

Cholangiocarcinoma following external beam radiotherapy: A report of two cases

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Abstract. Cholangiocarcinoma (CCA) is a relatively rare primary malignancy, with established risk factors that include primary sclerosing cholangitis, choledochal cysts and hepatolithiasis. In the present study, two cases of CCA, which occurred following abdominal external beam radiotherapy (EBRT) for non-Hodgkin's lymphoma, are reported. Case 1 and 2 were diagnosed with cholangiocarcinoma 30 and 4 years following treatment with combined chemotherapy and abdominal radiotherapy treatment, respectively. The patients received chemotherapy as treatment of cholangiocarcinoma; however, whilst their symptoms improved, they succumbed within 12 and 2 months respectively following the diagnosis with cholangiocarcinoma. Currently, the association between radiation exposure and hepatobiliary malignancy remains unclear, however, we hypothesize that biliary epithelium sensitivity to ionizing radiation may have contributed to the etiology of the secondary malignancies observed in these two patients. This study indicates that patients treated with abdominal EBRT may benefit from a heightened index of suspicion and more intensive surveillance for secondary biliary malignancies.

Introduction

Cholangiocarcinoma (CCA) is a relatively rare hepatobiliary malignancy, with an incidence of <1 case per 100,000 individuals, which accounts for 3% of all gastrointestinal malignancies worldwide (1,2). Known risk factors for the development of CCA include primary sclerosing cholangitis, choledochal cysts and hepatolithiasis, as well as liver flukes in Asian populations (2).

Patients with extra-hepatic cholangiocarcinoma often present with symptoms of biliary obstruction, including

painless jaundice, pale stools, dark urine and pruritis. Intra-hepatic disease may present differently, often with less specific symptoms, such as malaise, abdominal pain and weight loss (3).

Commonly used diagnostic imaging modalities for CCA include computed tomography (CT) and magnetic resonance cholangio-pancreatography. Endoscopic ultrasound and endoscopic retrograde cholangio-pancreatography are useful for imaging distal extra-hepatic lesions, as these techniques allow stenting to relieve biliary obstruction and cytological brushings to be obtained (3,4). Diagnosis may also be supported by elevated levels of the tumor marker, carcinoembryonic antigen 19-9 (4).

Surgical resection remains the standard treatment for cholangiocarcinoma, however 5-year postoperative survival rates remain poor at 27-37% for patients with extra-hepatic disease and 23-42% for patients with intra-hepatic disease and clear surgical margins (3,4).

In the current study, two cases of CCA, in patients who had previously undergone external beam radiotherapy (EBRT) for the treatment of non-Hodgkin's lymphoma (NHL), are presented. The clinical data of the patients are presented and the medical records of the patients are retrospectively reviewed. The study details the clinical history, investigations and outcome of these two cases of this rarely encountered phenomenon, which may ultimately be considered an unusual but important variant of CCA. We hypothesize that the biliary epithelium is particularly sensitive to EBRT and review the current literature to investigate the proposed etiology of secondary malignancies following EBRT.

Case report

Case 1. In August 1981, a 10-year-old female was diagnosed with metastatic abdominal NHL [Ann Arbor stage IV (5)], after presenting to Westmead Children's Hospital (Sydney, Australia) with massive hepatosplenomegaly. The patient was administered combined chemotherapy and radiotherapy with the LSA2L2 (6) protocol for 3 years, and received prophylactic cranial (24 Gy) and abdominal (7.2 Gy) irradiation for residual lymphoma. Abdominal irradiation was terminated early due to marrow suppression. The patient was well when discharged

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and was followed up in the hospital's Late-Effects Clinic for 22 years.

In July 2011, the patient presented with symptomatic cholelithiasis, and underwent an uncomplicated laparoscopic cholecystectomy (normal cholangiogram). However, at 2 months post-surgery, the patient presented with painless, obstructive jaundice. Endoscopic retrograde cholangiopancreatography (ERCP) proved technically difficult and following two failed attempts, a biliary stricture was identified. The stricture was subsequently dilated and stented using an antegrade, percutaneous transhepatic (PTC) approach (Fig. 1). The stricture was located 1 cm proximal to the common hepatic duct and 1 cm into the common bile duct. During follow-up ERCP, progression of the stricture was identified and a new plastic stent was inserted. No evidence of malignancy was identified on radiological or biochemical examination and thus, a benign bile duct stricture was presumptively diagnosed and the patient was referred for hepatico-jejunostomy.

During the hepatico-jejunostomy, widespread omental and abdominal metastatic disease was identified and thus, surgery was abandoned. Histopathological examination of the peritoneal biopsy demonstrated adenocarcinoma of pancreaticobiliary origin with a typical morphology and immunohistochemical profile [cytokeratin (CK)7⁺, CK20⁻]. Subsequent positron emission tomography (PET) scans showed uptake surrounding the biliary stent, and CCA was diagnosed.

The patient was administered 3 cycles (21 days/cycle) of combined chemotherapy with cisplatin and gemcitabine, which was changed to paclitaxel when disease progression was observed. A further PTC and ERCP with a metal stent were required to relieve the common bile duct obstruction. The patient was discharged to a palliative care unit and succumbed to the disease at 41 years of age, 31 years after the diagnosis of NHL and the delivery of EBRT, and 12 months after the diagnosis of CCA.

Case 2. In May 1997, a 42-year-old male was diagnosed with stage IVB NHL (5) following an inguinal node biopsy for a suspicious groin lymphadenopathy at Royal North Shore Hospital (Sydney, Australia). The patient subsequently underwent six cycles (21 days/cycle) of cyclophosphamide, hydroxydaunorubicin, vincristine and prednisone (CHOP) chemotherapy, achieving complete remission for 8 years. At this time in July 2005, the patient relapsed with widespread lymphadenopathy and was administered six further cycles of CHOP chemotherapy, achieving remission for another 3 years. The patient relapsed again 3 years later in May 2008, presenting with abdominal, back and flank pain. A PET scan revealed uptake in the left upper abdomen and para-aortic nodes. Four cycles (21 days/cycle) of rituximab, ifosfamide, carboplatin and etoposide salvage chemotherapy were subsequently administered and an autologous stem cell transplant was performed the following year. The transplant was followed by abdominal EBRT to the left upper mesenteric mass; a total of 38 Gy of radiation was delivered.

The patient was presented to the Upper Gastrointestinal Service 4 years later, in June 2012 with painless obstructive jaundice. Blood tests revealed a bilirubin level of 300 $\mu\text{mol/l}$ (normal range, 3–20 $\mu\text{mol/l}$) and a carcinoembryonic



Figure 1. Case 1: Intraoperative cholangiogram image. Stenting of the biliary stricture performed using an antegrade percutaneous transhepatic approach.

antigen 19-9 level of 15,120 U/ml (normal range, <37 U/ml). A CT scan revealed mid-common bile duct obstruction. An ERCP with stenting was performed and cytology confirmed the diagnosis of CCA due to the presence of adenocarcinoma on histological staining samples from the common bile duct. A staging laparoscopy revealed widespread metastatic disease. The patient was subsequently transferred to a palliative care facility in Sydney, Australia and succumbed to the disease at 58 years of age, 16 years after the initial diagnosis of NHL, 4 years after the administration of EBRT and 2 months after the diagnosis of CCA.

Written informed consent was obtained from the families of each patient for publication of the study data.

Discussion

Modern cancer therapies have led to increases in the quality of life and prognosis of cancer patients, allowing for the observation of long-term sequelae of cancer therapies. The risk of secondary malignancies following delivery of EBRT has been identified previously in a number of studies (7–10). Known risk factors for this include a younger age at diagnosis, high radiation dose and being of the female gender (11).

In 1948, Cahan and Woodard (12) proposed certain classic criteria that were required for the diagnosis of secondary malignancies due to prior radiotherapy treatment. These criteria remain widely accepted as a conservative guide and stipulate that affected patients must possess the following: i) A prior history of radiation treatment; ii) an asymptomatic latent period of several years; iii) occurrence of a second malignancy within the previously irradiated field; and iv) histopathology of a secondary malignancy distinct from that of the primary malignancy (12).

Primary cancers that have been consistently associated with a high risk of EBRT-associated secondary malignant neoplasm (SMN), include breast cancer, prostate cancer and lymphoma (including Hodgkin's and non-Hodgkin's subtypes) (11). The most commonly described SMNs vary with regard to primary cancer site and radiation field. In patients treated for NHL, the most common SMNs include leukaemia

and lung cancer (7-9,13) as well as melanoma in Australian populations (14).

At present, the association between ionizing radiation exposure and hepatobiliary malignancy remains unclear. Recently, Dores *et al* (15) reported an increased risk of pancreatic malignancy in patients treated with moderate to high doses of EBRT for Hodgkin's lymphoma. Furthermore, the study demonstrated that this risk was higher in patients treated with both EBRT and chemotherapy, which indicates a possible interaction between the two treatment modalities in contributing to SMN. Similarly, Morton *et al* (16) reported an increased risk of stomach cancer with EBRT, and showed that this risk was associated with the sub-diaphragmatic radiation dose.

Radiation exposure associated with hepatobiliary malignancy has previously been reported within the context of Thorotrast (17,18) and in survivors of atomic bomb fallout exposure in Nagasaki and Hiroshima (19,20).

In total, 5 cases of EBRT-associated CCA have been previously reported in the literature; 3 of these cases occurred 18-23 years after EBRT for urogenital carcinoma (21), and two cases occurred following abdominal EBRT for Hodgkin's lymphoma and teratocarcinoma, respectively (22). Radiation-induced liver disease is a known complication of EBRT (23), and there have also been reports of patients developing hepatocellular carcinoma (24) and benign biliary strictures (25,26) following EBRT.

The molecular mechanism of EBRT-induced biliary carcinogenesis remains unclear. However, it has been postulated that chronic inflammation secondary to biliary epithelial injury, and the accompanying disruption to bile flow, are important factors in the development of carcinogenesis (27-29). Persistent inflammation is hypothesized to damage DNA mismatch repair genes and tumor suppressor genes, thus promoting carcinogenesis (27). Cheng *et al* (23) previously suggested that hepatocytes may be more susceptible to radiation injury than the biliary epithelium, however, the susceptibility of these cell-types to radiation has not yet been reported.

In the present study, in the two cases reported, the histopathology was consistent with primary CCA. Considering the reported occurrence of CCA and other hepatobiliary complications (21-26,30,31), we hypothesize that chronic inflammatory reactions and resultant changes to the biliary epithelium following abdominal EBRT were fundamental to the development of CCA. However, it is unclear whether this represents a radiation-associated variant of the disease.

CCA continues to exhibit a poor prognosis. Thus, risk factors must be closely assessed to improve patient prognosis. Abdominal EBRT must be recognized as a risk factor of SMNs and thus, a heightened index of suspicion and more intensive surveillance of patients may facilitate an earlier diagnosis.

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