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LETTER TO THE EDITOR

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Tumor induced local fibrogenic effect by hepatic metastasis of insulinoma

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To the Editor:

Here we report an interesting phenomenon of peritumoral fibrotic architectural alteration of the non-tumorous liver, most likely induced by a diffusible, tumor-derived factor. A 47-year-old male Caucasian patient developed a metachronous hepatic metastasis of an insulinoma, which had been resected by partial pancreas tail-resection 13 years ago. Seven years later, recurrent hypoglycaemic episodes emerged and the patient received total pancreas left-resection, splenectomy and lymph node dissection. Several lymph node metastases were diagnosed in the peripancreatic fat tissue and the splenic hilus demonstrating malignancy. The patient now became symptomatic again with recurrent, spontaneous hypoglycemic episodes (serum glucose values lowered to 30 mg/dl). Neither abdominal ultrasound nor contrast-enhanced MRI detected a focal liver lesion, but liver metastasis was proven by a rise in serum insulin levels in the *vena hepatica propria* (3.2-fold increase of c-peptide and 9-fold increase of insulin values after selective intra-arterial calcium stimulation). Intraoperative ultrasound disclosed a single lesion in liver segment 6, which was resected. The gross specimen contained a relatively sharp demarcated, yellowish nodule, measuring 0.5 cm in diameter surrounded by liver tissue of micronodular texture. Immunohistologically, the tumor cells stained strongly for insulin (Fig. 1A). The immediately surrounding liver tissue showed severe fibrotic change, which was clearly demonstrable in connective tissue stains. The type of fibrosis was clearly discernible and different from tumor desmoplasia or capsule formation (Fig. 1B). Peritumorous focal nodular hyperplasia was ruled out by the lack of typical occluded or atypical vascular structures, well demarcated nodular hepatocellular proliferation, and by the fact that the fibrotic change faded out into the surrounding liver tissue, thus showing some kind of gradient formation [1]. The fibrogenic effect was not detectable in more than 1 cm distance from the metastasis and was also absent in a synchronous liver biopsy taken far away from the tumor (insert 1C). The restriction of the phenomenon to the immediate surrounding of the tumor with some kind of gradient formation strongly suggested activity of a tumor derived, diffusible factor. A likely candidate was insulin, which was highly expressed and secreted by the tumor cells. The growth-promoting effect of insulin appears to be mediated through activation of insulin-like growth factor I receptor (IGF-IR) and insulin receptor substrate-1 (IRS-1) [2]. In particular, it has been demonstrated that insulin stimulates proliferation and collagen type I expression of human hepatic stellate cells (HSC), which express insulin receptor, IGF-I-R, and IRS-1 [4]. Recently, Novosyadlyy et al. suggested that stimulation of the IGF axis by IGF-I and insulin is relevant in vivo for the process of fibrogenesis during acute and chronic liver injury [3]. Underlying stimulation and myofibroblastic transformation of HSC and/or portal fibroblasts in our case was suggested by smooth-muscle actin positive cells within the cirrhotic septa (Fig. 1D). Since the phenomenon was only detectable in the immediate surrounding, excessive insulin concentrations appear to be required to solely excert the fibrogenic effect in vivo. However, it remains an open question whether increased systemic insulin concentrations have confounding fibrogenic activity. Interestingly, patients with non-alcoholic fatty liver disease (NAFLD) associated with type 2 diabetes mellitus develop liver cirrhosis more frequently than non-diabetic patients [5]. In contrast to patients with

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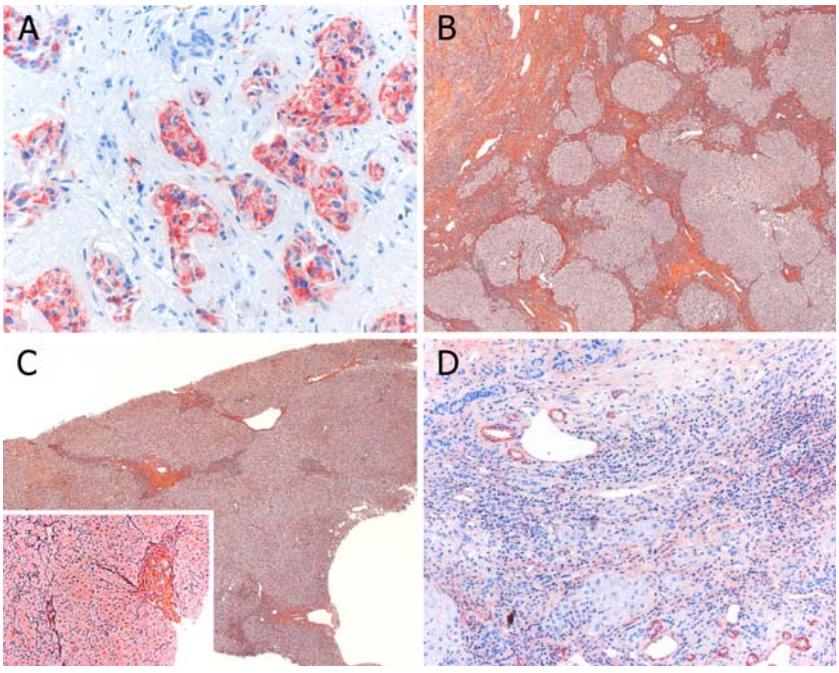

Fig. 1 Tumor cells stain strongly positive for insulin (**a**, original magnification 200×). The fibrotic architectural change of the nontumorous liver in the immediate surrounding of the insulinoma metastasis shows some gradient formation (**b**, 25×, modified Gomori's stain). Liver tissue distant to the metastasis (**c**, 25×, modified Gomori's stain) as well as an additional biopsy taken far away from the tumor (insert C, 50×) show only mild portal fibrosis. The fibrous septa as well as the vessels stain positive for alpha_smooth muscle actin (**d**, 25×)

NAFLD, we detected only mild steatosis in the parenchyma surrounding the metastasis, which was probably due to the absence of insulin resistance in these hepatocytes.

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