Digestive and Liver Disease 42 (2010) 635–641

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

Contrast-enhanced ultrasonography in evaluating hepatic metastases from neuroendocrine tumours

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ARTICLE INFO

Article history:
Received 14 July 2009
Accepted 14 January 2010
Available online 20 February 2010

Keywords:
Carcinoids
Contrast-enhanced ultrasonography
Gastroenteropancreatic neuroendocrine tumours
Liver metastases
Pancreatic endocrine tumours

ABSTRACT

Objectives: At presentation, gastroenteropancreatic neuroendocrine tumours (GEP NETs) frequently show prognostically negative hepatic involvement. The aim of this study was to characterise hepatic metastases of GEP NETs as revealed by contrast-enhanced ultrasonography (CEUS), which allows the fine definition of the microvascular system, and to correlate these findings to the biological behaviour of the tumour.
Methods: Eighteen out of 62 GEP NET patients examined between January 2007 and September 2008 had histologically proven hepatic metastases from primary ileal (#6), gastric (#1) or rectal (#1) carcinoids, pancreatic tumours (#7), or primary duodenal (#2) or occult gastrinomas (#1), and all underwent low mechanical index real-time CEUS with SonoVue® injection.
Results: Strong early enhancement in the arterial phase was observed in 15 cases (83%), and a rapid wash-out in the portal venous phase in 14 (78%). In the late venous phase, the lesions were hypoechoic in 12 cases (67%), isoechoic in five (28%), and hyperechoic in one (0.05%). The time of arterial enhancement correlated with the Ki-67 proliferative index ($r_s = 0.516$; $p = 0.028$).
Conclusions: Most of the neuroendocrine liver metastases showed increased arterial enhancement at CEUS, a behaviour that is similar to that of hepatocellular carcinomas and the opposite of that of other metastases. CEUS can be a useful diagnostic means of characterising such metastases.

1. Introduction

Gastroenteropancreatic neuroendocrine tumours (GEP NETs) are rare, accounting for only about 2% of all gastrointestinal tumours [1–3], and have strikingly varied symptoms and outcomes. Their clinical presentation depends on the site of the primary tumour and whether they are functioning (i.e. whether they secrete peptides that lead to symptoms). Most are non-functioning, and present fairly late with symptoms of mass effects or related to distant (usually hepatic) metastases, or both [1–5].

One of the most important prognostic factors affecting patient survival is the presence of liver metastases [1–7]. A substantial portion of patients with midgut or hindgut carcinoids present with liver metastases: up to 60–75% of patients with non-functioning tumours (i.e. those not associated with symptoms due to hormone hypersecretion) [7]. Liver metastases are the most common imaging finding at the time of the initial diagnosis of gastrointestinal endocrine tumours, being detectable in up to 40% of ileal, and 80% of caecal lesions [8]; furthermore, 59–80% of patients with pancreatic non-insulinoma tumours have synchronous liver metastases [9]. The site of the primary tumour also has prognostic significance: for example, the 5-year survival rate in patients with pancreatic tumours ranges from 30% in the case of non-functioning tumours to 97% in the case of benign insulinomas; on the other hand, gastrointestinal tumours have a 5 years survival rate of 60–90% [7].

Traditional contrast-enhanced examinations using diagnostic imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), show that the hepatic metastases of NETs avidly uptake the contrast medium in the early phase [8–11], whereas it is washed out in the later phases, which explains why metastases appear as enhancement defects. This behaviour is more similar to that of small primary hepatocellular carcinomas [12] than that of the metastases of adenocarcinomas, whose pattern is usually characterised by minimal or no enhancement during the arterial phase (rim-like enhancement, diffuse or mosaic-like enhancement). Diffuse enhancing metastases are observed in only 23–31% of cases, with complete contrast wash-out being seen in the late phases in almost all malignant lesions (84–100%) [13–16] (Table 1).

Ultrasonography (US) is widely used to detect liver lesions, even though it is usually considered to be less accurate than CT, MRI,

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1590-8658/$36.00
doi:10.1016/j.dld.2010.01.009

Table 1
SonoVue® enhancement of the more frequent focal liver lesions during the arterial, portal venous and late phases [13–15].

Diagnosis	Arterial phase (%)	Portal venous phase (%)	Late phase (%)
Malignant lesions (all)			
Hyper-enhancement	48–90	1	0
Hypo-enhancement	20	77	84
Iso-enhancement	25	19	7
HCC			
Hyper-enhancement	67–90	1	0
Hypo-enhancement	13	65	84–97
Iso-enhancement	15	33	14
Metastasis			
Hyper-enhancement	31–34	0	0
Hypo-enhancement	24	94.3	84–100
Iso-enhancement	38	1	0
CCC			
Hyper-enhancement	23	0	0
Hypo-enhancement	35	88	85
Iso-enhancement	10	8	0–4
Benign lesions (all)			
Hyper-enhancement	21	21	20
Hypo-enhancement	31	17	16
Iso-enhancement	24–48	41–62	43–64
Hemangioma			
Hyper-enhancement	27	60	63
Hypo-enhancement	60	30	20
Iso-enhancement	0–13	3–7	10–17
FNH			
Hyper-enhancement	100	38	23
Hypo-enhancement	0	62	8
Iso-enhancement	0	0	69

HCC = hepatocellular carcinoma; CCC = cholangiocarcinoma; FNH = focal nodular hyperplasia.

somatostatin receptor scintigraphy or histology, whose combination is considered the best possible way of evaluating patients. However, the availability of contrast-enhanced ultrasonography (CEUS) may improve the detection and characterisation of liver lesions as it allows much better definition of the microvascular system. The CT and MRI vascular patterns of metastases from NETs have been widely described [8–11,17–19], but there are fewer and more heterogeneous CEUS data concerning metastatic GEP NETs [20–25]; moreover, some of the CEUS studies concentrated on primary endocrine tumour [21,22].

The aim of this study was to characterise the CEUS patterns of hepatic metastases arising from GEP NETs.

2. Materials and methods

2.1. Patients

Between January 2007 and September 2008, 62 patients (32 males and 30 females; median age 60.5 years, range 21–82) were prospectively evaluated: 22 had neuroendocrine pancreatic tumours, 37 gastrointestinal neuroendocrine tumours, and three a primary occult gastrinoma. Eighteen patients (10 males and 8 females; median age 68 years, range 38–80) had hepatic metastases: three had a single hepatic lesion, 11 had 2–10, and four had more than 10 lesions, which were due to primary ileal tumours (6 cases), pancreatic endocrine tumours (7), a gastric carcinoid (1), a rectal carcinoid (1), duodenal gastrinomas (2) and a primary gastrinoma of occult origin (1) (Table 2).

The patients underwent a complete biochemical evaluation, including the plasma levels of chromogranin A (CgA, currently considered the most useful general circulating marker of NETs), transabdominal ultrasound and conventional radiological investigations (contrast-enhanced CT), somatostatin receptor scintigraphy, and histological characterisation of the NET on the basis of the WHO classification [26], with assessment of the Ki-67 proliferative index and TNM disease staging [27,28]. The CT examinations were performed within five days of CEUS. No histological evaluation was available for two patients with biochemically demonstrated occult gastrinomas without metastases.

Table 2
Patients' clinical characteristics.

Characteristics	All NET patients ($n = 62$)	Patients with liver metastases ($n = 18$)
Age (median, range)	60.5 (21–82)	68 (38–80)
Gender (male/female)	32/30	10/8
Location of primary (no. of patients)		
Pancreas	22	7
Stomach	13	1
Duodenum	5	2
Ileum	8	6
Appendix	5	–
Colon	2	–
Rectum	4	1
Occult	3	1
TNM staging at presentation (no. of patients)		
0/I/II/III/IV	1/23/7/5/26	–/–/–/–/18
Presence of clinical syndrome (no. of patients)		
Functional/non-functional tumours	20/42	13/5
Median CgA, range (U/L)	20 (16–1707)	469 (20–1707)
WHO classification (no. of patients)		
A, B, C[a]	34, 21, 5	1, 13, 4
Not available	2	–
Ki-67 (no. of patients)		
<2%	23	1
2–20%	32	14
>20%	4	3
Not available	3	–

[a] A = well-differentiated endocrine tumour; B = well-differentiated endocrine carcinoma; C = poorly-differentiated endocrine carcinoma.

The reference method for the diagnosis of hepatic metastatic lesions was the pathological examination of a liver biopsy. Each patient underwent a fine needle biopsy (FNB) of the target nodule and surrounding liver parenchyma performed using a 21-gauge trenchant needle for microhistology (Biomol, HS Hospital Service, Italy) of both intra- and extra-nodule liver parenchyma tissue. Five-micron thick formalin-fixed and paraffin-embedded sections of liver tissue were routinely stained with hematoxylin–eosin, Masson trichrome and PAS diastase. Immunohistochemical studies were performed, with neuroendocrine differentiation being proved by the reactivity of tumour cells to chromogranin A and/or synaptophysin antibodies. The proliferation index was determined on the basis of Ki-67 antigen reactivity.

The study was approved by our Local Ethics Committee, and all of the patients gave their written informed consent.

2.2. Imaging

2.2.1. US

The 18 patients with hepatic metastases underwent a B-mode ultrasonographic and colour Doppler examination using a 3.5 MHz multifrequency convex transducer (Philips iU22, Bothell, WA, USA). Lesion size and echogenicity were assessed at baseline. In the case of multiple lesions, the largest was used as the target for the contrast medium. All of the examinations were carried out by the same examiners (SM and SP), who have at least 2 years' experience of CEUS.