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Case Study

Radiation induced liver disease: is hereditary haemochromatosis a risk factor?

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Abstract

A 71-year-old man with Stage II gastric cancer developed rapid onset radiation induced liver disease after ceasing adjuvant chemotherapy and radiotherapy. Autopsy revealed moderate hepatocellular iron overload. Posthumously, he was found to be a compound heterozygote for hereditary haemochromatosis. Since both radiation and iron overload may induce liver damage through the activation of hepatic stellate cells, it is possible that hepatocellular iron overload may potentiate the effects of irradiation and predispose the patient to radiation induced liver disease.

Keywords

Radiation induced liver disease; veno-occlusive disease; iron overload; hereditary haemochromatosis, hepatic stellate cells

INTRODUCTION

Veno-occlusive disease (VOD) is characterized by non-thrombotic occlusion of the terminal hepatic venules and sublobular veins of the liver. Established causative agents include pyrrolizidine alkaloids in Jamaican bush tea, urethane, and oral contraceptives. There is an endemic form of the disease in Europe and Asia. Many chemotherapeutic agents have been shown to induce VOD.[1]

VOD has also been recognized as the morphological manifestation of radiation induced liver disease (RILD) since the 1960s.[2] RILD is usually a result of hepatic irradiation for the treatment of cancer.[3] Concurrent therapy with chemotherapeutic agents and pre-existing liver disease are thought to predispose the liver to VOD.[4] To our knowledge, there have been no reports linking hereditary haemochromatosis (HHC) with an increased risk of RILD. We hereby report a case with such an association.

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CASE REPORT

A previously well, 71-year-old man with normal liver function tests (LFTs) and negative hepatitis serology underwent distal gastrectomy for a poorly differentiated adenocarcinoma of the antrum. Metastases were present in omental lymph nodes.

To achieve loco-regional control, the patient was commenced on one initial cycle of 5-fluorouracil with folinic acid rescue followed by concurrent irradiation to the upper abdomen. The total radiation dose was 45 Gray in 25 fractions, five days per week, over approximately 2 months. The target volume was determined using computed tomography (AQsim). Dose volume histograms for critical normal organs were also

delineated using computed tomography and deemed to lie within normal tissue tolerance. The hepatic exposure was thus limited to <60% of the hepatic volume.

Within one week of ceasing radiotherapy, the patient developed increasingly abnormal LFTs and lethargy, anorexia and abdominal pain and distension. Two months post radiotherapy, LFTs were as follows: total protein 57 g/l, albumin 16 g/l, alkaline phosphatase 412 u/l, ALT 60 u/l, AST 104 u/l, bilirubin 310 umol/l. A clinical diagnosis of veno-occlusive disease was confirmed by a transcutaneous liver biopsy. The patient died from methicillin resistant, coagulase negative Staphylococcal bronchopneumonia. An autopsy was performed.

Genetic studies, initiated ante mortem, revealed that the patient was a compound heterozygote for mutations in the HFE gene, bearing one copy each of the C282Y and of the H63D mutations.

At autopsy, there was 900 ml of ascites. The liver weighed 1140 g. There were two distinct zones in the liver. The larger zone, corresponding to the irradiated field, included the left lobe and most of the right lobe, and had a mottled appearance. The smaller zone, corresponding to the unirradiated field, included the remainder of the right lobe and was uniform in colour. Intra-hepatic and extra-hepatic bile ducts were patent. There was some biliary sludge in the gall bladder lumen.

Microscopically, the irradiated zone of the liver revealed classical VOD (Figs 1 and 2) and marked hepatocellular iron deposition (3+ out of a total of 4+).[5] The unirradiated liver showed marked cholestasis and a moderate increase in hepatocellular iron stores (2+) without fibrosis. Microscopic foci of metastatic adenocarcinoma were present in portal tracts of the left lobe.

DISCUSSION

The classical histopathological features of VOD were present in the irradiated liver parenchyma. The unirradiated right lobe of liver showed features suggestive of large duct obstruction, possibly related to biliary sludge in the extrahepatic biliary system.

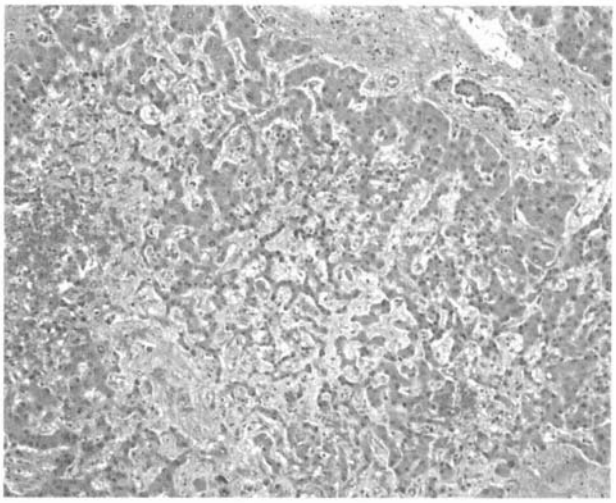

Figure 1. The central veins and perivenular sinusoids are obliterated by fibrous tissue. There is associated atrophy of zone 3 hepatocytes. (Hematoxylin and eosin stain, ×100)

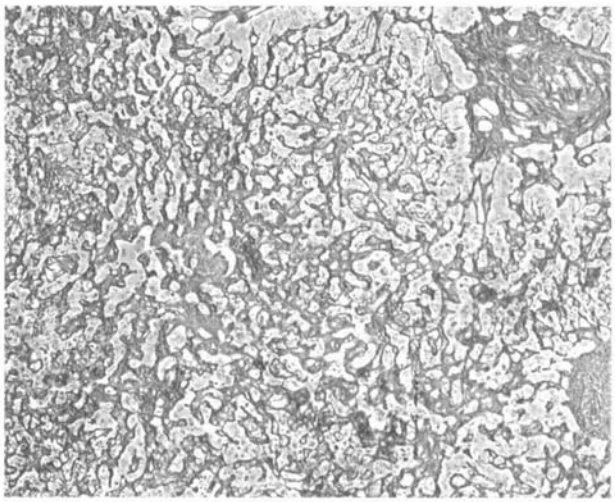

Figure 2. The reticulin stain highlights the fibrosis of the central veins and perivenular sinusoids. (Reticulin stain, ×100)

The pathogenesis of VOD after hepatic irradiation was first postulated in 1980.[1] Hepatic irradiation was thought to injure endothelial cells of the hepatic venules and/or zone 3 sinusoids, leading to the activation of the soluble clotting mechanism. Fibrin is deposited in the subendothelial space and lumina of these vessels. The fibrin serves as scaffolding for the deposition of reticulin and later, collagen, that gradually obliterates these vessels.[1]

Recently, the role of hepatic stellate cells (HSCs) in VOD has been investigated. HSCs,

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belonging to the family of myofibroblasts, may regulate sinusoidal blood flow. They are also involved in the development of hepatic fibrosis and cirrhosis.[6]

In the normal adult liver, activated HSCs, recognized by their immunohistochemical positivity with alpha smooth muscle actin (αSMA), are rarely seen. In irradiated liver, significant numbers of αSMA positive HSCs are identified in terminal hepatic venules and zone 3 sinusoids. Activated HSCs are thought to produce the reticulin and collagen that are deposited in these vessels in VOD.[7]

The stimulus for the activation of HSCs in RILD is uncertain; however, a likely candidate is the cytokine TGF-α1.[8] External beam radiation has been shown to induce release of TGF-α1 by injured hepatocytes, endothelial cells and/or Kupffer cells.[7]

Even when the radiation dose per volume of liver remains within prescribed guidelines, some patients still develop RILD. Certain chemotherapeutic agents, with the exception of the fluoropyrimidines[3] and pre-existing liver disease[4] can lower liver tolerance for radiation. The patient in this report, however, was treated with the fluoropyrimidine, 5-fluorouracil, alone. Thus, his chemotherapy is unlikely to have contributed to the development of VOD. In addition, this patient had no clinical evidence of pre-existing liver disease. Yet, he developed RILD even when the radiation dose administered was within the recommended range.[4]

The clinical presentation of RILD depends on whether the treatment has been with radiation alone, or whether chemotherapy has been combined with radiotherapy, i.e. combined modality therapy. Combined modality induced liver disease (CMILD) tends to be of more rapid onset, usually within one to two weeks after treatment, is more likely to cause abdominal pain, induces deeper jaundice with higher levels of bilirubin and AST, and has a 40 to 50% mortality. Radiation alone typically produces disease 4 to 8 weeks after treatment, produces only mild elevations in serum bilirubin and has a 10 to 20% mortality.[3]

In the absence of a hepatotoxic chemotherapeutic agent, this patient developed rapid onset RILD comparable to CMILD. This led us to postulate that this may be related to his hepatocellular iron overload.

HHC is the most common genetic disease in Caucasian populations.[9] The inheritance is autosomal recessive. The responsible gene is termed the HFE gene. Its protein product is a transmembrane glycoprotein (HFE) that modulates iron uptake.[10] Of the 37 allelic variants of HFE, two are significantly correlated with HHC.[11] These are the C282Y and H63D variants[10] and are the alleles found in this patient. The H63D allele is not associated with the same degree of iron overload as the C282Y allele.[12] There is no accurate data on the penetrance of these genes.[11] It is thought that compound heterozygotes may only partially express the disease or not at all.[13]

It is accepted that heavy iron overload causes parenchymal fibrosis in many organs. Lesser degrees of hepatic iron deposition also appear to exacerbate non-haemochromatotic liver disease. For example, patients with HFE mutations and co-existing alcoholic liver disease or chronic viral hepatitis are more likely to have advanced hepatic fibrosis or cirrhosis.[14,15]

Hepatic iron overload results in increased hepatic oxidative stress, presumably by the generation of free radicals. In turn, this may increase both lipid peroxidation and TGF-α1 expression, promoting injury and fibrogenesis.[16] In addition, it has been shown that in HHC, activation of HSCs becomes more prominent with increasing hepatic iron concentration.[17] Hence, the mere presence of increased iron stores endows a fibrogenic diathesis to the liver.

Increased hepatocellular iron may thus explain this patient's unusual clinical presentation. As the chemotherapeutic agent he received is not hepatotoxic, he should have presented clinically as classical RILD; however, he actually presented more like CMILD. The iron overload may have acted as the radiosensitizing agent simulating a chemotherapeutic drug.

As yet, there have been no reports associating RILD with HHC. Given that there are common pathogenic mechanisms in the liver disease of hepatic irradiation and of HHC, this report suggests

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that radiation and iron may act synergistically to produce liver damage. Further studies are thus required to confirm or refute this association. If the association is confirmed, the high prevalence of HFE mutations in Caucasian populations may render HHC an exclusion criterion for hepatic irradiation.

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