RESEARCH ARTICLE

Comparison of Clinical Characteristics between Occupational and Sporadic Young-Onset Cholangiocarcinoma

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Abstract

Background: Since seventeen employees of an offset printing company in Osaka, Japan developed cholangiocarcinoma it has become recognized as an occupational cancer. This study investigated the differences of clinical features between occupational cholangiocarcinoma and sporadic young-onset cholangiocarcinoma. Materials and Methods: Thirty-four young adults (<50 years old) with sporadic cholangiocarcinoma were extracted from the Rosai Hospital Group database (sporadic group) and their clinical features were compared with those of 17 patients with occupational cholangiocarcinoma (occupational group). Results: The 34 patients in the sporadic group were treated for cholangiocarcinoma at 16 different Rosai hospitals. There were significant differences of age (p<0.01), gender (p<0.01), abnormal laboratory tests (p<0.01), and tumor location (p<0.01) between the two groups. The percentage of patients with abnormal laboratory tests was significantly higher in the occupational group than in the sporadic group (p<0.001). Regional dilation of bile ducts, which is a characteristic of occupational cholangiocarcinoma, was not observed in the sporadic group. Conclusions: No cluster of cholangiocarcinoma cases was identified in the Rosai Hospital database. There were differences of clinical features between occupational and sporadic cholangiocarcinoma, which might be helpful for diagnosing occupational cholangiocarcinoma in the future.

Keywords: Occupational cholangiocarcinoma - juvenile cholangiocarcinoma - organic solvent

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Introduction

Recently, a cluster of cholangiocarcinoma cases was reported among relatively young workers in the offset color proof printing department of a printing company in Osaka, Japan (Kumagai et al., 2013; Kubo et al., 2014). In 2013, this type of cholangiocarcinoma was recognized as an occupational disease by the Japanese Ministry of Health, Labour and Welfare (Ministry of Health, Labour and Welfare. 2013). At the printing company in question, large amounts of dichloromethane (DCM) and 1,2-dichloropropane (DCP) were used in the printing process and the workers were exposed to high concentrations of these chlorinated organic solvents (Kumagai et al., 2013; National Institute of Occupational Safety and Health. 2012). From the estimated concentrations of DCP and DCM to which the workers were exposed and assessment of genotoxicity (Suzuki et al., 2014; Yamada et al., 2014), it was concluded that long-term exposure to high concentrations of DCP caused the development of cholangiocarcinoma. Although there is no definite evidence of carcinogenicity for DCM, it might also play a role in the development of cholangiocarcinoma (Yamada et al., 2015). Because of this event, the International Agency for Research on Cancer (IARC) upgraded the carcinogenicity of dichloromethane from Group 2B (possibly carcinogenic to humans) to Group 2A (probably carcinogenic to humans) and that of 1,2-dichloropropane from Group 3 (not classifiable as to carcinogenicity for humans) to Group 1 (carcinogenic to humans) in 2014 (Benbrahim et al., 2014).

The patients with occupational cholangiocarcinoma at the printing company were typically relatively young male workers with high serum levels of γ -glutamyl transpeptidase (γ -GTP) and regional dilatation of the intrahepatic bile ducts without obstruction by the tumor. In these patients, the primary cancer arose from a large bile duct (common hepatic duct, left or right hepatic ducts, or the first to third branches of the intrahepatic bile ducts) and they had co-existing precancerous lesions such as biliary intraepithelial neoplasia (BilIN) and intraductal neoplasms of the bile ducts (Kubo et al., 2014). These characteristics seemed to be different from the typical features of cholangiocarcinoma.

Up to October 30, 2014, 34 patients in Japan were recognized to have occupational cholangiocarcinoma by the Ministry of Health, Labour and Welfare. Therefore, it is important to determine whether occupational

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cholangiocarcinoma is widespread in Japan and if there is any doubt about the occupational etiology.

The Rosai Hospitals comprise 34 hospitals located throughout Japan from Hokkaido to Kyushu that treat patients with or without occupational diseases. At these hospitals, the occupational history of each patient is noted in the medical records, with the three previous occupations being registered in the database at the time of admission. This is a unique feature of the database for the Rosai hospitals (Rosai database).

The present study was performed to investigate the differences of clinical features between patients who developed occupational cholangiocarcinoma at the printing company in Osaka and young-onset patients with sporadic cholangiocarcinoma treated at the Rosai hospitals nationwide.

Materials and Methods

Cholangiocarcinoma is defined as young-onset cholangiocarcinoma if it develops in patients under 50 years old

A total of 34 patients with young-onset cholangiocarcinoma were extracted from the Rosai database by using keywords from the International Classification of Disease (9th and 10th edition), which were intrahepatic bile duct, extrahepatic bile duct, and biliary tract and parts unknown [ICD9:1551 (intrahepatic cholangiocarcinoma), ICD9:1561 (extrahepatic cholangiocarcinoma), ICD9:1569 (part undetectable); ICD10: C221 (intrahepatic cholangiocarcinoma), ICD10: C240 (extrahepatic cholangiocarcinoma), ICD10: C249 (part undetectable)]. The Rosai database contains 5.27 million medical records from April 1, 1984 to May 31, 2014, among which 2.79 million records include data on the occupational history. Cholangiocarcinoma was diagnosed in 7717 patients (including 5910 patients with occupational data) and 265 of them were under 50 years old (including 205 with occupational data).

Detailed medical records, including laboratory data and diagnostic imaging findings, were only available for 34 of the young patients. These 34 patients were employed in this study.

Exposure of the patients to DCM and/or DCP was estimated by using the Pollutant Release and Transfer Register (Ministry of Economy., 2014), indicating that five of the 34 patients had possible to exposure to DCM and/or DCP.

In this study, the 17 patients with occupational cholangiocarcinoma from the Osaka printing company were classified as the occupational group and the 34 patients with young-onset cholangiocarcinoma identified in the Rosai database formed the sporadic group.

We compared clinical features between the occupational group and the sporadic group, including lifestyle factors such as smoking and drinking (habitual drinking with an ethanol intake of 80g / day or more), laboratory data such as γ-GTP, carbohydrate antigen (CA) 19-9, and carcinoembryonic antigen (CEA), serum markers of hepatitis B and C virus, known risk factors for cholangiocarcinoma, diagnostic imaging findings (computed tomography, magnetic resonance imaging, endoscopic retrograde cholangiopancreatography, and magnetic resonance cholangiopancreatography), tumor location (intrahepatic or extrahepatic), and histological findings. We also compared clinical features between the occupational group and the 5 patients from the sporadic group with possible exposure to DCM and/or DCP (possible exposure group).

The diagnosis of cholangiocarcinoma was re-evaluated by a gastroenterologist from Kanto Rosai Hospital, who reviewed the medical records and imaging findings. Tumor

Table 1. Comparison of Characteristics between the Occupational Group and the Sporadic Group

	Occupational group (n = 17)	Sporadic group (n = 34)	P value
Age (years, mean)	25-45 (36)	23-49 (44)	0.009**
Gender (M:F)	17:0	23:11	0.009**
Alcohol abuse	3	14	0.12
Smoking	13	19	0.22
Symptoms	5	21	0.029*
Abnormal laboratory tests	12	4	0.001>**
Elevated γ-GTP	17	14(16)	0.23
Elevated CEA	10	5(14)	0.2
Elevated CA 19-9	13	9(16)	0.28
Tumor location			0.008*
Intrahepatic	10	7	
Extrahepatic	5	25	
Intra and Extrahepatic	2	0	
Unknown	0	2	
Tumor stage			0.07
I-III	2	9	
IVA and IVB	15	12	
Unknown	0	13	
Treatment			0.5
Surgery	12	12	
Chemotherapy and/or radiation	5	8	

*Elevation of γ-GTP, CA19-9, CEA indicates the number of patients with enzymes elevated at, the first admission. γ-GTP, γ-glutamyl transpeptidase; CA19-9, carbohydrate antigen19-9; CEA, carcinoembryonic antigen, Symptoms indicate the number of patients with complaints at the onset (abdominal pain, jaundice, pruritus, and anorexia), Abnormal laboratory tests shows the number of patients with abnormal test results.

location was classified according to the 'General Rules for Clinical and Pathological Studies on Cancer of the Biliary Tract (6th Edition). Tumors arising in a bile duct peripheral to the secondary branches were classified as intrahepatic cholangiocarcinoma, while tumors that developed in the so-called perihilar or distal sites were classified as extrahepatic cholangiocarcinoma. Pathological findings were recorded and described according to the World Health Organization classification of intrahepatic and extrahepatic cholangiocarcinoma (Bosman et al., 2010).

The χ^2 test or Fisher's exact test was used to evaluate significance of differences in categorical data between the groups. Statistical analysis was performed with Stata VER13 (Stata Corp. Texas, USA).

This study was approved by the ethics committee of Japan Labour Health and Welfare Organization Kanto Rosai Hospital.

Results

Clinical features of the sporadic group

The 34 patients with cholangiocarcinoma were treated at 16 different Rosai hospitals. Therefore, a cluster of young-onset cholangiocarcinoma was not found in the Rosai database accumulated from hospitals distributed throughout Japan.

In the sporadic group, 23 patients were male and 11 were female. The chief presenting complaint was abdominal pain in 11 patients, jaundice in 7, pruritus in 2, and anorexia in 1. Four patients presented to hospital because of abnormal laboratory test results. In the remaining 9 patients, the chief complaint was not specified. Two patients were positive for serum HBs antigen. Known risk factors for cholangiocarcinoma, such as primary sclerosing cholangitis, hepatolithiasis, pancreaticobiliary maljunction, or liver fluke infection, were not observed in the sporadic group.

The clinical stage at the time of diagnosis was stage 1 in 2 patients, stage 2 in 4, stage 3 in 3, stage 4A in 4, and stage 4B in 8. Detailed information about staging was not available for the other 13 patients. Seven patients had intrahepatic cholangiocarcinoma and 25 patients had extrahepatic cholangiocarcinoma, while the location of the primary tumor was unknown in 2 patients.

Surgical treatment was performed in 12 patients (pancreaticoduodenectomy in 8, right lobectomy in 1, and unknown operative procedure in 3). Seven patients underwent chemotherapy (tegafur-gimeracil-oteracil potassium in 3, gemcitabin in 2, cisplatin in 1, and intra-arterial fluorouracil in 1). The histologic diagnosis was adenocarcinoma in 26 patients, while the histology was unknown in the other 8 patients.

Comparison between the occupational group and the sporadic group.

Table 1 shows a comparison of clinical features between the occupational group and the sporadic group. The mean age was significantly younger in the occupational group than the sporadic group ($p<0.01$). All patients in the occupational group were male, while 23

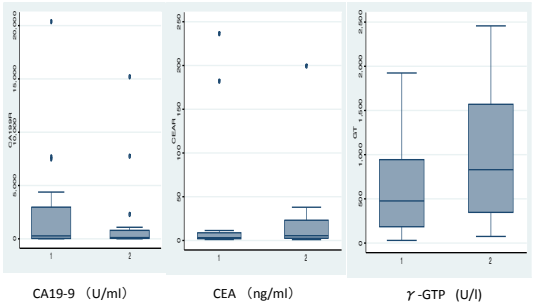

Figure 1. Comparison of Laboratory Data At Diagnosis. γ-GTP, γ-glutamyl transpeptidase; CA19-9, carbohydrate antigen19-9; CEA, carcinoembryonic antigen. Three abnormal outliers in the sporadic group were not incorporated in the main plot (CA19-9, 216394 U/ml; CEA, 8832 ng/mg; CEA, 2530 ng/mg). Although γ-GTP levels were higher in the occupational group, there were no significant differences

Table 2. Comparison of Characteristics between the Occupational Group and the Possible Exposure Group

	Occupational group (n = 17)	Possible Exposure group (n = 5)	P value
Age (years, mean)	25-45 (36)	44-49 (46)	0.001**
Gender (M:F)	17:0	4:1	0.23
Symptoms	5	4	0.12
Tumor location			0.03*
Intrahepatic	10	0	
Extrahepatic	5	5	
Intra and Extrahepatic	2	0	
Unknown	0	0	
Tumor stage			0.009**
I-III	2	4	
IVA and IVB	15	1	
Unknown	0	0	
Treatment			1
Surgery	12	4	
Chemotherapy and/or radiation	5	1	

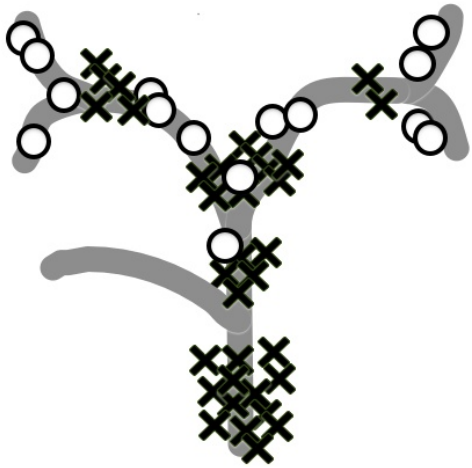

Figure 2. Tumor Locations. The sites of the main tumors are shown by open circles (occupational group) or by crosses (sporadic group). Two patients with both intrahepatic and extrahepatic tumors are not shown in the figure

patients were male and 11 were female in the sporadic group ($p<0.01$). With regard to lifestyle factors, there was no statistical difference in the number of patients with alcohol abuse or habitual smoking. Five patients in the occupational group presented to hospital because of symptoms, whereas 21 of 34 patients in the sporadic group presented because of symptoms ($p<0.05$). Twelve patients in the occupational group presented to hospital because of abnormal laboratory test results (tests performed for regular health checks in 11 patients and during treatment for another disease in 1 patient). The proportion of patients with symptoms was significantly higher in the sporadic group than in the occupational group ($p<0.05$). Serum γ-GTP was elevated in all patients from the occupational group, while it was elevated in 14 out of 16 patients tested in the sporadic group. The proportion of patients with elevation of CEA and CA 19-9 did not differ between the groups. Although there were no significant differences of γ-GTP, CA19-9, and CEA levels between the two groups, there was a trend for γ-GTP to be higher in the occupational group (Figure 1). On diagnostic imaging, regional bile duct dilatation without tumor obstruction was not observed in the sporadic group, unlike the occupational group.

In the occupational group, 15 patients had stage IV cholangiocarcinoma, while the carcinoma was classified as stage IV in 12 of 21 patients with data from the sporadic group. In the occupational group, 10 patients had intrahepatic cholangiocarcinoma, 5 had extrahepatic cholangiocarcinoma, and 2 had both intrahepatic and extrahepatic tumors (Figure 2). Most of the extrahepatic tumors were classified as so-called perihilar cholangiocarcinoma. In 13 of the 27 patients with extrahepatic cholangiocarcinoma from the sporadic group, the tumor was classified as distal cholangiocarcinoma. The proportion of intrahepatic cholangiocarcinoma was significantly higher in the occupational group than in the sporadic group ($p <0.05$). Eleven patients in the occupational group underwent hepatectomy and 1 underwent hepatectomy combined with pancreaticoduodenectomy. The proportion of patients undergoing hepatectomy was significantly higher in the occupational group than in the sporadic group ($p<0.01$).

Comparison between the occupational group and the sporadic group

Table 2 shows a comparison of clinical features between the 17 patients in the occupational group and five patients in the possible exposure group (a subgroup of the sporadic group). The mean age was significantly younger in the occupational group than the possible exposure group ($p<0.01$). In the possible exposure group, 4 patients were male and 1 was female. Although 5 of 17 patients in the occupational group presented to hospital because of symptoms, 4 patients visited hospital because of symptoms in the possible exposure group (jaundice, pruritus, and anorexia). Little data on γ-GTP, CEA, and CA19-9 levels was obtained from the medical records, so statistical analysis was not performed. All patients in the possible exposure group had extrahepatic cholangiocarcinoma, unlike the occupational group ($p<0.05$). In the possible exposure group, tumor stages were lower than in the occupational group.

Discussion

This study showed that there was no regional clustering of young-onset cholangiocarcinoma in the Rosai database for 16 hospitals around Japan. A previous study based on data from the Osaka Cancer Registry revealed that there was neither a change in trend nor regional clustering of cholangiocarcinoma in Osaka (Ikeda et al., 2013). It was also reported that the cluster of cholangiocarcinoma cases detected in Osaka may not be reproduced in the printing industry nationwide from analysis of the Japan Health Insurance Association claims database (Okamoto et al., 2013). Thus, the occurrence of occupational cholangiocarcinoma among workers of the Osaka company was not indicative of a wider problem.

This study also identified some differences of clinical features between occupational and sporadic cholangiocarcinoma. It is known that cholangiocarcinoma usually occurs in patients in their 60s-70s, while the patients with occupational cholangiocarcinoma were under 50 years old. When patients under 50 years old were extracted from the Rosai database for the sporadic group, the mean age of the occupational group was still significantly lower. Thus, the 17 patients with occupational cholangiocarcinoma were extremely young compared with patients developing sporadic cholangiocarcinoma. In addition, the proportion of male patients was significantly higher in the occupational group than in the sporadic group. In the relevant section of the printing company, most employees were young men and their for 6 to 19 years induced cholangiocarcinoma (Kubo et al., 2014). Thus, the gender difference between the occupational and sporadic groups is considered to reflect the low ratio of female workers exposed to organic solvents at the printing company.

The proportion of patients with symptoms was higher in the sporadic group than in the occupational group, whereas the proportion of patients with abnormal laboratory test results identified during regular health checks was higher in the occupational group. In some patients from the occupational group, elevation of the serum concentrations of γ-GTP, aspartate aminotransferase, and alanine aminotransferase was observed several years before the detection of cholangiocarcinoma (Kumagai et al., 2014; Kubo et al., 2014). These findings indicate that patients in the sporadic group generally presented to hospital after the onset of symptoms and that regular health checks are important for detecting occupational cholangiocarcinoma.

Although cholangiocarcinoma can develop at any site in the bile duct, more than 60 % are extrahepatic and only a small percentage of these tumors arise in the intrahepatic bile ducts (Razumilava et al., 2014). While these trends were seen in the sporadic group, many of the tumors developed in the large intrahepatic bile ducts in the occupational group. As a result, the proportion of patients who underwent hepatectomy was higher in the occupational group than in the sporadic group, while the proportion of patients undergoing

pancreaticoduodenectomy was higher in the sporadic group.

The characteristic findings in patients with occupational cholangiocarcinoma include regional dilatation of the intrahepatic bile ducts related to chronic bile duct injury, precancerous lesions including biliary intraepithelial neoplasia, and early cancerous lesions (Kaneko et al., 2014; Kubo et al., 2014; Sato et al., 2014; Suzuki et al., 2014; Tomimaru et al., 2015). In contrast, regional dilatation of the intrahepatic bile ducts was not observed by diagnostic imaging in the sporadic group. Thus, the process of carcinogenesis seems to differ between the occupational group and the sporadic group.

The differences that we identified between the occupational group and the possible exposure group were similar to those between the occupational group and the sporadic group. Although there is no detailed information about exposure to organic solvents in the possible exposure group, the extent of exposure might be lower in this group than in the occupational group. Occupational cholangiocarcinoma develops after long-term exposure to high concentrations of organic solvents. It is important to know the occupational history (including exposure to organic solvents) and the detailed clinical features of patients with cholangiocarcinoma because this information is useful for diagnosing occupational cholangiocarcinoma.

The present study identified some differences of clinical data between the occupational and the sporadic group, but evaluation was limited by the small number of young adult patients with cholangiocarcinoma. In fact, sufficient data were available for only 34 patients with sporadic young-onset cholangiocarcinoma, accounting for a mere 0.4% of all cholangiocarcinoma patients in the Rosai database. Therefore, the influence of selection bias cannot be ruled out. An unexpected finding was that clinical data did not include the occupational history in many cases. This may be due to technical problems such as different methods of data processing by each member of the Rosai Hospital group. In addition, availability of medical records is limited to five years in compliance with the law. Therefore, further improvements are necessary to allow studies to be performed with more precision.

In conclusion, this study showed that the cluster of occupational cholangiocarcinoma in Osaka was an isolated event and that there are differences of clinical features between occupational and sporadic cholangiocarcinoma. These findings might be helpful for diagnosing occupational cholangiocarcinoma in the future.

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