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TITLE PAGE

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Microangiopathic haemolytic anaemia caused by a signet-ring cell carcinoma of the intrahepatic bile duct.

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SUMMARY

Microangiopathic haemolytic anaemia (MAHA) originates from a mechanical injury of red cells, caused by vascular thrombosis or stenosis. Cancer is a cause of MAHA as a consequence of both chemotherapy and disseminated disease itself. Here we describe the case of a 60-year-old man who developed a signet-ring cell carcinoma originated from the intrahepatic bile ducts, complicated by bone marrow metastasis and MAHA.

INTRODUCTION

Cholangiocarcinoma is an uncommon adenocarcinoma of bile ducts, with an annual incidence rate in Europe of 1.5 cases per 100,000. [1] The frequency is higher in patients with biliary-enteric surgical drainage, mainly in those who develop recurrent biliary infections. [2]. In parallel, cirrhosis is a risk factor for the development of intrahepatic cholangiocarcinoma.

Signet-ring cell carcinoma (SRCC) is an extremely rare and dedifferentiated subtype of bile ducts carcinoma. Only a few cases of SRCC of the bile ducts are described in literature, all of them originating from extrahepatic bile ducts.

Microangiopathic haemolytic anaemia (MAHA) is a form of haemolytic anemia deriving from a mechanical injury of red cells, caused by vascular thrombosis or stenosis. An essential feature of

this anaemia is the detection of red cell fragments (schistocytes) on peripheral-blood smear. [3] Cancer can be a cause of MAHA, as a consequence of both chemotherapy and disseminated disease itself.

Here we describe the case of a 60-year-old cirrhotic patient who developed a signet-ring cell carcinoma originated from the intrahepatic bile ducts twenty years after a transduodenal sphincteroplasty and complicated by bone marrow metastasis and MAHA. To the best of our knowledge, this is the only case of MAHA caused by bile duct carcinoma and of signet-ring cell carcinoma of the intrahepatic biliary system.

CASE REPORT:

A 60-year-old man was admitted to our hospital for worsening anaemia (Hb 5.6 g/dl), dyspnoea and diffused spontaneous haematomas. Past medical history included dextrocardia, alcohol-related cirrhosis, chronic obstructive pulmonary disease (COPD), cholecystectomy and transduodenal sphincteroplasty.

The patient underwent an emergency esophagogastroduodenoscopy (EGD) showing haemorrhagic gastritis with oozing haemorrhage (Forrest Ib) treated with injection of dilute adrenaline. Subsequently, he received red blood cell transfusions along with platelet infusions because of the detected thrombocytopenia (PLTS 24,000/mm^3).

Despite transfusion therapy, anaemia continued to worsen. Laboratory analysis showed high levels of lactate dehydrogenase (LDH) (4,546 IU/l), total bilirubin (4.6 mg/dl), indirect bilirubin (2.6 mg/dl), reticulocytes (258 * 10^9/l), and alkaline phosphatase (ALP) (296 UI/l) accompanied by low levels of haptoglobin (<10 mg/dl) while direct Coombs test was negative. Coagulation tests were abnormal (INR 1.38; aPTT 47 s). Supposing an haemolytic anaemia the blood smear was analysed

and it revealed the presence of anisopoikilocytosis with abundant schistocytes (25% of the erythrocytes). On the basis of these findings a diagnosis of MAHA was made while thrombocytopenia and coagulation abnormalities were considered related to the underlying cirrhosis.

On the other hand, high levels of Carcinoembryonic Antigen (2,125 ng/ml) were also detected while Carbohydrate Antigen 19-9 (CA 19-9) and Alpha Fetoprotein (AFP) were within the normal range. Several examinations were performed in order to find out the presence of an occult carcinoma. Colonoscopy and EGD results were negative but the abdominal computed tomography (CT) showed adenopathy at the porta hepatis and pneumobilia in the left part of the intrahepatic biliary system associated to distension of the extrahepatic bile ducts and a fistula connecting the second duodenal portion and the common bile duct.

A bone marrow biopsy was also performed and it demonstrated a metastatic invasion from signet-ring shaped cells derived from an adenocarcinoma (Fig. 1-2). Immunohistochemical analysis was positive for cytokeratin 7 (CK7) and pancytokeratin (AE1/AE3) while cytokeratin 20 (CK20), caudal type homeobox transcription factor 2 (CDX2), thyroid transcription factor-1 (TTF-1) and acid phosphatase stains were negative (Fig. 3).

Positron Emission Tomography (PET) scanning with 18-fluorodeoxyglucose (18-FDG) revealed an increased uptake of radionuclide in all skeletal portions, in the intrahepatic biliary system (segment S2 and S4) and at the porta hepatis and celiac trunk (Fig.4).

According to PET scanning and to the histological result the location of the primary tumour was identified as the intrahepatic bile ducts.

Patient’s clinical condition worsened, with the progression of dyspnoea and the onset of bone pain. The patient died 17 days after the admission.

DISCUSSION:

MAHA can complicate the course of tumoural disease and it is frequently associated with bone marrow metastasis [4, 5], but its pathogenesis in cancer remains unclear. It seems that substances secreted by tumour cells (in particular cytokines and mucine) can cause endothelial injury, with subsequent red blood cells fragmentation. The presence of bone marrow metastasis can simultaneously worsen the anaemia by adding an hyporegenerative component.

Typical features of MAHA are high levels of LDH, indirect bilirubin, reticulocytes and a decrease in haptoglobin levels with schistocytes on peripheral-blood smear and negative direct Coombs test [6]. All these features were identified in our patient,. In this case, anaemia was worsened by the concomitant chronic liver disease (mainly because of the associated hypersplenism) and by alcohol intake and bone marrow metastasis (both causing an hyporigenerative anaemia).

Bone marrow biopsy showed a metastatic invasion from signet-ring shaped cells (SRCC), which is an extremely rare subtype of bile ducts carcinoma. It is a dedifferentiated adenocarcinoma, histologically characterized by round-shaped cells, with peripherally placed nuclei and cytoplasmic vacuoles filled with mucin [7, 8]. SRCC is usually located in the stomach but can also be found in other tissues like prostate [9], breast [10], testis [11] and ovary [12], bladder [13], lung [14], colon [15], gallbladder [16] and Vater ampulla [17]. To the best of our knowledge only 5 cases of SRCC of the bile ducts are described in literature, all of them referring to extrahepatic bile ducts SRCC [18, 19, 20, 21, 22].

According to the PET scanning results, the primary location of the SRCC in our patient was the intrahepatic biliary system (segment S2 and S4). At the same time, our patient had a history of transduodenal sphincteroplasty that supports this theory. Sphincteroplasty was a procedure used for treating benign distal common bile duct obstruction. It is a mucosa-to-mucosa suture, either of duodenum to bile duct alone (biliary sphincteroplasty) or of bile duct to pancreatic duct in addiction

(pancreatic sphincteroplasty). This procedure creates a permanent destruction of the Oddi's sphincter [23, 24].

It is known that the frequency of bile duct carcinoma is higher in patients with biliary-enteric surgical drainage, mainly in those who develop recurrent biliary infections. A study pointed out an incidence of bile duct carcinoma of 5.8% after transduodenal sphincteroplasty. [2] It seems that bile and pancreatic secretions can cause a chronic injury in bile ducts, resulting in premalignant or malignant changes in the biliary epithelium. Recurrent cholangitis can contribute to the chronic mucosal damage. Cholangiocarcinoma arising after a biliary-enteric drainage are often multifocal, supporting the hypothesis of toxic carcinogenesis affecting the biliary epithelium, causing a field change, even involving intrahepatic ducts. At the same time, our patient had alcohol-related cirrhosis, that is an additional risk factor for cholangiocarcinoma. [25]

This is the only case of SRCC deriving from the intrahepatic biliary system and the only case of MAHA related to a bile duct carcinoma.

Cancer – related MAHA is more frequently associated to respiratory symptoms and bone pain than non-cancer-related MAHA, and our patient developed both. [26] The prognosis of cancer - related MAHA is poor and a standard therapy is not well established. [3, 27]

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