

Cutaneous metastases from carcinoma of the bile duct

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To the Editor,

A 68-year-old woman was admitted because of painless obstructive jaundice of three days duration when she noticed yellow colored sclerae and dark colored urine. Two months before presentation, she noticed a reddish, gradually enlarging, skin nodule at the neck above the left supraclavicular area whereas a second lesion was noticed on the chest above the xyphoid 20 days before her admission. On physical examination the skin and sclerae appeared yellow. The nodule at the neck was well circumscribed with erythema, measuring approximately 2 cm in diameter (Fig. 1A) whereas the chest lesion was a 0.8-cm red papule (Fig. 1B). Both lesions were asymptomatic, hard on palpation, not fixed to the underlying tissues and non-tender. Abdominal examination revealed mild tenderness in the right upper abdominal quadrant but no mass was palpable. There were no enlarged neck, axillary or inguinal lymph nodes.

Laboratory tests showed elevated total bilirubin, 11.8 mg/dL (0.3-1.2 mg/dL); direct bilirubin, 8.2 mg/dL (< 0.2 mg/dL); alkaline phosphatase, 328 U/L (30-120 U/L); AST, 168 U/L (< 35 U/L); ALT, 266 U/L (< 45 U/L); and γ -GT, 498 U/L (9-55 U/L). Serum CA 19-9 level was increased at 340 U/mL (< 37 U/mL) with normal CEA levels, 0.9 ng/mL (0.9-5.4 ng/mL).

Abdominal ultrasonography, cholangiography and CT showed dilatation of the intrahepatic bile ducts and an obstructing mass at the hepatic hilum. Cholangiocarcinoma arising at the confluence of the hepatic ducts (Klatskin's tumor) was suspected. This was confirmed at operation where an unresectable locally extended tumor was found at the hepatic hilum. No distal lymph node or liver metastases were evident. Biopsy was taken from the tumor and a T-tube was inserted into common bile and right hepatic ducts for biliary drainage. A skin biopsy was also taken from the lesion at the neck. Histopathology revealed nests of moderately differentiated tumor cells located among fibrotic tissue in both specimens. Tumor cells were pleomorphic, with hyperchromatic atypical nuclei, cuboidal or low columnar in shape, arranged in glandular or tubular structures and

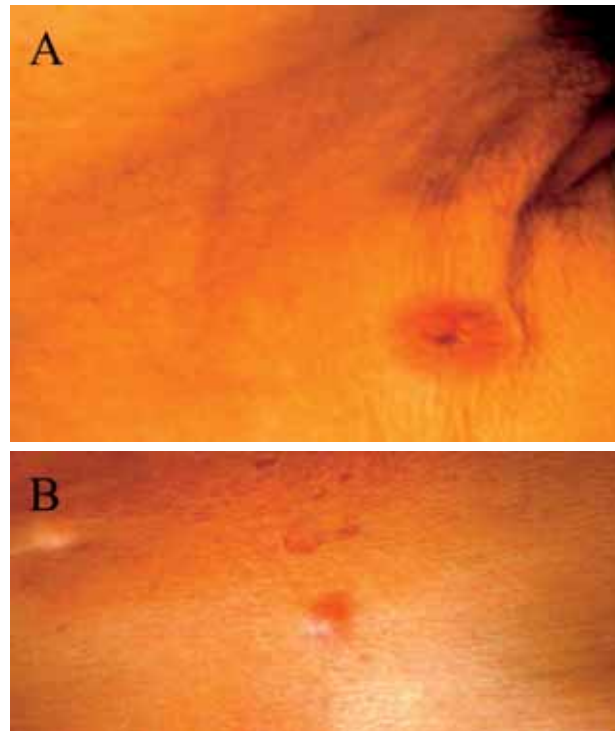


Fig. 1. — The reddish skin nodule at the neck (A) and the red papule on the chest (B).

positive for cytokeratins 8, 18 and 19, and for CEA but negative for alpha-fetoprotein by immunohistochemistry. Based on these findings, a diagnosis of skin metastases from a Klatskin tumor was made. The patient refused any further treatment and eventually died three months later.

Carcinomas of the extrahepatic or intrahepatic bile duct (cholangiocarcinomas) are rare tumors with poor prognosis. They locate mostly proximally in the duct or arise at the confluence of the left and right hepatic ducts (Klatskin tumors) and spread by local invasion into adjacent tissues or by metastasis to regional lymph nodes

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whereas hematogenous distant metastases to other organs are relatively uncommon (1). Accurate histological diagnosis of these tumors sometimes may be difficult especially in biopsy specimens. Immunohistochemically cytokeratin (CK) profiling has been used as a diagnostic tool to distinguish cholangiocarcinomas from hepatocellular (HCC) or metastatic carcinomas along with other markers. Normal hepatocytes express CK 8 and 18, whereas normal bile duct cells express CK 7, 8, 18 and 19, and this immunophenotype is generally preserved in their malignant counterparts. In this context, CK 7 and/or CK 19 positivity are relatively specific for cholangiocarcinoma although some HCCs occasionally exhibit CK 7 or CK 19 positivity. In contrast, a CK 8 and 18 positive and CK 7 and 19 negative immunophenotype is suggestive of HCC (2,3). Other markers, namely CEA and alpha-fetoprotein may also be useful in differential diagnosis; alpha-fetoprotein expression although of limited sensitivity is consistent with HCC since cholangiocarcinomas are alpha-fetoprotein negative as in our case. A bile canalicular staining pattern with polyclonal antibodies against CEA (pCEA) or absence of immunostaining with monoclonal antibodies (mCEA) is highly specific for HCC. Cytoplasmic pCEA staining is also observed in HCC but this pattern of staining is nonspecific and is also seen in both metastatic carcinomas and cholangiocarcinomas as in our patient where diffuse cytoplasmic staining was observed by pCEA immunohistochemistry.

Cutaneous metastases from cholangiocarcinomas have been described in the catheter tracts after percutaneously performed biliary catheterizations as a result of direct tumor cell seeding (4-6), whereas distant metastases to the skin are rare, with only seven cases reported so far (7-11). The primary tumor was located into the liver in 4 cases (7-9), in the lower third of the common bile duct in one case (11) and two cases were Klatskin tumors (8,10). In most cases skin metastases occurred several months after diagnosing the primary tumor in the presence of advanced disease but in our patient and in one other previously described (10), these were present before detecting the underlying cholangiocarcinoma. The development of cutaneous metastases was an ominous prognostic indicator associated with short survival.

The lesions were described as red, asymptomatic or slightly tender, firm to hard, cutaneous or subcutaneous nodules varying in size 0.5-2 cm. Only one case was described as fixed, indurated, painless ulcer (10).

The most common site for metastases was the scalp, 5 out of 7 cases (7-10), with one patient having additional lesions on the chest and the knee (8). In two reports, the lesions were located on the shoulder and chest (7), and in the lumbar and cervical areas (11), respectively. Lu *et al.* (8), suggested that metastasis to the scalp may be associated with the presence of communications between the intracranial venous sinuses and the valveless vertebral venous plexus and therefore with the veins of the chest, abdomen, and pelvis.

In conclusion, distant cutaneous metastases arising from adenocarcinoma of the bile duct may occur before diagnosing the primary tumor. A high index of suspicion should be maintained and biopsy performed when facing such lesions in order to detect the underlying carcinoma.

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