

Multimodality treatment of unresectable hepatic metastases from pancreatic glucagonoma

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Abstract

Glucagonomas are pancreatic islet cell tumors arising from the alpha cells which belong to neuroendocrine tumors. They frequently metastasize to the liver. We report the case of a 52-year old man with a pancreatic glucagonoma with synchronous multiple liver metastases treated by surgery, transarterial chemoembolization, percutaneous radiofrequency thermal ablation and long-acting octreotide. Our report confirms that a multimodal approach is very effective in patients with unresectable liver metastases from pancreatic endocrine tumors providing long-lasting palliation and probably prolonging survival.

Case Report

A 52-year old man was referred to our hospital because of weight loss, chronic diarrhea and an erythematous rash with bullae and erosions on the feet (Figure 1), in the groin and on the face. Blood chemical analyses showed mild anemia (hemoglobin 10.8 g/dL), and an impaired fasting glucose test. As a part of the diagnostic work-up, he underwent an abdominal computed tomography which showed a large tumor of the pancreatic tail and multiple hepatic lesions (Figure 2). Histological examination of a specimen obtained by ultrasound-guided percutaneous biopsy of a liver lesion revealed a tubulo-acinar structure of moderately atypical cells positive for chromogranin (Figure 3). ¹¹¹In-octreotide scan showed hepatic and pancreatic uptake without evidence of extrahepatic metastases. A high level of glucagon in the plasma (950 pg/mL) confirmed the diagnosis of glucagonoma. Long-acting octreotide was started with partial improvement of the symptoms. The patient was then treated with hepatic transarterial chemoembolization (TACE) combined with percutaneous radiofrequency thermal ablation (RFTA) in an effort to reduce the hepatic tumor burden. Two sessions of TACE, one month apart, were performed using polyvinyl alcohol-based

microspheres (DC Bead™, Biocompatibles UK Ltd., Farnham, UK) pre-loaded with 100 mg of doxorubicin. One day after each TACE procedure we performed ultrasound guided percutaneous radiofrequency. The radiofrequency system consists of an expandable electrode with insulated outer needle of 2.2 mm of diameter that houses nine deployable curved tines (Starburst XL; Rita Medical Systems). Abdominal enhanced CT scan at one month after the last RFTA procedure showed minimal arterial contrast enhancement in two lesions of the right lobe. The pancreatic tumor was then surgically removed and the residual vital hepatic tumors were treated with four sessions of radiotherapy with Y-DOTATOC, a radiolabeled somatostatin analog. Thirty-two months after diagnosis the patient was well, he had regained his normal body weight and the erythema had completely disappeared.

Discussion

Glucagonomas are pancreatic islet cell tumors arising from the alpha cells which often produce elevated levels of circulating glucagon.¹ The characteristic feature of the glucagonoma syndrome is a skin rash termed necrolytic migratory erythema. Other findings include a mild insulin-resistant diabetes, glossitis, cheilosis, weight loss, venous thrombosis constipation and mood changes.² Glucagonoma is a neuroendocrine tumor (NET) which frequently metastasize to the liver.³ The particular biological behavior of NETs, characterized by a long natural history, even in the presence of liver metastases, has important therapeutic implications.^{4,5} Surgical resection is to be considered when the metastases are resectable and no extrahepatic disease is present. Unfortunately, neuroendocrine metastases are

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Key words: neuroendocrine tumors, liver metastases, hepatic transarterial, chemoembolization.

Received for publication: 15 June 2009.
Accepted for publication: 29 June 2009.

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Rare Tumors 2009; 1:e6
doi:10.4081/rt.2009.e6

usually multiple and diffuse and therefore radical resection is feasible only in 10-20% of patients.⁶ Surgical resection of liver metastases with curative intent is associated with 5-year survival rates of 73-85%^{7,8} but, in unresectable disease, surgery is not useful as a palliative tool unless more than 90% of the tumor load can be debulked.⁹ In this setting, systemic chemotherapy and octeotide have proved more useful in controlling the endocrine syndrome.^{10,11} On the experience of the efficacy of transarterial chemoembolization (TACE) in hepatocellular carcinoma that shares vascular findings with neuroendocrine hepatic metastases, TACE has been effectively used in the palliative management of these tumors.¹²⁻¹³ TACE has also been used in adjuvant settings to reduce tumor load before hepatic resection, hepatic transplantation or tumor ablation techniques.^{4,14,15} Preliminary results show that the new drug-eluting microspheres now available seem to optimize TACE procedures. In fact, these microspheres are capable of loading the drugs and slowly delivering them directly into the tumor, thus achieving high intratumoral



Figure 1. Necrolytic migratory erythema on the feet.



Figure 2. Abdominal CT scan shows multiple hepatic lesions.

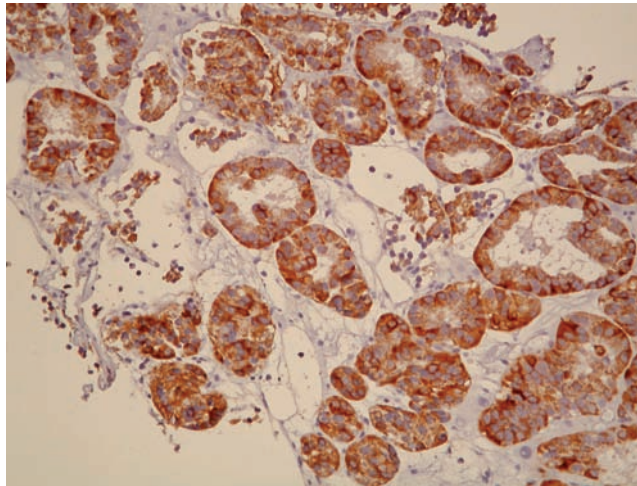


Figure 3. Liver biopsy reveals a tubulo-acinar structure of moderately atypical cells positive for chromogranin (x100).

concentrations and low plasma concentrations.^{16,17} The results with microspheres loaded with doxorubicin have been promising, showing an advantageous pharmacokinetic profile and good clinical response when compared with conventional TACE both in patients with unresectable HCC¹⁸ and in patients with liver metastases from well differentiated NETs.¹⁹ Local therapy using RFTA provides a minimally invasive procedure that decreases tumor volume, preserves most of the normal liver and can be repeated several times.²⁰ Nevertheless, histological data from liver specimens of HCC patients who underwent RFTA showed that tumor size has a significant impact on the local effect of this treatment. Indeed, vessels adjacent to the tumor cause heat loss due to perfusion-mediated cooling.²¹ Balloon catheter occlusion or TACE increase the efficacy of RFTA by reducing tumor arterial supply.²² In our patient we performed each RFTA exactly one day after the TACE to obtain an increase of the necrotic area induced by thermal ablation. After two procedures of both TACE and RFTA, the hepatic tumor load was considerably reduced, so that we were then able to perform four sessions of somatostatin receptor mediated radiotherapy using ⁹⁰Y Tyr-octreotide, which is capable of binding to the residual vital tumor. Our report confirms that a multimodal approach is very effective in patients with unresectable liver metastases from pancreatic endocrine tumors providing long-lasting palliation and probably prolonging survival.

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