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Abstract

Purpose

This study aimed to establish an efficient strategy for screening and surveillance for occupational cholangiocarcinoma.

Methods

We evaluated the consecutive changes in laboratory findings during regular health examinations and in abdominal ultrasonography findings before the diagnosis of occupational cholangiocarcinoma in nine patients. The results of laboratory tests and abdominal ultrasonography at the time of diagnosis were also examined.

Results

In all patients, the serum γ-glutamyl transpeptidase (γ-GTP) activity increased several years before the diagnosis of cholangiocarcinoma. The serum alanine aminotransferase (ALT) activity also increased several years before the diagnosis, following an increase in the serum aspartate aminotransferase (AST) activity in most patients. Abdominal ultrasonography before the diagnosis revealed regional dilatation of the bile ducts, which continued to enlarge. At the time of diagnosis, the γ-GTP, AST, and ALT activities were increased in nine, seven, and seven patients, respectively. The regional dilatation of bile ducts without tumor-induced stenosis, dilated bile ducts due to tumor-induced stenosis, space-occupying lesions, and/or lymph node swelling were observed. The serum concentrations of carbohydrate antigen 19-9 (CA 19-9) and/or carcinoembryonic antigen (CEA) were increased in all patients.

Conclusions

Regular health examinations with a combination of ultrasonography and laboratory tests including the γ-GTP, AST, ALT, CA 19-9, and CEA levels are useful for screening and surveillance for occupational cholangiocarcinoma.

Keywords: occupational cholangiocarcinoma, screening and surveillance, health examination, organic solvent

Abbreviations

γ-GTP	γ-glutamyl transpeptidase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CA19-9	carbohydrate antigen 19-9
CEA	carcinoembryonic antigen
DCM	dichloromethane
DCP	1,2-dichloropropnae
PSC	primary sclerosing cholangitis
MRI	magnetic resonance imaging
MRCP	magnetic resonance cholangiopancreatoraphy
ERCP	endoscopic retrograde cholangiopancreatography

Introduction

An outbreak of cholangiocarcinoma among workers at a printing company was recently reported [1, 2]. Although the mechanism underlying the development of cholangiocarcinoma is still unknown, long-term exposure to chemicals that include high concentrations of dichloromethane (DCM) and/or 1,2-dichloropropane (DCP) is strongly suspected to be a cause of the disease [1-3]. The Ministry of Health, Labour and Welfare of Japan classified this type of cholangiocarcinoma as "occupational cholangiocarcinoma" on October 1, 2013 [3]. Thirty-six patients, some of whom have been described in previous reports [2, 4], had been diagnosed with occupational cholangiocarcinoma as of February 2015.

Early detection of cholangiocarcinoma is essential, because the treatment outcomes for cholangiocarcinoma are still unsatisfactory [5-10]. Of 17 patients diagnosed with occupational cholangiocarcinoma following employment in the aforementioned printing company in Osaka, 11 patients were diagnosed on further examination after a regular health examination revealed abnormal findings on either laboratory tests or ultrasonography [2]. This demonstrates the importance of regular health examinations for screening and surveillance for occupational cholangiocarcinoma. In addition, previous studies reveled that abnormal liver function test results were observed several years before the diagnosis of cholangiocarcinoma [11,12]. However, an efficient strategy for the detection of occupational cholangiocarcinoma during the health examinations of workers with long-term exposure to high concentrations of organic solvents remains to be elucidated. The aim of this study was to establish an efficient strategy for screening and surveillance for occupational cholangiocarcinoma through the evaluation of changes in the results of laboratory tests in nine patients with occupational cholangiocarcinoma. These patients were selected because the consecutive results of laboratory tests performed prior to the diagnosis of cholangiocarcinoma could be obtained for this group. The consecutive results of abdominal ultrasound studies performed before the diagnosis of cholangiocarcinoma were also available and evaluated in two patients.

Patients and methods

The subjects included in this study were nine patients with occupational cholangiocarcinoma (Table 1). Of the nine patients, six worked at a single printing company in Osaka (Company A) [2], two worked at another company (Company B), and one worked a third company (Company C) [4]. Of the nine patients, seven patients (patients 1, 3-8) were exposed to a high concentration of DCP, one (patient 9) was exposed to a high concentration of DCM and one (patient 2) was exposed to high concentrations of both DCP and DCM. In four patients, cholangiocarcinoma was diagnosed while they were currently working at the printing companies, while the cholangiocarcinoma was diagnosed after the end of the exposure in the remaining patients. The interval between the end of the exposure

and the diagnosis of cholangiocarcinoma ranged from three years and 10 months to 12 years. The consecutive results of laboratory tests that were performed at regular health examinations before the diagnosis of cholangiocarcinoma were available for all nine patients. The changes in the serum activities of γ-glutamyl transpeptidase (γ-GTP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were evaluated because abnormal results on these tests have often been observed at the diagnosis of occupational cholangiocarcinoma [2, 4]

In two patients, the consecutive results of abdominal ultrasound studies were obtained from two hospitals where these two patients were followed up because of abnormal liver function tests. We evaluated tumor lesions, such as space-occupying lesions in the liver, papillary or protruding tumorous lesions in the bile duct, dilatation of the bile ducts, and lymph node swelling detected by ultrasonography.

This study was approved by the ethics committee of Osaka City University (No. 2368), and all subjects or their legally authorized representatives (for deceased patients) provided written informed consent.

Results

Changes in laboratory test results

The consecutive results of tests of the serum activities of γ-GTP, AST and ALT are shown in Figures 1A, B, and C. In all nine patients, the serum γ-GTP activity was increased several years before the detection of cholangiocarcinoma. The serum ALT activity also increased several years before the detection of cholangiocarcinoma, following an increase in the serum AST activity in most patients. In patients 3, 4 and 5, the serum activities of γ-GTP, AST and ALT increased gradually after the end of the exposure. In patient 5, cholangitis occurred one month before the diagnosis of cholangiocarcinoma. Patient 6 retired from printing company A because of extremely increased activity levels of γ-GTP, AST and ALT, and the activity levels gradually decreased after retirement.

Changes in abdominal ultrasonographic images

In patient 5, regional dilatation of the bile ducts in the posterior segment and the lateral segment was detected five months before the diagnosis of cholangiocarcinoma, and these were subsequently enlarged (Fig. 2). At the diagnosis of cholangiocarcinoma, regional dilatation of the bile ducts without tumor-induced stenosis and tumorous lesions in the bile duct with thick walls in the lateral segment was observed. In patient 6, regional dilatation was first detected five years and three months before the diagnosis of cholangiocarcinoma, and the ducts continued to enlarge gradually (Fig. 3). At the diagnosis of cholangiocarcinoma, regional dilatation of the bile ducts, dilatation of the intrahepatic bile ducts due to tumor-induced stenosis, space-occupying lesions, and/or lymph node swelling were observed

in the nine patiens.

The results of laboratory test results and abdominal ultrasonography

At the time of diagnosis of cholangiocarcinoma, the serum activities of AST and ALT were elevated in seven of the nine patients. The serum γ-GTP activity was elevated in all nine patients (Table 1). The serum concentrations of carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA) were elevated in eight and three patients, respectively; the serum concentrations of CA 19-9 and/or CEA were elevated in all nine patients. Among the nine patients, ultrasonography detected tumorous lesions in six patients, space-occupying lesions in the liver (Fig. 3k) in three patients (patients 1, 6, and 7) and tumorous lesions in the bile ducts (Fig. 2f) in four patients (patients 2, 3, 5, and 9). Ultrasonography also showed wall thickening of the bile ducts (hyperechoic wall) (Fig. 2f) in one patient (patient 5). Dilated intrahepatic bile ducts with tumor-induced stenosis (Fig. 3f) were detected by ultrasonography in six patients (patients 1, 3, 4, 6, 8, and 9). Regional dilatation of the intrahepatic bile ducts without tumor-induced obstruction (Figs. 2 and 3), which is a characteristic of patients with occupational cholangiocarcinoma [2, 4], was detected in two patients (patients 5 and 6). Lymph node swelling (Fig. 3e) was observed in one patient (patient 6). Abnormal findings indicating the possibility of malignant disease were detected by ultrasonography in all nine patients.

Discussion

Early detection of cholangiocarcinoma, while it is still in the resectable stage, is essential ,because complete resection is the most effective and curative treatment. However, the early diagnosis of cholangiocarcinoma is difficult, because the signs and symptoms of the disease are often nonspecific. Of 17 patients who were diagnosed to have occupational cholangiocarcinoma following employment at a printing company in Osaka, 11 patients were diagnosed on further examination after a regular health examination revealed abnormal findings on either laboratory tests or ultrasonography [2]. This demonstrates the importance of regular health examinations for screening and surveillance for occupational cholangiocarcinoma.

Exposure to organic solvents induced liver dysfunction in the patients diagnosed with occupational cholangiocarcinoma. In previous studies, pathological examinations of resected specimens demonstrated chronic bile duct injury and/or cholestasis due to cholangiocarcinoma [2, 4, 13]. In the current study, the serum γ-GTP activity was found to have increased several years before the diagnosis of cholangiocarcinoma. The serum ALT activity was also increased several years before the detection of cholangiocarcinoma, following an increase in the serum AST activity in most patients. As a result, the serum γ-GTP activity was elevated in all nine patients with occupational cholangiocarcinoma. These

findings suggest that the observed liver dysfunction might be related to chronic bile duct injury and that the development of precancerous lesions and/or cholangiocarcinoma was due to the exposure to chlorinated organic solvents. Therefore, consecutive assessment of the liver function with tests for AST, ALT and γ-GTP is useful for the evaluation of bile duct and liver injury, and for estimating the risk of cholangiocarcinoma during regular health examinations. However, these tests cannot detect cholangiocarcinoma itself, and are not a definitive method for diagnosing cholangiocarcinoma.

The serum concentration of CA 19-9 is elevated in 60-80% of patients with intrahepatic cholangiocarcinoma [5-7, 14-16]; testing the serum concentrations of CA 19-9 is currently widely used to detect cholangiocarcinoma, particularly in patients with primary sclerosing cholangitis (PSC), which is a risk factor for cholangiocarcinoma [14, 17-21]. It is also known that the serum concentrations of CEA are often elevated in patients with cholangiocarcinoma [5, 15, 16] and high serum concentrations of CEA suggest intrahepatic cholangiocarcinoma in patients with hepatolithiasis [22, 23]. In the current study, the serum concentrations of CA 19-9 and CEA were increased at the time of diagnosis of cholangiocarcinoma in three patients and eight patients, respectively. The serum concentrations of CA 19-9 and/or CEA were elevated in all nine patients at the time of diagnosis. This demonstrates that measurement of the serum concentrations of CA 19-9 and CEA is useful in indicating the possibility of cholangiocarcinoma.

In this study, abdominal ultrasonography revealed the gradual enhancement of the regional dilatation of the bile ducts before the diagnosis of cholangiocarcinoma in two patients in whom consecutive ultrasonography results were available. Ultrasonography detected abnormal findings (tumorous lesions and/or dilated bile ducts) in all nine patients at the time of diagnosis of cholangiocarcinoma. Thus, although it is difficult to use ultrasonography to obtain a definitive diagnosis of cholangiocarcinoma, ultrasonography is useful for screening and surveillance for occupational cholangiocarcinoma because of its high rate of detection of abnormal findings and its noninvasive nature.

For the surveillance for cholangiocarcinoma in patients with PSC, a combination of the measurement of the serum concentrations of CA 19-9 and ultrasonography or magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) is recommended [24]. Endoscopic retrograde cholangiopancreatography (ERCP) is reserved for patients with an increased serum concentration of CA 19-9 or imaging evidence of dominant strictures. For regular health examinations, noninvasive and cost-effective methods are preferred. The results of the current study demonstrate that a combination of ultrasonography and laboratory tests including the γ-GTP, AST, ALT, CA 19-9 and CEA levels is useful for screening and surveillance for occupational cholangiocarcinoma in workers who are exposed to chlorinated organic solvents.

For patients with PSC, measurement of the serum concentrations of CA19-9 and

ultrasonography at 12-month intervals is recommended for the screening and surveillance for cholangiocarcinoma [17, 24]. The incidence of cholangiocarcinoma seems to be higher in printing company workers (17 out of 101 workers in the offset color proof-printing department at the printing company in Osaka [2]) than in patients with PSC (their risk of subsequent development of cholangiocarcinoma was 0.5 - 1.5% per year [25, 26]). Therefore, health examinations with laboratory tests and ultrasonography at least every six months may be recommended for workers who are exposed to high concentrations of chlorinated organic solvents. When ultrasonography or laboratory test results are abnormal, computed tomography, MRI, and/or MRCP should be performed to detect possible cholangiocarcinoma. Furthermore, ERCP with biopsy and/or cytology, or a liver biopsy, is recommended to obtain a definitive diagnosis (Fig. 4). However, it is necessary to evaluate this strategy in a prospective cohort study.

The longest period between the end of the exposure to the chlorinated organic solvents and the diagnosis of cholangiocarcinoma was 12 years. Thus, it is necessary to monitor the workers long-term even after they switch jobs or retire.

In conclusion, regular health examinations with a combination of ultrasonography and laboratory tests including the γ-GTP, AST, ALT, CA 19-9 and CEA levels is useful for screening and surveillance for occupational cholangiocarcinoma in workers who are exposed to high concentrations of chlorinated organic solvents. Health examinations at least every six months, and for the long-term even after the discontinuation of exposure are warranted.

Acknowledgments

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Author contributions

Study design: SK. Acquisition of data: SK, ST, ST, TN, MK, GH, TI, MA, MA, KN, SH, AM, YO, and SK. Data analysis and interpretation: SK, ST, ST, TN, MK, and GE.
Drafting the manuscript: SK.
All authors reviewed the manuscript.

Conflict of interest statement: Shoji Kubo and co-authors have no conflicts of interest.

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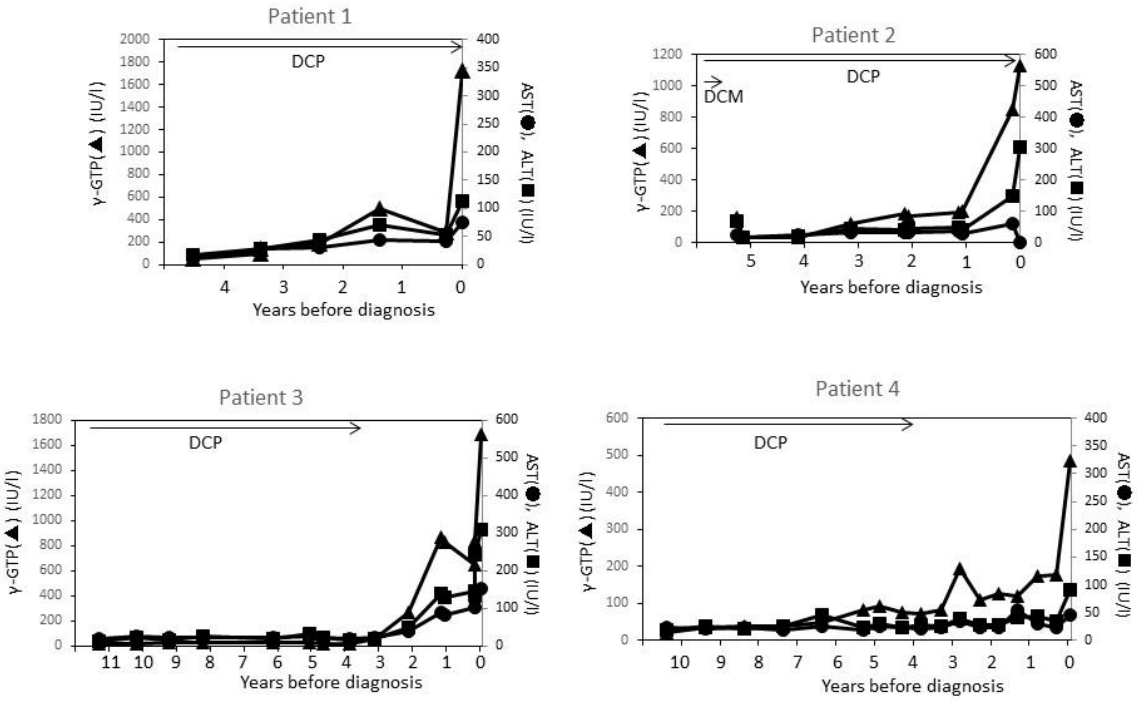
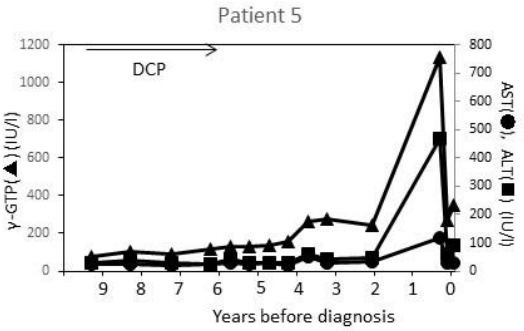
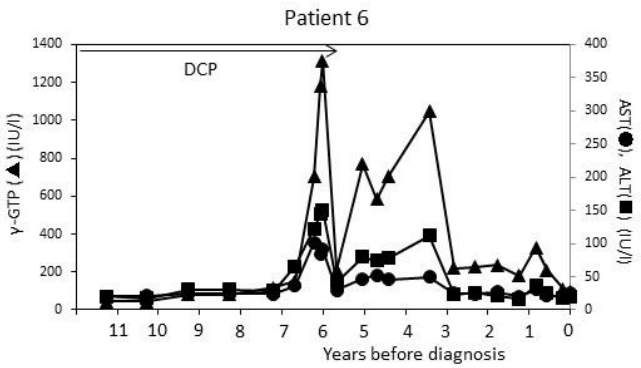
2004;99:523-6

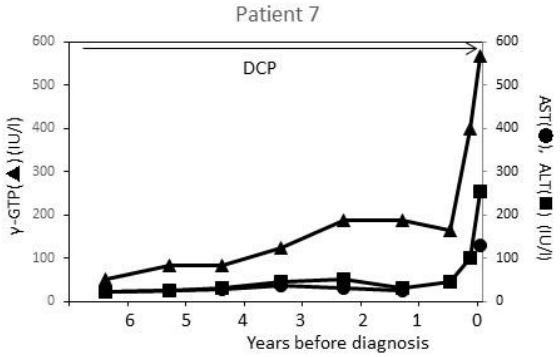
Figure legends

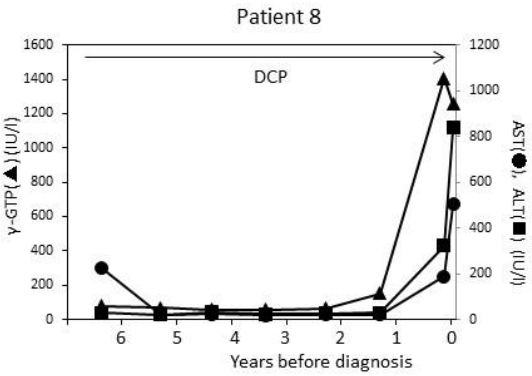
Figure 1. The changes in the laboratory test results before the diagnosis of cholangiocarcinoma.
A-C. Closed triangles show γ-GTP; closed circles show aspartate aminotransferase; closed squares show alanine aminotransferase. The arrows show the term of the exposure to 1,2-dichloropropane (DCP) and dichloromethane (DCM).




Patient 5
DCP
γ-GTP(▲) (IU/l)
AST(●), ALT(■) (IU/l)
Years before diagnosis


Patient 6
DCP
γ-GTP(▲) (IU/l)
AST(●), ALT(■) (IU/l)
Years before diagnosis


Patient 7
DCP
γ-GTP(▲) (IU/l)
AST(●), ALT(■) (IU/l)
Years before diagnosis


Patient 8
DCP
γ-GTP(▲) (IU/l)
AST(●), ALT(■) (IU/l)
Years before diagnosis

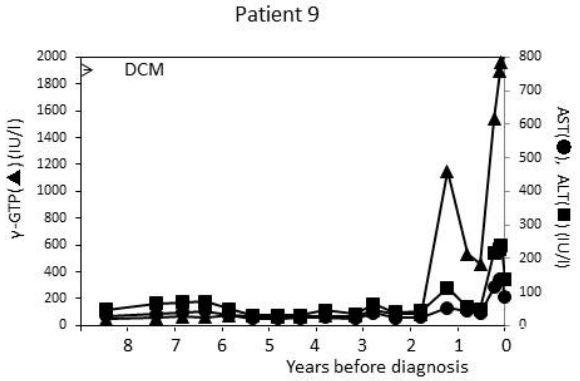

Patient 9
DCM
γ-GTP(▲) (IU/l)
AST(●), ALT(■) (IU/l)
Years before diagnosis

Figure 2. The changes in the findings of abdominal ultrasound studies before the diagnosis of cholangiocarcinoma in patient 5.

The times indicate the duration before the detection of cholangiocarcinoma. Short arrows show the regional dilatation of the bile ducts without tumor-induced stenosis. The long arrow shows a tumorous lesion in the bile duct with wall thickening (hyperechoic wall).

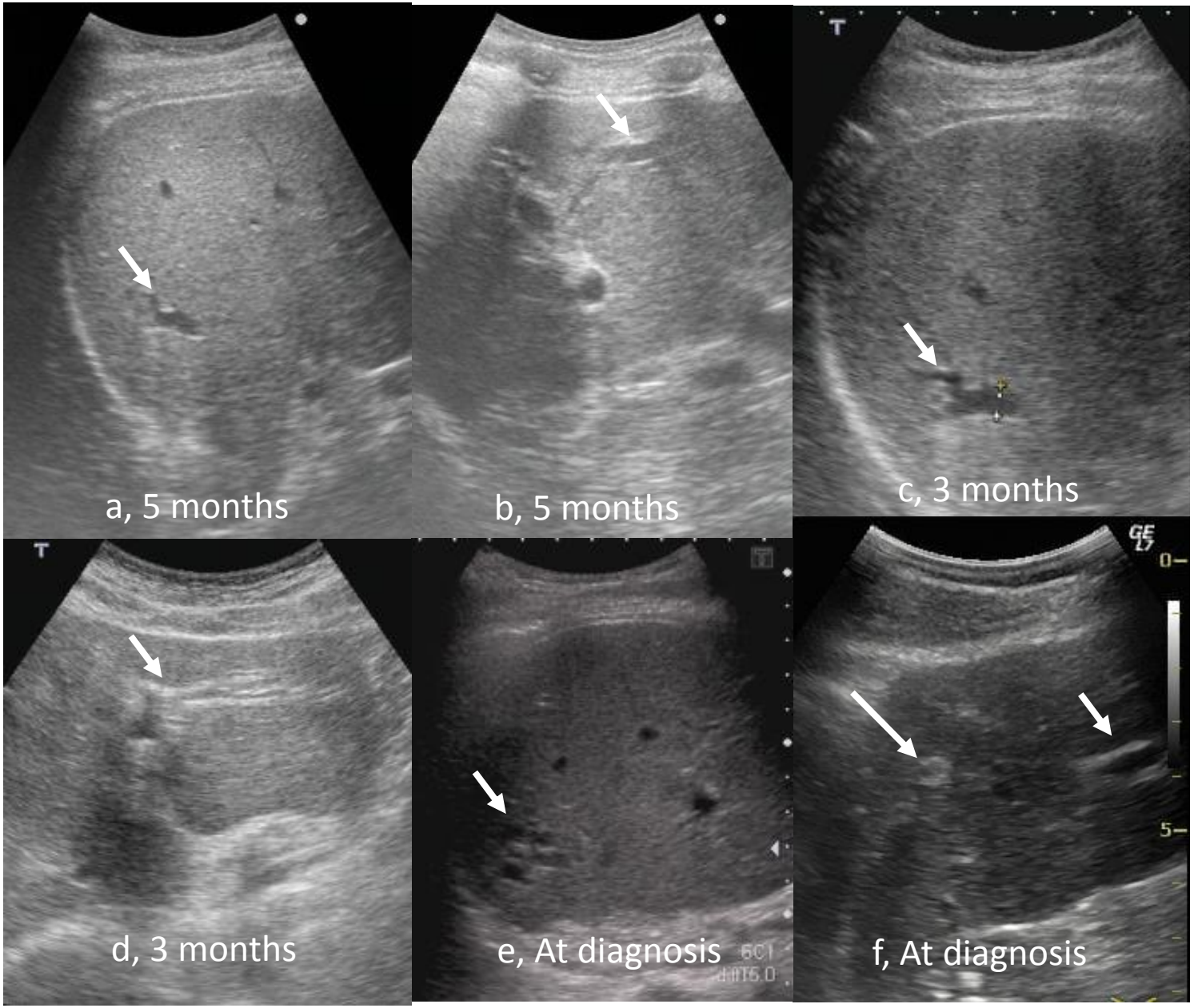

a, 5 months
b, 5 months
c, 3 months
d, 3 months
e, At diagnosis
f, At diagnosis

Figure 3. The changes in the findings of abdominal ultrasound studies before the diagnosis of cholangiocarcinoma in patient 6.

The times indicate the duration before the detection of cholangiocarcinoma. Short arrows show the regional dilatation of the bile ducts without tumor-induced stenosis. Long arrows show a space-occupying lesion in the liver. The dotted arrow shows dilatation of the bile duct due to tumor-induced stenosis. The arrow head shows lymph node swelling.

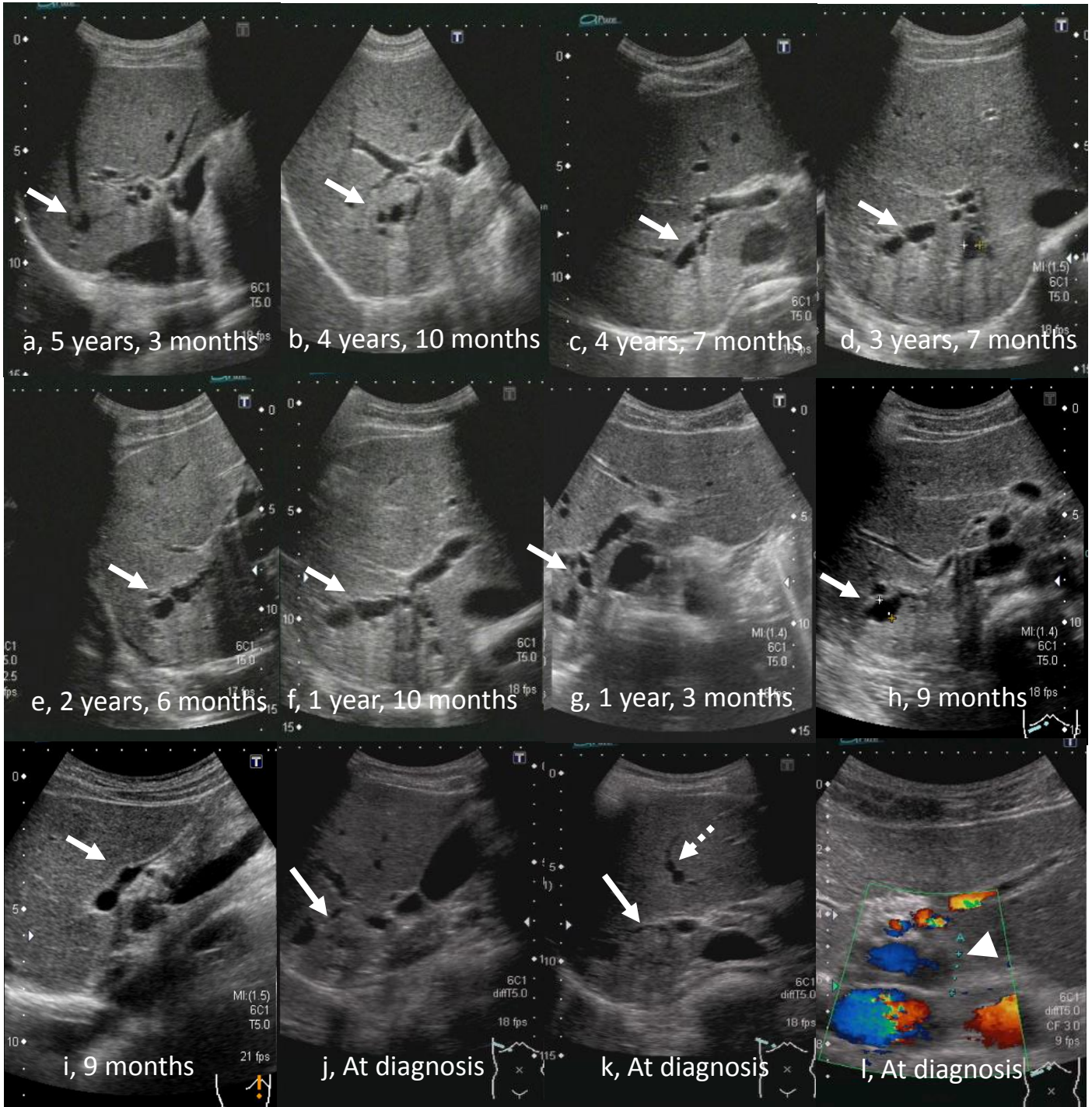

a, 5 years, 3 months
b, 4 years, 10 months
c, 4 years, 7 months
d, 3 years, 7 months
e, 2 years, 6 months
f, 1 year, 10 months
g, 1 year, 3 months
h, 9 months
i, 9 months
j, At diagnosis
k, At diagnosis
l, At diagnosis

Figure 4. The proposed program for the screening and surveillance for cholangiocarcinoma in workers exposed to chlorinated organic solvents.