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DIAGNOSTIC DIFFICULTIES, REMISSION CRITERIA OF AUTOIMMUNE PANCREATITIS

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Autoimmune pancreatitis (AIP) is an inflammatory disease of the pancreas (PG) with the characteristic clinical, radiological, serological, histological features. In the pathogenesis of this disease the autoimmune mechanisms are involved. Currently, AIP is often considered as a part of systemic pathology, such as IgG4-related sclerosing disease, which becomes apparent through AIP, the sclerosing cholangitis, cholecystitis, sialadenitis, retroperitoneal fibrosis, tubulointerstitial nephritis, interstitial pneumonia, prostatitis, inflammatory pseudotumors and lymphadenopathy, associated with the increasing the titre IgG4 [1, 2, 3].

The peculiarities of the clinic symptoms of this disease are similar to those with the pancreas cancer, and it requires the differential diagnosis between these diseases. The correct diagnostics is essentially important, since AIP, in contrast to pancreas cancer, is the reversible process, and the treatment may be effective when using the steroid medicines. The retrospective analysis demonstrates how to perform the pancreatic duodenal resectionsin patients with AIP in connection with a suspected tumor of the pancreas. In the USA, for example, according to the results of histology after the pancreas resection, the AIP was retrospectively detected in 10–11% of cases [2, 4].

By the AIP the local affections, according to the computer tomography data (CT), are presented with the hypotension or isotention zone, localized mainly in the pancreas head. When contrasting these areas slowly increase the density and differ little from the cancer [5]. The surgical treatment is performed, because it is

completely impossible to exclude the pancreas or bile passages tumor. Analysis of the foreign clinics and Vishnevsky Institute of Surgery data revealed, that all pancreas resections, performed on the occasion of AIP, were accompanied by the greater technical complexity, blood loss, duration and the large number of complications in comparison with the operations concerning the pancreas cancer [6, 7].

In 2011 the AIP was included in the classification of chronic pancreatitis TIGAR-O, in 2007 — M-ANNHEIM as the separate item, because it has differences in the etiology, the courseand prognosis from the other forms of pancreatitis [8, 9]. The Japanese pancreatic society, Mayo Clinic, Korean pancreatologists proposed the diagnostic criteria of the AIP. In many countries the criteria HISORt are often used (Histology — histology, Imaging — imaging, Serology — serology, Other organ involvement — involvement of other organs, Response to corticosteroid therapy — response to corticosteroid therapy), proposed by Mayo Clinic. The latest revision was carried out in 2009 [2, 10].

The natural course and the long-term prognosis are not well studied yet. H. M. Kim et al. (2010), on the basis of analysis of the literature data for last 10 years, proposed to divide the remissions of AIP into 5 categories: 1 — symptomatic, 2 — serologic, 3 — radiological, 4 — histological, 5 — functional. By the symptomatic remission, the resolution of obstructive jaundice and abdominal pain syndrome occurs. The serologic remission means the normalization of serum IgG or IgG4. By the corticosteroid therapy, serum IgG4 decreases in all patients, but it does not always return to the normal level. By the radiological remission, the size of the pancreas reduces and the irregular narrowing of the main pancreatic duct takes place. The histological examination practically is not carried out for the estimation of the remission in the clinical conditions. By the functional remission, the restoration of exocrine and/or endocrine pancreatic functions occurs. The clinical complete remission includes symptomatic, serologic and radiological. The partial remission includes only 1 or 2 of these categories. The partial remission means the partial normalizationof each category [11, 12, 13, 14, 15]. By the AIP, the corticosteroid medicines are considered the first-line therapy. The dose and the duration vary in the

clinical centers, because the treatment protocol is not standardized. The dose of 30 to 40 mg per day during 1 month has become almost the standard for the inductionof the AIP remission. The symptomatic remission can occur during 2–3 weeks, and the achievement of the serologic and radiological remission takes from several weeks to months. By the ineffectiveness of the corticosteroid therapy, the immunosuppressants are used in the treatment of the AIP [16].

So, the AIP is the difficulty diagnosed and severe coursed disease due to low learning of it.

This publication presents the case of the three-year monitoring for the patient, suffering from the AIP, which clearly demonstrates the difficulties of diagnosis and treatment.

The patient G., 56 years old, was examined in the department of the pancreas pathology of CRIG in 2009, 2010, 2011 years. The last hospitalization was from 29.03 to 12.04.2012.

From the anamnesis we know that she has been illsince January 2009, when the first persistent moderate pains in the right upper hypochondrium and weakness appeared. By April 2009 she noted the decrease in body weight of 10 kg, the onset of nausea, bitter taste in the mouth, the periodic vomiting the eaten food, the increased weakness, and therefore she was hospitalized to the CCH of MP St. Aleksiy. By the ultrasonic scanning, the diffuse enlargement of the pancreas size was revealed: 40-25–30 mm, the moderate dilatation of the intrahepatic ducts, and the thickening of the gallbladder walls up to 6 mm. The increase of aminotransferase up to 9–10 norms drew attention in the biochemical analysis of blood. On the basis of the performed examinations the diagnosis was given: the exacerbation of the chronic pancreatitis.

In May 2009 the icteritiousness of skin and sclera appeared, and the patient was again hospitalized. Considering the ineffectiveness of the performed therapy, on the 20th of May, 2009 the patient was underwent the operation — the formation of cholecystoenteroanastomosis and enteroenteroanastomosis. In the biochemical analysis bilirubin decreased from 216.1 μmol/l (direct 108.7) to 70.4 (direct 33.9), ALT decreased from 137 u/l to 79, AST — from 104 u/l to 55.

After the discharge, the patient continued to have jaundice, itching, weakness. 29/07/09 she was hospitalized to the Vishnevsky Institute of surgery. In the blood analysis it was noted leukocytosis to $22.5x10^9$/l, the ESR increase up to 37 mm/h, the increasing glucose to 7.45 mmol/l, AST — 203 u/l, ALT — 162 u/l, ALP — 2160 u/l, and other parameters and tumor markers CEA, CA 19-9 — within limits. According to data of the abdominal cavity ultrasonic scanning, the dimensions of the pancreas were 37x15x21 mm, the zone of low echogenicity in the pancreatic head, the biliary hypertension, the diffuse changes of the pancreas and the liver were detected. The CT of the abdominal cavity did not confirm the pancreas tumor. It was noted the diffuse dilatation of the pancreas, main pancreatic duct (MPD) was not observed. The MRI of the abdominal cavity revealed: the CP signs, the difference between the areas of the inflammatory infiltration and tumor, the symptoms of chronic cholangitis and extensive stricture of the intrapancreatic part of hepatic choledoch. It was performed the endoscopic ultrasonography (EUS) to make the differential diagnosis between autoimmune pancreatitis and the pancreas tumor, accompaniedby the total affection of the organ. The fine-needle aspiration biopsy of the pancreas head was done. According to the cytology examination data, there were numerous red blood cells, the elements of inflammation, the crystal-like structures, the fragments of fibrous tissue, the cells of the ductal and glandular epithelium without peculiarities. The tumour affection was not revealed in the examined material. It was performed the endoscopic retrograde cholangiography, the papillosphincterotomy, the balloon dilatation of the walls of the terminal part of the choledoch. The biopsy from the terminal part of the choledoch: there were small fragments of glandular epithelium with no signs of atypia, with the chronic inflammatory infiltration and the surrounding blood clots and fibrin. The ultrasonic scanning of the pancreas revealed: the diffuse goiter, the massive formation of both lobes and isthmus. When copying ESR, the white blood cells and glucose levels normalized, other indexes decreased: AST — 174 u/l, ALT — 182 u/l, ALP — 746 u/l. The patient was discharged with the diagnosis: Chronic autoimmune pancreatitis. There were observed in the patient the stricture of the terminal part of the choledoch,

the chronic recurrent cholangitis, the biliary hypertension, the overlay of cholecystoenteroanastomosis on 20/05/09, the insular diabetes of the specific type, the diffuse goiter grade 3.

According to the CT data of the abdominal cavity from 09/01/09: the hypotension zone (bezelHalo) was present along the outline of the pancreas. When contrasting, the density gradually increased with the highest figures during the venous phase of the examination. MPD was partially traced. Common bile duct (CBD) was dilated up to 13 mm, in the intrapancreatic part — 7 mm. 29/09/09 the patient was hospitalized to CRIG to decide on the feasibility of steroid therapy. In the blood analysis it was noted the increase in total bilirubin up to 84.8 μmol/l, direct — up to 48 μmol/l, AST — 247.1 u/l, ALT — 211.5 u/l, ALP — 1543.8 u/l, GGT — 831.3 u/l, glucose — up to 8.1 mmol/l, ESR up to 36 mm/h, IgG4 — 2.8 mg/ml (norm 0.08–1.4). Considering the clinical symptoms of the disease, the data of the pancreas visualization, the results of the serologic examinations, the involvement of other organs (chronic cholangitis, accompanied by stenosis of choledoch in the intrapancreatic part), it was decided to hold the corticosteroid therapy. The availability of insular diabetes of the patient determined the addition to the treatment of the short-term and intermediate-term acting insulin using the control of blood glucose during the steroid therapy. The initial dose of prednisolone was 0.6 mg per 1 kg of body weight (under 50 kg) — 30 mg/day with the following reduction during the 30-day period to 5 mg and the cancellation of the drug in 1.5 month.

18/11/2009 the patient was hospitalized to the Vishnevsky Institute of surgery with the clinical improvement to remove the stent and to evaluate the state of the duct system. The MRI revealed the slight negative trend in the form of narrowing of the intrapancreatic part of the hepatic choledoch, the proximal part was dilated up to 1.2 cm. In the intrapancreatic part, the hepatic choledoch was narrowed to 0.4 cm and then over the distance of 2.0 cm to the zone of the major duodenal papilla (MDP) was not traced. 27/02/10 the patient was hospitalized to the CRIG with complaints of weakness, mild pains in the right upper hypochondrium. When performing the EUS, CBD lumen was visualized throughout and free, the CBD walls were significantly

thickened all the way along up to 7–8 mm, hypoechoic with hyperechoic internal lining, the CBD lumen was from 7 mm on average to 1.0 mm in the distal section. The MPD walls were irregularly thickened from 1.0 to 3.5 mm, the lumen was from 2.0 mm in the proximal part to 1.0 mm in the distal section (fig. 1, 2, 3). In the analysis of blood the increase of indexes continued: AST — 128 u/l, ALT — 113 u/l, ALP — 709, GGT — 503 u/l, glucose — 6.8 mmol/l. Results of immunological test were: IgG1 — 18 mg/ml (norm 4.9–11.4 mg/ml); IgG2 — 12.4 mg/ml (norm 1.5–6.4 mg/ml); IgG3 — 2.8 mg/ml (norm 0.2–1.1 mg/ml); IgG4 — 2.0 mg/ml (norm 0.08–1.4 mg/ml). Considering the negative trend according to the EUS data (the narrowing of the distal section of the choledoch to 1 mm), the continuing increase of immunoglobulin G, it was decided to course the treatment with infliximab at a rate of 5 mg per 1 kg of body weight and with ursodeoxycholic acid (UDCA) at a dose of 750 mg/day. Once, 300 mg of infliximab were injected intravenously by drops in the physiologic saline. The patient was recharged with the recommendation of the subsequent hospitalization to CRIG for the purpose of re-injection of infliximab. But later, the patient fell ill with acute bronchitis, and then by the examination of the external respiration function, it was noted the decrease of the pulmonary ventilation capacity due to malfunctions of the restrictive type, which was estimated as the clinic functional symptoms of the chronic obstructive bronchitis, and therefore it was decided to abandon the re-injection of infliximab. According to USS data of the abdominal cavity the negative dynamics of the hepatobiliary systemwas not revealed, the pancreas was of normal size, the MPD was traced in diameter up to 2 mm. It was recommended to continue taking UDCA.

In May 2011 there was the next hospitalization to CRIG. The weakness and the pains in the right upper hypochondrium continued. The indexes were the following: IgG4 — 2.0 mg/ml (norm 0.08–1.4 mg/ml), the levels of ALT and AST — 4 norms, GGT and ALP — 5 norms, glucose — 8.62 mmol/l. According to the EUS data there was no significant dynamics in comparison with the previous analysis. Considering the remaining symptoms of the autoimmune pancreatitis and cholangitis, according to the EUS, the high level of IgG, it was decide to add to the treatment azathioprine at a

rate of 3 mg per 1 kg of body weight (50 mg 3 t/day). Hereinafter the patient took the medicine for 6 months, and then in April 2012 she was hospitalized to the department of the pancreas pathology of CRIG again.

On the admission she complained of the pains in the right upper hypochondrium, increased after eating, bloating, shapeless stool 1–2 times, rarely — constipation, weakness, increasing to the evening.

By the objective examination, the painfulness was noted during the deep palpation in the right and left hypochondria. When performing the laboratory and instrumental analyses, it was noted the significant improvement of indexes: ALT — 33 u/l, AST — 63 u/l, GGT — 68 u/l, ALP — 336 u/l, glucose — 7.0 mmol/l, AMA M2 — 1.7 (norm 0–20 U/ml), ANA — 0.4 (norm less than 1.0), IgM — 115 (norm 50–130), IgG — 1610 (norm 750–1300), IgA — 158 (norm 90–230), IgG4 — 1.8. According to the EUS data there was the positive dynamics: the intrahepatic bile ducts were not dilated; CBD — all over with the thickened walls maximum up to 3–5 cm, the lumen in the proximal section was 2 mm, in the middle part — 9 mm, then narrowed down to 2–3 mm, the internal lining of the walls was hyperechoic, in the lumen of the proximal section of the CBD was gas, the pancreas — the parenchymal echogenicity was diffusely reduced, Wirsung’s duct walls were not thickened, the lumen was 2.5–3 mm in diameter and free.

Thus, against the background of cytostatic therapy, the positive dynamics is noted — the general state of the patient improved, the pain syndrome decreased. According to the EUS data, the thickness of the CBD and MPD walls decreased slightly. The MPD was traced all over the length. The pancreas size was normal. There was the significant improvement of biochemical indexes: ALT, AST, GGT, ALP. The level of IgG4 decreased, but not normalized. The dose of azathioprine was reduced to 100 mg/day (2 mg per 1 kg of body weight), such dose the patient takes to the present.

In this case, the partial remission was achieved, as the partial normalization of the clinical, serologic and radiological indexes.

The given case shows the difficulties of diagnosis in the early stages of the disease, when the surgical intervention was performed for the treatment of obstructive jaundice in the AIP patient — the overlaying of cholecystoenteroanastomosis and enteroenteroanastomosis, because of the suspecting of tumor. To diagnose the AIP, the number of the instrumental analyses was done (CT, MRI, EUS) in the dynamics and the serologic tests. The results of the cytology did not allow making a diagnosis, but excluded the presence of the pancreas tumor. The use of steroid therapy did not lead to the remission, and the partial remission was achieved only due to the appointment of cytostatic medicines.

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Diagnostic difficulties, remission criteria of autoimmune pancreatitis

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The paper describes a clinical case in a 56-year-old female patient who has been suffering from chronic autoimmune pancreatitis, chronic recurrent cholangitis for three years. It demonstrates diagnostic difficulties at the early stage of the disease, the specific features of its course, the sequence of treatment in the patient, and problems in choosing a therapy option to achieve a remission.

Examination data of the patient G., 56 years

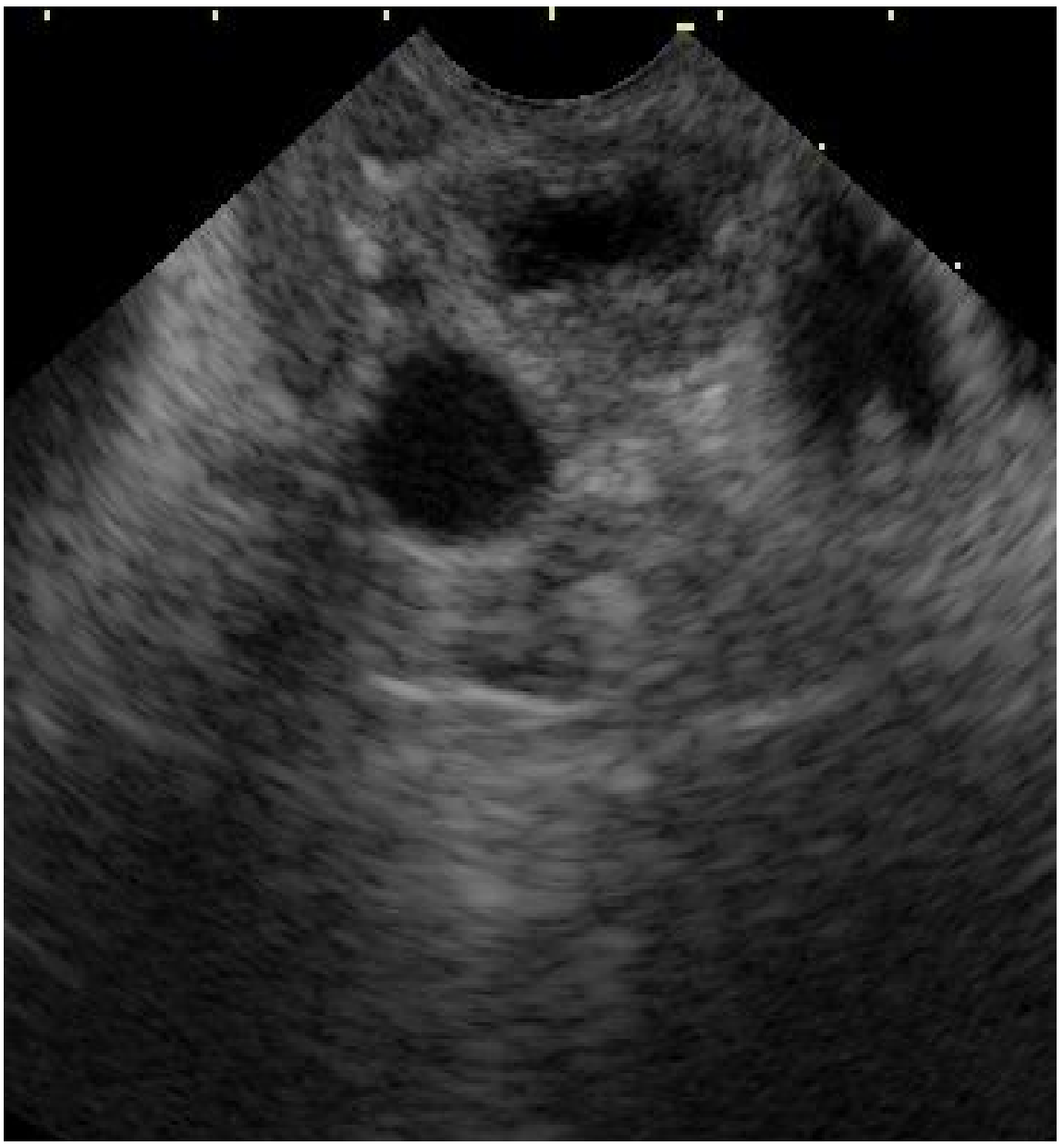

Fig. 1. CBD wall thickening

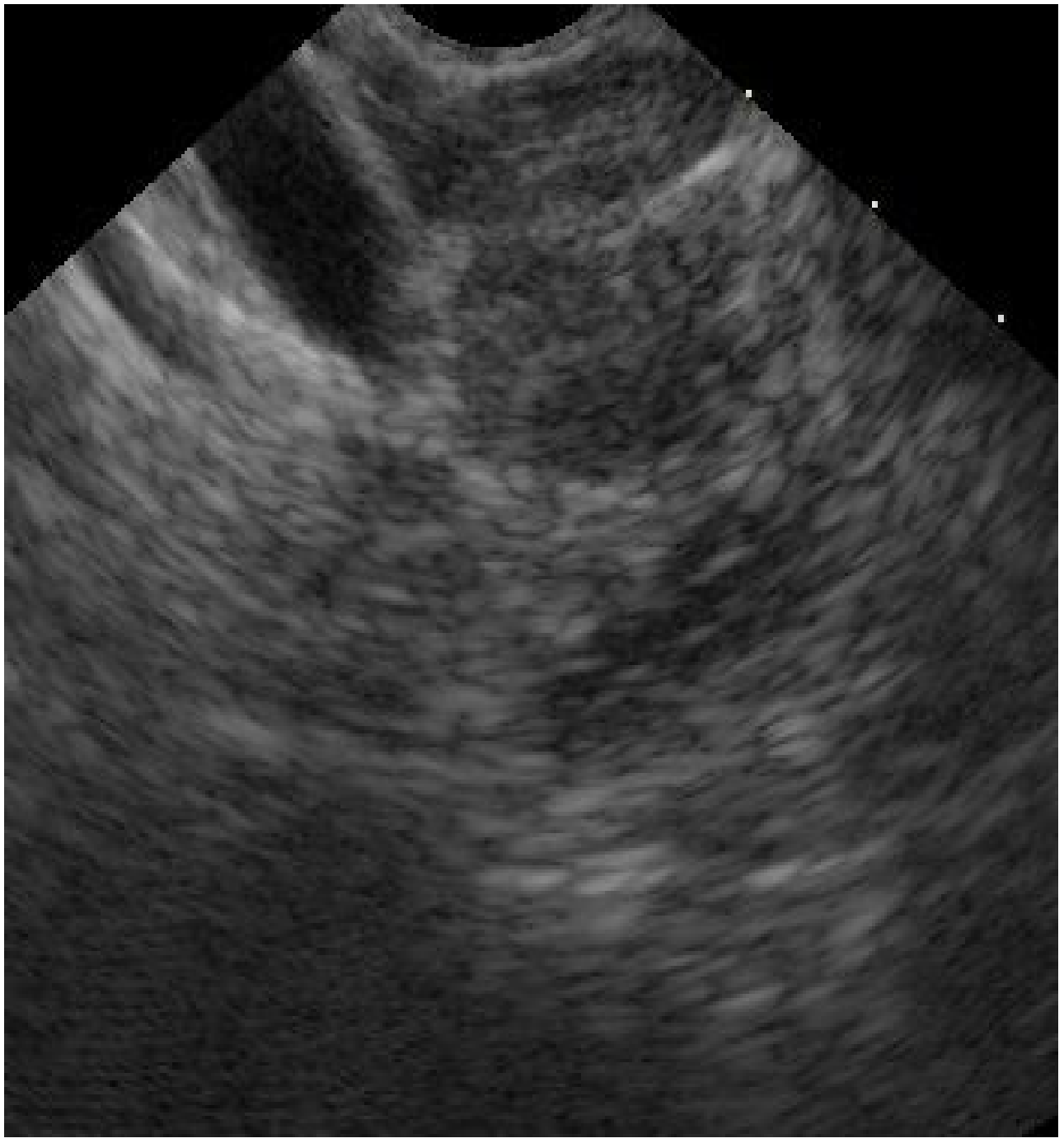

Fig. 2. Narrowing of CBD distal part

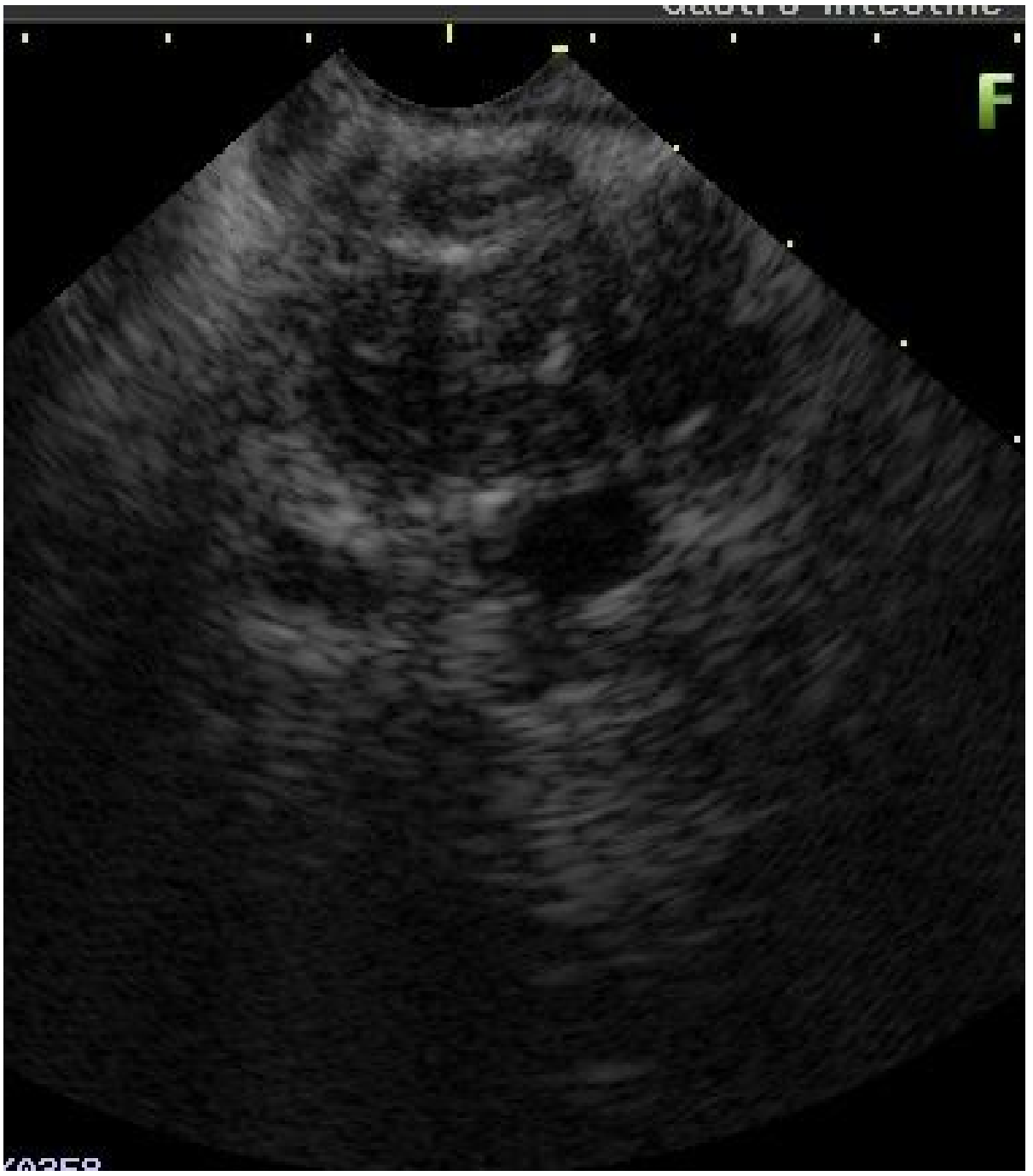

Fig. 3. Hyperechoic lining areas of MPD and CBD