Intrabiliary metastasis from rectal cancer mimicking peripheral papillary-type cholangiocarcinoma.

and depth. The relationship between the site characteristics and mean overall quality score were analysed by means of univariate and multiple logistic regression analysis. The probability of an 'insufficient' score was calculated in relation to the above-mentioned variables, with an odds ratio (OR) of >1 indicating insufficient quality.

The overall rating score was sufficient (≥ 3) in 51% (95% CI: 38–65%) of cases. The majority of the sites (73%) were aimed at patients rather than physicians. Commercial sponsorship was significantly more frequent among the CH sites (45%) than among the HH (15%) or CA sites (0%) ($p = 0.002$); 61% of the commercial sites did not include a financial disclosure. Results from both univariate and multiple logistic regression analysis are given in the Table 1. Interestingly, at multivariate analysis, the only variable independently related to the poor quality was the presence of commercial sponsorship, with an odds ratio (OR) of 18.1 (95% CI: 1.7–192.5).

Overall, these results indicate that the quality of hepatological web sites on the Internet is low and negatively affected by the presence of mainly undeclared commercial interests. Thus, considering that most of these sites are addressed to patients, guidelines for the certification and surveillance of web sites relating to liver diseases are warranted.

Mirella Fraquelli[1], Dario Conte[1], Calogero Cammà[2], Giovanni Casazza[3], Daniele Prati[1,4]

[1]*Postgraduate School of Gastroenterology, Padiglione Granelli 3° piano, IRCCS—Ospedale Maggiore, Via F. Sforza 35, 20122 Milan, Italy*
[2]*National Council of Research, IBIM and Cattedra di Gastroenterologia Palermo, Italy*
[3]*Department of Clinical Sciences, Ospedale 'L. Sacco', Milan, Italy*
[4]*Department of Transfusion Medicine and Hematology, Ospedale Alessandro Manzoni, Lecco, Italy*
E-mail address: mfraquelli@yahoo.it

References

[1] Winker MA, Flanagin A, Chi-Lum B, White J, Andrews K, Kennett RL, et al. Guidelines for medical and health information sites on the internet: principles governing AMA web sites. JAMA 2000;283:1600–1606.
[2] Kim P, Eng TR, Deering MJ, Maxfield A. Published criteria for evaluating health related web sites: review. BMJ 1999;318:647–649.
[3] Berland GK, Elliott MN, Morales LS, Algazy JI, Kravitz RL, Broder MS, et al. Health information on the internet: accessibility, quality, and readability in English and Spanish. JAMA 2001;285:2612–2621.

doi:10.1016/j.jhep.2004.03.009

Intrabiliary metastasis from rectal cancer mimicking peripheral papillary-type cholangiocarcinoma

To the Editor:

Metastatic lesions from colorectal cancer (CC) have been described in the common bile duct [1,2], whereas their occurrence in the intrahepatic biliary tree is extremely rare. We describe the case of a 75-year-old man who underwent an anterior rectal resection for a lower third rectal adenocarcinoma at moderate degree of differentiation initially infiltrating the muscular layer but none out of the 21 examined nodes (Dukes A; Jass 1; Astler-Coller B1; T2 N0 Mx). Twenty-eight months after surgery, the patient complained abdominal pain in the right upper quadrant, mild and transient jaundice without nausea and/or vomiting and fever. Liver function tests were as follow: ALT 47 U/L; AST 57 U/L; alkaline phosphatase level 138 U/L; gamma-glutamyltransferase level 246 U/L; total bilirubin 1.76 mg/dl. Hepatitis A, B and C markers were negative. CEA level was 36.6 ng/ml (n.v.: 0.0–5.0) and Ca 19–9 Gica was 120.6 ng/ml (n.v.: 0.0–37.0).

US revealed an irregular sectorial (triangular shaped) mostly hyperechogenic area placed in V–VI–VII segments (Fig. 1(A)). MR examination showed a sectorial area with apex pointed to the hilum, hipo-iso-intense in T1, slightly and irregularly hyper-intense in T2-weighted acquisition/image, containing some little dilated biliary vessels and with clear enhancement at the hepatic arterial phase (HAP) (Fig. 1(B) and (C)) after administration of contrast media. Direct and enhanced CT confirmed the findings (Fig. 1(D)). None of imaging techniques was be able to demonstrate a neoplastic nodule. Consequently, the imaging diagnosis was: 'Arterial compensatory phenomena probably due to a hidden nodule causing biliary vessels dilatation and partial portal flow stoppage. Suspect cholangiocarcinoma'. The patient underwent a right hemi-hepatectomy extended to the common bile duct and to the limphonodes anastomosing the left bile duct to a Roux-en-y jejunal loop. The specimen showed a papillary tumour with intra/extra-biliary growth (approximately 1 cm) of the right bile duct near the confluence with the left (Fig. 1(E)), located at the apex of a triangular area of congested liver parenchyma and corresponding to the sectorial enhancement area evidenced by MR/TC. Two additional papillary tumours (both less than 1.0 cm in diameter) were found in this area (Fig. 1(E)).

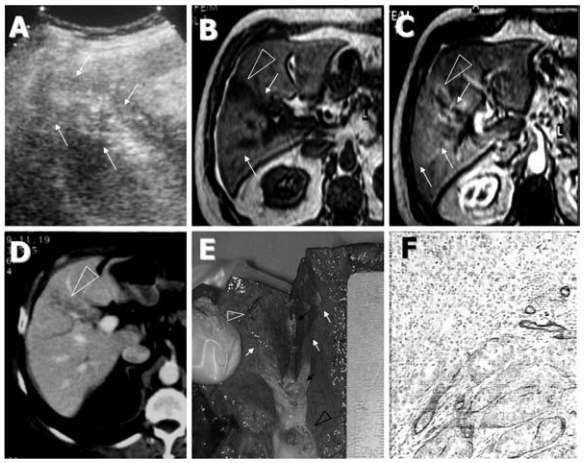

Fig. 1. (A) Ultrasonography, axial scan. Magnetic resonance, axial scans T1 weighted, (B) direct and (C) after paramagnetic contrast agent intravenous administration, hepatic arterial phase. (D) Spiral computed tomography, axial scan after iodinated contrast agent intravenous administration, portal venous phase. Triangular congested parenchymal area (white arrows); dilated biliary vessels (white arrowheads). (E) Surgical specimen. Opening longitudinally from the hilum to the glissonian surface. Triangular congested parenchymal area (white arrows); dilated biliary vessels (white arrowheads); main papillary tumour at the apex of congested parenchyma (black arrowhead); others papillary tumours within the congested area (black arrows). Note the correspondence between MR imaging and specimen. (F) Immunostaining for laminin-5 (cryostat sections) in metastatic tissue.

Microscopically, metastatic tissue stained positive for cytokeratin 20 and was distributed both in the lumen of the biliary duct and extraductally. The cytokeratin 20 positive epithelium was clearly distinct from the epithelium of the biliary duct showing positivity for cytokeratin 7. Cytokeratin 7 was 100% negative in the tumour mass. In reason of the prognostic value attributed to laminin-5 in metastatic colon cancer [3,4], laminin 5 immunostaining was performed on cryostat sections of primary tumour and metastatic tissue. Positive staining was detected in the stroma of pseudoglandular structures of the primary tumour. In liver tissue distant from the metastatic areas, positive staining for laminin-5 was found only in the basal membrane of biliary ducts in portal areas. In metastatic tissue, staining for laminin-5 was identical to that observed in the primary tumour and was concentrated in stromal areas around pseudoglandular structures (Fig. 1(F)). Final diagnosis after pathology was ‘Intra and peribiliary metastasis from CC’.

Parenchymal arterialisation areas have been known for a long time as transient hepatic attenuation differences (THAD) [5,6]. However, being observed only during HAP, they were rarely seen at non-breath-hold imaging. Diffusion of spiral CT and high performance MR has led to higher detection rates of such arterialisation areas with resulting interpretation problems [7]. The hepatic parenchyma is provided with a dual blood supply, receiving 70% of blood form the portal vein and 30% from the hepatic artery. Compensatory relationships exist between the two inflows, so arterial flow increases when portal flow decreases [5]. THAD usually result from a secondary increase in arterial inflow, compensating for a reduced portal inflow (e.g. portal thrombosis or stoppage) with repercussions on the entire territory downstream from the obstruction, following portal dichotomy and producing an arterial reaction with a sectorial, triangular shape. Moreover, in case of bile duct dilatation, a collapse of the peribiliary plexus that surrounds biliary tree like a meshwork and lacks muscular walls, is observed. Since this plexus provides an additional portal inflow, its impairment or failure, results in a further decrease in the portal inflow and increase arterial reaction. In the case described herein, it is likely that both causes of portal flow reduction were responsible for the THAD. Therefore, a sectorial THAD may be the only warning sign of a hidden nodular lesion and may herald pathology, preceding its clear CT detection. Consequently, the HAP must be always performed even if no focal lesions are expected.

The histopathological examination of this case provides in addition some interesting clues about the biology of CC metastasis developing within the biliary tree. Several studies have proposed a link between laminin-5 expression and invasive activity of CC cells. In particular, laminin-5 has been shown to act as a potent stimulator of cancer cell migration [3,4] and its high expression in CC is correlated with higher degree of liver metastasis. It is possible that some forms of CC requires a specific ‘soil’ for developing metastasis in distant organs such as the liver: in the present report, it is likely that biliary structures, normally expressing laminin-5 in their basal aspects, may offer advantageous conditions for the ‘seeding’ of metastatic cells derived from CC with a particular dependency from laminin-5 for their spreading and invasive capability.

Stefano Colagrande[1], Giacomo Batignani[2], Luca Messerini[3], Massimo Pinzani[4]

[1]*Dipartimento di Fisiopatologia Clinica, Unità di Radiodiagnostica, Università degli Studi di Firenze, University of Florence, School of Medicine, Viale Morgagni 85, 50134, Florence, Italy*

[2]*Dipartimento di Fisiopatologia Clinica, Unità di Chirurgia; University of Florence, School of Medicine, Viale Morgagni 85, 50134, Florence, Italy*

[3]*Dipartimento di Patologia Umana e Oncologia; University of Florence, School of Medicine, Viale Morgagni 85, 50134, Florence, Italy*

[4]*Dipartimento di Medicina Interna, University of Florence, School of Medicine, Viale Morgagni 85, 50134, Florence, Italy*

E-mail address: s.colagrande@dfc.unifi.it

References

[1] Riopel MA, Klimstra DS, Godellas CV, Blumgart LH, Westra WH. Intrabiliary growth of metastatic colonic adenocarcinoma: a pattern of intrahepatic spread easily confused with primary neoplasia of the biliary tract. Am J Surg Pathol 1997;21:1030–1036.
[2] Blot E, Heron F, Cardot F, Kerleau JM, Metayer J, Michot F, et al. Villous adenoma of the common bile duct. J Clin Gastroenterol 1996; 22:77–79.
[3] Pyke C, Salo S, Ralfkiaer E, Romer J, Dano K, Tryggvason K. Laminin-5 is a marker of invading cancer cells in some human carcinomas and is coexpressed with the receptor for urokinase plasminogen activator in budding cancer cells in colon adenocarcinomas. Cancer Res 1995;55:4132–4139.
[4] Orian-Rousseau V, Aberdam D, Rousselle P, Messent A, Gavrilovic J, Meneguzzi G, et al. Human colonic cancer cells synthesize and adhere to laminin-5. Their adhesion to laminin-5 involves multiple receptors among which is integrin alpha2beta1. J Cell Sci 1998;111:1993–2004.
[5] Itai Y, Moss AA, Goldberg HI. Transient hepatic attenuation difference of lobar or segmental distribution detected by dynamic computed tomography. Radiology 1982;144:835–839.
[6] Itai Y, Hachiya J, Makita K, Ohtomo K, Kokubo T, Yamauchi T. Transient hepatic attenuation differences on dynamic computed tomography. J Comput Assist Tomogr 1987;11:461–465.
[7] Colagrande S, Carmignani L, Pagliari A, Capaccioli L, Villari N. Transient hepatic attenuation differences (THAD) not connected to focal lesions. Radiol Med 2002;104:25–43.

doi:10.1016/j.jhep.2004.03.027

Epstein-Barr virus (EBV)-induced liver failure in the absence of extensive liver-cell necrosis: a case for cytokine-induced liver dysfunction?

To the Editor:

Epstein-Barr virus (EBV) related liver failure is a very rare occurrence, especially in the immunocompetent patient. Severe hepatitis has been seldom reported and about 17 cases of fulminant hepatitis appeared in the literature, one being treated by orthotopic transplantation [1, 2]. In the reported cases, liver failure occurred as a complication of extensive hepatocellular necrosis as seen in fulminant viral hepatitis of other origins. We report the case of an immunocompetent patient in whom EBV primary infection led to liver failure and hepatic encephalopathy in the absence of extensive parenchymal necrosis and in whom one may raise the hypothesis of liver dysfunction related to an indirect effect of T-cell soluble products.

A 42-year-old man was referred from another hospital for severe acute hepatitis. Two weeks earlier, he experienced fever (39 °C), headache, arthralgia, right upper quadrant discomfort and tremor. He was also slightly jaundiced. His past medical history was unremarkable except for a cranial traumatism at the age of 20 complicated by epilepsy and hypertension. Since that time, he had taking valproate (500 mg two times daily) and captopril (100 mg daily). He did not take any alcohol. At presentation, blood cell count showed: WBC: $3 \times 10^3/mm^3$ (61% neutrophils; 36% lymphocytes), INR was 1.6 (N : 0.9–1.3), AST 218 IU/L (N : 0–37), ALT 135 IU/L (N : 0–40), alkaline phosphatase 344 IU/L (N : 100–280), total s. bilirubin: 3.53 mg/dl (N : 0.2–1); serum valproate was 26 mcg/ml (therapeutic range = 50–100). Serological markers for hepatitis A, B, C, CMV, Leptospirosis, Herpes and HIV were all negative. The Paul-Bunnell test was positive with positive IgM antibodies against EBV viral capsid antigen (anti-VCA) at 0.4 (N : <0.2) while EBV-VCA IgG antibodies were negative.

The worsening of clinical picture with confusion together with increased biochemical cholestasis prompted referral to our centre. At admission, the patient was jaundiced, disoriented and complained of sore throat and upper dysphagia. Clinical examination showed a diffuse German measles like rash and an erythematous throat together with hepatosplenomegaly and a coarse flapping tremor. INR was 2.29 (N : 0.9–1.3), fibrinogen 73 mg/dl (nl: 150–400), LDH 1144 IU/L (N : 98–192), AST 483 IU/L (N : 6–33), ALT 177 IU/L (N : 14–63), total s. bilirubin 16.8 mg/dl (N : 0.3–1.2), direct s. bilirubin 12.2 mg/dl, s. albumin 2.3 g/dl with fasting venous ammonia at 140 mcg/dl ($N <$ 100).

Serum EBV-VCA IgM antibodies were positive, IgG EBV-VCA antibodies were slightly positive at 26 U/L at admission, raising up to 170 U/L after 10 days. Search for EBV nuclear antigen antibodies was negative. Search for EBV-DNA sequences by PCR [3] remained positive at 270 copies EBV/mcg DNA 10 days after admission. Electroencephalogram showed a slow rhythm interpreted as grade I hepatic encephalopathy (graded from 0 to 4 following Child's scoring).

At transjugular hepatic vein catheterization performed 7 days after admission, the wedged hepatic vein pressure gradient was slightly increased at 6 mmHg (N : 1–4). Transjugular liver biopsy showed a slight mononuclear cell infiltrate of the portal tracts together with multiples inflammatory aggregates scattered into the parenchyma as well as a diffuse lymphocytic infiltration of the sinusoids. There was a centrilobular drop-out as well as centrilobular cytoplasmic cholestasis (Fig. 1(A) and (B). At in situ hybridization assay, EBER (Epstein-Barr virus Encoded RNA) was positive in several nuclei of lymphocytes in the