CLINICAL CASE

Radiation-induced cholangitis with hepatocellular carcinoma

*Cholangite postradique et carcinome hépatocellulaire*


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**Summary** There are no reports of hepatocellular carcinoma complicating postradiotherapy cholangitis. We report the case of a 45-year-old patient who had undergone upper abdominal radiotherapy for Hodgkin’s disease, 21 years before, which was complicated years later by cholangitis with stricture of the common bile duct. Biliodigestive anastomotic surgery was scheduled due to recurrent angiocholitis, and hepatocellular carcinoma was discovered. The patient died from carcinoma some months later.

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**Introduction**

The liver is an organ, which is sensitive to radiation. Thus, abdominal radiotherapy can result in serious hepatic lesions [1,2], which include acute and delayed injuries [2,3]. Acute injury may include veno-occlusive disease due to endothelial cell damage 2 weeks to 4 months after radio-
therapy [1–4]. Chronic radiation injury is characterized by parenchymal fibrosis [1,2]. Liver cancers have rarely been related to radiation such as cholangiocarcinoma, malignant hemagioendothelioma, angiosarcoma or hepatocellular carcinoma [5–7]. It has been reported that hepatocytes may be more susceptible to radiation than epithelial biliary cells [8]. However, several clinical and experimental studies have demonstrated that radiotherapy can also cause shrinking of the biliary tree [9–12].

We report the case of a patient who developed radiation cholangitis and stricture of the common bile duct with the development of hepatocellular carcinoma 21 years after upper abdominal radiotherapy for Hodgkin’s disease. To our knowledge, this is the first reported case of hepatocellular carcinoma associated with radiation-induced cholangitis.

Case report

A 45-year-old man had a history of Hodgkin’s disease diagnosed in 1976 when he was 16. He was treated with a combination of a chemotherapy and radiotherapy, including a Y radiation of the epigastric area and the left lobe of the liver with a total dose of 40 Gy over a 4-week period. The patient was considered to be in complete remission and remained healthy until 1997 when he presented with an episode of abdominal pain in the right upper quadrant. The pain recurred in 1998 and 1999 associated with abnormal liver tests.

In May 1999, the patient was admitted for abdominal pain once again associated with jaundice. Laboratory blood test results showed total hyperbilirubinemia (60 μmol/L) associated with elevated alkaline phosphatases (260 IU/L) and cytolysis (AST 400 IU/L and ALT 51 IU/L). Serological determination of hepatites A, B and C viruses and human immunodeficiency virus were negative. The patient did not take alcohol or drugs. Ultrasound examination showed an absence of gallbladder lithiasis. Endoscopic ultrasound of the biliary tree showed that the diameter of the common bile duct was normal. Choledocolitiasis was suspected in the presence of hyperamylasemia and hyperlipasemia identified at admission to the hospital. Systematic endoscopic sphincterotomy (ERCP) was performed because of the appearance of forced papilla. However, abdominal pain recurred after only 8 days associated with cytolysis. In July 1999, a laparoscopic cholecystectomy was performed which showed the left lobe of the liver was atrophical and appeared cholestatic. There were patterns suggesting radiation injury: increased thickness of Glisson’s capsule with a retractable appearance, telangiectasia in the peritoneal cavity with maximal localisation in the sternal manubrium. There were no gallstones in the excised gallbladder. Peroperative cholangiography revealed a clear thin common bile duct with some irregularities of the intrahepatic ducts. Radiation-induced cholangitis with secondary migration of intrahepatic stones was suggested to explain the abdominal pain. The patient started pharmacological treatment with ursodeoxycolic acid 15 mg/kg/day, simvastatine 20 mg/day and pentoxifyline 800 mg/day. However, recurrent abdominal pain of the right upper quadrant continued. In 2003, pain became more intense and frequent and was associated with jaundice, pruritus and sometimes with fever.

Blood analysis revealed total bilirubin 324 μmol/L, alkaline phosphatases 260 IU/L (N < 109), gamma glutamytransferase 105 IU/L (N < 82), aspartate aminotransferase 63 IU/L, and alanine aminotransferase 70 IU/L (N < 60). Magnetic resonance cholangiography (MRCP) and ERCP showed 1 cm of stricture in the common bile duct associated with dilatation of the intrahepatic biliary ducts, predominantly in the right biliary tree. Dilatation of the left intrahepatic biliary ducts appeared irregular. Enhancement on the periphery of the main biliary duct and of left intrahepatic biliary ducts was pathological. A biliary stent was inserted to relieve obstruction. Persistent jaundice justified a second ERCP. The biliary stent was removed and the patient underwent balloon dilatation of the structured area, resulting in partial regression of the jaundice. The cytolological examination of bile brushing for malignant cells was negative and bile concentration of CA-19-9 was normal.

In May 2004, an MRCP showed total atrophy of the left lobe of the liver and a hilar stricture that extended to the secondary right ducts associated with marked dilatation of right intrahepatic biliary ducts (Fig. 1). No tumour was detected. Blood CA-19-9 was normal at 3 IU/mL (N < 37).

In August 2004, the patient again presented with jaundice. As a result, two biliary stents were endoscopically inserted. The patient’s jaundice persisted so that in September 2004 the patient underwent surgery. At laparotomy the left lobe of the liver was totally atrophic; the right lobe appeared cholestatic. A tumour of the left liver was unexpectedly found to be associated with a tumoral thrombus of the portal vein and of the biliary convergence. A left hepatectomy with hilar and common hepatic duct resection were performed. A small tumoral lesion (1 cm) was also removed in segment VIII. A Roux Y right hepaticojejunostomy permitted to establish biliary continuity. The macroscopic examination of the left lobe of the liver revealed total atrophy. The parenchyma had a green-brown cholestatic colour at the incision and a nodule of approximately 4 cm in diameter was located in segment IV. Histological examination showed a moderately differentiated hepatocellular carcinoma (Fig. 2). The majority
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Figure 2  Microscopic examination. Upper figure: hematoxylin-eosin-saffron staining (original magnification × 4). Moderately differentiated hepatocellular carcinoma (arrows) invading fibrous atrophic liver tissue. Blood vessels with marked endarteritis are highly characteristic of postradiation injury. Lower figure: paraffin sections immunostainings (original magnification × 20). Few tumor cells express c-Kit antigen whereas most of them are positive for both Hepar 1 and CK19, suggesting a progenitor cells origin of the tumor.

of tumoral cells demonstrated peculiar phenotype with coexpression of the Hepar antigen and of cytokeratin 19. In addition, small basophilic cells also expressed c-Kit antigen. The expression of alpha-fetoprotein (AFP) in malignant cells was around 30% (Fig. 2). These immunohistochimical data suggested that the hepatocellular carcinoma had developed from progenitor cells. This malignancy surrounded and invaded the biliary ducts, as well as the parenchymal blood vessels, which were damaged by fibrosis and endarteritis with calcifications considered to be postradiation injuries. Histopathological changes of the non-tumoral liver revealed mild portal and periportal fibrosis (metavir scoring F1).

Postoperative blood AFP was found to be increased at 138 ng/mL (N < 6) as well a retrospective pre-operative determination on the frozen sample: 575 ng/mL (N < 8.6). In the subsequent months, AFP levels increased to a maximum of 2880 ng/mL and further imaging procedures revealed multiple tumour recurrence in the right liver. The patient underwent three sessions of palliative lipiodol arterial chemoembolization of the liver. In December 2005, blood AFP levels were 1641 ng/mL and the patient was in good condition and had gone back to work activity. In January 2006, the patient noted an increase in fatigue with weight loss and effort dyspnea. Unfortunately, the clinical course was unfavorable with the development of neoplastic pleurisy, major asthenia and denutrition. The patient died in November 2006.

Discussion

In this case, the first clinical symptoms (right upper quadrant pain) were attributed to cholangitis with intrahepatic lithiasis. The irregularity of the biliary ducts suggested a diagnosis of cholangitis. The macroscopic findings (at laparoscopy and laparotomy) were characteristic of delayed radiation injuries: atrophy of the left liver and typical macroscopic vascular lesions. The diagnosis of radiation-induced cholangitis was finally confirmed by pathological examination (arteriopathy and fibrosis). The biliary stricture was initially attributed to cholangitis, which can explain the diagnostic delay. A liver tumor was identified during surgery and finally the stricture was linked to this neoplasm.

We suggest that, in our patient, radiation therapy is the most likely cause of the cholangitis and hepatocellular carcinoma. Three arguments support this hypothesis: chronological and topographical relationships and pathological lesions. First, the patient received abdominal radiotherapy and the diseased part of the liver (atrophy, vascular lesions, fibrosis, cholangitis and hepatocellular carcinoma) matched the field of radiation as evidenced by skin tags. Second, the time frame between radiation and the first symptoms — 21 years — is compatible with other published reports of delayed radiation injury[13,16]. Third, the macroscopic findings were characteristic of latent radiation-induced injury and the histological findings were characteristic of late radiation injuries.

Cholangitis and biliary strictures are rare complications of radiotherapy. We have only found a few reports in the literature describing this association. Two experimental animal studies demonstrated that radiation produces obvious lesions of the bile duct with sclerosis and obliteration of capillary vessels [17,18]. There were marked changes in the duodenal papilla [17,18]. Besides, patients who received intraluminal brachytherapy for bile duct cancer, experienced complications with abdominal pain, cholangitis and
recurrent biliary obstructions that were compatible with cholangitis [3,19]. Several studies have described hepatic duct strictures after external radiotherapy for biliary cancer [11,12,20]. The strictures were located in different parts of the biliary tract, usually in the middle portion of the common bile duct which is less vascularised. Usually, jaundice is the first clinical symptom in these patients [9,10,14,21,22]. In one report, biliary stricture was associated with radiation-induced lesions of papilla [15].

The occurrence of liver cancer (cholangiocarcinoma, malignant hemagioendothelioma, angiosarcoma and hepatocellular carcinoma) has been described after internal alpha-particle-emitting radiological contrast thorotrast [23,24]. There have been reports identifying the appearance of cholangiocarcinoma after radiotherapy. Three cases of biliary tract carcinoma have been reported 18–23 years after radiotherapy performed after surgical treatment for an urogenital carcinoma [25]. Two cases of biliary duct carcinoma were described 17 years after abdominal irradiation for a teratocarcinoma and Hodgkin’s disease [13]. One patient developed postradiation cholangitis associated with pancreatitis and cholangiocarcinoma 23 years after the treatment of Hodgkin’s disease [16].

Hepatocellular carcinoma is the most frequent primary liver cancer [26,27]. However, the occurrence of hepatocellular carcinoma after radiation has rarely been described. Two experimental animal studies documented the occurrence of malignant liver tumours including hepatocellular carcinoma after external radiation [28,29]. A high incidence of primary liver cancer was documented in a group of survivors of the atomic bomb in Hiroshima: hepatocellular carcinoma was mostly detected, with a higher incidence among males [6]. There are only two reports in the literature describing the occurrence of hepatocellular carcinoma after abdominal radiation treatment. The first reported a case of “hepatoma” occurring two decades after hepatic radiation in a patient with non-malignant hepatic haemangiomata [7]. The second case of hepatocellular carcinoma occurred in a patient 17 years after treatment of a peripheral neuroectodermal tumour [5]. Risk factors for secondary malignancies after Hodgkin’s lymphoma have been reported in two studies but none of them described a case of hepatocellular carcinoma [30,31]. It is important to note that the risk of developing a solid tumor after radiotherapy is increased in patients treated at a younger age [30]. Only one case of hepatocellular carcinoma as a probable consequence of radiation for Hodgkin’s lymphoma has been reported in the literature [32]. In the two cases, radiotherapy was delivered during adolescence and hepatocellular carcinoma occurred more than 20 years later. In the present case, hepatocellular carcinoma was unusual suggesting it had developed from progenitor cells. Stem cells are assumed to be more sensitive to the radiation injury than hepatocytes and more susceptible to neoplastic transformation [33,34]. Liver injury can induce progenitor cell activation and proliferation, making these cells a very likely carcinogen target [35]. The tumour surrounded and invaded the biliary ducts and the vessels with postradiation injuries. Other possible risk factors of hepatocellular carcinoma (viral infections, alcohol) were eliminated in our patient. Thus, we suggest that the hepatocellular carcinoma is probably secondary to radiation injuries.

In conclusion, the present case is the first report of hepatocellular carcinoma as a probable complication of radiation-induced cholangitis. We suggest during abdominal radiotherapy for curable malignancy when the liver lies within the field of radiation, patients should undergo long-term follow-up for early diagnosis of hepatic radiation-induced injury such as cholangitis to screen for complications such as hepatocellular carcinoma.

Conflicts of interest

None to be declared.

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References

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