Hyperparathyroidism: pancreatitisandothergastrointestinalmanifestations

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Key words:hyperparathyroidism, gastroduodenal ulcers, acute and chronic pancreatitis, pancreatic calcification, pathogenesis, treatment

In clinic of internal diseases, syndromes "distant" from the localization of the true causeare not uncommon. This is typical for endocrine diseases in which different organs and systems are involved in the pathological process. Let us consider the problem of hyperparathyroidism (HPT). TheincidenceofprimaryHPTis 25-50 per 10,000 ofpopulation [3, 4].

HPT is a pathological condition caused by an increased inflowof parathyroid hormone (PTH)in the blood, leading to a disruption of normal metabolism of calcium and inorganic phosphorus in the body [4]. Increased levels of PTH in the blood often occur upon hyperplasia of the parathyroid glands, rarer—as the result of an adenoma or cancer of these organs (Fig. 1).

Fig. 1. Parathyroid adenoma (macropreparation).

The total number of the parathyroid glands and their location is not always the same. Besides conventional localization — backwards thyroid gland — they may be located in its parenchyma, in the thymus tissue,in the mediastinum, in deep neck tissues (tissue surrounding the trachea, esophagus, carotid arteries, vagusand recurrent nerves) and even in the pleural and pericardial cavities [3, 4] (Fig. 2).

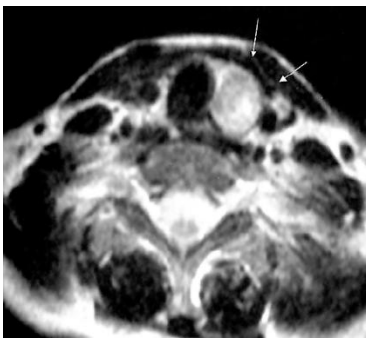

Fig. 2. Magnetic resonance imaging of the neck. Rounded tumor with a size of 2×2 cm (arrows) is detected— parathyroid adenoma.

Elevated levels of PTH in the blood lead to a "washout" of calcium from the bones, their structure is broken, the bones become porous and brittle. If calcium loss is compensated, HPT may be asymptomatic, without radiological manifestations that occur in one third of HPTcases. Excess calcium is excreted by the kidneys, where calcareous concrements are often formed [5]. The deposits of calcium salts also form in other organs (liver, gallbladder, pancreas, spleen, heart, wall of the colon and stomach, lungs, the walls of arteries, soft tissues). Depending on the primary lesion,HPT forms aredistinguished: bone, kidney, gastrointestinal (often with the involvement of the biliary tract and pancreas), skin and mixed [4].

The negative impact of excessive levels of calcium in the blood is manifested not only in the form of the formation of calcareous concrements and calcifications in tissues. Calcium is an important component of physiological arousal of secreting cells (e.g., of the pancreatic acinar cells or secreting epithelial cells of the gastric mucosa). Under the action of cholecystokinin, acetylcholine or bombesin in vitro dose-dependent response of the secretory cells is normally observed as a rise of intracellular calcium concentration, followed by a plateau period of excitation. Primary peak of calcium concentration provides by anintracellular depot (specialized structures of the endoplasmic reticulum are probably responsible for this), while the subsequent concentration plateau depends on calcium entry from the outside of the cell. Thus, upon breach of calcium metabolism on the background of HPT, secreting parenchyma of various organs is in a state of hyperfunction, which in turn may lead

to the development of the relevant pathology, such as peptic or duodenal ulcer, acute or chronic pancreatitis. This was also confirmed by experimental and clinical data: the intravenous infusion of solution of calcium salts in healthy volunteers increased production of acid in the stomach. Patients with Zollinger-Ellison syndrome noted calcium-induced release of gastrin from gastrinomas and vice versa — reducing basal acid production and gastrin levels in the blood after parathyroidectomy, leading to a decrease in calcium concentration in blood [1,2].

Let us considerthe peptic ulcer. Gastroduodenal ulcers on the background of HPT are symptomatic. Among such patients women prevail,although peptic ulcer occurs 4 times more frequently in malesas the primarydisease.

H. Rogers in 1946 first suggested a causal relationship between HPT and a stomach or duodenalulcer. Until now, this question remains open: some researchers are convinced in the ulcerative HPT effect, while others believe the connection between these two facts is a random association. According to various researchers, the formation of gastroduodenal ulcers is observed in 4,3-12,0% of patients with HPT. This difference may be explained by that gastroenterological symptoms are usually paid attention to when they appear before bone changes. Much less peptic ulcer is the only manifestation of HPT[2].

The pathogenesis of ulcer formation in primary HPT is ambiguous. Excess PTH in blood leads to increased secretion of hydrochloric acid, pepsin and increasing gastric motility. But the direct negative PTH impact on the organ mucosa is also assumed. The most common ulcer develops in diffuse hyperplasia of the parathyroid glands and is usually localized in the stomach, at least — in the duodenum. Less than a quarter of cases, the ulcer has a dual location — both in the stomach and duodenum [2,4].

The clinical picture in most cases is typical: epigastric pain immediately after eating or delayed, late, hungry, night pain — depending on the level of the lesion. Also, almost all the patients have dyspeptic syndrome: heartburn, loss of appetite, nausea, sometimes vomiting, constipation. Time fromdiagnosing the primary HPT to the development of peptic ulcer takes 10-26 yearsat the average. The course of peptic

ulcer on a background of multiple adenomas of the parathyroid glands in the presence of HPT is of particular severity (severe pain, nausea, vomiting), resistance to the usual treatment (sometimes worsening of the condition is marked after the appointment of antacids), frequent development of complications — gastrointestinal bleeding, perforations.

If you suspect HPT, manifested in gastroduodenal peptic ulcers, along with the standard methods of detection of ulcers of the stomach and duodenum, it is necessary to investigate the levels of PTH, calcium, phosphorus, alkaline phosphatase in the blood; to determine the secretory function of the stomach; to conduct rthe adiography of bones to identify structural changes, osteoporosis (Fig. 3). To determine the localization of tumors of the parathyroid glands ultrasound and computed tomography are used. If the level of total calcium in the blood increases periodically or stays within the normal range, fractions of ionized calcium should be examined. Sometimes there is a combination of peptic ulcers and hypercalcemia associated not with HPT, and caused by excessive consumption of milk and milk products, but not HPT[2].

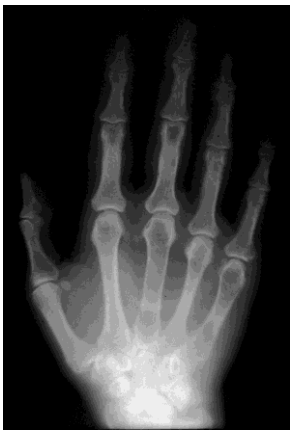

Fig. 3. X-ray of the hand. Severe osteoporosis in patient with HPT.

Treatment of peptic ulcers in patients with primary HPT must be primarily directed to surgical removal of adenomas or hyperplastically changed parathyroid glands. In some cases, surgery can be avoided by prescribing calcitonin and antisecretory drugs. Some authors propose to maintain removed glands frozen for autotransplantation in case of postoperative HPT condition. Sometimes, parathyroid

adenomas are associated with other endocrine tumors, such as gastrinomas, that is causing ulcer recurrence and the development of dangerous complications. If the surgeryis successful and other endocrine tumors were not missed, a persistent scarring comes.

Another gastroenterological HPT manifestationis anacute or chronic pancreatitis. There is a certain relationship between HPT intensity and the degree of morphological lesionof the pancreas. Evidence may include: firstly, data on HPTcorrelation with hyperamylasemia resistance in chronic pancreatitis; secondly, the relationship between HPT and the violation of exocrine pancreatic function in humans and animals. Moreover, one of the pathogenic mechanisms of chronic pancreatitis (formation of calcium stones in the ducts of the pancreas, it parenchymal calcification) is associated with parathyroid imbalance and excess calcium in a pancreatic secretion. Calcium stimulates the exocrine pancreatic function, activates trypsinogen by intraorgan ways, which leads to the emergence of foci of autolysis [6,7,8].

Association of HPT and acute pancreatitis is still a debatable issue, as well as the results of clinical observations. T. R. Kelly observed 242 patients with primary HPT, among which only 7 (2.9%) patients had pancreatitis [4]. C. G. Mixter et al. point to a higher frequency — 7-19% [6]. C. W. Imrie had examined 880 patients admitted to hospital with acute pancreatitis for 14 years, of which only 2 (0.23%) patients had HPT [8]. Thus, the connection of hypercalcemia and acute pancreatitis is still being discussed by various authors, while the connection of hypercalcemia and chronic pancreatitis is more specific.

Electron microscopy allowed to verify the structure of the pancreatic calcinations and calcifications inHPT: a large number of calcium carbonate crystals, surrounded by sponge-like mass with the remnants of the destroyed cells. This structure confirms the two-phase theory of the formation of the pancreatic stones: firstly, protein "plugs"appearin its ducts, then the calcium salts are deposited, and to a lesser extent — some other salts. Biochemical analyzes confirm the identity of the protein in the "plugs" and protein contained in the composition of pancreatic stones.

The precursor of the protein "plugs" — lithostathine — is normally determined in the pancreatic juice. It plays the role of agent binding an excess of calcium ions in the supersaturated pancreatic juice. According to other data, litostatin acts as a crystallization inhibitor of calcium salts. Therefore, this protein is a component which prevents formation of stones in the ducts of the pancreas. But under certain conditions (for example, premature activation of trypsinogen in the pancreas), soluble lithostathine fractions S2-S5 are transformed into virtually insoluble fraction S1, which forms the centers of the precipitation of calcium salts,where the pancreatic stones are formed[6].

Common diagnostic approaches are similar toabove-discussed in the description of the primary HPT association and symptomatic gastroduodenal ulcers. To determine the extent of the structural changes of the pancreas, the number, location and size of pancreatic stones, transabdominal sonography, computed tomography, endoscopic retrograde cholangiopancreatography and endoscopic ultrasound are used (Fig. 4).

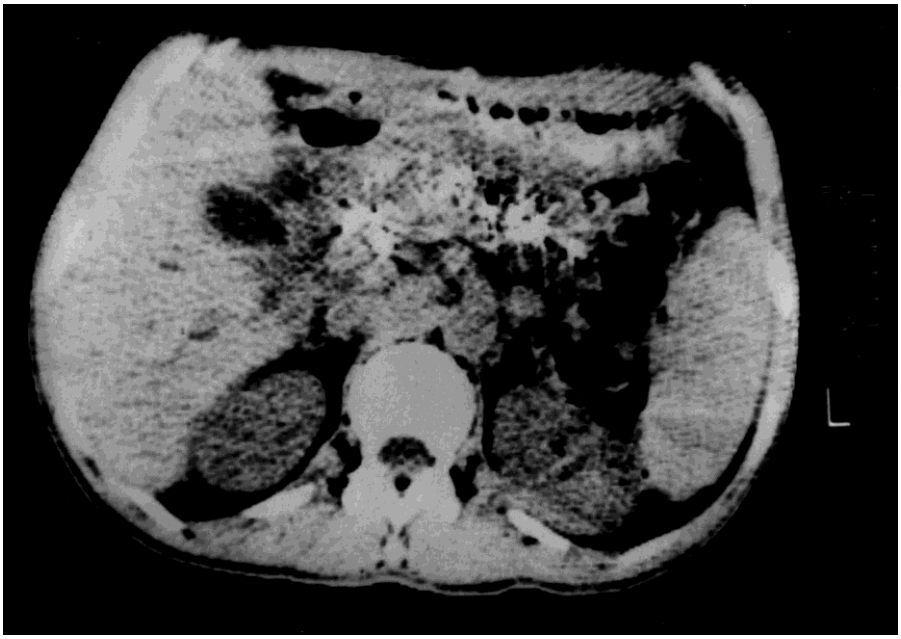

Fig. 4. Computed tomography: HPT withpancreolithiasisand calcifications of the pancreatic parenchyma (observation by the Department of Internal Medicine n. a. Prof. A. Y. Gubergrits of the Donetsk National Medical Universityn. a. M. Gorky).

The basic principles of HPT treatment are also discussed above. In addition to the surgical techniques, calcitonin is used, which reduces the production of pancreatic enzymes by reducing the level of calcium in the blood (suppresses its way out of the bones). The drug does not affect the motility of the digestive tract, has analgesic effect. It is prescribed in a dose of 5 IU/kg of body weight intramuscularly, 2 times a day for chronic pancreatitis or intravenously — in acute pancreatitis [7].

Attempts to dissolve stones by oral pancreatic citrate, which theoretically should reduce the pH of pancreatic juice and transform insoluble calcium salts in soluble ones, have not given appreciable clinical outcome [8].

Inpancreolithiasis, sphincterotomy followed by extraction of stones from Wirsung's duct is used. But itseems possible only in the case of a very close location of the large stone of the main pancreatic duct to the duodenal lumen. Extracorporeal shock wave lithotripsy is combined with oral citrate for breaking stones and the subsequent dissolution of the remaining small fragments. According to various authors, the effectiveness of this method varies from 50 to 100%. There are no serious complications, although exacerbation of chronic pancreatitis is possible in 10% of cases. With the combined treatment, a rapid relief of pain is achieved faster, but long-term results are not as satisfactory: steady decrease in pain occurs only in 33-88% of cases [1].

The possibility of the formation of calcareous concretions in the gallbladder in HPTshould be kept in mind (Fig. 5).

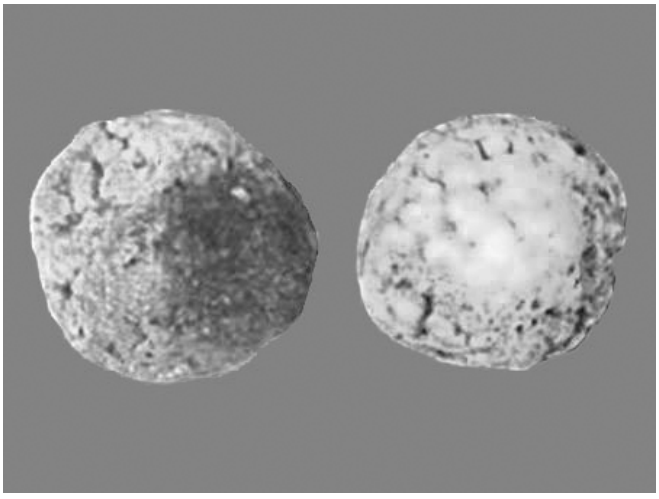

Fig. 5. White (calcareous) concrements of the gall bladder in HPT.

Therefore, therapies should be directed not at the elimination of pancreatic stones as the main goal (as seen from the results, it is only a temporary measure for the relief of pain), but to the elimination of the root cause of their appearance, i.e. HPT correction.

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Article analyzes the literature data on the frequency of lesions of the digestive system upon hyperparathyroidism, as well as the pathogenesis of gastroduodenal ulcers in this pathology. Particular attention is paid to acute and chronic pancreatitis upon hyperparathyroidism, pathogenesis of pancreatic lesions, diagnostics and treatment. Possibility of the formation of calcareous concrements in the gall bladder is also pointed out.