# *Hemocromatose associada a carcinoma hepatocelular e neoplasias extra-hepáticas*

## *Hemochromatosis combined with hepatocellular carcinoma and extrahepatic neoplasms*

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## RESUMO

A hemocromatose caracteriza-se pelo acúmulo excessivo de ferro no organismo, que é depositado predominantemente no fígado, e resulta ou de um defeito genético determinando uma absorção excessiva de ferro ou da administração parenteral deste íon. O ferro em excesso determina alterações celulares através da peroxidação lipídica, estímulo da deposição de colágeno e interação com o oxigênio reativo e DNA. Os autores relatam um caso de hemocromatose em paciente portador de cirrose hepática associada ao desenvolvimento de hepatocarcinoma, hemangioma hepático, adenocarcinoma prostático e carcinoma renal, e apresentam uma discussão geral deste processo, frequentemente associado ao desenvolvimento de neoplasias.


UNITERMOS: Doenças do Metabolismo do Ferro, Hemocromatose, Carcinoma Hepatocelular, Carcinoma de Células Renais, Adenocarcinoma, Cirrose Hepática.


## ABSTRACT

*Hemochromatosis is characterized by excessive accumulation of iron in the body, which is deposited primarily in the liver. It results either from a genetic defect determining an excessive absorption of iron or from parenteral administration of this ion. The excess iron determines cellular changes through lipid peroxidation, stimulation of collagen deposition, and interaction with reactive oxygen and DNA. The authors report a case of hemochromatosis in a patient with liver cirrhosis associated with development of hepatocellular carcinoma, hepatic hemangioma, prostate adenocarcinoma and renal cell carcinoma, and provide a general discussion of this process often associated with the development of neoplasias.*


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KEYWORDS: *Iron Metabolism Disorders, Hemochromatosis, Hepatocellular Carcinoma, Renal Cell Carcinoma, Adenocarcinoma, Liver Cirrhosis.*

## INTRODUCTION

Hemochromatosis defines a state of body iron overload that results in tissue injury, and the term hemochromatosis, from the Greek haima (blood) and Chromatos (color), created by Von Recklinghausen in 1889. Hereditary hemochromatosis is an inherited recessive disorder associated with increased absorption of iron due to the presence of C282Y and/or H63D hemochromatosis gene (HFE), which is allocated on chromosome 6. The secondary hemochromatosis is an acquired disorder that occurs in the context of diseases with known causes for metabolic overload of iron, such as hemolytic anemia, blood transfusions and liver cirrhosis (1, 2, 3).

The iron corresponds to the most abundant transition metal ion in the body, and its overhead determines tissue injury through lipid peroxidation by free radicals, stimulation of collagen deposition and reactive oxygen interactions with DNA. The development of liver cirrhosis related to iron overload is associated with development of hepatocellular carcinoma (1, 2, 3, 4).

The authors report a case of hereditary hemochromatosis associated with liver cirrhosis, hepatocellular carcinoma, hepatic hemangioma, renal carcinoma and prostatic adenocarcinoma, and present a general discussion of this process.


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## CASE REPORT

Male patient, 63 years, white, reported low back pain. The medical history revealed arterial hypertension, cerebral ischemic attack, family history of brain tumor and renal cell carcinoma, and prior diagnosis of prostate adenocarcinoma of Gleason score 9 (Figure 1). He denied alcohol consumption, and had negative serology for HBV and HCV. Bone scintigraphy showed multiple areas of increased uptake involving almost the entire skeleton. Bone biopsy revealed metastatic adenocarcinoma. The CT scan identified two liver nodules, one compromising segments VI and VII, and one in segment IV, which measured 4.3 cm and 2.3 cm, and an expansive nodule in the upper pole of right kidney, measuring 5.7 cm. The microscopic evaluation of the resected liver parenchyma showed two distinct liver lesions, the biggest one corresponding to a trabecular pattern of hepatocellular carcinoma, grade II / III of Edmondson-Steiner (Figure 2), and the smallest corresponding to a hemangioma (Figure 3). The kidney lesion corresponded to a renal clear cell carcinoma (Figure 4), grade 2 of Fuhrman. Table 1 shows the immunohistochemical

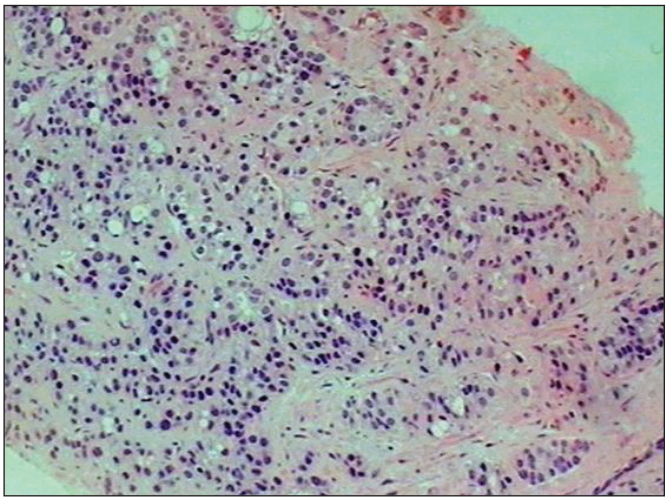


**FIGURE 1**

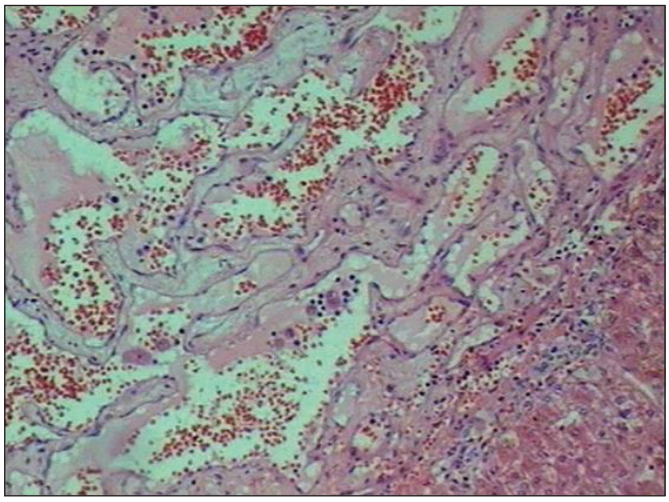


**FIGURE 3**

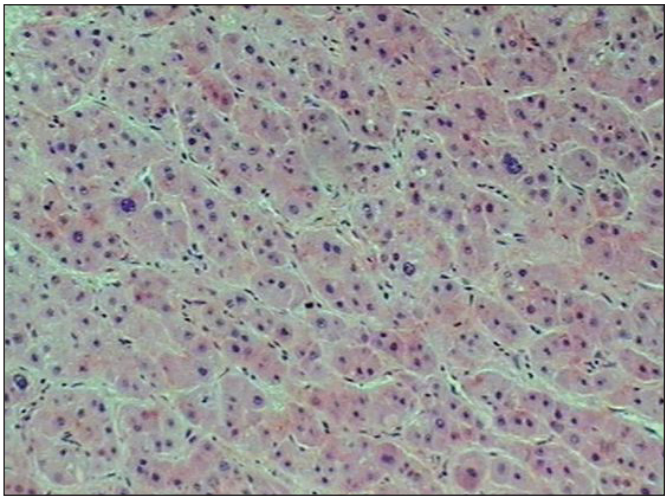


**FIGURE 2**

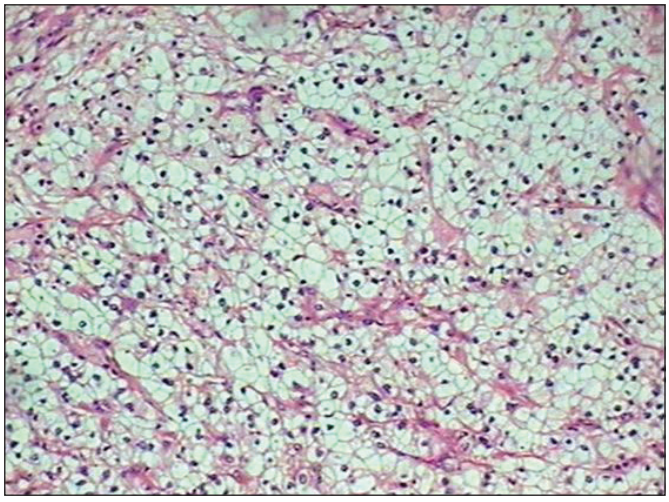


**FIGURE 4**

**TABLE 1** – Immunohistochemical profile of tumors

| NEOPLASMS / ANTIBODY | PSA | CD10 | HSA | CK8/18 | VIMENTIN | S100 | CA19.9 |
|---|---|---|---|---|---|---|---|
| HEPATOCELLULAR CARCINOMA | - | - | + | + | - | - | - |
| RENAL CARCINOMA | - | + | - | + | + | - | - |
| PROSTATIC ADENOCARCINOMA | + | - | - | - | - | - | - |

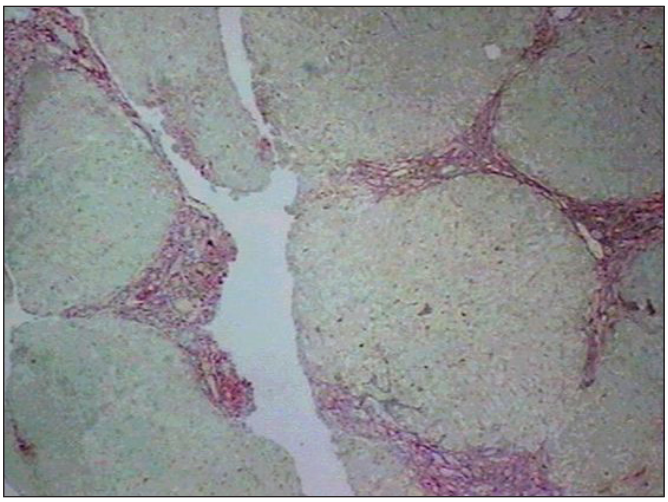


**FIGURE 5**

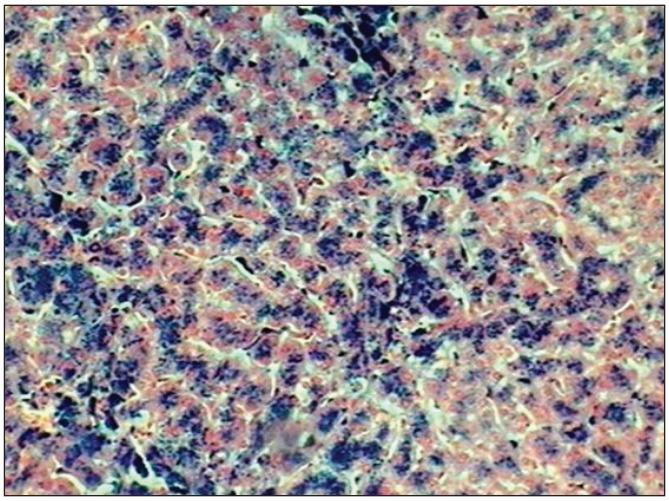


**FIGURE 6**

profile of tumors (using streptavidin-biotin-DAKO). The liver also showed micronodular cirrhosis (Figure 5) with accumulation of hemosiderin (4 + / 4 + on a scale of Scheuer – Figure 6). Perls staining was positive (1 + / 4 +) in renal cell carcinoma. Serum iron was 174ug/dl (normal = 50-150ug/dl), transferrin saturation corresponded to 96% (normal = 20% -50%), and glucose was equal to 82.0 mg / dl. The diagnosis of hemochromatosis was then suggested.

## DISCUSSION

Iron accumulates as ferritin and hemosiderin in almost all body cells. In hereditary hemochromatosis, the liver is the target organ because iron absorbed from the intestinal tract crosses the hepatic parenchyma before reaching the systemic circulation. Initially the deposit occurs in the hepatocytes of zone 1 of Rappaport, progressing to the surrounding parenchyma. With progressive accumulation, occurs formation of fibrous septa from the portal spaces, which may progress to cirrhosis (1, 2, 3).

Iron acts as a catalyst in the generation of reactive oxygen species in pathological conditions, which are associated with carcinogenesis by inducing tissue damage through lipid peroxidation and DNA damage. Lipid peroxidation is a critical step for fibrosis (the activation of stellate cells) and hepatocarcinogenesis, and iron may initiate these mechanisms. Iron overload increases the number and activity of CD8 T lymphocytes and inhibits the proliferation and activity of CD4 T lymphocytes, determining the generation of cytotoxic T cells, changes in immunoglobulin secretion and suppression of the complement system (1, 2, 4).

The diagnosis of hereditary hemochromatosis is based on the accumulation of iron excess in parenchymal cells in the absence of known causes of iron overload and in the presence of C282Y mutation in HFE. Liver biopsy quantifies the iron deposit and determines the presence of fibrosis or cirrhosis. The determination of liver iron content is also a safe diagnostic method, exceeding 1.9 mmol / kg / year. The factors that predate the clinical expression of hemochromatosis are: male sex, alcoholism, infection with HBV / HCV, food rich in iron and vitamin C and deficiency of alpha-1-antitrypsin. Up to five individuals in 1000 are homozygous for the disease in the USA, France, Sweden and the UK, where about 10% of the Caucasian population is heterozygous. From 64% to 100% of patients with hereditary hemochromatosis in Caucasian descent are homozygous for C282Y, being the heterozygous state more frequent in men (1, 2, 3, 5, 6).

Hepatocellular carcinoma is a possible complication of cirrhosis in hereditary hemochromatosis, accounting for 45% of the deaths. The relative risk of developing hepatocellular carcinoma in patients with hemochromatosis and cirrhosis is approximately 200 times. The follow-up of patients with alcoholic cirrhosis or hepatitis B has shown that patients with elevated serum ferritin or liver iron concentration have a higher risk of liver cancer than patients with normal or low stocks of iron. Foci of hepatocellular hyperplasia are more frequent in macro-regenerative iron--positive nodules (73%) than macro-regenerative iron-negative nodules (21%). Foci free of iron can be found in hereditary hemochromatosis, being those areas associated with the early stages of hepatocellular carcinoma. Even with iron overload, the precancerous lesions dont seem to show ion accumulation, suggesting that their depletion is one of the early changes of cancer cells. The iron also has an effect on promotion of hepatocellular carcinoma in the presence of HBV infection, because it promotes viral replication and tumor cell growth. HBV is more likely to infect and replicate in hepatocytes with increased ferritin (1, 2, 4, 7). The possible relationship between hepatocellular carcinoma and heterozygosity for the C282Y mutation is not defined, although the homozygous for C282Y in the

absence of blood loss, always develop iron overload, while in heterozygotes that risk is lower (3, 4, 5, 6, 7).

If the relationship between hemochromatosis and risk of hepatocellular carcinoma appears to be well documented, the association of hepatocellular neoplasms and hereditary hemochromatosis seem indefinite (1, 3, 4, 8, 10, 11). It is suggested the iron as a promoter of carcinogenesis by altering the immune system and promoting lipid peroxidation (3, 8, 9, 10, 11). Geier et al found 13 cases of non-hepatocellular carcinoma in 59 patients with hemochromatosis, being the colon, stomach, prostate, breast and hematopoietic tissue the primary sites (10). Elmberg et al., among 1847 patients with hereditary hemochromatosis, found 62 cases of hepatocellular carcinoma and 128 non-hepatobiliar neoplasm (8). Shaheen et al. suggested that mutations in the HFE gene are associated with increased risk for colon carcinoma (11). Osborne et al. reported that HFE C282Y homozygotes have twice the risk of colorectal and breast cancer compared with those without the C282Y variant, although male C282Y homozygotes were not at increased risk for prostate cancer (12). Gannon et al described that C82Y mutation may increase the risk of developing ovarian carcinoma, and may be associated with poor outcomes. Dorak et al described a strong association between C282Y mutation and childhood acute lymphoblastic leukemia. Kallianpur et al reported a high prevalence of C282Y alleles in female breast cancer, and its association with more aggressive forms of the tumor (15).

The HFE gene is a major histocompatibility class I--like molecule, that, when mutated, may cause hereditary hemochromatosis. HFE associated with the major protein responsible for cellular iron uptake, namely the transferrin receptor (TfR). The association of HFE with TfR at the cell surface lowers TfR affinity for the circulating iron--transporter transferrin, thereby limiting iron uptake and thus directly implicating HFE in the modulation of cellular iron levels. A failure to appropriately express HFE at the cell surface, as is found in the C282Y mutation, may result in an enhanced ability to capture iron and may induce tumor cell proliferation. In addition, it looks that high level of free iron may accentuate the effects of other carcinogenic agents, such as ethanol and ionizing radiation. Iron-catalyzed oxidative stress causes lipid peroxidation and protein modification, DNA damage with consequent promotion of mutagenesis, and leads to the depletion of antioxidant defenses (12, 13).

## FINAL COMMENTS

Although it is not possible to attribute a direct cause--effect relationship between hemochromatosis and the neoplasms, especially after reviewing the literature, the presence of a basic metabolic disease and four tumors induces the hypothesis of a common cause for the development of these tumors. At diagnosis of hemochromatosis, done by the research of iron in the liver tissue and by abnormal levels of iron and transferrin saturation, should perform the study for genetic mutations in the HFE gene for confirmation of homozygosity. Given the natural history of disease, it is necessary to track patients with hemochromatosis for the early detection of complications such as cirrhosis and cancer.

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