Cholangiocarcinoma: Demographic Characteristics, Diagnostic Modalities, Therapeutic Options and Risk Factors in an Endemic Area of Human Fascioliasis, Guilan Province North of Iran

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Abstract

**Background:** Although there is no report about association of Cholangiocarcinoma (CCA) and fascioliasis, but the role of other liver flukes has been defined in developing Cholangiocarcinoma. We decided to evaluate the demographic characteristics, diagnostic modalities, therapeutic options and risk factors of CCA in an endemic area of human fascioliasis.

**Materials and Methods:** Twenty two patients with CCA and 48 control subjects were enrolled in this study. Controls included twenty four healthy subjects and twenty four in patients with gastrointestinal malignancy and without liver or other systemic disease. All cases and controls were carried out from 2010 to 2011. The medical records and information about liver diseases, family history, past medical history, smoking, and alcohol consumption were collected on both groups. Blood from all participants was tested for HBV and HCV and fasciola markers and then analysed.

**Results:** Twenty two cholangiocarcinoma cases with a median age of 68 years were included. Twentyone were extrahepatic and only one intrahepatic CCA. Thirteen (59%) had jaundice and abdominal pain at presentation. Using of CT scan with ERCP or MRCP findings and elevated tumour markers (CA19-9, CEA) were the most diagnostic procedure in patients. The prevalence of smoking and alcohol consumption were not significantly different between cases and controls. Compared with controls, patients had not a higher prevalence of positive HCV Ab (Eliisa) and HBs Ag. Anti Fasciola Ab was negative in all cases and controls.

**Conclusions:** These findings support that there is no positive association between smoking, alcohol consumption and infection with HBV, HCV and Fascioliasis with Cholangiocarcinoma in Guilan province. However, the number of patients was fairly low in our study and this limits our ability to detect actual association between these factors and Cholangiocarcinoma.

Keywords: Cholangiocarcinoma; Endemic; Fascioliasis

Introduction

Cholangiocarcinoma (CCA) is malignant tumours arising from the biliary tract [1]. They are second most common primary liver cancer and accounted for an estimated 15% of primary liver cancer worldwide [2]. Though it is a rare malignancy, the incidence of Cholangiocarcinoma is raising globally [3]. There is extensive variation among the incidence rates of CCA in different parts of the world, and the incidence is reported to be higher in East Asia [4]. Cholangiocarcinoma occurs with a varying frequency in different areas of the world. Some of the variations in incidence rates can be explained by distributing risk factors in different geographic regions and ethnic groups. Several accepted risk factors for Cholangiocarcinoma include infestation with liver flukes, primary sclerosing cholangitis, hepatolithiasis, choledochal cysts, cirrhosis, and infusion of some chemical agents [2,5]. Approximately, 90% of patients diagnosed with cholangiocarcinoma do not have a recognized risk factor for the malignancy [5]. CCA has a severe outcome and a poor prognosis with a median survival of less than 24 month [6]. The 5-year survival is about 5% and it depends on the stage and histological type of the tumour [7]. The high fatality rate has been attributed to the poor knowledge of the tumour pathogenesis and the paucity of effective methods of diagnosis and management. Unfortunately, both intra and extrahepatic CCA are most commonly diagnosed at advanced stages because of absence of specific symptoms, physical examination findings or laboratory abnormalities in early or premalignant stages. Currently, diagnostic modalities for CCA include serum tumour markers, radiological and endoscopic imaging, and pathological analysis of biopsies or endoscopic brushings [8]. Surgical resection is the only curative option for cholangiocarcinoma, but only a minority of patients are suitable for resection [9].

In Iran, human fascioliasis was sporadic until 1987, when an outbreak occurred in Guilan province, northern Iran affected more than 10000 people [10]. The second outbreak occurred 10 years later in which several thousands of people were again infected [10]. Reports of several hundred cases of human disease during inter epidemic periods and then after, show that Guilan province has become an important endemic area for human fascioliasis [10]. Although there is no report...
about association of CCA and fascioliasis, but the role of other liver flukes such as *Opisthorchis viverrini* and *Clonorchis sinensis* has been defined in developing Cholangiocarcinoma. Even in a recent study the association of parasites such as biliary ascariasis or liver schistosomiasis and hilar CCA has been considered [11]. We decided to evaluate the demographic characteristics, diagnostic modalities, therapeutic options and also attempted to investigate whether fascioliasis can be as a risk factor for CCA in Guilan province (North of Iran) or not.

**Materials and Methods**

Between April 2010 to April 2011, we identified all patients diagnosed as Cholangiocarcinoma in the five referral hospitals in Guilan province. This study was done with twenty two cases. Diagnosis of cholangiocarcinoma was based on clinical presentation, imaging, cytophotic and histopathologic findings. Cholangiocarcinoma was classified as intrahepatic and extrabiliary type. All cases were interviewed individually using a specially structured questionnaire for this study (Questionnaire as supplementary material). The main questions were divided in three categories: demographic information, Cancer data and history of exposure to predisposing factors. Major questions included age, gender, education, region of living, job, initial manifestations of the disease, anatomical site of tumour, method of diagnosis, surgical or palliative therapy, smoking or drinking habits and past medical history including family history of liver disease or malignant neoplasm, history of infestation with liver flukes and hepatitis B or hepatitis C viruses, diabetes, primary sclerosing cholangitis, hepatolithiasis, choledochal cysts, cirrhosis, cholecytitis and Cholecodocolithiasis. Heavy alcohol consumption and heavy smoking were defined as drinking more than 80 gram of ethanol per day for more than 10 years and smoking more than 1 pack per day for more than 10 years, respectively. Moreover laboratory data (Serum Aspartate Aminotransferase (AST), serum Alanine Aminotransferase (ALT), Alkaline Phosphatase (ALP), total and free bilirubin and serum tumour markers (CA 19-9, CEA)) were recorded. Two control groups matched by sex and age (± 4 years) to the cases were selected. Selection criteria for Controls I were patients with gastrointestinal malignancy and without liver or other systemic disease. They were selected from the same hospitals that the cases were enrolled. Three esophageal cancer, fourteen gastric cancer and seven colon cancer were in Controls I. Controls II (healthy controls) were enrolled. Three esophageal cancer, fourteen gastric cancer and seven colon cancer were in Controls II. Controls I (healthy controls) comprised healthy people who had visited the Non-Communicable Disease Control Center of the same hospital for a routine check-up. Past history of human fascioliasis and ELISA test (Anti fasciola Ab) were two criteria for diagnosis of fascioliasis in subjects. Moreover serological tests for hepatitis B (HBsAg) and hepatitis C (Anti HCVAb) were done in all cases and controls.

Statistical data were analyzed using SPSS 18.0 for Windows. Descriptive statistics including mean, ranges and standard deviation values were calculated for all the demographic characteristics. To identify risk factors for CCA using chi-square univariate and if was significant unconditionallogistic regression multivariate analyses. Variables with a P value<0.05 were considered statistically significant.

**Results**

Twenty two patients were diagnosed as cholangiocarcinoma in study period. One patient as Intrahepatic and twenty one as extrahepatic cholangiocarcinoma. The mean age of patients were 68.55(SD: 11.392). The demographic and baseline characteristics of patients and controls has been shown in table 1. Initial manifestations were jaundice with abdominal pain in 13(59.1%) patients, whereas 8(36.4%) presented with painless jaundice and one with cholangitis symptoms.

Table 2 displays the frequency of diagnostic procedures was used in patients with cholangiocarcinoma. Using of CT scan with ERCP or MRCP findings and elevated tumour markers were the most diagnostic procedure in patients. The family history of cholangiocarcinoma was in one patient. A history of at least one predisposing factor was recognized in 36% of patients, one with chronic hepatitis B, one with chronic hepatitis C, one with Cholecystolithiasis, one with Choleodocolithiasis and three with Diabetes mellitus. There was a suspicious history of typhoid in one patient too. No primary sclerosing cholangitis, cirrhosis, Caroli’s syndrome, congenital hepatic fibrosis, choledochal cyst or occupational chemical exposure was found.

Table 3 shows frequency of drinking and smoking habits and serologic findings in patients and controls. The prevalence of obesity, cigarette smoking and alcohol consumption were not significantly different between the patient and control groups. Heavy consumption of alcohol and heavy use of tobacco were present in one (4.5%) and 6(27.3%) CCA cases, respectively. Compared with the controls, CCA patients had a higher prevalence of HBsAg and HCV Ab seropositivity, (HBsAg: 13.6% vs. 4.2% and HCV Ab: 4.5% vs. 0%), but it was not statistically significant in Univariate analysis (p=0.127 and0.331, respectively). anti-fasciola antibody was negative in all patients and controls. Also there was no past history of fascioliasis in subjects.

Symptomatic therapy with medication and Palliative biliary drainage was the most therapeutic procedures that were performed in 21 patients (95.5%). One case (one intrahepatic CCA) was managed with painless jaundice and one with cholangitis symptoms.

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**Table 1: Demographic and baseline characteristics of patients and controls.**

| Variables             | Cholangiocarcinoma No (%) | Control I (GI Malignancy without liver disease) No (%) | Control II (Healthy population) No (%) |
|-----------------------|---------------------------|------------------------------------------------------|--------------------------------------|
| Sex: Male             |                           |                                                      |                                      |
|                       | Female                    |                                                      |                                      |
| Total                 | 13(59.1)                  | 14(58.3)                                             | 14(58.3)                             |
|                       | 9(40.9)                   | 10(41.7)                                             | 10(41.7)                             |
| Age                   |                           |                                                      |                                      |
| ≤ 65 years            | 12(54.5)                  | 14(58.3)                                             | 14(58.3)                             |
| ≥ 65 years            | 10(45.5)                  | 10(41.7)                                             | 10(41.7)                             |
| Minimum               | 45                        | 45                                                   | 45                                   |
| Maximum               | 86                        | 83                                                   | 86                                   |
| Mean age              | 68.55(SD: 11.392)         | 68.21(SD:10.134)                                     | 67.88(SD:10.991)                     |
| Education level       |                           |                                                      |                                      |
| Illiterate            | 9(40.9)                   | 6(25)                                                | 0                                    |
| Primary               | 12(54.6)                  | 14(58.3)                                             | 19(79.1)                             |
| Secondary             | 1(4.5)                    | 4(16.7)                                              | 5(20.9)                              |
| Occupation            |                           |                                                      |                                      |
| Farmer                | 10(45.5)                  | 7(29.1)                                              | 5(20.9)                              |
| Non-farmer            | 12(54.5)                  | 17(70.9)                                             | 19(79.1)                             |

**Table 2: Diagnostic modalities in patient with cholangiocarcinoma.**

| Diagnostic Modality | CTA | ERCP/MRCP+Elevated tumor markers |
|---------------------|-----|---------------------------------|
| Pathology           | 1(4.5) | 13(59.1)          |
| CT scan             | 13(59.1) | 8(36.4)          |
and radiological findings. In the absence of other explainable causes results should not rule out CCA in the presence of appropriate clinical stool and hyper pigmented urine. Non-diagnostic cytology or biopsy symptoms related to biliary obstruction such as itching, clay-colored

On the other hand, ECC usually present with painless jaundice and rarely during physical exams, as asymptomatichepatic masses. ICCs are often diagnosed by imaging tests, region. CCAs are usually clinically silent or associated with nonspecific symptoms in early stage. Although the incidence of cholangiocarcinoma is relatively rare with a poor prognosis and a lower quality of life [7]. CCA accounts for around 10–25% of the primary liver cancers in most parts of the world with Age-Standardized incidence Rates (ASRs) between 0.3 and less than 1.5 per 100 000 in western countries [13]. In the USA, approximately 5000 new cases are diagnosed yearly. CCA is divided into extra or intrahepatic CCA. ECCs is further divided into hilar or distal tumour. Although the incidence of ICC is rising, the occurrence of ECC is trending down suggesting that different risk factors may be involved. The average age at presentation is the seventh decade of life with a male to female ratio of 1.5 to 1 [14].

The distribution of age and sex among the patients in our province was similar to other worlds and like other study majority of patients were identified in seventh decade of life or later. According to National Statistics Office 2011 report, Guilan province had a population of 2.5 million in 2011. Identification of 22 patients in this province during study period shows that Cholangiocarcinoma is a rare malignancy in this province during study period shows that Cholangiocarcinoma is a rare malignancy in this province. Most of the cases are developed with some abnormalities other than normal liver. However, in approximately 10% of cases, CCA is preceded by a chronic inflammatory disease process of the bile ducts that might induceprogressive changes in the biliary epithelium that culminate in cancer. Examples of such diseases are Primary Sclerosing Cholangitis, liver fluke infestations and hepatolithiasis [16].

The most common predisposing factor for CCA is Primary Sclerosing Cholangitis (PSC) which has been reported in up to 40% of patients suffering from a specific malignancy. In addition, patients with intrahepatic biliary stones have a 10% risk of developing CCA, while up to 70% of patients with histologically confirmed CCA have hepatolithiasis. Moreover, biliary malformations such as Caroli’s disease and congenital fibropolycystic disease carry a 10% to 15% risk of malignancy. Chronic pancreatitis, non-specific liver cirrhosis, history of biliary-enteric drainage for benign disease, exposure to environmental toxins, increased body mass index, smoking and consumption of alcohol have also been associated with a higher prevalence of CCA [17-23].

We evaluated role of smoking, consumption of alcohol and past history of obesity in developing cholangiocarcinoma in Guilan province. Comparison of patients and controls group showed that there was no association between these factors and developing cholangiocarcinoma in our study. On the other hand, the role of these factors has not confirmed in all studies and there are some differences in results of various studies [20-26]. For example, the case-control study by Parkin et al. [21] and a study by Hsing et al. [22], reported no association between cholangiocarcinoma and tobacco smoking, but opposite in Honjo et al. [23] study found that smoking had slightly increase association with cholangiocarcinoma.

Although we studied role of several factors such as smoking, alcohol consumption and history of obesity with developing of CCA in our region but it was not a main goal of present study. Alcohol consumption and partly smoking tobacco is very low in Guilan province because of culture and religious believes of People in this area. On the other hand obesity was a self-reported response and we didn’t access to reliable index such as patient’s BMI, before the illness presented clinically. Also the number of patients was fairly low in our study and these results need limitation. If these conditions put together we can say that smoking and obesity were not risk factors for developing cholangiocarcinoma in our study.

The second most common risk factor for developing cholangiocarcinoma is history of liver disease. In our study, chronic liver disease (CH), including hepatitis C, alcoholic and non-alcoholic fatty liver disease, was the most important risk factor for developing CCA, with a significantly increased risk of 13.50 compared with patients with no history of liver disease. However, other studies have not confirmed this relationship. There are many causes for this difference, such as the differences in the antibody tests used, the selection criteria of patients and controls, and the specific populations investigated.

A univariate analysis among Cholangiocarcinoma cases and controls according to selected variables is presented in Table 3. The results show that patients with a history of alcohol consumption had a significantly increased risk of developing CCA compared with controls (OR 3.12, 95% CI 1.14-8.49, p = 0.025). Anti-HCV Ab Positive have a higher P value

Discussion

Primary Liver Cancer (PLC) encompasses hepatocellular carcinoma, intrahepatic cholangiocarcinoma, and a few other rare histological types. PLC is the fifth most common cancer in the world and the third most common cause of cancer death worldwide [12].

Cholangiocarcinoma is relatively rare with a poor prognosis and a lower quality of life [7]. CCA accounts for around 10–25% of the primary liver cancers in most parts of the world with Age-Standardized incidence Rates (ASRs) between 0.3 and less than 1.5 per 100 000 in western countries [13]. In the USA, approximately 5000 new cases are diagnosed yearly. CCA is divided into extra or intrahepatic CCA. ECCs is further divided into hilar or distal tumour. Although the incidence of ICC is rising, the occurrence of ECC is trending down suggesting that different risk factors may be involved. The average age at presentation is the seventh decade of life with a male to female ratio of 1.5 to 1 [14].

The distribution of age and sex among the patients in our province was similar to other worlds and like other study majority of patients were identified in seventh decade of life or later. According to National Statistics Office 2011 report, Guilan province had a population of 2.5 million in 2011. Identification of 22 patients in this province during study period shows that Cholangiocarcinoma is a rare malignancy in this region. CCAs are usually clinically silent or associated with nonspecific symptoms in early stage. ICCs are often diagnosed by imaging tests, and rarely during physical exams, as asymptomatichepatic masses. On the other hand, ECC usually present with painless jaundice and symptoms related to biliary obstruction such as itching, clay-colored stool and hyper pigmented urine. Non-diagnostic cytology or biopsy results should not rule out CCA in the presence of appropriate clinical and radiological findings. In the absence of other explainable causes of biliary strictures, patients should be considered as having CCA and treated, accepting that 10% to 15% will have benign lesions on final pathology [14].

Jaundice with abdominal pain was the most presenting symptom in our study. In thirteen patients Endoscopic Retrograde Cholangiography (ERCP) and/or Magnetic Resonance Cholangiography (MRCP) plus CT scan and elevated tumour markers were used for the diagnosis. Cytological examination and pathologic confirmation was got in eight and one respectively. As noted above confirmation of cholangiocarcinoma can be very difficult because of a wide spectrum of alternative diagnosis, including other carcinomas, metastasis and benign biliary strictures, so multidisciplinary investigative approaches are needed to overcome this problem [15].

In low incidence areas of cholangiocarcinoma, risk factors for the tumours are poorly characterized. Because of its sporadic nature, the etiology of CCA remains enigmatic and evaluation of risk factors poses a difficult puzzle. There are few well-established risk factors for CCA. Most of the cases are developed with some abnormalities other than normal liver. However, in approximately 10% of cases, CCA is preceded by a chronic inflammatory disease process of the bile ducts that might induceprogressive changes in the biliary epithelium that culminate in cancer. Examples of such diseases are Primary Sclerosing Cholangitis, liver fluke infestations and hepatolithiasis [16].

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| Variables                  | Cholangiocarcinoma | Control I (GI Malignancy without liver disease) | Control II (Healthy population) | P value |
|---------------------------|--------------------|-----------------------------------------------|--------------------------------|---------|
| Past history of obesity no yes | 6(27.3)            | 7(29.2)                                      | 3(22.9)                         | 0.325   |
| Smoking history no moderate heavy | 15(68.2)           | 17(70.8)                                     | 20(83.3)                        | 0.259   |
| Drinking history no moderate heavy | 19(86.6)           | 21(87.5)                                     | 24(100)                         | 0.260   |
| HBsAg Positive negative | 3(13.6)            | 1(4.2)                                       | 0                               | 0.127   |
| Anti-HCV Ab Positive negative | 1(4.5)             | 0                                            | 0                               | 0.331   |
| Anti fasciola Ab Positive negative | 0                  | 0                                            | 0                               | 0.000   |

Table 3: Univariate analysis among Cholangiocarcinoma cases and controls according to selected variables.
Second to tobacco use, infections are the most important preventable source of human malignancies [27]. Although Chronic infectious liver diseases, such as HBV and HCV infection, were not significantly associated with cholangiocarcinoma in our study but It has been shown that HBV is an independent risk factor for CCA in Chinese and Korean population [21,27]. Recent studies from Korea, Japan and Italy showed that HCV is associated with cholangiocarcinoma too [27-29]. Studies in aggregate, suggest that HBV and HCV infection are potential risk factors for CCA, but their impact might be different across different countries or areas and most of these has been reported from endemic area of HBV or HCV [27-33].

The association between the occurrence of CCA and liver flukes has been known for about 50 years. Infection by *Opisthorchis viverrini* has been demonstrated as a definite cause of human CCA, whereas infection by *Clonorchis sinensis* has been linked to a higher incidence of CCA [17]. Most of the data about *O. viverrini* come from Thailand, which has the highest incidence rates of CCA in the world. In the largest case-control study of CCA among 103 patients with CCA in Thailand investigators found a strong positive association between *O. viverrini* and CCA (unadjusted odds ratio [OR]=4.8; 95% CI, 2.3 to 9.8). This association has been confirmed in several studies in endemic area of these flukes [30-33]. Human fascioliasis is geographically widespread and recognized as a serious public health problem in some endemic areas, which includes countries in South America, Northern Africa, areas in Western Europe as well as Iran and some other Asian countries. The main problem with regard to fascioliasis in Iran is concentrated in the Guilan province on the Caspian Sea coast in the north. The first large outbreak of human fascioliasis in this region, in which more than 10000 to 20,000 people were infected, was reported in 1987 and 1988. Another outbreak with about 2,000 infected individuals occurred ten years later [10,34-35].

Surveying the association of CCA and fascioliasis was one of the most goals of our study. This hypothesis formed based on association of other liver flukes (*Opisthorchis viverrini* and *Clonorchis sinensis*) with CCA, relatively similar pathogenesis of fascioliasis and these flukes cause chronic inflammation of bile duct epithelium and high prevalence of fascioliasis in our province. Even in a recent study, the association of parasites such as biliary ascariasis or liver schistosomiasis and CCA has been considered [11].

Although the results of present study didn’t confirm this hypothesis, but some limitation diminish the accuracy of present study. First, the small cases in our study were a main limitation to assess the association of CCA and fascioliasis, exactly. Also, we cannot reject this association definitely, because anti-fasciola antibody was negative in all samples, therefore rejection of this association is not possible statistically. We suggest further study in endemic area of fascioliasis to explore the role of this liver fluke in the development of CCA. Assessment CCA in positive anti-fasciola antibody patients is an alternative suggestion too.

**Conclusions**

Cholangiocarcinoma is rare in Guilan province. Most patients diagnose at end stage of disease and curative therapy is not possible in majority of them. None of the known cholangiocarcinoma risk factors were associated to developing CCA in this region. Also there was no association between fascioliasis and CCA but we cannot reject this association definitely, because anti-fasciola antibody was negative in all samples, therefore rejection of this association is not possible statistically. We suggest further study in endemic area of fascioliasis to explore the role of this liver fluke in the development of CCA.

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