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Double metachronous cutaneous metastases from recurrent hepatocellular carcinoma: a case report

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Summary. Cutaneous metastases from hepatocellular carcinoma (HCC) are rare. We report an unusual case of metachronous double skin metastases to the left nostril and the buttocks in a patient with HCC. The lesions were discovered during clinical and radiological follow-up and appeared as solitary, painless, reddish-blue nodules that bleed easily, prompting suspicion of metastatization of HCC to the nose. This is the fourth reported case of cutaneous skin metastasis to the nose. Besides the highly unusual skin sites, another peculiarity of this case is the long survival of the patient, given that the survival rate after a diagnosis of HCC is generally about 5 months. The clinical course and histopathology are compared with other similar cases. This case suggests that skin metastasis in patients with HCC who present with skin nodules should be included in the differential diagnosis of lesions arising in unusual localizations.

Key words: hepatocellular carcinoma, cutaneous metastases, chemotherapy

«METASTASI CUTANEA DA CARCINOMA EPATOCELLULARE RECIDIVO: PRESENTAZIONE DI UN CASO CLINICO»
Riassunto. Le metastasi cutanee da carcinoma epatocellulare (CE) sono rare. Riportiamo un insolito caso di metastasi cutanee metacrone insorte contemporaneamente in due sedi differenti: narice sinistra del naso e sede glutea in un paziente affetto da CE. Le lesioni sono state evidenziate durante il follow-up clinico-radiologico e apparivano isolate, asintomatiche, in forma di noduli rosso-blu facilmente sanguinanti, ponendo il sospetto di metastatizzazione di CE al naso. Questo è il quarto caso riportato in letteratura di metastasi cutanee al naso. Oltre alla sede cutanea, decisamente poco comune, un'altra peculiarità di questo report è la lunga sopravvivenza del paziente, dal momento che il tasso di sopravvivenza dopo una diagnosi di CE metastatico è generalmente di circa 5 mesi. L'evoluzione clinica ed istopatologica sono state confrontate con altri casi simili. Questo caso suggerisce che le metastasi cutanee in pazienti con CE che presentano noduli cutanei dovrebbero essere incluse nella diagnosi differenziale di lesioni che insorgono in sedi inusuali.

Parole chiave: carcinoma epatocellulare, metastasi cutanee, chemioterapia

Introduction

Cutaneous metastasis could be the first sign of an internal neoplasm and it is estimated to occur in 0.7-9% of patients with internal cancers (1). Cancers metastasizing to the skin may follow hematogenous or lymphatic routes, direct contiguous tissue infiltration or iatrogenic implantation. Hepatocellular carcinoma

(HCC) has a worldwide incidence of approximately 500,000 to 1 million new cases per year and its incidence is increasing in recent years, with metastasis detected in more than 50% of patients. The most frequent localizations are the lungs, abdominal lymph nodes, diaphragm and skeleton (2). Hu et al. (1) observed a rate of cutaneous metastases of 0.34% in a series of 12,146 patients with internal malignancies. Magana et al. (3) reviewed skin metastases from HCC, reporting 39 cases of metastatization to this site as of 2009. Skin metastases are very rare; the majority appear to originate from needle tracks or surgical wound contamination. We present an unusual case of metachronous double cutaneous metastases from recurrent HCC confirmed by histology. To our knowledge, this is the first report of metachronous cutaneous metastases from HCC.

Case report

A 65-year-old man was observed. His medical history included previous hepatitis B virus (HBV) infection and myocardical infarction for which he underwent percutaneous transluminal coronary angioplasty (PTCA). A liver lesion in S6-7 discovered during routine laboratory and radiological exams in July 2005 was reportedly diagnosed as HCC. The lesion was deemed resectable and right hepatectomy (S5-8) was performed. Postsurgical histology described a multifocal HCC, with moderately differentiated trabecular, solid and pseudoglandular patterns (G3 in the Edmondson-Steiner grading system), pT2-N0, in HBV-related chronic hepatitis with steatosis (1-2%); the resection margins were negative (R0), without neoplastic vascular invasion (Figure 1).

Clinical and radiological follow-up was started according to international guidelines. Recurrence of HCC was diagnosed in October 2006. A computed tomography (CT) scan revealed a new liver lesion in S2 (diameter, 21 mm). Considering the lesion diameter and the previous oncological history, treatment with percutaneous radiofrequency ablation was elected. A subsequent CT scan was negative for residual liver disease.

Clinical and radiological follow-up continued until June 2007, when lung disease was suspected. A

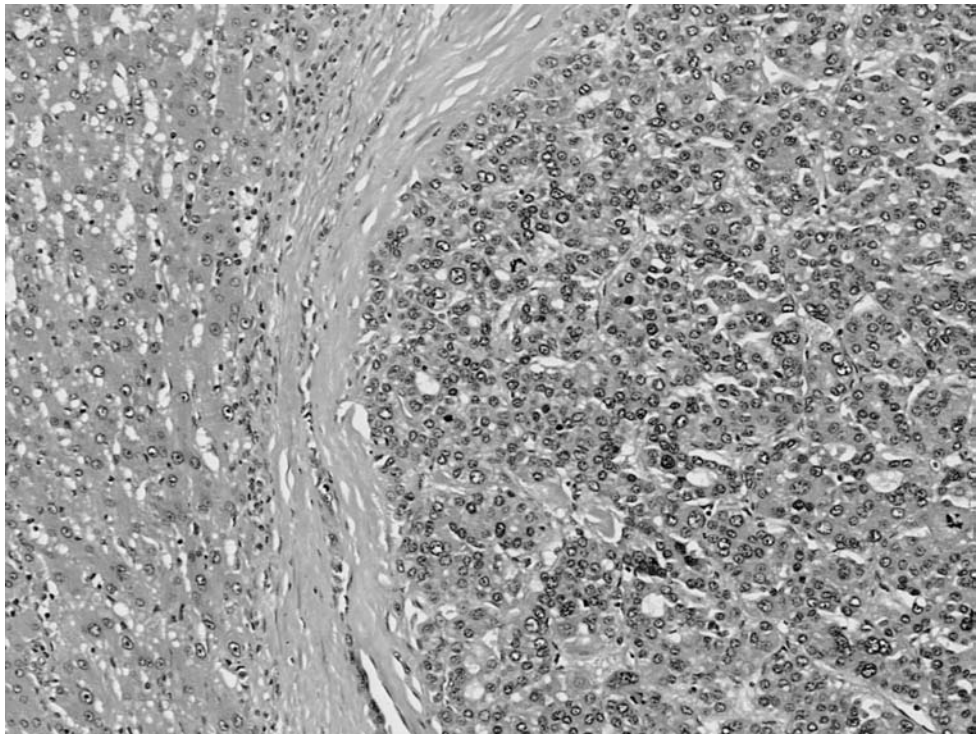

Figure 1. Primary tumor. Interface of tumor and non-neoplastic liver: in the left hepatocellular carcinoma, with pseudoglandular patterns, moderately differentiated, G3 according to Edmondson-Steiner grading system. In the right: the lobular parenchyma shows macrovesicular steatosis. Hematoxylin & Eosin, original magnification 100x.

needle biopsy of a lung lesion (diameter, 25 mm) revealed secondary spread of HCC to the lung, which was treated with radiofrequency ablation. No recurrences or secondary lesions were observed at follow-up visits over the next 12 months. In June 2008 a solitary, painless, reddish-blue nodule (diameter, 21 x 16 mm) that easily bled was observed on the left nostril (Figure 2).

A CT scan showed slight protrusion into the nostril lumen. No radiological signs of liver or lung recurrences were observed. Histological exam of a skin biopsy revealed cutaneous metastasis from HCC. Testing with serum alphafetoprotein was normal.

In August 2008, given the disease stage and the patient's clinical status (Eastern Cooperative Oncology Group [ECOG] 1 - Child A), treatment with Sorafenib (800 mg/day) was carried out. Toxicity was negligible and no increase in lesion size was observed at examination 6 weeks later.

In September 2008, Sorafenib (800 mg/day) therapy was suspended and the lesion was excised in October 2008.

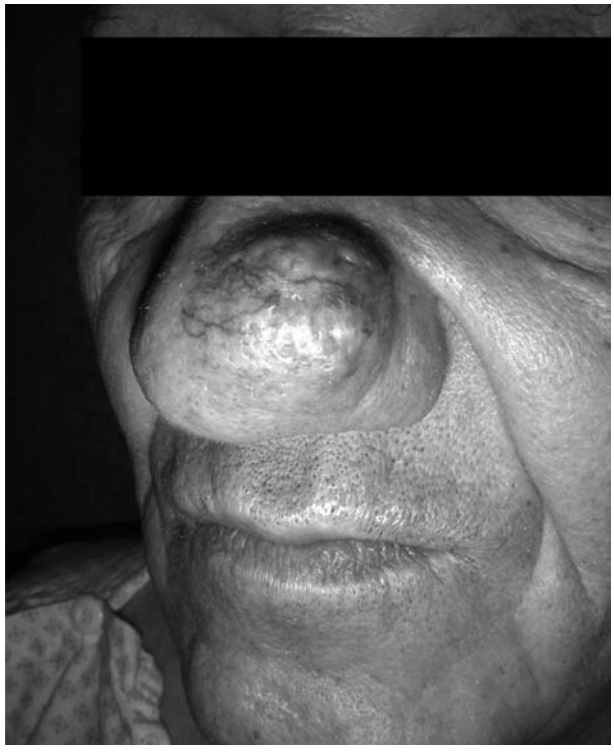

Figure 2. Metastasis from hepatocellular carcinoma localized to the left nasal wing.

Microscopic examination of the subepidermal connective tissue stroma showed proliferations of solid nests and macrotrabecules of atypical cells with abundant cytoplasm and irregular nuclei and numerous atypical mitoses (Figure 3). Strongly granular cytoplasmatic immunostaining in the tumor cells was observed with antibodies to hepatocyte paraffin 1 (HepPar 1) (Figure 4). The resection margins were negative.

The maximal Sorafenib dose was resumed without significant toxicity until May 2009, when a secondary osteolytic lesion of the left iliac wing and recurrence of lung disease were diagnosed. Chemotherapy with Sorafenib was again discontinued, and the osteolytic lesion was treated with chemoembolization, osteoplasty, calcium therapy, and infusion of Zoledronic acid (4 mg/fl every 28 days).

Over the ensuing 16 months, bone and lung disease stabilized without further cytostatic treatment. A new lesion arose on the buttocks in October 2010. The mass was found to deeply infiltrate the small gluteal muscle and was removed. Histological exam of the surgical specimen revealed further metastases from HCC.

The patient is currently alive, 3 years after excision of the first cutaneous metastases.

Discussion

We present an unusual case of metachronous double metastases from HCC. HCC is the most widespread type of malignant liver cancer and more than 80% of cases are associated with cirrhosis. Its incidence is increasing (4). Metastases from HCC usually spread to the lungs, adrenal glands, bone and regional lymph nodes. Skin metastases from internal neoplasms are infrequent, accounting for 0.7 to 9% of metastases, and are generally of pulmonary or breast origin (1).

Although cutaneous metastasis may occasionally present as the first clinical sign of HCC (4), it is a very uncommon manifestation of HCC. Magana et al. (3) reported 39 cases of metastatization to the skin described as of 2009. Further reports were published (5-12), accounting for a total of 50 patients with cuta-

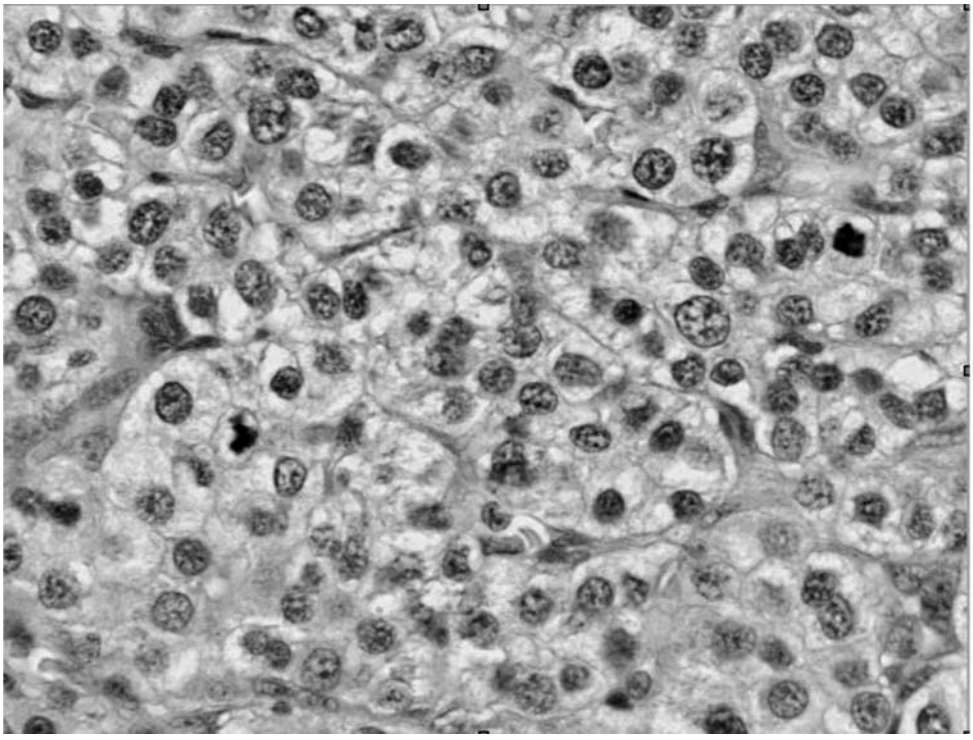

Figure 3. Tumor cells with prominent nuclei, nucleoli, and granular clear cytoplasm, and numerous atypical mitoses (Hematoxylin & Eosin, 400x).

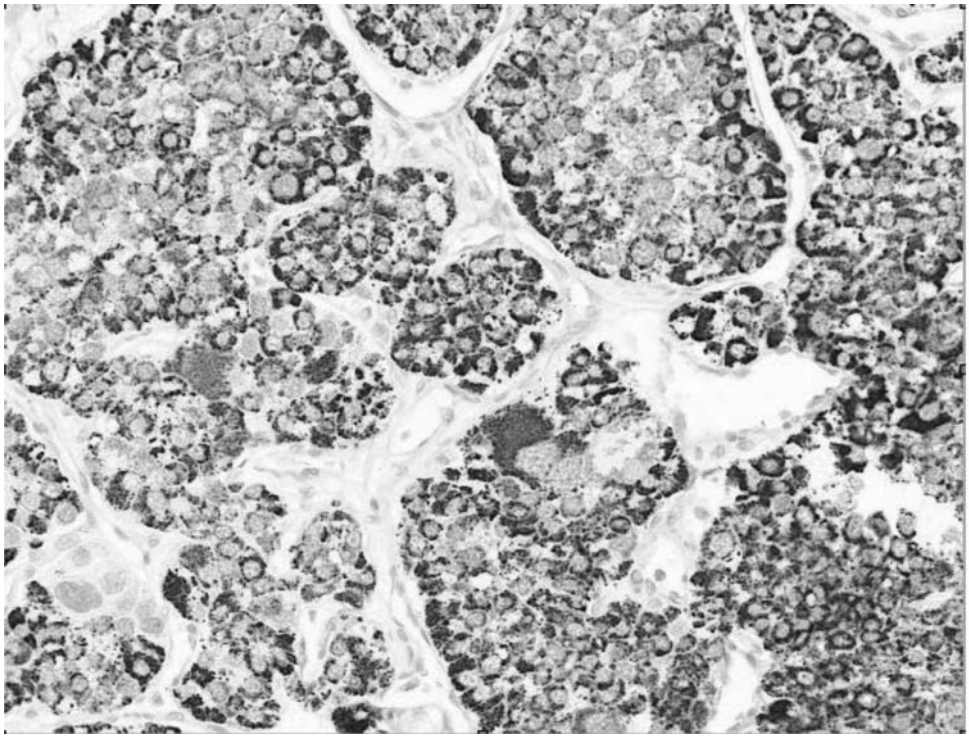

Figure 4. Strongly granular cytoplasmatic immunostaining with antibodies to hepatocyte paraffin 1 (Hep-Par1) in tumor cells (Immunoperoxidase, 200x).

neous metastases from HCC to date. The present case is the fourth to describe skin metastasis localized to the nose. Its peculiarity is the appearance of metachronous cutaneous metastases and the long survival of the patient, given that survival rate is generally about 5 months (13-14).

Histologic tumor grade has a strong impact on time to recurrence and overall survival in patients affected by HCC. Moderate and poorly differentiated tumor is a strong negative predictor of the outcome. In fact our patient developed hepatic recurrence of the disease and metastatic extrahepatic disease respectively 1 year and 2 years after surgery. However prolonged administration of Sorafenib, an oral multikinase inibitor, has recently been shown to improve overall survival in patients with advanced HCC. Also an earlier recognition and resection of the recurrent or metastatic lesions could increase the longevity of these patients.

Metastatic skin lesions from HCC follow a characteristically rapid growth pattern, typically arise on the face, scalp, chest and shoulders (15), and appear as solitary or multiple lesions, usually presenting as firm, painless, reddish-blue nodules measuring 1-5 cm without ulcerations (4, 16-17). They may be necrotic or purulent and exhibit massive bleeding when ulcerated or traumatized (17). They may occur following hematogenous or lymphatic cell dissemination (16, 18-20), or be of iatrogenic origin caused by needles in transcutaneous procedures. They may sometimes mimic pyogenic granuloma, making it an important element in the differential diagnosis of these patients (17).

Immunohistochemical analysis with alphafetoprotein, cytokeratins 8 and 18, and HepPar 1, a monoclonal antibody that reacts with an epitope of liver mitochondria, may be useful for establishing the diagnosis (3, 11).

In brief, because they generally arise from systemic dissemination of the primary cancer, cutaneous metastases are often a sign of poor prognosis. The recurrence of an implanted nodule after surgical excision and the incidence of needle-track seeding from HCC after an ultrasound-guided procedure are more frequent than cutaneous metastases. In other sites, cutaneous nodules in patients with HCC should be considered as metastases. Histology is necessary to confirm the diagnosis. Metastases from HCC should be included in the differential diagnosis of patients with the disease and skin lesions arising in unusual localizations.

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