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Cholangiocarcinoma in Patients with Crohn's Disease

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Abstract

Cholangiocarcinoma is an uncommon malignancy that increases with age. Cholangiocarcinoma has been linked to inflammatory bowel disease, and a relationship between inflammatory bowel disease, anti-tumour necrosis factor alpha antibody (Infliximab) and cholangiocarcinoma has been suggested. Although cholangiocarcinoma is usually associated with ulcerative colitis, recently more cases are being seen in association with Crohn's disease. The risk of cancer in patients treated with Infliximab has been discussed, and whether Infliximab is associated with an increased risk of cholangiocarcinoma is not clear. Cholangiocarcinoma is an uncommon malignancy and it is difficult to establish a clear correlation with Infliximab treatment. A large number of reports are needed to further address these issues.

Keywords

Cholangiocarcinoma, Crohn's, Inflammatory Bowel Disease, Infliximab

Cholangiocarcinoma is a malignant tumour arising at any portion of the biliary tree, divided into intrahepatic (peripheral) or extrahepatic [1] [2]. The distinction is important, since epidemiology, natural history and pathology differ significantly [1] [3]. Cholangiocarcinoma is an uncommon malignancy that increases with age, with most cases occurring in patients over 65 [4]. Despite the decline in the incidence of extrahepatic cholangiocarcinoma, the incidence of and mortality from intrahepatic cholangiocarcinoma has increased [5]. Cholangiocarcinoma is characterized by bad prognosis and poor response to therapies [1].

Few years ago, a 30-year-old man with a long history of moderate Crohn's disease was operated on at our surgical department for a large intrahepatic cholangiocarcinoma (**Figure 1**) and died from the disease one

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year later. He was treated with Azathioprine along with Infliximab for a short period of time. An induction regimen of 3 single-dose infusions of 5 mg per kg of Infliximab at 0, 2, and 6 weeks was used. Patient slightly improved but 3 months later developed painless obstructive jaundice and was diagnosed with cholangiocarcinoma.

The introduction of Infliximab has offered new treatment options in patients with Crohn's disease and changed disease outcome [5]. The risk of cancer after anti-TNF therapy is controversial [6]-[8]. However, it is difficult to prove a link between exposure and tumour development in these patients, since they may already be predisposed to cancer as a consequence of their underlying disease [9].

The correlation between Infliximab therapy and the development of cholangiocarcinoma in our patient was claimed. Liver function disorders were excluded before treatment. However, dimension at diagnosis suggested that the tumour was probably already present when Infliximab was administered. In this case, cholangiocarcinoma is likely a complication of Inflammatory Bowel Disease rather than of Infliximab infusion. It could be questioned whether immunosuppression might have increased the rate of tumour growth in our patient. Due to the liver toxicity of Infliximab and the risk of hepatic and biliary complications in Crohn's patients, liver function and imaging should always be carefully evaluated before Infliximab administration [10]. Cholangiocarcinoma is an uncommon but know extra-intestinal cancer complicating Inflammatory Bowel Disease [11]. Patients with Inflammatory Bowel Disease have a four-fold increased risk of developing cholangiocarcinoma, especially when they suffer from Ulcerative Colitis [12]. To our knowledge, only five studies in the literature reported an association between cholangiocarcinoma and Crohn's disease, with a total number of 9 cases (see **Table 1**) [13]-[17]. Most patients were female, young, and with a long duration of the disease before development of cholangiocarcinoma, with a severe prognosis and low survival. Tumour location was prevalently the hilum. Infliximab therapy was only recorded in one case, in association with Azathioprine and previous long course of Metronidazole, which safety is also controversial [17].

The risk of cancer in patients treated with Infliximab has been discussed, and whether Infliximab is associated

Figure 1. CT scan showing in segment 8 and 4 a large liver mass measuring 60 × 85 mm in the axial axes and about 9 cm in height, associated with multiple smaller peripheral lesions and responsible for an important dilatation of bile ducts.

Table 1. Patient characteristics from the review of the literature.

Reference	Number of patients	Sex	CD[a] (age at diagnosis, *years*)	Location of CD[a]	CD[a] (age at diagnosis, *years*)	Treatment of CD[a]	Mortality for CCA[b]	Disease duration (*years*)	Location of tumor
Berman (1980)	1	F	30	Small bowel	43	N/A	N/A	13	Hilar
Krause (1985)	1	M	10	N/A	31	MT[d]	N/A	21	N/A
Altaee (1991)	4	F	N/A	N/A	57±17	N/A	N/A	8.5	Hilar
Choi (1994)	1	F	27	N/A	57	N/A	YES	30	Hilar
Biancone (2006)	1	M	25	N/A	48	MT[d] + AZA[e] + IFX[f]	YES	23	N/A
Present report (2013)	1	M	20	Right colon	30	AZA[e] + IFX[f]	YES	10	Intrahepatic
Summary	**9**	**6F/3M**	**Range 10 - 48.5**	-	**Range 30 - 57**	-		**Range 10 - 30**	-

Abbreviations: [a]CD: Crohn's Disease; [b]CCA: Cholangiocarcinoma; N/A: Not applicable; [d]MT: Metronidazole; [e]AZA: Azathioprine; [f]IFX: Infliximab.

with an increased risk of cholangiocarcinoma is not clear. Possible correlation of Infliximab administration and cholangiocarcinoma deserves more accurate designed studies, large case series, than single case reports.

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