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Efficiency of the confocal method of laser endomicroscopy in complex diagnoses of diseases of common bile duct

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Abstract. One of the more frequent manifestations of diseases of the bile ducts are its’ strictures or stenoses that could be of either malignant or benign nature. Current methods of diagnosing this pathology include computer tomography (CT) scan, magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP). However, these methods are not always informative, which makes this a current and topical problem.

A fundamentally new method that broadens the capabilities of ERCP when diagnosing diseases of the bile duct accompanied by the development of strictures or stenoses is probe-based confocal laser endomicroscopy (pCLE). The method is based on the principle of confocal fluorescence microscopy.

The most elaborate complications arise with the presence of the pre-existing pancreatobiliary pathology: pseudotumoral chronic pancreatitis, acute cholangitis, etc. Early stage cholangiocarcinoma diagnosis can be difficult (and not always possible) even with the help of modern research methods. For the timely diagnostic it is advantageous to conduct pCLE and targeted biopsy of the zone with most manifested changes.

In all instances, the first use of the pCLE method for diagnostic purposes allowed us to clarify and correctly verify the diagnosis.

When concerning the diseases of the bile duct, the modern stage of pCLE development can be of critical importance when other methods are not effective.

1. Introduction

One of the most prevalent manifestations of the bile ducts disease are their strictures or stenoses, which may have both malignant and benign nature and may be accompanied by the syndrome of obstructive jaundice.

The most frequent reasons of formation of strictures or stenoses of bilious channels are the following malignant diseases: cholangiocarcinoma, pancreatic cancer, cancer of a gall bladder. Occur among benign diseases: syndrome of Mirizzi, primary sclerosing cholangitis, autoimmune pancreatitis, iatrogenic intraoperative damages of bilious channels, strictures of a biliodigestivny anastomosis [1].
A.C. Burner et al., have analyzed these literatures over the last 10 years, chose 17 large publications including the description of 1556 cases of various diseases bilious ducts with the diagnosed stricture where the endoscopic retrograde cholangiopancreatography and a brush biopsy were a final diagnostic method [2]. Results of this research show rather low level of sensitivity – only 41%, and the prognosis of a negative outcome made 58% that allows to speak about need of further search of additional methods of intravitil bilious ducts diseases diagnostics which are followed by development of strictures or stenoses.

Malignant tumors of bilious ducts are the most dangerous and complex in timeous diagnostics. Cholangiocarcinoma (carcinoma of the bile ducts) is a relatively rare malignant tumor originating from mutated epithelial cells of the bile ducts, which in its histological structure refers to adenocarcinoma. In Europe and North America the incidence of cholangiocarcinoma is 1-2 cases per 100 000 population per year, but its level have been increasing for recent decades [3]. The tumor affects mainly extrahepatic bile ducts: 60-80% in the liver gates (Klatskin’s tumor) and 10-30% in the distal duct. Generally, cholangiocarcinoma develops on the background of primary sclerosing cholangitis (PSC), accompanied by ulcerative colitis. It is believed that the risk of cholangiocarcinoma increases with the following congenital cystic diseases: liver fibrosis, cystic enlargement of the intrahepatic ducts (Caroli syndrome), cysts of the common bile duct, cystic liver, microanatomy (complexes of von Meyenberg), as well as biliary cirrhosis [1]. At the same time, there is no specific factor in the anamnesis at most patients with a cholangiocarcinoma.

Some authors mark the fact that the risk of developing carcino of the extrahepatic bile ducts in 10 years or more after cholecystectomy significantly reduces, that may indicate the relation between the tumor and biliary stones [3, 4].

Timeous diagnostics of cholangiocarcinoma, even when it is possible to do a radical operation, represents certain difficulties and depends on the capabilities of available diagnostic equipment and the qualifications of diagnosticians. That fact that the early stage of a disease lack of any symptomatology and discovery of it is an fortuity, makes diagnostics more difficult.

In cases when the patient already has an accompanying pathology of pancreatobiliary area, early diagnostics of a cholangiocarcinoma is greatly hampered in consequence of the existing morpho-functional changes of this area, and also by focus of the doctor on the pathology established earlier.

Diagnostics at patients with a cholangiocarcinoma with suffering chronic pseudo-tumorous pancreatitis, a cholangitis, cicatrical strictures of extrahepatic bilious ducts is especially difficult, because in many cases one of components of complex treatment is endoscopic prosthetics or stenting of bilious ducts. The stent which is stays in a duct makes the capture of biopsy material for cyto- or histological research impossible without its preliminary removal. Besides, long-term presence of a stent in a bile duct necessarily causes visual and morphological changes of the epithelium, which complicates timely diagnosis of cholangiocarcinoma [2].

A number of authors believe that a long course of chronic indurative pancreatitis or sclerosing cholangitis in excess of 10 years, may be accompanied by the development of pancreatic cancer or cholangiocarcinoma [1, 4]. Surgical treatment of cholangiocarcinoma is ineffective, mainly due to the low accessibility of tumor and its late diagnosis. Most patients have recurrence to medical help at the stage when the tumor is inoperable, because in the early stages disease runs oligosymptomatic. In this case, the main methods of treatment are adjuvant chemotherapy and radiation therapy, palliative care. The argument in favor of endovascular and endoscopic interventions for inoperable tumors is the elimination of jaundice and itching from dying patients.

The methods and ways of diagnostics of this pathology including the spiral computer tomography (SCT), a magnetic resonance cholangiopancreatography (MRHPG), endoscopic ultrasonic research (EUZI), an endoscopic retrograde cholangiopancreatography (ERHPG) which are available now, but aren’t always informative, leaving a problem of early cholangiocarcinoma diagnostics actual and didn’t solved until the end. In this regard, the growing demand for new technologies with high reliability to detect pancreatic cancer or cholangiocarcinoma in patients with chronic pseudo-tumor-
like pancreatitis, cicatricial stenosis of the common bile duct and obstructive jaundice who had undergone endoprosthesis of the bile ducts.

A fundamentally new method which allows to expand the possibilities of diagnostic ERCP in diseases of the bile ducts, accompanied by the development of strictures or stenosis, is probe confocal laser endomicroscopy (Clem) (probe-based Confocal Laser Endomicroscopy – pCLE) [5, 6, 7]. This study is conducted using the device of Cellvizio®, developed by Mauna Kea Technologies (Paris, France).

The method is based on the principle of confocal fluorescent microscopy. At the fiberoptic probe is a transfer of laser radiation at a wavelength of 488 nm from a workstation. Falling on the biological tissue, a portion of the light is absorbed and laser-induced fluorescence effect causes the illumination of the tissue, which is identified by confocal microscope and processed by computer, allowing to obtain dynamic monochrome image with a frequency 11 Hz and with a resolution of 600 mkn. (figure 1).

![Figure 1. Scheme of Probe-based Confocal Laser Endomicroscopy (pCLE).](image)

Only certain tissues in living organisms possess autofluorescence. The main endogenous luminescing biological tissues include the following groups of substances: flavins, proteins and porphyrins. Each of the luminescing has a characteristic spectra for absorption and emission. Mostly they are concentrated in tissues rich in collagen and elastin that does not require the introduction of additional fluoresceins [8]. Epithelial cells of the gastrointestinal tract, as well as tumors do not have sufficient volumes of these structures, in this regard, the induction of fluorescence effect using parenteral administration of sodium fluorescein (Novartis) [9-14].

For investigation of the bile duct apply a probe of Holangioflex which resolving power reaches 3,5 mkn, and the optical field makes 600 mkn, with a depth of research of 0-50 mkn. After performance of ERHPG, the minisand is carried out on system of delivery to an interest zone. For this purpose use a catheter of "OASIS Wilson-Cook" with X-ray positive tags or its analogs. Just before the beginning of scanning enter sodium fluorescein in a dose from 0,5 to 1,0 ml.

Considering the low frequency (11 Hz) of change of a personnel, it is important to get a picture without blur effect, i.e., the moving speed of the probe relative to the tissue should be minimal. The study is a preliminary evaluation of data, with further detail when viewing recorded movies. Video analytics using the classification of microendoscopic images, which lay in the basic for the evaluation
of the shape, color, size, visible structures and estimation of dynamic components [15-17]. The following elements are important for an assessment of the endomicroscopic picture received at research of bilious ducts. Thin and light strips, mainly meet at bening whereas increase in their width testifies in favor of a neoplasia. Inflammatory changes are shown by numerous white strips, dark granular structures with the repeating deepenings, a thickening of strips of a reticular network.

As examples, showing the high diagnostic capability of the Clem method in the early diagnosis of cholangiocarcinoma or exception, against the background of other diseases of the pancreatobiliary zone, describe our own clinical observations.

2. Clinical observation

2.1. Clinical observation №1. Patient G., born in 1960, was observed in the Federal scientific clinical center of FMBA of Russia since 2005 courses of inpatient treatment in the departments of gastroenterology and surgery, with a clinical diagnosis of chronic pseudo-tumor-like pancreatitis. It is known from the anamnesis that at the beginning of 2005 the patient rubbed through pancreateonecrosis. In July, 2005 in connection with the stenosis of a duodenum which developed after the postponed pancreateonecrosis operation is executed: a laparotomy, a gastroenterostomy on a long loop with an interintestinal anastomosis according to Brown. On June 30, 2006 concerning mechanical jaundice ERHPG is made, symptoms of pseudo-tumorous pancreatitis, a prelum of an intrapancreatic part of the general bilious duct inflammatory infiltrate of a head of a pancreas, expansion of the general bilious and pancreatic ducts come to light. Produced biliodigestive endoprosthesis effect, the jaundice resolved.

During 2007 – 2010 years to the patient planned X-ray endoscopic interventions on replacement of stents, nazo-biliary drainage for the purpose of a decompression of biliary system were carried out. It should be noted that during the periods between hospitalization the patient did not keep to a diet, abused alcohol, did not accept the appointed drugs and refused possible radical operation (a gastropankreatoduodenalny resection). In October, 2010 there was a recurrence of mechanical jaundice in this connection, in a hospital on a sore point operation was executed: the laparotomy, external drainage of the general bilious duct, jaundice is stopped.

In 2010 - 2011 passed numerous hospitalization concerning chronic pseudo-tumorous pancreatitis, an acute purulent cholangitis, complex conservative therapy with an effect was carried out. In March, 2011 at control inspection considering categorical refusal of the patient of radical operation, short service life of plastic endoprosthesis in connection with their constant obturation biliary sludge and big losses of bile on the external drainage sick the nitinolous self-expanding stent of uncovered type with simultaneous removal of an external drainage from the general bilious duct (figure 2) was established. In May, 2012 in connection with recurrence of the mechanical jaundice caused by stent obturation a hyperplastic mucous membrane of the general bilious duct, to the patient it is executed transdermal and transhepatic external - internal drainage of the general bilious duct (figures 3, 4). When performing a fistulography and EGDS with survey of a big duodenal nipple there were suspicions on possible tumoral defeat of a distal part of the general bilious duct. The brush biopsy was executed, however convincing data were not received for oncological process.
For the purpose of clarification and possible verification of the diagnosis for the first time in Federal research and clinical centre of FMBA of Russia was used new method – Clem, which was mastered and implemented endoscopic service Center in 2011 with the aim of differential diagnostics of lung diseases.

Via the created duct of a hepaticocholedochostomy the flexible EB-530T endoscope is carried out. Via the tool channel of the endoscope by means of a miniprobe of "Cholangioflex" it is executed CLEM (figure 5) at which the hyperplasia of fabrics in the field of standing of a stent, and also signs of focus of a cholangiocarcinoma is revealed that it is confirmed with results of planned histological research after the executed biopsy (figures 6,7). The patient is advised by the oncologist, adjuvant chemoradiotherapy is appointed.

Considers himself ill since August 2013, when he first began to note pain in the right upper quadrant and epigastric, change in urine color, later came the yellowness of the skin. Was admitted to the hospital at the place of residence, the examination diagnosed with cholelithiasis, chronic calculous cholecystitis, stricture of the common bile duct. Routinely laparotomy, cholecystectomy, drainage of the common bile duct by Pikovsky. The postoperative period was uneventful, after removal of the drainage on the 9th day, patient was discharged in satisfactory condition. In November 2013 he had a relapse of jaundice, in connection with which the patient was performed percutaneous external-internal drainage of the bile ducts. Attempted ERCP at that time failed. Sent to Federal research and clinical centre for diagnosis and definition of further tactics of treatment.
At admission clinical laboratory tests within normal limits. Ultrasound of internal organs of the abdominal cavity from 30.01.2014: the condition after cholecystectomy. Diffuse changes of the liver and pancreas. Intrahepatic bile ducts not enlarged, increased echogenicity, visualized a single haplotype include "comet tail" – pneumobilia, in the projection of the right equity and the common bile duct – drainage. The diameter of the common hepatic duct 1.3 cm, walls thickened, low echogenicity, with irregular contours that do not allow the exclusion reprocess. Determined by a single reactive modified l/nodes in the course hepatoduodenal ligament. At the time of inspection free fluid in the abdominal cavity and the pelvis is not defined.

At gastroduodenoscopy, ERCP from 07.02.2014 g. revealed a long stricture of the common hepatic duct (figure 8), produced crustacea replacement percutaneous drainage of the bile duct. Conclusive for malignancy, compression from the outside is not received. The result of cytological examination number: 2013-19/14 (brush biopsy): clusters of cells are proliferating epithelium of the duct with a tendency to the formation of large papillotomy structures.

10.02.2014 was completed radial endosonography ULTRASONIC transducer, confocal laser endomicroscopy (figure 9). Confirmed cholangitis, reactive hyperplasia of the mucosa of the common bile duct, signs of neoplasia in the area of the stricture histological examination not revealed. In connection with the exception of cancer the patient was discharged from the hospital 11.02.2014. recommendation for readmission after 2 week in Federal Research and Clinical Centre for endoscopic stenting of the common bile duct.

2.3. Clinical observation №3. Patient Z., born in 1937, was hospitalized in the surgery Department, Federal scientific clinical center of FMBA of Russia 09.04.2013, for examination with complaints on a periodic aching pain in the epigastrium, heartburn, belching air, lack of appetite, weight loss of 7 kg over the last month, change the color of the skin 2 weeks before admission.

At admission the clinical picture of obstructive jaundice. Biochemical analysis of blood from 7.04.2013 g.: total bilirubin. 87.7 µmol/l, AST 405 U/l, AST 405 U/l, alkaline phosphatase 745 U/l, glucose 12.2 mmol/l Other changes in clinical laboratory tests no.

Ultrasound of internal organs of the abdominal cavity from 09.04.2013 g: the common bile duct is dilated at the level of the gate of the liver to 1.41 cm, in the region of the distal common hepatic duct is determined volumetric education up to 3.2 cm, decreased echogenicity, heterogeneous structure. Intrahepatic bile ducts are dilated to the level of subsegmental ducts. The gallbladder is enlarged, the lumen thick bile.
Figure 9. Dynamic monochrome microendoscopic the image with a picture of cholangitis and reactive hyperplasia of the mucosa of the common bile duct.

10.04.2013 was completed videogastroduodenoscopy, ERCP identified a biliary hypertension, signs of tumors of the common hepatic duct, taken by brush biopsy. With the aim of biliary decompression produced naso-biliary drainage of the common hepatic duct (figure 10). The result of cytological examination number:7317-20/13: expressed proliferation of epithelium of the ducts with formation of branching and papillary structures.

Figure 10. Cholangiogram made through nasobiliar drainage installed in the common hepatic duct. Identified during stucture the common bile duct.

When abdominal CT with contrast enhancement (12.04.2013,) and microcholangiography (16.04.2013) identify changes to best meet the neoplastic process of the common bile duct, signs of biliary hypertension. In order to clarify the diagnosis 26.04.2013 G. performed confocal laser endomicroscopy (figure 11). Revealed the formation of the common bile duct, solid structure, tight and rigid relative to the surrounding tissues during instrumental palpation, stenosing the lumen of the duct. Conclusion: visual and microscopic picture of the adenomatous structure with signs of malignization, most likely adenocarcinoma. The planned histological study confirmed the diagnosis of cholangiocarcinoma. Radical surgery because of severe concomitant cardiac pathology is not recognized by the portable produced endoscopic stenting of the common bile duct self-expanding nitinolous stent uncovered type. The patient was seen by oncologist assigned to adjuvant chemoradiotherapy.
Figure 11. Dynamic monochrome microendoscopic image: painting adenomatous structure with signs of malignancy.

3. Discussion

Most difficult diagnosis of malignant neoplasms of the bile duct on the background of already existing diseases of the pancreatoduodenal zone, for example, chronic pancreatitis. Hyperplastic (pseudo tumor) chronic pancreatitis occurs in 4-6% of patients with chronic pancreatitis. Complications of disease of this form happens in 30% of patients and develop approximately 7-15 years [1]. Sclerotic processes in the head of the pancreas lead to the clinical picture, resembling a compression of the ducts of the biliary tract and pancreatic duct (Wirsung duct). The violation of outflow of bile in such cases causes mechanical jaundice. In alcoholic and hereditary chronic pancreatitis there is a reaction of precipitation of calcium and proteins inside the pancreatic ducts. Normal precipitation is prevented PSP-proteins that are secreted arealine cells. The level of this protein in patients with chronic pancreatitis significantly reduced, thereby increasing calcium in pancreatic juice, its microcrystallization. In the lumen of the duct are formed calcification, plugging of ducts, there is a pressure increase in them. Ultimately, developing fibrosis.

In recent years, endoprosthesis of bile duct is widely used for the treatment of chronic pancreatitis complicated by development of stenosis of the common bile duct, obstructive jaundice. For the first time endoprosthesis of common bile duct produced by Soehendra and Reuynders Frederix in 1979 [4]. In the hands of an experienced endoscopist, this method did not seem so difficult, and its low injury rate and effectiveness make it attractive in clinical practice. Currently uses a variety of stents - nitinol self-expanding stents and plastic stents. The main disadvantage of the latter is high probability of obstruction of the prosthesis after 2-6 months after the setting as a result of deposition in it of salts of bile acids and bacterial films. To maintain their free clearance require regular remedial endoscopic lavage of the lumen of the prosthesis, which in the end does not increase their duration, but only allows you to save for a short time, their drainage function [2].

Self-expanding metal stents maintain patency longer than plastic, about 6 months or more. The use of metal stents is associated with a risk of germination hyperplastic tissue epithelial duct or a tumor that requires subsequent recanalization. Over time, standing uncovered biliary stent may be complicated by hyperplasia of the cuboidal epithelium of the common bile duct, leading to obstruction of the stent. To eliminate this effect use of covered nitinol stents, in which between cells sealed in a plastic membrane that prevents its germination. On this background, regardless of the type of stent cholangiocarcinoma diagnosis is delayed because of changes to the zones, technical difficulties in performing biopsies and orientation of doctors to another, previously established pathology.

The suspected cholangiocarcinoma occurs when unexplained etiology of biliary obstruction. Laboratory studies reflect only the degree of cholestasis. Diagnosis is based on ultrasound or CT. If these methods do not allow to verify the diagnosis, you must hold MRCP or ERCP with percutaneous transhepatic by cholangiographies. In some cases, ERCP not only diagnose the tumor, but also allows you to perform a tissue biopsy brush that provides a histological diagnosis without fine-needle biopsy
under ultrasound or CT scan. For diagnosis verification it is necessary to perform a biopsy with subsequent histological examination of the obtained material [1].

Applied in our clinical observations, the Clem method allows not only to clarify but also to verify the diagnosis when other modern diagnostic methods proved to be uninformative.

To date, there are only a few foreign works devoted to the method of Clem in the pathology of hepatopancreatoduodenal region. Three multicenter studies conducted in Europe and the United States demonstrated a high specificity 73-88% and sensitivity 83-97% intraductal the Clem for strictures of the bile ducts of unknown etiology [18]. Some foreign authors consider that at the present stage of development of the Clem diagnosis in diseases of the bile ducts may be critical for the inefficiency of other methods [5, 6].

4. Conclusion
Diagnosis of cholangiocarcinoma at an early stage of the disease even with the help of modern methods of research are complex and not always possible. The greatest difficulties arise in the development of tumors on the background of already existing pancreatobiliary pathologies: chronic pseudo-tumor-like pancreatitis, supplicative cholangitis, etc. For timely diagnosis appropriate to the conduct of the Clem and target biopsy of the area with the most pronounced changes. This clinical case shows the need for further controlled studies to determine specificity and sensitivity of the method, the Clem case of various pathologies of the bile and pancreatic ducts.

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