Hereditary pancreatitis: tactics of diagnostics and differential diagnostics (clinical case)

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Heredity is the omnibus, in a torus of us accompany our ancestors; every now and then someone of them put out there, stunning us with their appearance

Oliver Holmes,
American writer

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Among the many etiological factors that cause pancreatic pathology, perhaps the least studied is heredity. A number of diseases of the pancreas are associated with a genetic predisposition. But the main ski caused by genetic e not endocrine organ diseases cystic fibrosis believe, hereditary pancreatitis (HP) and hereditary pancreatic cancer. Not randomly on the Midwest logo Mult i center Pancreatic Study Group, created for the comprehensive study of hereditary pathology of the pancreas gland (epidemiology, pathogenesis, clinical manifestations, prognosis, etc.), these three diseases are indicated (Fig. 1). Furthermore they are inherited as: Shvahmana syndrome, Johanson-Blizzard syndrome, congenital e constant prices sideroblasticheskaya anemia with exo to rinnoy insufficiency of the pancreas, Clarke-Hedvilda syndrome, Andersen's syndrome, izolirovan Nye insufficiency separate pancreatic enzymes (lipase, kolipazy, amylases, trypsinogen), a syndrome of enterokinase deficiency, macroamylasemia, α_1 deficiency -antitrypsin, and other [16]. Of course, genetically determined are also the malformations of the development of the pancreas: pancreas divisum, pancreas annulare, pancreas aberrans, congenital e ki nnye with you RV et al. [7, 8, 24].

Let's stop at the NP. For the first time NP was described by M. W. Comfort and A. E. Steinberg in 1952, which examined about a hundred families in the different countries of the world (most examined were Caucasians, but Asian and East Indian residents also included in one district the observations). They noted that the NP is an autosomal dominant mode of inheritance with incomplete

penetrance s w (about 80%), m. E. Probability manifestations of the disease with the appropriate genetic predisposition for STI [24].

However, before the exact explanation of the pathogenesis of the TM, there were assumptions about the relationship of the disease with the hereditary pathology of the ducts. According to this hypothesis, the anomalies of the duct system of the pancreas are primary, and the development of pancreatitis is secondary (due to a violation of the outflow of pancreatic secretions). This hypothesis was based on the fact that changes in the duct system of the pancreas are often detected in the NP. DEF is also put forward thetheory and QUO antioxidants in pancreas tissue, according to which primary importance in the pathogenesis and DIDP valos oxidant stress [7, 8, 16].

In 1996. D. C. Whitcomb et al. gene on those developed tory explaining the development of NP and linking it with a mutation of the gene encoding three sinogen claim[19]. Tion and associative NP gene with a mutation in the long arm of chromosome VII (7 q 35) was shown to inheritance relationship of NP specific markers of known chromosomal loci proved. With this mutation proish dit replacement of arginine for histidine at position 117 of the molecule trypsinogen — R 117 H (for n o howling nomenclature — R 122 H) [5, 7]. The proof of a genetic predisposition to the development of pancreatitis in 5% of cases has found its reflection in the e classification of risk factors for chronic pancreatitis — in the classification of TIGAR — O. In this abbrevi a round letter «G» stands for «genetic» [14]. NP stands out also and at tion and classification M — ANNHEIM ("H -" hereditary ") [29]. O ne of the genetic predisposition is usually not enough for the development of pancreatitis — ating in and needs an external factor (often used zloupotreLenie alcohol, biliary pathology, viral infection, and others.), Promoting e Manifa habitats disease. Of course, genetic predisposition is the basis for a more likely development of the same alcoholic pancreatitis [24]. NP is equally common in men and women, has no differences of race and depending on the [7, 8, 16].

Later, mutations of the serine — protease inhibitor Casal type I (SPINK I) in patients with idiopathic chronic pancreatitis, about half of the cases of tropical pancreatitis and part of the bladder of idiopathic chronic pancreatitis with the mutation SPINK I (No. 291) [13, 17, 21, 22, 25].

At present, it can be assumed that a wide range of possible associations gene on the type / phenotype NP BK and Luciano direct autosomal domi nating features of the disease with five hours of full penetrance Stu (dominant gene mutation PRSS1), and "soft" genetics cal risks without evidence of Mendelian heritage of

Bani (gene mutationsSPINK I and trans — membrane controller cystic fibrosis (CFTR), chymotrypsinogen (CTRC), etc.) [4, 18, 26, 30].

Given that the pancreas synthesizes a variety of digestive enzymes, there are a number of duplicating mechanisms that prevent autolysis of the organ tissue (Figure 2) [8,27] :

– production of enzymes of the pancreas in inactive form (in the form of proenzymes);

– separation of products in the space processes and activation of enzymes (in dven and dtsatiperstnoy intestine under the action of enterokinase);

– localization of enzymes in the zymogen granules of acinar cells, preventing s in the course of the enzymes in the cytoplasm;

– low concentration of calcium ions in the cytoplasm of acinar cells, as a result of which the probability of activation of trypsinogen decreases;

– secretion of SPINK I ;

– the ability of the enzymes of the pancreas to autolysis;

– Products α_1 -antitrypsin and α_2 -microglobulin in the liver, binding of providing activated pancreatic enzymes in the blood and Perithia nealnoy of liquid.

Basically, any mutation of the gene encoding the pancreas self-defense mechanisms, m about Jette lead to the development of pancreatitis with external triggering factors.

Let us analyze in detail the pathogenesis of NP associated with the mutations R 122 H and N 291. Trypsin molecule composed of two subunits joined e nGOVERNMENTAL polypeptide chain (Fig. 3). At position 117 of this chain is arginine. Between the two subunits three sina n is an active center which is capable of recognizing arginine and lysine and implement the location of the connection of these amino acids is the lysis of the polypeptide chain. That m and Kim manner trypsin mezotripsin Y and enzyme inactivated 80% intrapancreatic trypsinogen and trypsin [8, 28]. The remaining 20% inactivation intrapancreatic prot e az provided SPINK I (Figure 4). This inhibitor is a specific su b striations for trypsin. SPINK I irreversibly binds trypsin serine to lysine in its acti Foot center. It is important that SPINK I is synthesized in an amount 20 times smaller than the amount of trypsinogen produced by the pancreas. In this regard, SPINK I can completely inhibit trypsin of Vat in body tissue only when the level of activity of trypsin low. In these cases, SPINK I prevents the subsequent autoactivation of trypsinogen and blocks the cascade of activation of pancreatic enzymes and autolysis of the pancreas (Figure 5). With intensive activation of trypsinogen SPINK I not able to it ina-activated. In this case, trypsin and other trypsin-like enzymes as described above, are lysed polypeptide chain obedinyayusch th 2 subunit of trypsin, at

position 117, ie. E. At the junction of a p ginina and lysine. When mutation of cationic trypsinogen R 122 Harginine is replaced by gi with tidin, so trypsin is not capable of lysing the molecules of trypsinogen and trypsin. Mo ni Nosta SPINK I in these cases is not enough to block the autoactivation of trypsinogen, the cascade of activation of pancreatic enzymes and the autolysis of the pancreas are continuing [8, 16]. With the mutation SPINK I (N 291) reduces the degree of inactivation of trypsin and when exposed to powerful provoking F torus (alcohol) also develops NP (Fig. 6).

NP is divided into:

1) classical (autosomal dominant, with penetrance 80%, gene cationic three n sinogen PRSS1, R122H, N291) ;

2) idiopathic.

Separately isolated special forms of OP: pancreatitis giperamino tsiduriey and (e isolated with amino acids of the urine as a result of a genetic defect tubular); gemorragiche sky pancreatitis with increasing separation of electrolytes through sweat; pancreatitis due n ny violation of calcium metabolism.

In connection with new ideas about the role of gene mutations in the pathogenesis of chronic pancreatitis, it can be assumed that the two leading forms of idiopathic pancreatitis — with an early and late onset — are due to different genetic mechanisms. Moreover, the version with a late start can be modified by environmental factors, such as, forexample, alcohol. In accordance with this hypothesis, it is possible that among alcoholics, chronic pancreatitis develops only in people with a genetic predisposition for Stu to this pathology. This assumption is confirmed by the fact that alcohol xp about nical pancreatitis is diagnosed in only a small portion of people who abuse alcohol. This agrees with the fact that the clinical manifestation of the proven NP appears usually in Raste of 3-10 years and has a second peak at the age of 20-25 years, when most patients start with e m of alcohol [6, 8, 16].

In the development of the NP, the value of other mutations has been proved [18]. Particular attention is paid to the mutation of CFTR — gene trans from the membrane regulator of cystic fibrosis. This mutation and mutation SPINK I are inherited by autosomal recessive type. If a patient has a CFTR mutation, flour develops about viscidosis or genetically determined hypoenzymatic pancreatitis. Such an option is also possible in case of insufficiency of production and violation of activation of three n synogenes [16].

Identification of NP by traditional methods is impossible, since there are no specific morphological and biochemical markers [5]. When examining each patient, it is necessary to carefully collect the anamnesis, take into account

heredity, nicotine-alcoholic hung and bridge, weight loss. Although NP is characterized by an early onset (in 80% of patients falls to the age of up to 20 years), but almost always — late diagnosis, the formation of calcification of the pancreate form (in 50% of cases (Figure 7)), pseudocyst.Its initial manifestations are similar to the clinic of acute pancreatitis. Typical repeated episodes of abdominal pain and dispep t nical syndromes with a gradually increasing frequency and severity of relapses, increase of degree tional functions of RV failure (15-20% of patients revealed marked steatorrhoea), resulting in the development of chronic pancreatitis. But with the passage of time, an increase in the duration of remission is characteristic of NP. In the late stages of the disease, diabetes mellitus develops (joined after 8-10 years in 20% of patients), thrombosis of large veins (portal, spleen, nocturnal, lower hollow), hemorrhage [8, 23]. Pancreatic attacks with NP not ex and are not similar to other forms of chronic pancreatitis. However, recent studies proof and if that can not be considered abuse of alcohol or the presence of cholelithiasis factors, and we conclude with the NP. This suggests that the change in trypsin is only a background. Mut and tion does not lead to increased activation of trypsin, but only violates one of the protective fur-organisms and acinar cells. For the occurrence of the disease, the onset of clinical symptom of the MoU needed initiate factors that vyzv and Would this activation.Therefore, verification of the mutation of trypsinogen with the help of sex and a merase chain reaction is necessary to verify the diagnosis of NP [2].

Eneticheskо e r e test for suspected NP allows [14]:

✓ determine whether kationicheskogo trypsinogen mutation is indeed the cause of isolator ment and pancreatitis;

✓ justify the symptoms of patients;

✓ to carry out early diagnosis of NP in children for further rational tactics of monitoring them ;

✓ to determine the degree of risk in the patient's relatives;

✓ APPLY be a preventive therapy w th: lifestyle changes to reduce the risk of possible development of pancreatitis.

Other methods of diagnosis of NP are traditional for the verification e Skog chronic pancreatitis at all.

One of the main dangers of NP is a sharp increase in the risk of developing RV cancer. Thus, the epidemiology of NP was studied in two independent studies in the US and Europe, which revealed an increase in the risk of developing RV cancer in NP patients by 50-70 times. These studies were based on the databases of the International Hereditary Pancreatitis Study Group and European register NP and cancer RV (EUROPAC — European Registry of Hereditary Pancreatitis and

Pancreatic Cancer). The risk of pancreatic cancer and povysh etsya, since 40 years, and up to 40-70% at age 70 (especially if the NP is traced through the male line). In most cancer Global Developing a camping infamilies with mutations 122 R H, N 291 or without mutations, but with obvious NP phenotype [16].

At the same time, in genetic studies of patients with NP, no changes in oncogenes or tumor suppressor genes have been detected [32]. This suggests that the cause of the incidence of RV cancer in the IR is a higher level of activity of the inflammatory process and its longer duration. This extra argument for the fact that the very chronic inflammation is a predisposing factor ra of Vitia pancreatic cancer. Probably has a value of duration of the inflammatory process, otsuts m Wier causal therapy for NP. In other studies, in contrast, show a but that the pancreas carcinoma that developed as a result of the NP, the mutation of the oncogene K — ras are found in the cells swelled to whether, and in areas adjacent to its tissues, as well as NP zones epithelial hyperplasia Archpriest of Cove [3, 15]. Mutations of oncogenes can be detected with a pancreas biopsy or in the study of e secretion (typically for him to get e have involved sekretinovy or secretin-pankreoziminovy tests). The pathogenesis of the development of RV cancer in NP is shownin Fig. 8.

Most of the tumors outcome and that of the protozoal epithelium of the pancreas. At present, there is no evidence to confirm the difference in the pathogenesis of pancreas cancer in patients with infarction and in the case of banal cronchronic pancreatitis, as well as with initially intact RV [16].

If the patient with NP developed clinical signs suspicious against pancreas cancer, it is necessary to conduct an endoscopic retrograde cholangiopancreatography (ERCP) with biopsy pancreatic direct current of the cells [10]. It is proved that a precancerous condition against pancreas adenocarcinoma is pancreatic dysplasia (n pas kreaticheskaya intraductal neoplasia — PanIN). There are 3 degrees of PanIN [16] :

– PanIN I — Intraepithelial ductal hyperplasia;

– PanIN II — low-grade dysplasia (Figure 9);

– PanIN III — High-grade dysplasia or carcinoma in situ (Figure 10).

For screening of dysplasia of the epithelium and carcinoma in situ on the background and so forth NP change endoscopic sonography (endoUZI), ERCP, spiral computedmografiyu a m (CT), determining levels karboantigena 19 — 9 (CA 19 — 9) and kartsiembrionalnogo and ant gene (CEA) in the blood. However, only endo ultrasound and ERCP can be considered informative enough. Signs of pancreatic dysplasia in endoUZI consider the heterogeneity and n renhimy, the presence of hyperechoic foci and / or hypoechoicnodules (Fig. 11, 12). P on the

results of ERCP features associated with dysplasia, according to the uneven expansion of the ducts sometimes sacciform extensions (Fig. 13). Symptoms DISPLAY sion ductal epithelium and RV, which are detected at endoUSD and ERCP, pre presented in Table d. 1.

Table 1

Symptoms associated with ductal dysplasia of the pancreas [16]

endoUSD	***ERCPR***
Heterogeneity of parenchyma	The unevenness of the lumen of the mainflow pas n kreaticheskogo
Hyperechoic foci in the parenchyma	Uneven luminal side of prot Cove
Increase in echogenicity of the walls of the main pancreatic duct	Extension of lateral ducts
Hypoechoic nodules	Sack-shaped expansion of pancreate andductal ducts
Focal changes of the parenchyma	

In April 2001 g of. in Milan (Italy), the III International Symposium on hereditary diseases of the pancreas was held, where the Consensus was adopted on the prevention, screening and treatment of pancreas cancer in NP [16]. This onsensuse K indicated that, in the absence of any vaccines or other prophylactic agents for the prevention of pancreas cancer bol s nym NP should avoid or seek to reduce the influence of the main cancer-causing factors, such as smoking or alcohol abuse. These measures are necessary, as well as banal preventive actions that reduce cha with Toty cases of acute pancreatitis and acute exacerbation of chronic pancreatitis. This, in its e och red, reduces the risk of developing pancreatic cancer. Thus, the basic recommendation should be boiling th: at complete abstinence from alcohol and smoking e ma; refusal of pancreotoxic honey and vitamins;correction of metabolic disorders (hypertriglyceridemia or hypercalcemia); PAC and cients NP should be periodically Toolmaker s e observation by I (endoUSD, ERCP, CT) for timely identifying e Nia and correction of structural defects (e.g., choledocholithiasis, stri to pancreatic duct tours) that may contribute to recur and NIJ acute pancreatitis attacks и трансформации заболевания в хронический панкреатит.

Until now, there are no effective screening schemes for examining patients at risk for pancreatic adenocarcinoma (in particular, patients with NP). This is due to the following reasons:

1) a small number of patients with a verified NP;

2) lack of sensitivity and specificity, and therefore the prognostic value of tumor markers in comparison with diagnostic value Radiologica e ray methods (much cheaper than it would be used for the screening of tumor markers, if they were informative enough);

3) Sun e is insufficient sensitivity radiological techniques (helical CT, endoUZI, ERCP, magnet n orezonansnoy tomography and cholangitis about pancreatography and) to detect tumors in resectable stage. There are no prospective studies showing the benefits of using and economic benefits of a method for the early diagnosis of pancreas cancer in patients with NP. Lack of e f ciency of the available methods for screening NP explained very early metastasizes to vaniem even small tumors limited sensitivity range of methods in chronic pancreatitis and high cost of diagnostic percent e fools.

At the same symposium in Milan, the following data were given [16]. Jerzy d ny screened 250 patients with NP aged 40-50 years for 5 years using cn and tral CT, ERCP, endoUZI, with the definition of tumor marker s serum and pankre well -static secret was worth an average of 362 857 USD for one set diagnosis cancer of the pancreas. While the annual survey of such a group of patients with Execu s mations endoUZI fence and blood and pancreatic secretions for storage (without research) cost in 69943 USD for a diagnosis of pancreas cancer. Despite neoptimist and cal conclusions to the onsensus adopted in Milan, says that patients with NP older than 40 years must undergo annual screening against cancer of the pancreas. Currently, the most informative is endoUZI, although the final conclusion is formulated on Vat esch ie early, as research continues to improve diagnostic meth about Dick.

Specific treatment of NP is not developed. Given the rapid progression of functional pancreatic insufficiency, shows the assignment of enzyme t e rapii already in the early stages of the disease. Unconditional in but the drug of choice in this respect is Creon having significant advantages over other enzyme prep and ratami (minimikrosfericheskaya release form, the high activity of enzymes, particularly lipases, acid-shell minimicrospheres, the presence of other lipolytic fe p cops optimum ratio kolipaza / lipase and other).

In some cases, should be the appointment of non-narcotic analgesics in large q on Zach, including children [5]. In individual studies have shown that when e m high doses of antioxidant and Dante reduces the need for analgesics. So, the effectiveness of the antioxidant vitamin-mineral complex has been proved (sulfadenosyl methionine 800 mg / day, vitamin C 180 mg / day, vitamin E 30 mg / day, vitamin A 2.4 mg / day, selenium 75 μg / day). Introduction to the treatment

of this complex NP contributed to the reduction of pain intensity and con b Nosta analgesics [8, 31].

Подходы к ведению больных НП с аденокарциномой ПЖ не отличаются от таковых при опухоли отличного от НП генеза. В К онсенсусе высказывается мнение, что у пациентов с НП и аденокарциномой ПЖ нужно проводить панкреатэктомию. Панкреатэктомия выпо л няется также как профилактическая мера при выявлении протоковой дисплазии, обнаруже н ной с помощью биопсии панкреатического протока, особенно у пациентов старше 30 лет [15]. Хотя р е зультаты таких мероприятий and are not verified by any of the prospective studies, logical reasoning proves the necessity of removing the entire body, since the NP to pancreatic tissue regeneration processes are expressed and contribute significantly increased frequency maligniz a tion.

Here is our clinical observation, which, as far as we know, is the first case of diagnosis of NP in Ukraine.

Patient B., 52 th year, head. grocery store.

Complaints about periodic pain in epigastrium, left hypochondrium, irradiating in the lower back, girdling. The pain intensified soon after when th food ma, especially spicy, fatty, fried, sweet st. Sometimes there are abdominal pain undetectable e constant localization, are alleviated after eating. The chair is regular, decorated, without pathological processes and joints. Dispep t ble no complaints. She notes gradual weight loss — by 7 kg for the last 6 months (binds with a diet with a tripot), a general weakness. Disturb pain in the joints (knee, ankle), sometimes their swelling. Periodically notes b ol and discomfort in the submandibular salivary glands. The temperature is within the normal range.

Anamnesis of the disease. He considers himself a patient from the age of 35 years (about 17 years), when they began to disturb pains in the stomach, you put yalsya diagnosis cholecystopancreatitis. At US kaltsifik a tion pancreatic not detected. Since h e tkih exacerbations of pancreatitis was not.

In the beginning of 2017. He was treated in a neurological hospital about distsirkulyato p Noah encephalopathy, then hospitalized in February allergenic sta of bunks on the hives. During the examination, HCV infection was detected. Fibroscan 08.03.2017, the — the F 1-2. From March to mid June, 2017. received Hepzinat. After HCV RNA treatment otr. until now. During his stay in the hospital carried out allergological plan on -hand ultrasound of the abdominal cavity (02.03.2017 g) — revealed hypoechoic areas with uneven h e with contours of size 16, 0 × 11, 0 × 7.6 mm, 6.4 × 3.8 mm in the area of the body of the pancreas. In withdrawal: acute pancreatitis. However, due to the lack of clinical and laboratory data for acute pancreatitis, such a diagnosis is not indicated in the extract. At the

same time, an increase in amylase — 159 U / l (at a rate of up to 100 U / l) and blood glucose — 8.09 mmol / l was detected. Proksium received, Duspatalin, without Mezim h e rcoh effect.

On its own initiative carried out CT scans of the abdomen and retroperitoneal, etc. of the space (07/02/2017 g) (Fig. 14). PZ : head — 25 mm, body — 22 mm, tail — 20 mm. Structure for inhomogeneous MF e r multiple calcifications up to 5 mm. The pancreatic duct is not pa with panded. Free fluid in the abdominal cavity is not determined. Silesia e NCA — 107 × 44 mm ; d obovochnaya slice — 9 mm ; with elez e nocturnal vein — 10 mm. Portal vein — 14 mm. Conclusion: to alkul e zny pancreatitis.

EGD (18.05.2017 g) — reflux esophagitis Article Epen A. erythematosus gastropatia on the background of duodenal reflux. Post-ulcer deformity of duodenal bulb, light degree.

07/12/2017 STUL- test for Helicobacter pylori — positive.

The results of biochemical blood tests (June s 2017 g of.): Amylase Blood — 154 U / L (normal — 100 U / l), creatinine — 91 pmol / l (norm — 80 pmol / l), alkaline phosphatase — 117 U / l (the norm is up to 104 U / l); ALT, AST, GGTP, bilirubin general and direct, general blood test — within the norm s.

The glomerular filtration rate is 50 ml / min. (norm — 100 — 120 ml / min.). Rheumatoid factor +, C-reactive protein (CRP) +++.

5.07. 2017 turned to the clinic Into-Sana (Odessa) to prof. N. B. Gubergrits which set forth the following iagnoz: determining f nny chronic pancreatitis, kaltsifits and ruyuschy. Recall that according to the classification of M — ANNHEIM defined e nnym, t. E without producing. Th conductive doubt, pancreatitis believe that if there is at least one of cl e blowing signs of calcification of the pancreas; pronounced changes in pancreatic ducts; cord e barking exocrine insufficiency of the pancreas (steatorrhea), inferior to substitution enzyme therapy; histological changes in the pancreas tissue that correspond to chronic pancreatitis [29]. H and the presence of calcification in our patient RV is sufficient reason to assume pancreatitis have not e determined e constant.

Anamnesis of life. Work with physical activity, hazard has never been a Saint I linked. At the age of 20 years, a duodenal ulcer was detected, then exacerbations were observed thrice.

In 2016. parotid sinial adenitis is diagnosed. In ultrasound, the 24/05/2016 : okolou br Nye right salivary gland is slightly increased, the heterogeneous structure, with areas of reduced echogenicity contains small hyperechoic inclusions to 0.6 mm.

For many years, the patient, and e e a mother suffering from urolithiasis, as evidenced by so camping at repeated sonography (last 21.09.2017 city).

Objectively. The general condition is relatively satisfactory. N adequate and Tania. Peripheral lymph nodes are not enlarged. Skin and visible mucous membranes are clean, of normal color. Joints are not externally changed. Submandibular and parotid salivary glands are sensitive to palpation.

Percussion above lungs clear lung sounds, auscultation breath vesicles River Noe. The boundaries of the relative dullness of the heart within the normal range, the activity of the heart pu t Michna, heart rate — 66 per minute, blood pressure — 135/85 mm Hg. Art.

Tongue moist, coated with white cash is, is. Abdominal palpation soft surface, determined by a straight sensitivity of body projections and RV tail. With deep palpation pain in areas Chauffard and Guba p Grits — Skulsky. Segments of the colon of ordinary properties. Liver to 1 cm below edge p e Bernier arc, elastic, painless, rounded edge e n, flat, smooth surface. Sel e zenka is not clearly palpable. Peripheral edema is absent. Pasternatsky's symptom is weakly positive on both sides.

Data of additional survey methods.

July 21, 2017 n Anticreatic elastase in the stool — 374 mcg / g (the norm is more than 200 mcg / g) ; to the program — neutral fat was not detected.

The biochemical blood test (15.09.2017): and the total blood methylase is 164 U / l (the norm is up to 100 U / l), and the pancreatic milase is 34 U / l (the norm is up to 53 U / l), and the milase urine — 226 U / l (the norm is up to 447 U / l), and the blood capacity is 33.1 U / l (the norm is up to 60 U / l) ; g of blood glucose, HbA 1 c within the norm.

Magnetic resonance imaging of the abdominal cavity with cholangiography (July 19, 2017) (Figure 15). PZ : head — 30 mm, body — 18 mm, tail — 16 mm. Diffusely inhomogeneous structure for MF e r calcifications, contours h e tkie. The projections on the upper body contour single small cysts and 6 — 7 mm without h e mended communication with pancreatic duct. Virsungianov duct in the body with a maximum diameter of 6.34 mm. Free fluid in the abdominal cavity is not determined. Silesia e NCA — 115 × 53 × 10 7 mm; with Elez e nocturnal vein — 9 mm. Portal vein — 12 mm. Conclusion: MR-picture of calcifications and single cysts of the pancreas. Splenomegaly, indirect signs of portal hypertension.

Although the CT scan revealed the expansion of the portal vein, and when m agnitnorezonansnoy tomography — splenomegaly, we had no reason to think of liver cirrhosis. His symptoms had neither clinical nor on the results of Fibroscan (see. Above), HCV RNA after antiviral therapy cr on vie undetectable. It was

decided to control the diameter of the portal vein and dimensions sat e h e APIS dynamics.

The diagnosis was determined e nnogo calcification chronic pancreatitis caused no doubt, but it was necessary to clarify the etiology of the disease.

To clarify the etiology of pancreatitis, the following hypotheses were put forward:

- alcoholic pancreatitis (but the patient denies abuse of alcohol, GGT within norms s when repeated studies);
- Hyperparathyroidism (this hypothesis is advanced in connection with the combination of calcifying pancreatitis with urolithiasis);
- Viral pancreatitis (associated with mumps virus (pain in the salivary glands, sialoadenitis in the anamnesis), hepatitis C virus);
- drug pancreatitis (patient taking a plurality of medicines, but not those that differ TSS e tlivoy likely cause drug pankre and tit : valproate, diuretics, ceftriaxone, azathioprine, 5-aminosalicylates, etc.; impact on RV sofosbuvir ledipasvira and members of the Hepcin and ta, not studied);
- autoimmune pancreatitis (pancreatitis combination with joint pain, increased index C. RB, positive rheumatoid factor);
- tropical pancreatitis (but the patient did not visit exotic countries);
- Pathology of the pancreas on the background of chronic renal failure due to urolithiasis;
- NP (although family history is not burdened th district, but the patient knows only maternal relatives and his father died many years ago, and kinship n nicks on from tsovskoy line patient does not know).

To exclude hyperparathyroidism were the following studies were performed: to Alzen common — 2.42 mmol / l (norm — 2,15-2,5 mmol / l) to Alzen ionized — 1.3 mmol / l (norm — 1,16- 1.32 mmol / l), n aratgormon — 33.1 pg / ml (rate — 15 — 65 pg / ml) (07.19.2017 g). Ultrasound of the parathyroid glands (July 21, 2017) is the norm.

Densitometry (July 28, 2017) — osteopenia of the lumbar vertebrae, requiring honey and kametoz correction ; The right and left thighs are normal. However, hyperparathyroidism is characterized by a diffuse pronounced osteoponosis of roses.

Regarding exceptions pancreatitis, parotitis associated with viral performed e us the following studies: a ntitela IgM in mumps virus — 1.26 (above 1.1 — positive result), and ntitela IgG virus Mumps — 5.4 (greater than 1, 1 — positive result) (July 19, 2017). In dynamics (09.15.2017 g): a ntitela IgM in mumps virus

— 0.71 (above 1.1 — positive result), and ntitela IgG virus Mumps — 5.8 (above 1.1 — a positive result).

Ultrasound of salivary glands (July 21, 2017) — no pathology was detected.

19.09.2017 was a review of price per head. Department of Infectious Diseases of Odessa National Medical University prof. TV Chaban — there are no clinical and laboratory data for viral parotitis. Single insignificant s Noe rate increase antibody IgM in mumps virus, probably due to blocked e Stn s mi immune responses.

With regard to the association of pancreatitis with HCV infection, it is questionable. Not described hundred eh cord e Loe defeat RV hepatitis C virus. In addition, currently the virus in the blood is not detected, and pancreatitis is progressing (increased blood amylase activity).

Further, a study was conducted to exclude autoimmune pancreatitis and si from a dark disease : a. Antinuclear antibodies less than 1: 100 (normal) (July 19, 2017); antibodies a to cytoplasmic antigens of neutrophil granulocytes (p — A NC A, c — A NC A) are found, but in a low titer of 1:10 ; Ig G 4 — 1.4 g / l (norm — 1.2 g / l) — slight increase is not diagnostic and physical significance (07.26.2017 g).

Protein in daily urine (July 31, 2017) — 58 mg / day. (the norm is less than 100 mg / day).

Radiography of chest organs (August 1, 2017) is the norm.

08.02.2017 city to onsult th e rheumatologist th, d. Med. n. TV Anikeyeva : when reading a virus hepatitis in an anamnesis, the presence of ANCA and an increase in CRP may be due to this diagnosis. However, increasing creatinine speed reduction club h kovoy filter to 50 ml / min. testimony th tons of kidney disease. It is impossible to exclude ANCA- associated vasculitis. Appointed a follow-up.

August 14, 2017 CRP — 0.02 mg / dL (norm — less than 0.5 mg / dL), circulating immune complexes — 66.0 units (the norm is up to 120 units).

18.08.2017 a qualitative definition of p — ANCA, with — ANCA — otr.

Re-examination of the med. T.V. Anikeeva: there is no data for ANCA-associated va with coughs (recommended monitoring of glomerular filtration rate, general urine analysis, daily urine analysis for protein). At the time of examination, there is no evidence confirming Sjogren's syndrome (lacrimal glands function, saliva is produced in sufficient quantity, there is no dryness in the mouth, the profile of antinuclear antibodies is negative).

Given urolithiasis and chronic renal failure, we might think about the defeat of the pancreas, St. I bound with chronic renal failure. However, the development

of such pancreatitis is questioned in principle. In addition, pancreatic hyperfermentemia develops with a creatinine level in the blood above 300 μmol / l [1].

To exclude the NP, a genetic study (August 11, 2017) was carried out : gene cationic trypsinogen PRSS 1, polymorphism R 122 H — A / a (heterozygote); g of secretory inhibitor of trypsin SPINK I, polymorphism N 34 S — A / A (norm).

In the mother (74 years) and daughter (19 years) of the patient, polymorphism R 122 H — A / A (norm).

M atheromas and daughter patsie ntki performed ultrasound of the abdomen (09.21.2017 g) in daughter structural pathology signs pancreas were found in kidneys small hyperechoic inclusions 2 — 3 mm on both sides ; from mother moderate diffuse changes of the pancreas, m ochekamennaya disease concretions of both kidneys, chronic renal failure (thinning of the parenchyma).

CA 19-9 (06.11.2017) — 13.4 U / ml (norm up to 34 U / ml).

Thus, after the conducted studies, we formulated the *final diagnosis* :

on he primary : a limit e nny calcifying hereditary pancreatitis in the acute stage;

a Companion : m ochekamennaya disease localization of concrements in both h Kah, CRF II. Chronic viral hepatitis C, RNA (-). Peptic ulcer dvenadtsatipers m hydrochloric intestine inactive phase, with the presence of deformation postyazvennoy twelve bulbs and duodenal ulcer associated with Helicobacter pylori.

We consider it necessary to mention several positions regarding the disease of our patient.

It is important that, despite the presence of calcification of the pancreas and the expansion of the main pankre and cal flow, results of fecal elastase test are normal. This indicates that the newly developed pancreatitis (possibly in February 2017 g., When the im- p stems were found increased rates of amylase and blood glucose changes of the pancreas at sonography). If pancreatitis developed earlier, with high probability it would be expected decrease of exocrine pancreatic function (according to the literature, in neshnese to retornaya RV failure with a combination of th e calcification and expansion virsungian about of the duct is present in 90% of cases [1 2]). The above circumstance (Intact pancreatic exocrine function) indicates the need for effective therapeutic action (see. Below) without delay e Nia.

Conservative therapy of our patient is certainly not very promising. Given the expansion of virsungianova flow, we hypothesized that a high probability of the presence of calculi in n e m. St. I have communication with this patient held and endosonography I pancreatic and bile ducts for the subsequent decision on the

need to perform ERCP and endoscopic and whether surgery. EndoUZI pancreas and biliary tract performed 6.11.2017 g (Fig. 16) in the center of OLYMED (city of Kiev), a study conducted head. endoscopic department SV Music. Based on the results of endometrial pancreatitis not increased, contours th e smooth, h e tkie. Ehogennost RV uneven predominantly in the head and in the body are determined focal anechoic inclusion size 4-5 mm, Length hyperechoic e nnye inclusion virsungianova duct wall thickening. The duct diameter is uneven (with expansion sites up to 5 mm in the head and 4 mm in the body), inclusions in the duct are not visualized. Vnepech e night bile ducts are not dilated, without inclusions. Enlarged lymph nodes in the tissue, surrounding the stomach and pancreas, are not visualized. Conclusions: endosonographic signs of chronic pancreatitis. Recommended observation in the gastroenterologist, endometrial pancreatitis in the dynamics.

The manifestation of NP at the age of 52 years is atypical (usually it manifests itself earlier). We assume that the resolution was a factor in HCV - infektsiya and / or against a viral therapy.

Required periodic control CA19-9 and endosonography RV (orientirovo h but 1 every 6 months.).

Given urolithiasis with chronic renal failure in a patient mother, the most sick and m a chekisly diathesis, the patient's daughter, we consider it appropriate to recommend participation in g th -kinetic program of urolithiasis (genes of VEGFA — vascular endothelial growth factor A, the VDR — of vitamin D receptor, of TNF -α — tumor necrosis factor-α), which is held in German diagnostician and centers were binding. Paul (city of Odessa).

Currently, the patient is prescribed the following *treatment* : Nolpaz 20 mg morning and evening 30 minutes before meals 1 month, Buskopan 1/2 table. 3 p aza daily before meals 1 m e syats, glutathione 1 capsule (250 mg), 2 times a day for 1 month. By reducing the index of fecal elastase test and after normalization is active on the STI blood amylase enzyme preparations to be appointed, the dose of which will depend e t s by step e or pancreatic insufficiency. It was decided to postpone the eradication of Helicobacter pylori.

Unauthorized- e n with f m of alcohol even in the minimum amount and also smoking chickens e of, when f m in acute food, sour, bitter, very fatty and is very sweet.

We assume that NP is not such a rare pathology. Physicians should be aware of in the of possibility of such pancreatitis. Genetic studies have become more affordable, and you need to claim on Nima, in which cases it is advisable to direction A five patients at a study.

We are only at the source of studying the IR in all its aspects. NP — this is one of s and gadochnyh pancreatology sides that we have to learn. Sun is, it is not necessary in all cases with pancreatitis of unknown etiology for the doctor to consider them hereditary. For m and one judgment needed only genetic test results to a Thoroe, unfortunately, currently not enough available for practitioners in Ukraine. At about t absence of such results, relying solely on empirical judgments, it is easy to make a speculative conclusionabout the NP, because: "Genetics — the science explaining n about what you look like your father, if you like, and why did not like him, if so get and elk "(Oliver Holmes).

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FIGURES

Fig. 1. The Midwest Multicentre Pancreatic Study Group logo (according to P. Durie et al., 2002 [16]).

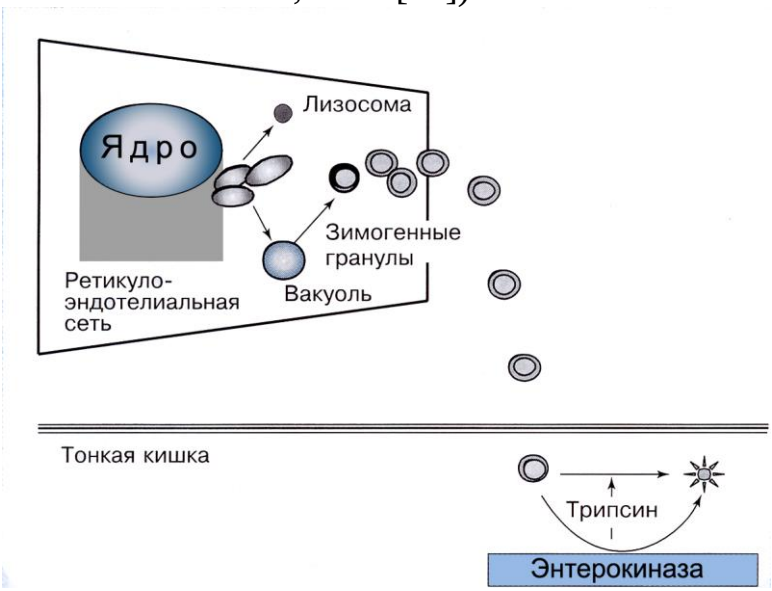


Fig. 2. Mechanisms of protection against premature activation of the pancreas enzymes (according to AV Okhl about bystinu, 1999 [9]).

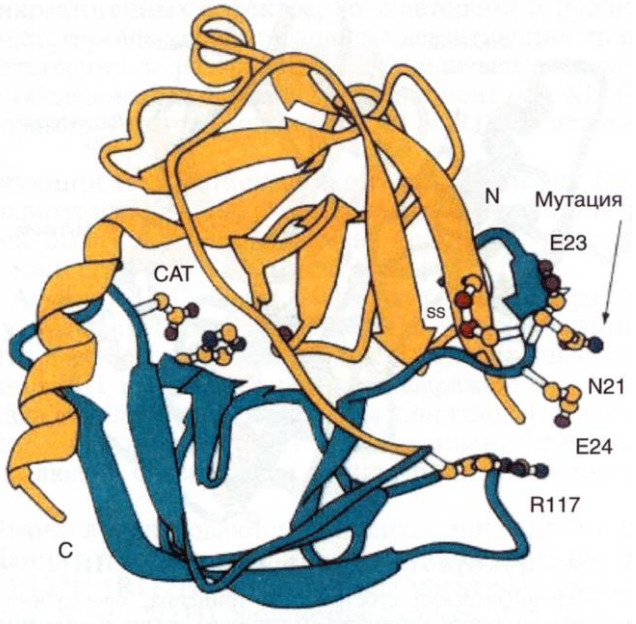


Fig. 3. Structure of human trypsinogen (according to IV Mayev et al., 2005 [8]).
CAT — catalytic triad;
R 117 is the site of the mutation of cationic trypsinogen;
N 21 — the location of the mutation SPINK I ;
SS — disulfide bond;
E 29 / E 24 — glutamic acid;
C is the carboxylic end of the region;
N is the amino terminus of the region.

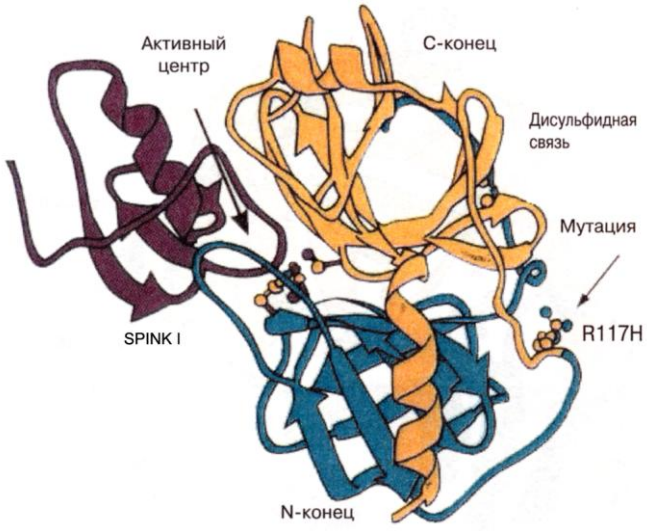


Fig. 4. Structure of the trypsinogen- SPINK I complex (according to IV Mayev et al., 2005 [8]).

Fig. 5. The proteolytic cascade — RV basis autolysis (for M. W. B u chler et al, 2004 [11]).

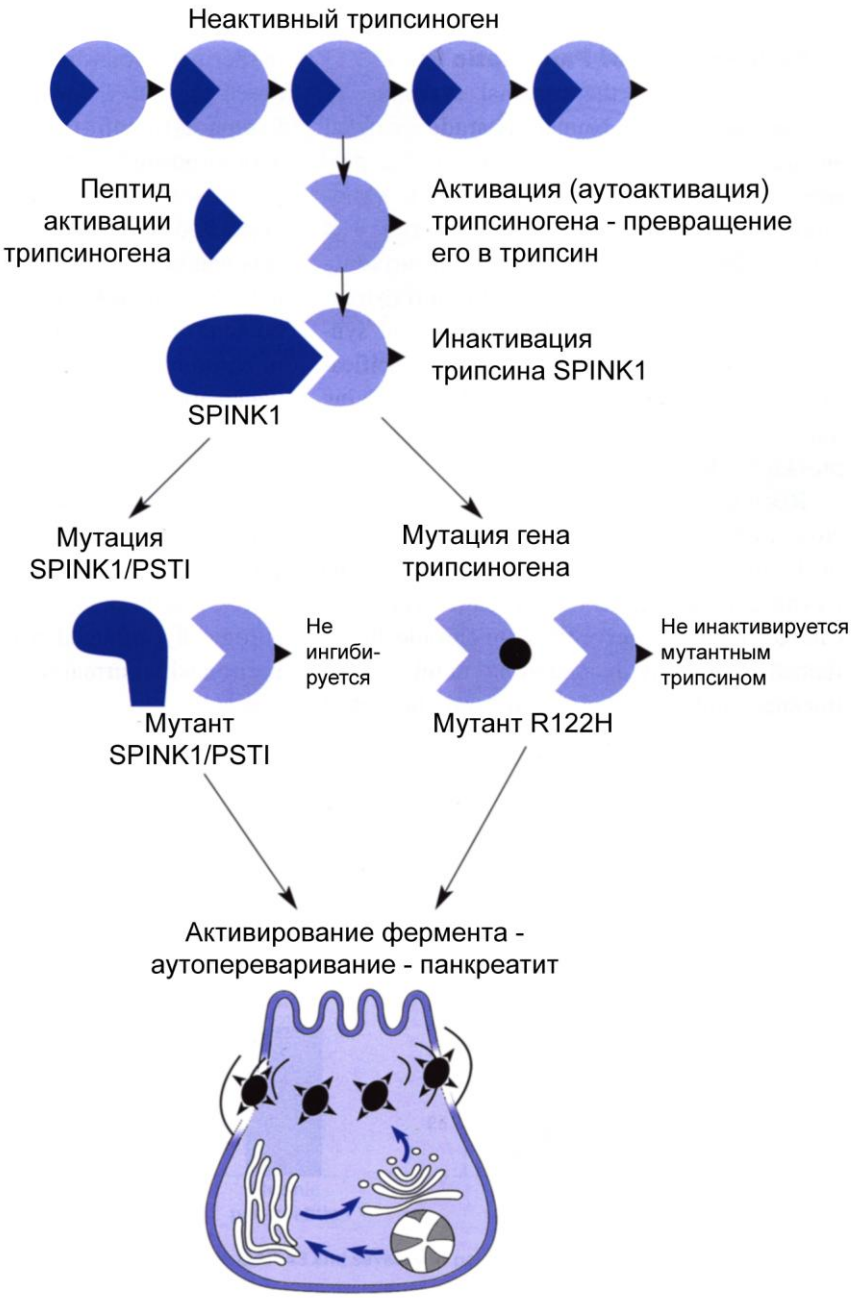


Fig. 6. Intrapancreatic trypsinogen activation and genetically dete p mined anomalies defense mechanisms against excessive activation of intraorgannoy etc. of the enzyme (for M. W. B u chler et al., 2004 [11]).

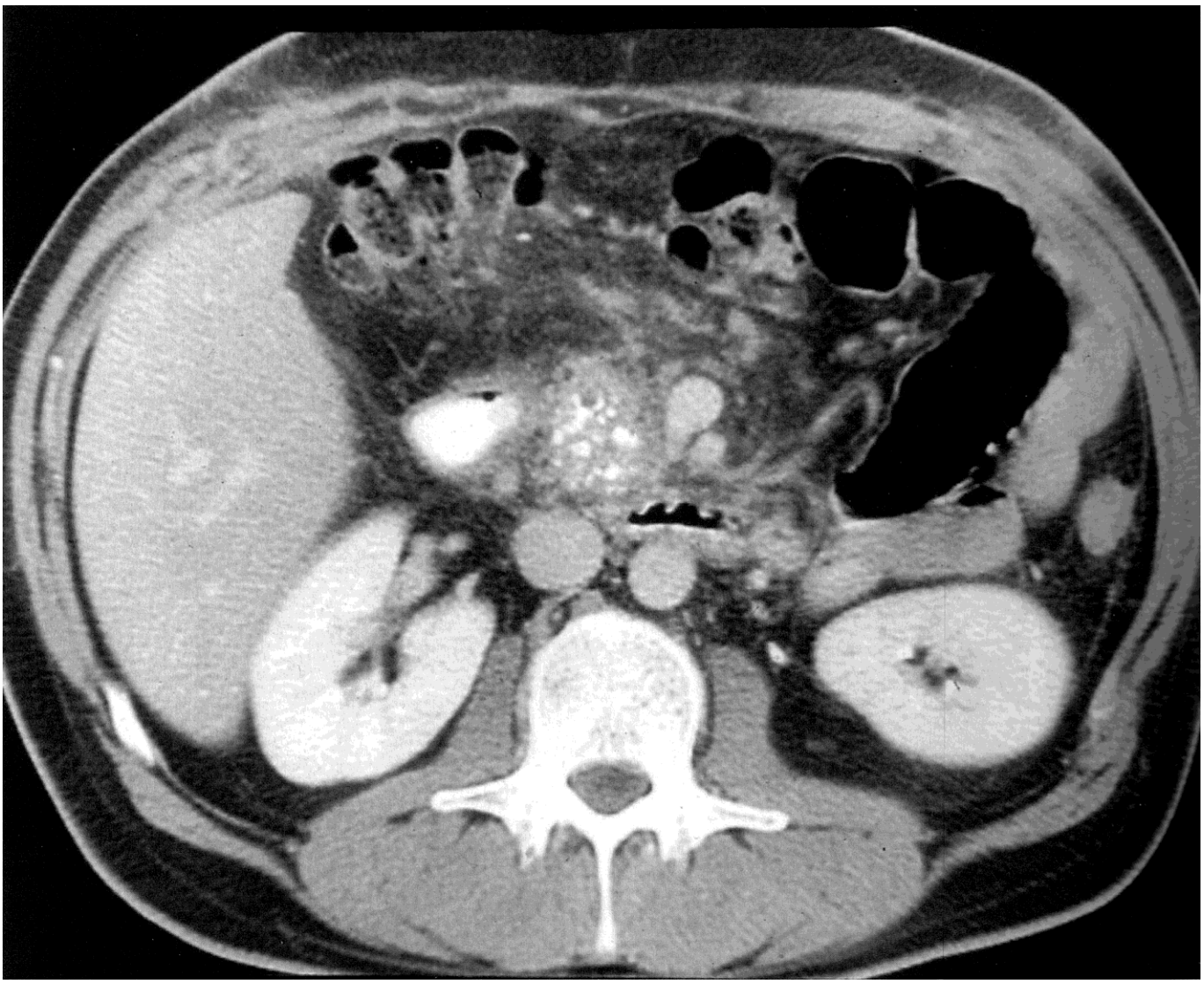


Fig. 7. When CT patient with NP determined multiple cal s tsifikaty in the pancreatic head. In peripancreatic tissue — adhesive process (for C. D. Johnson et al, 2005 [. 20]).

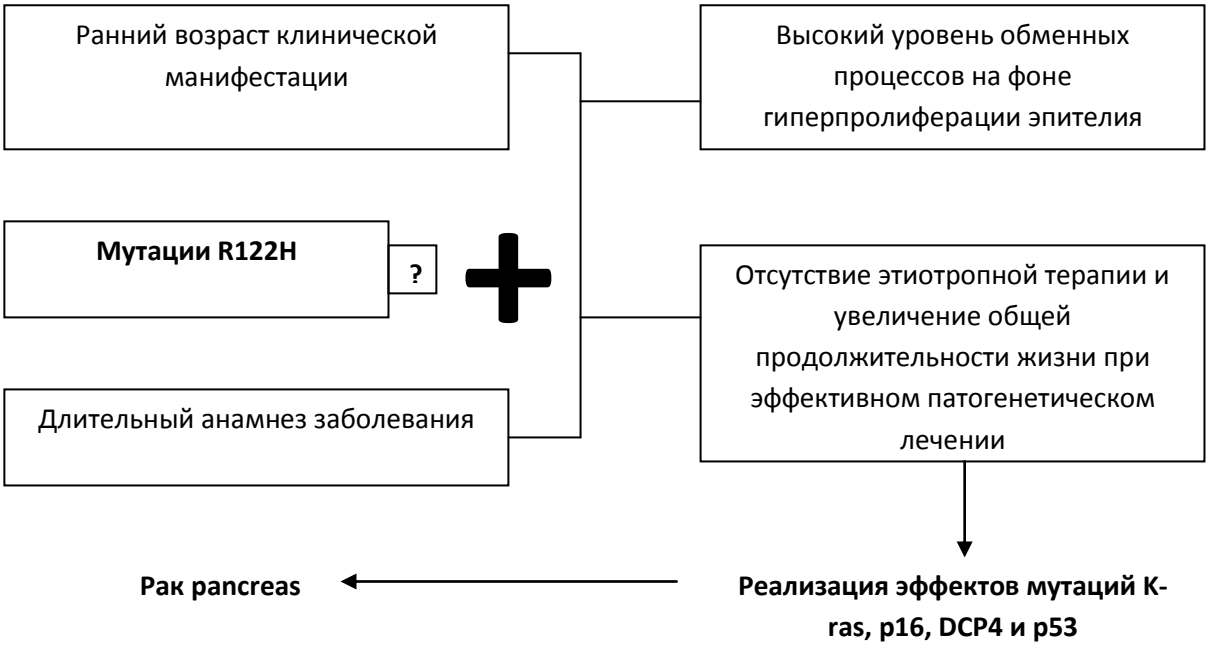


Fig. 8. The causes of high incidence of pancreas cancer in NP (according to IV Mayev et al., 2005 [8]).

K — ras — oncogene encoding a protein homologous to epidermal and transforming th present growth factors;

p 16, p 53, DPC 4 — tumor suppressor genes.

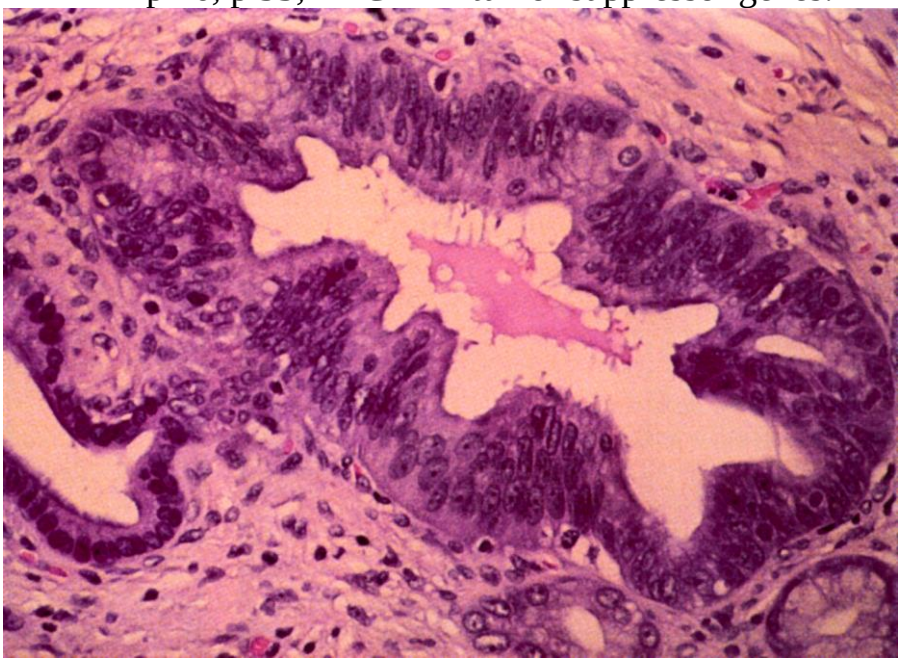


Fig. 9. PanIN II — dysplasia of low-grade protocol epithelium. Flow of vy layered epithelium cells enlarged, hyperchromatic nuclei compared with the normal straight on current epithelium (in the lower left corner of p and sunka) [16].

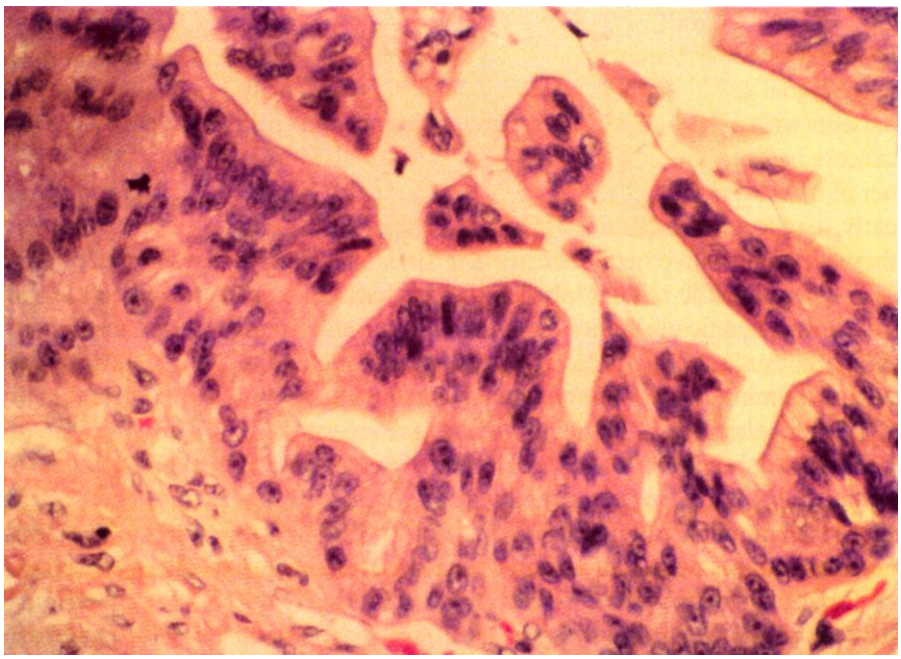


Fig. 10. PanIN III — dysplasia of high-grade protocol epithelium (carcinoma and noma in situ). Expressed papillary images determined as Nij, aberration nuclei, loss of cell polarity [16].

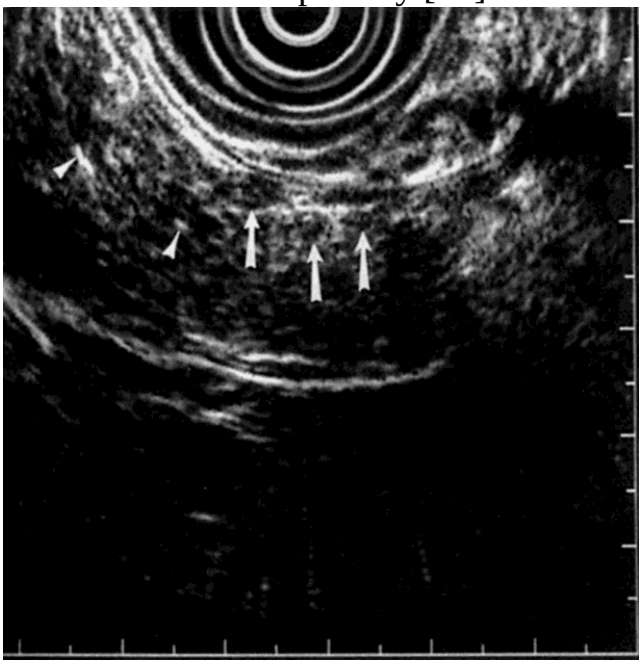


Fig. 11. When endoUZI patient with NP determined signs of ductal dysplasia ep and Telia: hypoechoic lesions (nodules), indicated by arrows, and hyperechoic f of Coosa (indicated only arrowheads) in the tail of the pancreas. Histological and to follow a patient identified DISPLAY and Zia in a plurality of ducts [16].

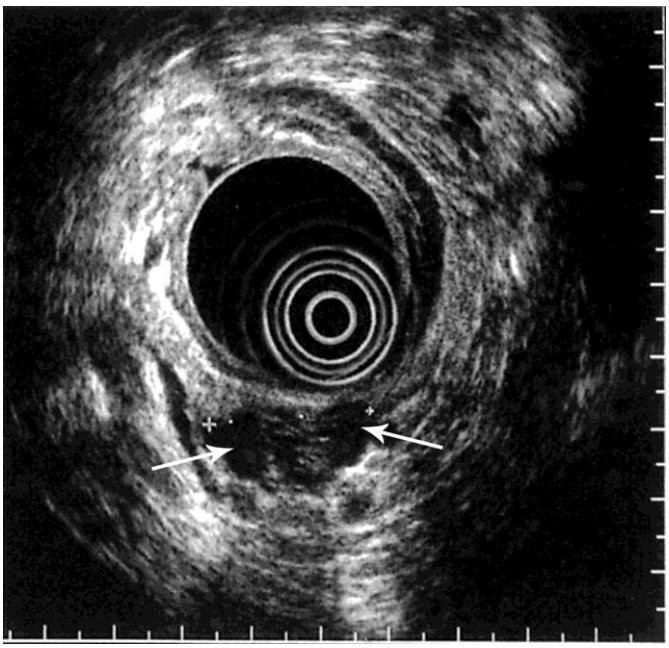


Fig. 12. When endoUZI patient with NP determined hypoechoic heterogeneous images and of the head in the pancreas (arrowhead). When resection in the preparation revealed a large area of dysplasia (PanIN III — carcinoma in situ) [16].

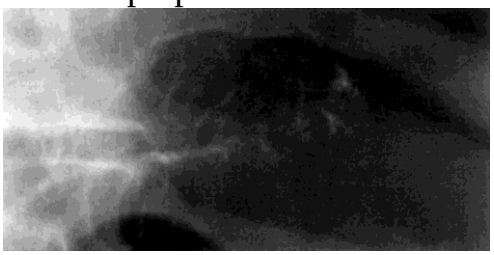


Fig. 13. A patient with NP detected during ERCP unevenness lumen SFA in Nogo duct with an extension of the side duct in the tail of the pancreas [16].

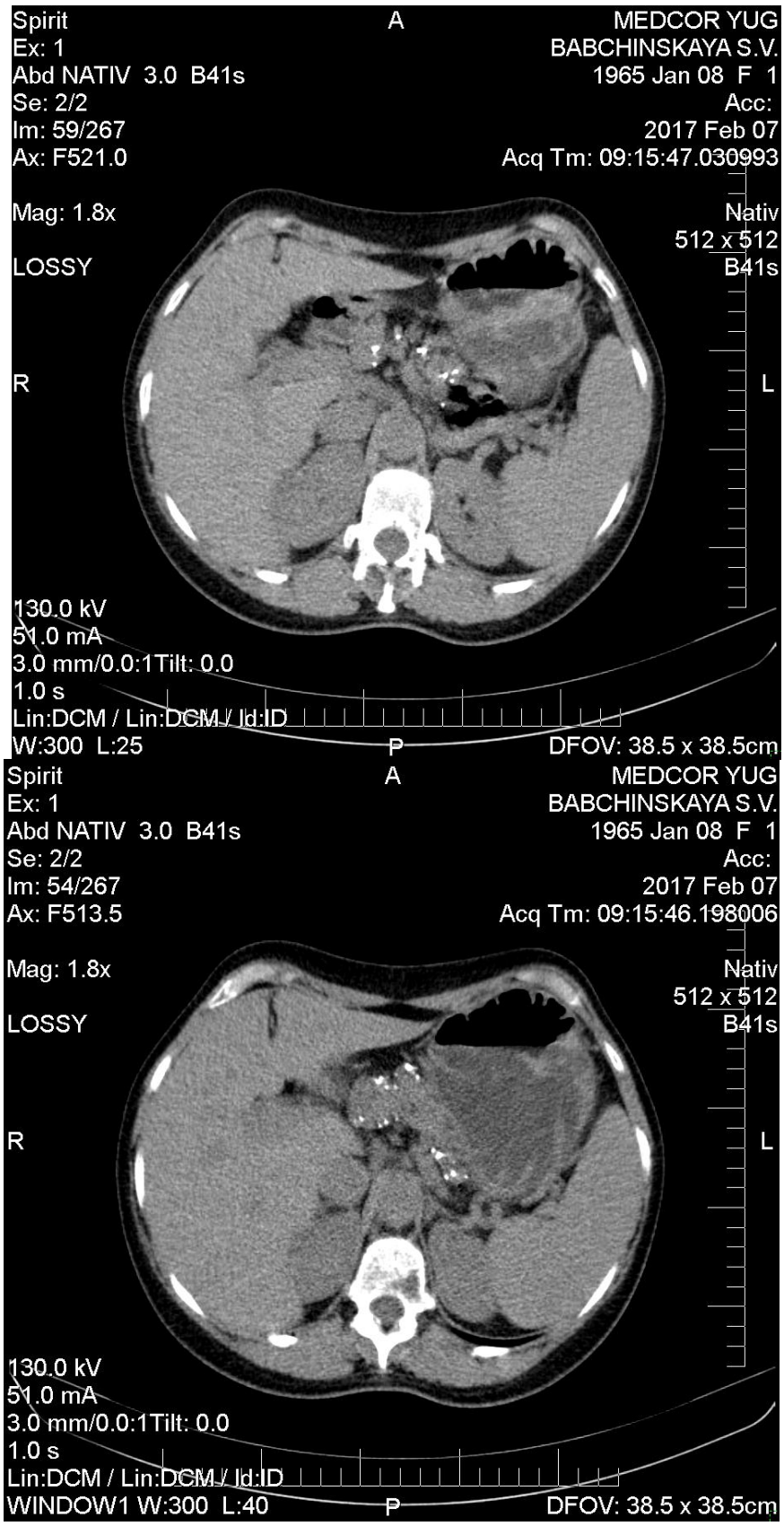


Fig. 14. CT of the abdomen and retroperitoneum patient B. (without counterstain as Nia due to the presence in the patient CRF) (explanation in the text).

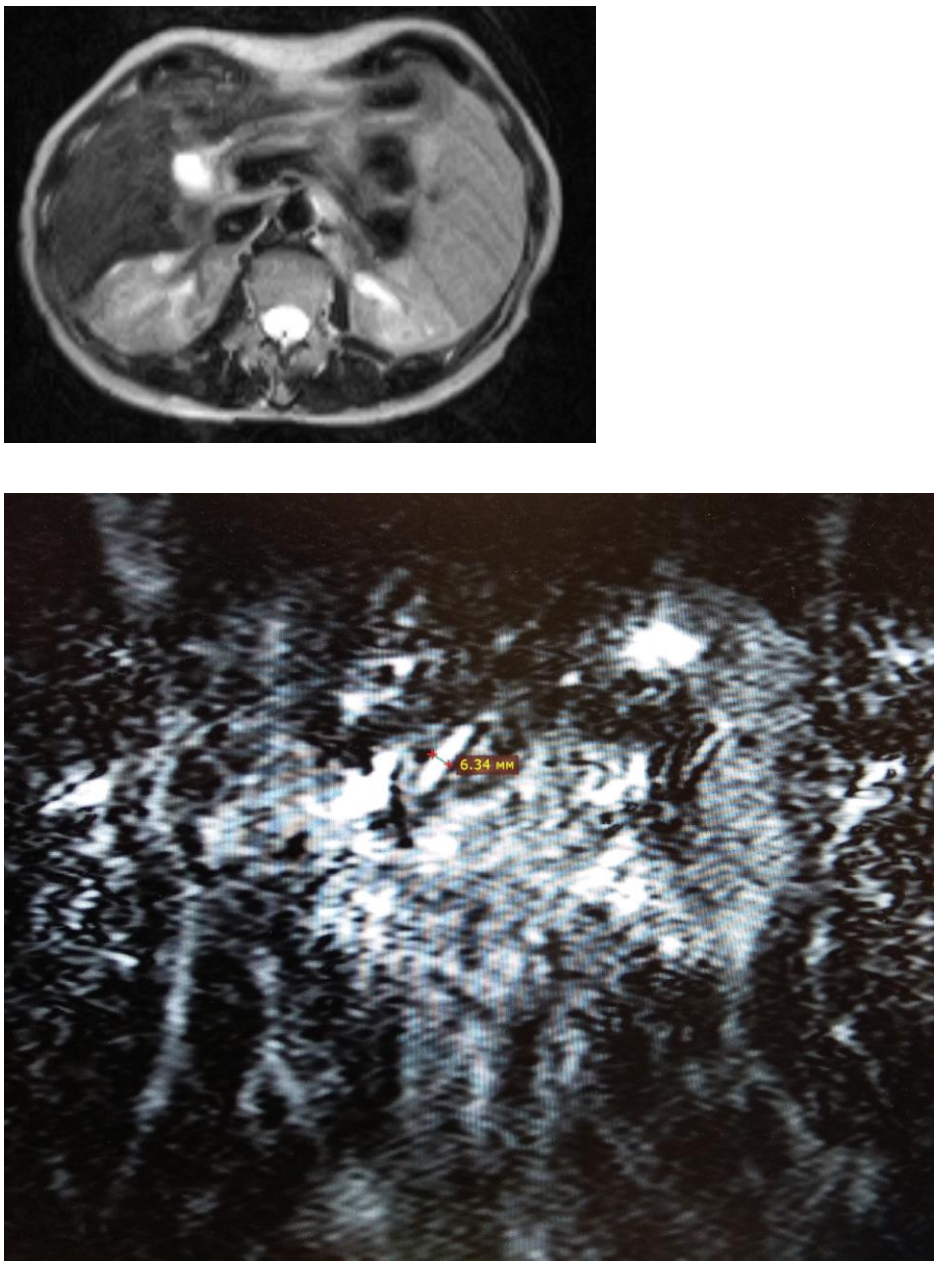
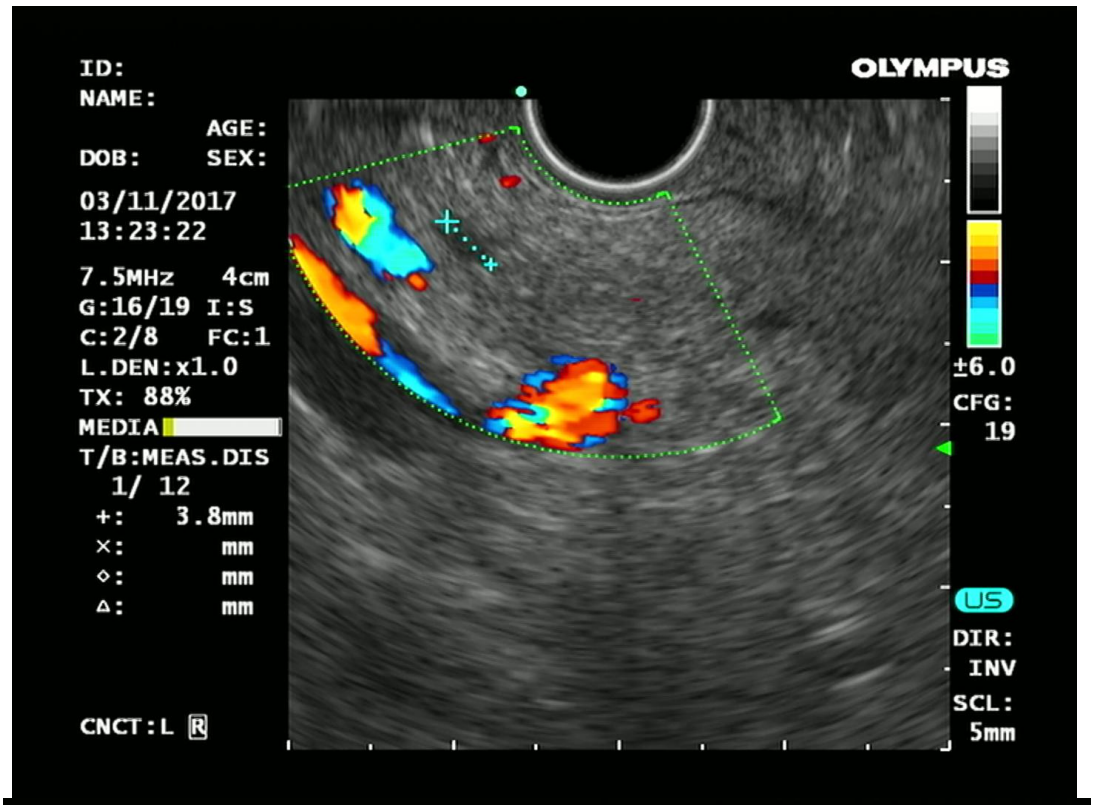


Fig. 15. M Agnita n orezonansn Single tomography I abdominal patient B. (explanation in the text). a) MR sequence T2 VI ; b) magnesium t norezonansnaya cholangiopancreatography.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TX: 88%
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+: 3.8mm
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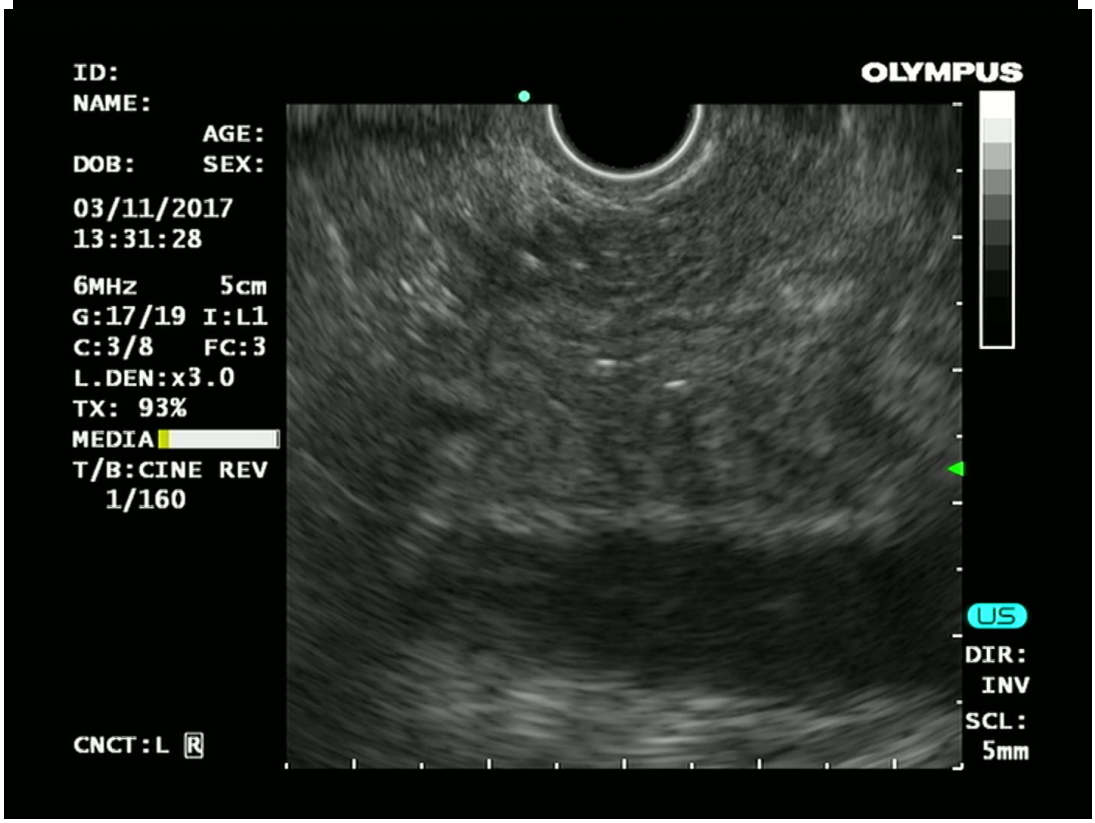
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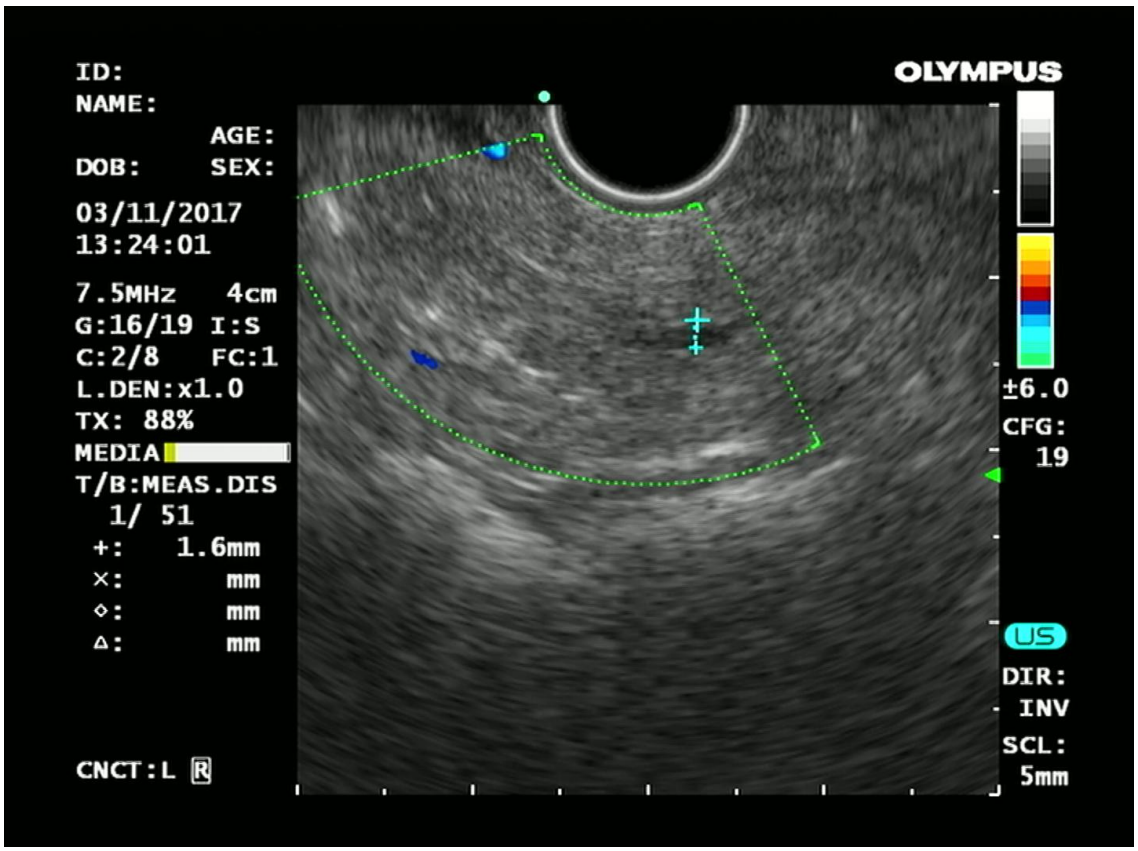

Fig. 16. The results of the endosarcoma of the pancreas of the patient B. a) anechogenous area in the parenchyma; b) hyperechoic inclusions, probably calcifications; c) uneven duct clearance, expansion site.

Hereditary pancreatitis: tactics of diagnostics and differential diagnostics (clinical case)

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Key word: pancreas, hereditary pancreatitis, mutation of the cationic trypsinogen gene, risk of pancreatic cancer, clinical observation

The article presents a literature review on the main genetic mutations leading to the development of pancreatitis, analyzes the pathogenesis of hereditary pancreatitis and the high risk of pancreatic cancer upon this disease. The authors described their own clinical case of calcificating pancreatitis that developed in a patient with a mutation of the cationic trypsinogen gene. The tactics of treatment and observation is discussed.