycin were administered and the size of tumours in the liver decreased. In October 1983, he showed telangiectasia of the face, massive ascites and hepatomegaly. Abnormal laboratory data included (normal values in parentheses): alkaline phosphatase (ALP), 480 IU/l (88–271); prothrombin time, 15.9 s (11.9–13.9); and fibrinogen, 106 mg/dl (170–410). He died in January 1984.

At autopsy, a tumour 1.5 cm in greatest diameter was found in the pancreatic head. Multiple metastases were found in the liver and also in the rectovesical pouch. Histologically, the tumour showed ribbon-like and tubular patterns (Fig. 1) and a number of tumour cells were positive by aldehyde fuchsin stain as well as for chromogranin A. Insulin was positive in the pancreatic tumour, though other peptide hormones examined were negative in both the pancreatic and metastatic hepatic tumours. A diagnosis of primary endocrine tumour of the pancreas was made.

The liver, with multiple metastatic nodules, was markedly enlarged (10800 g). The non-metastatic portions of the liver showed diffuse, whitish, fine nodulations and intervening darker areas. Microscopically, these whitish nodules were 2–3 mm in size and were composed of normal-appearing hepatocytes arranged in a two or multi-cell thickness (Fig. 3). Hepatocytes were compressed and sinusoids were congested between these nodules. These findings were diagnostic of NRH. There were on occasion tumour thrombi in the intrahepatic portal vein branches. The patient had mild splenomegaly (220 g) but clear evidence of portal hypertension was found at autopsy.

Case 2

A 64-year-old Japanese man complained of epigastric pain in January 1988 and was admitted to a local hospital. The early medical history disclosed an operation for perforated gastric ulcer at 60 years of age. Several imaging modalities disclosed multiple metastatic tumours in the liver but failed to show pancreatic masses. A high serum gastrin was found and the diagnoses of gastrin producing tumour of unknown primary focus and Zollinger-Ellison syndrome were made. Progressive anaemia developed, and he was transferred to our hospital in july 1990. Laboratory data were as follows: white blood cells 1400/mm^3; ALP, 699 IU/l; and serum gastrin, 29333 pg/μl. Serum vasoactive intestinal polypeptide (VIP) was 7.1 pg/ml (<100). During admission acute myelogenous leukaemia (smouldering type) was found by bone marrow puncture. He developed fever and complained of dyspnoea, and died in October 1990.

At autopsy, a tumour 1.5 cm in its greatest diameter was found in the pancreatic body. Multiple metastases were found in the liver. Histologically, this tumour showed a tubular pattern admixed with rosette-like or compact formation (Fig. 2). A number of tumour cells were positive by the aldehyde fuchsin stain and for chromogranin A. Insulin, glucagon, gastrin and VIP were positive in pancreatic tumours and the latter two were found in liver metastases. A diagnosis of primary endocrine tumour of the pancreas was made. Bone marrow showed moderate infiltration of leukaemic cells.

The liver was markedly enlarged (3200 g), and there were multiple metastatic nodules. In the non-neoplastic parts, there were diffuse fine nodulations without a fibrous rim (Fig. 4A). Microscopically, the nodules were composed of hyperplastic hepatocytes without a fibrous rim, with intervening atrophic and compressed hepatocytes (Fig. 4B). These changes were consistent with a diagnosis of NRH. There were occasional tumour thrombi in the intrahepatic portal vein branches.

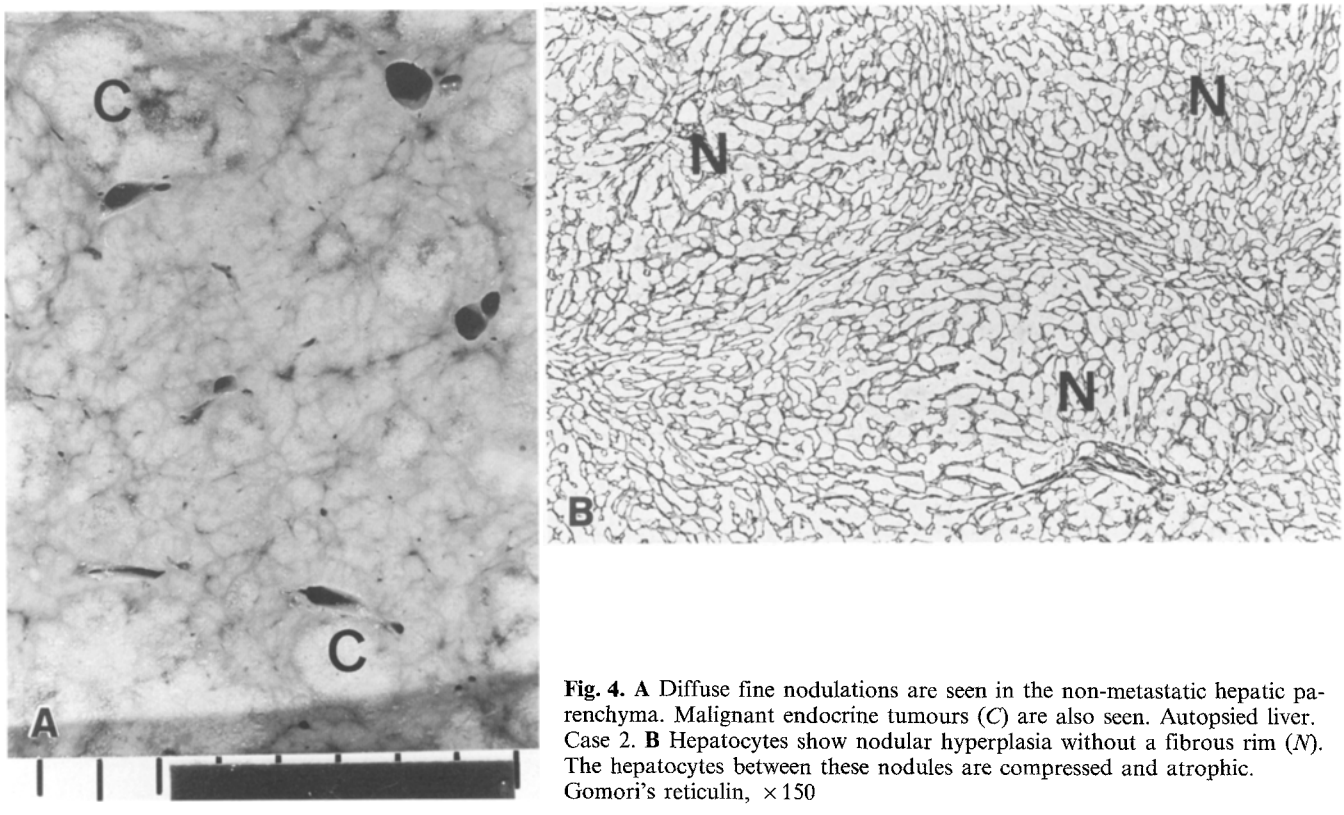


Fig. 4. A Diffuse fine nodulations are seen in the non-metastatic hepatic parenchyma. Malignant endocrine tumours (*C*) are also seen. Autopsied liver. Case 2. **B** Hepatocytes show nodular hyperplasia without a fibrous rim (*N*). The hepatocytes between these nodules are compressed and atrophic. Gomori's reticulin, ×150

Control cases

NRH was sought in 35 consecutive autopsied non-cirrhotic livers with multiple liver metastases (mean age, 66 years; age range, 33–86 years; male to female ratio, 25:10). Livers with portal fibrosis, hepatitis as well as considerable autolytic changes were not included. Endocrine tumours were also not included.

There were no cases showing changes diagnostic of NRH.

Discussion

There have been no reports of NRH in the liver bearing primary or metastatic tumour(s) in the literature, apart from a brief description in a recent paper by Wanless (1990), who surveyed 2500 autopsy cases and found that 12.5% of 64 cases of NRH were associated with massive liver metastases; he speculated that portal venous tumour thrombosis might be pathogenetically related to the development of NRH. However, the clinicopathological data on these cases, such as the primary focus of malignancy and the degree of portal venous thrombosis, were unclear.

The pathogenetic mechanism(s) of NRH in our two cases can only be the subject of speculation. De Sousa et al. (1991) have proposed two modes of pathogenesis for NRH, the first related to the persistent sinusoidal congestion. Wanless (1990) suggested that NRH is a secondary and non-specific tissue adaptation to heterogeneous distribution of blood flow within the liver and does not represent a specific entity (Wanless 1990). The second hypothesis relates to the prolonged exposure of hepatocytes to blood-borne hepatotrophic substances, such as glucagon and insulin. Thung et al. (1982) reported one NRH patient who had maturity-onset diabetes with elevated serum insulin. Moran et al. (1991) made a report on NRH in children, in which one case of Donohue's syndrome was included, where hyperplasia of the pancreatic islets might have been related to the development of NRH. It is possible that hepatotrophic peptide hormones may be involved in the development of NRH and De Sousa suggested that the cooperative action of these two processes may be the mechanism leading to the development of NRH (De Sousa et al. 1991).

In our cases, tumour microthrombi were occasionally found in the intrahepatic portal vein branches. Metastatic nodules and these tumour thrombi might have caused disturbance of intrahepatic circulation; however, nodular hyperplasic changes of the hepatocytes were not topographically related to the portal venous thrombi or metastatic nodules. These findings suggest that disturbed intrahepatic circulation due to metastases alone is insufficient for the development of NRH in the liver.

The tumour cells in our two cases were positive with aldehyde-fuchsin stain and also for chromogranin A, characterizing endocrine tissue (Lloyd et al. 1990). Of interest was that glucagon and insulin, both being hepatotrophic hormones stimulating regeneration and proliferation of hepatocytes (Leffert et al. 1982), were found in tumour cells in case 2, and insulin was found in case 1. It seems likely that these hepatotrophic hormones might have had endocrine and possibly paracrine effects on the hepatocytes, and contributed to the development of NRH. In addition, gastrin and VIP were also positive immunohistochemically within some tumour cells and the serum gastrin was elevated in case 2. VIP is known to act on smooth muscle cells of vessels causing dilatation of vessels (Straus and Raufman 1985), and might have acted on the vessels within the liver here and caused changes in the hepatic circulation which contributed to the development of NRH.

We conclude that the combination of intrahepatic circulatory disturbance due to multiple liver metastases and prolonged exposure to hepatotrophic hormonal factor(s) produced in endocrine tumours may be a factor in the development of NRH in our cases.

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