PATHOLOGICA 2022;114:55-63;
DOI: 10.32074/1591-951X-709

Review

Congenital anomalies of the gastrointestinal tract: the liver, extrahepatic biliary tree and pancreas

Kathrin Ludwig[1], Luisa Santoro[1], Giuseppe Ingravallo[2], Gerardo Cazzato[2], Cinzia Giacometti[3], Patrizia Dall'Igna[4]

[1] Department of Pathology, Azienda Ospedale-Università Padova, Padua, Italy; [2] Department of Emergencies and Organ Transplantation, Section of Pathology, University of Bari, Bari, Italy; [3] Department if Services, Pathology Unit, ULSS 6 "Euganea", Camposampiero, Italy; [4] Department of Emergencies and Organ Transplantation, Pediatric Surgery, University of Bari, Bari, Italy

Summary

Congenital anomalies of the liver, biliary tree and pancreas are rare birth defects, some of which are characterized by a marked variation in geographical incidence. Morphogenesis of the hepatobiliary and pancreatic structures initiates from two tubular endodermal evaginations of the most distal portion of the foregut. The pancreas develops from a larger dorsal and a smaller ventral outpouching; emergence of the two buds will eventually lead to the fusion of the duct system. A small part of the remaining ventral diverticulum divides into a "pars cystica" and "pars hepatica", giving rise to the cystic duct and gallbladder and the liver lobes, respectively. Disruption or malfunctioning of the complex mechanisms leading to the development of liver, gallbladder, biliary tree and pancreas can result in numerous, albeit fortunately relatively rare, congenital anomalies in these organs. The type and severity of anomalies often depend on the exact moment in which disruption or alteration of the embryological mechanisms takes place. Many theories have been brought forward to explain their embryological basis; however, no agreement has yet been reached for most of them. While in some cases pathological evaluation might be more centered on macroscopic evaluation, in other instances small biopsies will be the keystone to understanding organ function and treatment results in the context of congenital anomalies. Thus, knowledge of the existence and histopathological characteristics of some of the more common conditions is mandatory for every pathologist working in the field of gastrointestinal pathology.

Key words: biliary atresia, extrahepatic, choledochal cyst, congenital, annular pancreas, heterotopic tissue, abnormalities

Received and accepted: December 7, 2021

Correspondence
Patrizia Dall'Igna
Department of Emergencies and Organ Transplantation, Azienda Ospedaliero-Universitaria Consorziale, Ospedale Pediatrico Giovanni XXIII, via Giovanni Amendola 207, 70126 Bari, Italy
E-mail: patrizia.dalligna@uniba.it

Conflict of interest
The Authors declare no conflict of interest.

How to cite this article: Ludwig K, Santoro L, Ingravallo G, et al. Congenital anomalies of the gastrointestinal tract: the liver, extrahepatic biliary tree and pancreas. Pathologica 2022;114:55-63. https://doi.org/10.32074/1591-951X-709

Introduction

Initial morphogenesis of the hepatobiliary and pancreatic structures begins during the 3rd to 4th week of gestation, initiating from two tubular endodermal evaginations of the most distal portion of the foregut [1].

The pancreas develops from two endodermal buds, a larger dorsal and a smaller ventral outpouching, arising at the junction between the fore- and midgut endoderm during the 5th week of gestation.

The smaller ventral outpouching gives rise to the inferior portion of the pancreatic head and uncinate process, while the larger dorsal bud forms the upper portion of the pancreatic head, neck, body and tail. During foregut elongation, the ventral bud (developing ventral pancreas) rotates clockwise posterior to the duodenum and joins the dorsal pancreas in the retroperitoneum. The duct of the dorsal pancreas opens into the du-

odenum proximally to the duct of the ventral pancreas and the common bile duct. The latter two, linked by their embryonic origins, typically show a common entrance into the duodenum at the major papilla. Fusion of the ventral and dorsal buds leads to the fusion of the duct system, in which the duct deriving from the ventral bud becomes the duct of Wirsung, and the dorsal duct remains patent, forming the minor duct of Santorini [2,3].

Subsequently, a small part of the remaining ventral outpouching/diverticulum divides into a "pars cystica" and "pars hepatica". The "pars cystica" gives rise to the cystic duct and gallbladder, while the "pars hepatica" divides and forms the right and left liver lobes. Both, subsequently, mingle with proliferating mesenchymal elements of the septum transversum to give rise to all the structures of the adult gallbladder, extrahepatic bile ducts and liver. The epithelial components of the liver originate from the most cranial portion of the "pars hepatica", while the connective tissue framework with its stromal elements have a mesodermal origin, deriving from the septum transversum and the lining cells of the coelomic cavity [2,4-6].

Disruption or malfunctioning of the complex mechanisms leading to the development of liver, gallbladder and pancreas can result in numerous, albeit fortunately relatively rare, congenital anomalies in these organs. Type and severity of anomalies often depend on the exact moment in which disruption or alteration of the embryological mechanisms takes place.

This article will focus on the key clinical, macroscopic and histological features of some of the more common congenital malformations of the liver, extrahepatic biliary tree and pancreas.

Liver

Liver Agenesis

Liver agenesis is incompatible with life and is usually encountered during fetal/perinatal autopsies. Other severe anomalies are normally associated [7]. Agenesis of one liver lobe (usually the right) is rare and is frequently associated with anomalous localization of the gallbladder (retrohepatic or suprahepatic gallbladder).

Accessory liver lobe

An accessory lobe is defined as the presence of a benign portion of liver, distinct from the main organ, but connected to it by a segment of tissue; in contrast to ectopic liver tissue, which has no anatomical continuity with the normal liver [8]. The presence of accessory liver lobes, considered morphologic variations and related to excessive hepatic development, is rare [9,10]. The reported frequency varies greatly in the literature, ranging from less than 1 to 10%, depending on whether the Riedel lobe is considered an accessory lobe in the particular study design or as a separate entity [10].

Accessory lobes, generally located in the right liver, differ vastly with regard to form and size, and can be described as either sessile or pedunculated according to their type of attachment. When pedunculated, the pedicle contains vessels and bile ducts.

Pedunculated accessory lobes can be located either within the abdominal or the thoracic cavity. In the latter case, the pedicle passes through the diaphragm and cases have been mistaken for intrathoracic tumors [8,9,11,12].

The term Riedel lobe is mainly used to describe an accessory lobe extending/originating anteriorly from liver segments V and VI into the right flank and/or iliac fossa, immediately beneath the anterior abdominal wall. Riedel lobe, usually with the gallbladder on its left border, can locate either anteriorly to the right colonic flexure or else dislocate the flexure medially [8] This accessory lobe can range in size from a few mm to more than 10 cm.

Histologically, Riedel lobe is generally identical to normal liver tissue and in its classic form receives portal, arterial and biliary structures, while venous drainage connects to branches of both, the median and right hepatic vein [10]. Small accessory lobes missing bile ducts and portal veins have been described, frequently causing nodular regenerative hyperplasia [8].

The whole range of primary hepatic tumors, as well as metastatic tumors, can occur in the accessory lobes [10,13].

Most accessory lobes, which are frequently located infrahepatically, are without clinical importance and are diagnosed post-mortem or as an incidental finding during surgery for other causes. In some rare cases, especially when pedunculated, they are revealed by pain due to torsion of the pedunculus and subsequent imaging studies. In the rare instance of torsion of the pedunculated accessory lobe, histological findings can range from patchy zone infarction to extensive infarction [8].

Ciliated Hepatic Foregut Cyst

Congenital cysts of the liver are thought to be uncommon. However, with increasing and widespread use of imaging their prevalence appears to increase [14].

Congenital Hepatic Foregut Cyst (CHFC) is thought to arise from embryonic foregut remnants. Despite its supposed congenital origin, of the less than 100 cases reported to date, only a minority have been identified in pediatric patients [15-17].

Extrahepatic biliary tree

Biliary Atresia

Biliary atresia (BA) is a disorder of infants in which the obliteration or discontinuity of the biliary ducts obstructs bile flow. BA is a rare disease, generally presenting within the first few weeks of life, and is the most frequent cause of surgical jaundice in children.
Although universally characterized by an obliterative fibrosing cholangiopathy of the intra- and extra-hepatic bile ducts, BA is not a single condition with a well-defined etiology, but rather a group of diseases with overlapping appearance by the time of presentation.
Prevalence of BA varies widely, ranging from an estimated 0.5 to 0.8 per 10,000 live births in the Western countries to 1.1 and 1.5 in 10,000 live births, respectively in Japan and Taiwan [18-21].
Based on etiology and pathogenesis, four different variants of BA can be distinguished with the help of clinical and/or laboratory features [22].

1 BASM (BA Splenic Malformation): polysplenia, situs inversus, preduodenal portal vein.
2 Cystic BA (cystic change in an otherwise obliterated biliary system).
3 CMV BA: Viral-associated BA (particularly Cytomegalovisrus); infants have IgM antibodies to CMV.
4 Isolated BA (90%): lacking all the above.

Some authors prefer the names perinatal and embryonic BA with reference to the time of onset of symptoms, the presence of extrahepatic malformations and molecular analysis.
For the purpose of this article, we will concentrate on those entities considered to have a likely developmental origin, namely BASM, cystic BA and a subgroup of isolated BA.
The commonest classification for clinical use is the Japanese Association of Pediatric Surgeons (JAPS) classification (Fig. 1), which recognizes three types of BA, on the basis of the level of lumen obliteration:
Type 1 (3-5%): patency of proximal extrahepatic bile ducts with atresia of the distal (correctable biliary atresia)
Type 2 (2-6%): atresia of the common hepatic duct at different levels with the presence of a cyst at the hilum in about 5% of cases
Type 3 (> 90%): non patency of the entire extrahepatic biliary system and intrahepatic bile ducts at the hilum; in 20% of cases, gallbladder, cystic duct and common bile duct are patent. In the French classification, this subtype is the Type 3, while the Type 4 is the complete atresia

BA Splenic Malformation (BASM)

BA can present together with other congenital anomalies or be part of a syndrome. The term BASM was proposed by Davenport and colleagues to describe a subset of mainly female patients who present with BA and laterality defects such as polysplenia, asplenia, situs inversus and other associated anomalies. These associations have raised the hypothesis of a possible link between alterations in specific genes relevant for early liver development and BA. In fact, studies in mice, investigating effects of overexpression and in-

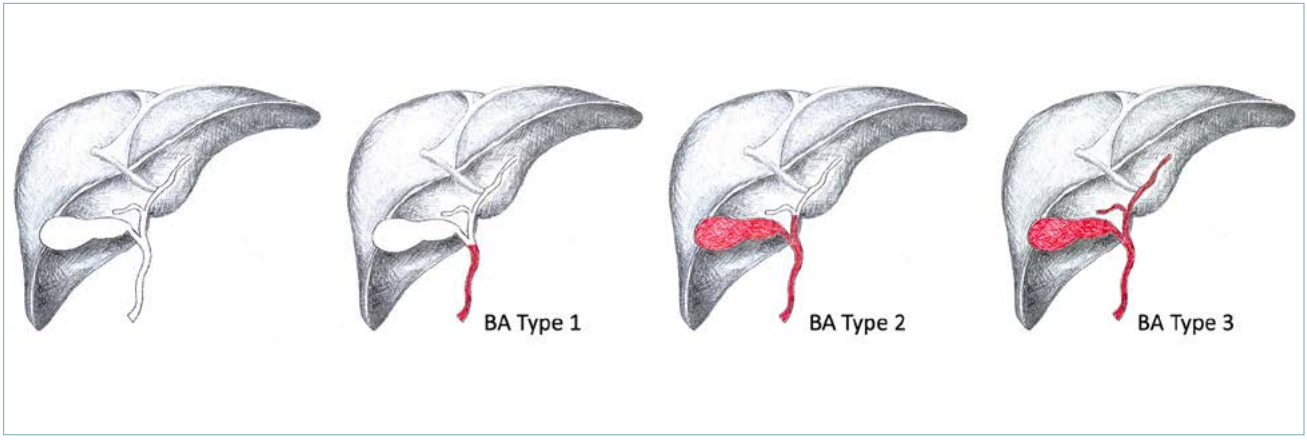

Figure 1. Types of biliary atresia (BA) according to the Japanese Association of Pediatric Surgeons (JAPS) classification. Type 1 BA is characterized by patency of proximal extrahepatic bile ducts with atresia of the distal tract (correctable biliary atresia); Type 2 BA with atresia of the common hepatic duct at different levels and the presence of a cyst at the hilum in about 5% of cases (correctable biliary atresia); Type 3 BA with non-patency of the entire extrahepatic biliary system and intrahepatic bile ducts at the hilum.

activation of genes involved in left-right patterning (for example *Invs* and *Lgr4*) have shown disruption of normal extrahepatic biliary system development. However, no gene mutations with a causative link to BA have so far been described in humans [23].

In a minority of cases there is an association with other congenital anomalies, such as esophageal or jejunal atresia, in the absence of laterality defects. These cases are different from the BASM spectrum.

While BASM is not currently considered a syndrome by the Online Inheritance in Man database (https://www.omim.org/), there are other recognized genetic syndromes which include BA, and for which a specific genetic cause has been identified. These syndromes include Mitchell-Riley Syndrome (caused by mutations in the Regulatory Factor X, 6 [*RFX6*]), Fanconi anemia complementation group Q (caused by mutations in the Excision-Repair Cross-Complementing group 4 [*ERCC4*]), and others.

Cystic BA

Cystic BA constitutes about 5-10% of cases, independently of geographical extraction, and is characterized by cystic dilatations in an otherwise obliterated biliary tract [22]. In a minority of cases cystic alterations are confined to the intrahepatic biliary ducts. Though difficult, due to its overlapping features with choledochal cysts on imaging, cystic BA can be detected prenatally by ultrasound scans [24,25]. Cysts have been shown to contain either mucus or bile, which in the case of the latter would imply an onset after establishment of continuity between the intrahepatic and extrahepatic bile ducts [22].

Isolated BA

Isolated BA, with a negative serological profile for hepatotropic viruses and in the absence of a syndromic pattern or specific causes, forms the largest clinical group of BA [22]. Little is known about the actual cause. However, some existing data address the presence of elevated direct bilirubin levels in neonates with a subsequent diagnosis of BA, raising the possibility of a biliary obstruction already present at birth, thus supporting the hypothesis of a possible developmental defect, at least in a subgroup of patients [26]. BA as a consequence of potential defects in prenatal circulation, supported by cases of BA with anatomic variants of the hepatic artery, has also been hypothesized.

All patients with BA present with a varying degree of jaundice, clay-colored stools and dark yellow urine. The severity of jaundice increases steadily. Failure to thrive, coagulopathy and anemia may also occur, and some infants will present with signs of advanced disease and cirrhosis (ascites, hepato-splenomegaly, prominent abdominal veins, respiratory discomfort). In comparison to the European or North American experience, most cases in developing countries present late.

Direct (conjugated) hyperbilirubinemia is the clinical and laboratory key feature of BA. Progression to end-stage cirrhosis, when untreated, is inevitable, thus the initial goal of clinical management is a prompt diagnosis.

The clinical diagnosis in infants less than 60 days of age can be difficult. Abdominal ultrasound may not visualize the gallbladder, but this finding is not absolute. A percutaneous liver biopsy can be considered to distinguish BA and other causes of neonatal jaundice; however, a fast response is mandatory to avoid the deleterious effect of uncorrected obstruction.

Interpretation of liver biopsies in this setting is challenging as the differential diagnosis of infantile cholestasis is vast and includes numerous obstructive and non-obstructive disorders. In addition, histological alterations of many of these conditions vary/evolve with time.

Generally liver histology displays signs compatible with obstruction of large ducts. These include edematous expansion of the portal areas, together with

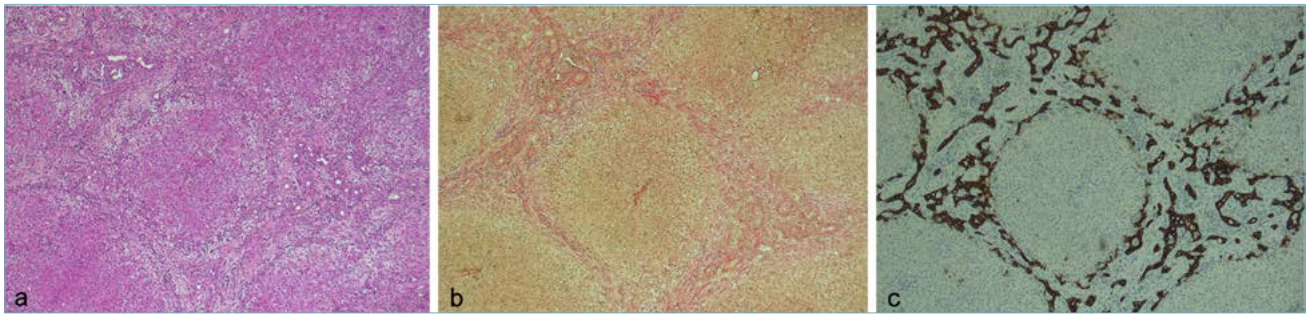

Figure 2. Biliary atresia, wedge biopsy in a 8 weeks old infant (a); H&E, x 50. (b); Van Gieson's elastic fibers stain, x 50. (c); Cytokeratin 7, x 50). Portal expansion, bridging fibrosis with significant bile duct and ductular proliferation.

prominent ductular proliferation and bile plugs (Fig. 2). Interlobular bile ducts appear tortuous with deformed contours and show degenerative changes of the lining epithelium. An intense inflammatory reaction, with activated mononuclear cells, can be present and tends to progress with time.

After the first few weeks of life nearly all portal areas are expanded by fibrosis, giving way to bridging fibrosis and early nodular transformation which will eventually lead to secondary biliary cirrhosis.

The Biliary Atresia Research Consortium (BARC) has developed a standardized histologic reporting system for evaluation of liver biopsies from infants with cholestasis, which recommends assessment of 26 discrete histological features [27].

Apart from its diagnostic role, histology also holds the possibility to identify prognostically significant histological features, helpful in the prediction of possible outcomes after Kasai portoenterostomy.

Sometimes the interpretation of a biopsy can be difficult as there is marked overlap in the histological finding of BA and neonatal hepatitis.

Currently BA is being managed in two stages. The first stage involves the Kasai operation, which should be performed before 6-8 weeks of age, because hepatic fibrosis progresses rapidly. Essentially, all extrahepatic biliary remnants are excised, leaving a denuded portal plate, to which a Roux-en-Y jejunal loop is anastomosed to reconstruct the biliary tract (portoenterostomy). The key observation at laparotomy is presence or absence of bile in the gallbladder. In most infants, the gallbladder is absent or fibrotic, which makes cholangiography impossible. If the gallbladder is present, injection of radiographic contrast shows whether bile ducts are patent from the liver to the duodenum. If BA is confirmed, then the operation is carried on. If the bile flow is not restored by the Kasai procedure, then consideration should be given to liver transplantation as a second stage. In these patients, transplantation is planned within 12-16 months. In infants who remain jaundiced but with stabilization of the progression of liver disease, extended survival can be expected. However, most patients will ultimately require a liver transplantation within a few years [28].

Choledochal Cysts (*Congenital Choledochal Malformation*)

Choledochal cysts (CC) are congenital bile duct anomalies, characterized by cystic segmental dilatations of the extrahepatic biliary radicles, the intrahepatic biliary radicles, or both [29].

The anomaly is very rare in Western Countries, occurring in 1 in 150,000 live births, while it is more frequent in Asia, and particularly in Japan (1 in 1000 to 1 in 1750 live births) [30]. The M:F ratio is 4:1 and although it is thought to be congenital, patients often present later in childhood or adulthood [31,32]. Most frequently, choledochal cysts are classified according to the Todani revision of the initial classification by Alonzo-Lej and colleagues in 1959 [33].

The anatomic classification recognizes five main variants, of which type I is by far the most frequent (Tab. I). Type I accounts for 50-80% of cases, while type II, III, IV and V account for 2%, 1.4-4.5%, 15-35% and 20%, respectively [34].

The precise etiology of choledochal cysts has yet to be elucidated. Multiple theories have been postulated, the most popular of which hypothesizes an anomalous pancreaticobiliary junction at the base of the cyst development in types I and IV, and was brought forward by Babbitt in 1969 [35]. Others have hypothesized a purely congenital etiopathogenesis due to a reduction of ganglionic cells in the distal common bile duct, thus leading to dilatation of its proximal segment [36]. For type II and type III, biliary duplication cysts and ciliary/duodenal duplication cysts respectively have been discussed to be causative, while type V, commonly known as Caroli disease, is thought to be caused by a premature arrest in the ductal plate remodeling. Caroli disease is also associated with both, autosomal recessive and dominant polycystic kidney disease [34].

CC has been widely accepted to be a premalignant state with cancer occurring more often and earlier in these patients [34]. The risk of cancer increases with age. A meta-analysis found that 11% of almost 3000 patients developed cancer with a poor 5-year survival rate of approximately 5% [37]. The associated cancer types in decreasing frequency are adenocarcinoma (73-84%), anaplastic carcinoma (10%), undifferenti-

Table I. Choledochal cysts according to the Todani Classification.

Type	Description
Type I	Cystic or fusiform dilatation of the common duct; right and left hepatic ducts and intrahepatic bile ducts are normal
Type II	Diverticular malformation of the common bile duct; the entire intrahepatic and extrahepatic biliary tree is normal
Type III	Choledochocele (cystic dilatation of distal common bile duct, which enters the duodenum)
Type IV	Multiple cysts of either intrahepatic and extrahepatic, or exclusively extrahepatic bile ducts.
Type V	Single or multiple intrahepatic cysts with normal extrahepatic bile ducts; when cysts are associated with fibrosis, they have been referred to as Caroli's disease

ated cancer (5-7%), squamous cell carcinoma (5%) and others (1,5%) [34]. In Caroli's disease, the risk for developing cancer is 7-15%.
With regard to age and time of presentation, there are two clinical distinct groups of patients.
Infants less than 6 months of age present with obstructive jaundice and hepatomegaly. Bile flow may cease after 3 to 6 weeks, indicating that the dilated duct may angulate and obstruct. Fever from cholangitis may be frequently present. This form is indistinguishable from that of biliary atresia.
In older patients, symptoms occur after 2-4 years of age and are mostly abdominal pain and jaundice. Pain may be related to distension of the cyst or cholangitis. Children may also have intermittent biliary obstruction or recurrent bouts of pancreatitis [38].
In case of jaundice, laboratory tests demonstrate conjugated hyperbilirubinemia and hyperamylasemia. The abdominal ultrasound is the technique of choice for the diagnosis of a choledochal cyst, and it is also diagnostic during the prenatal period [39]. MRI may help in delineating the anomaly and the surrounding structures [40,41].
The treatment of choice for choledochal cysts is complete excision of the cyst with construction of a biliary-enteric anastomosis to restore continuity with the gastrointestinal tract, which can also be performed through a laparoscopic procedure [42-44].

Pancreas

Pancreatic Agenesis and Hypoplasia

Agenesis or hypoplasia of the whole pancreas are very rare anomalies with only a few cases reported so far [45-47]. Agenesis of the dorsal pancreas (ADP) is slightly more frequent and around 100 cases have been published in the literature [48]. ADP is characterized by the absence of the pancreatic body and tail, while absence of the pancreatic tail only is defined as partial ADP. Most patients are asymptomatic, and ADP is an incidental finding on abdominal imaging. Little is known about the pathogenesis of ADP, but an association with pancreatitis, either acute or chronic, has been observed [48].

Pancreas Divisum

Pancreas divisum (PD), resulting from failed fusion of the ventral and dorsal pancreatic ducts, is the most frequent malformation of the pancreas with a prevalence of about 10% in Western populations [49].
In this anatomic situation, the dorsal pancreas drains through the duct of Santorini, while the ventral pancreas drains through the duct of Wirsung. The exact mechanisms underlying the failed fusion of the ventral and dorsal parts has yet to be elucidated. This congenital anomaly has been identified in 3-7% of patients undergoing ERCP, while its incidence in autopsy cases has been described to be as high as 9% [3].
PD is asymptomatic in most cases and it has been estimated that less than 5% of people with PD develop symptoms due to altered anatomy [50]. An obstruction to pancreatic exocrine secretory flow due to a relative stenosis of the minor papilla with subsequent pancreatitis appears to be the cause of symptom onset [51,52].
Three clinical conditions are associated with PD: recurrent acute pancreatitis (characterized by recurrent episodes of abdominal pain with increase in amylase and lipase in the absence of changes suggestive of chronic pancreatitis on ERCP, MRI, and CT scan); chronic pancreatitis, characterized by pain associated with the presence of pancreatic calcifications, intraductal stones, pseudocysts; "pancreatitic-like" abdominal pain without evidence of clinical and radiological pancreatitis [53].
In about 15% of cases, PD is associated with cystic dilatation of the terminal portion of the pancreatic duct (so called Santorinicele), first described by Eisen et al in 1994, characterized by a stenotic appearance of the minor papilla, which worsens after administration of secretin [54].

Annular Pancreas

Annular pancreas (AP) is a rare congenital anomaly, with an estimated incidence of 1 in 1000-6000 people, in which a ring of pancreatic tissue encircles completely or partially the second portion of the duodenum [55,56]. In 1978 Johnston described two different forms of AP, extramural and intramural [57]. Extramural AP is characterized by a flat band of pancreatic tissue overlaying the duodenum and an anteriorly born duct which encircles the duodenum and joins the main pancreatic duct. Intramural AP is characterized by ectopic pancreatic tissue within the duodenal wall. In this scenario, numerous small ducts drain directly into the intestinal lumen.
Two main hypotheses, the theories of Lecco and Baldwin, have been proposed in order to explain the etiopathogenesis of extramural AP. Lecco's theory postulated the adherence of the right ventral bud to the duodenal wall with subsequent encircling of the intestine as a consequence of normal foregut rotation, while in Baldwin's theory it's the persisting left ventral bud, which encircles the duodenum. Intramural AP is associated with duodenal atresia [58]; in extramural AP, the duodenal atresia/obstruction appears related to a mechanical effect [59,60].

In the neonatal period, the clinical picture is dominated by epigastric distension with non-biliary vomiting, as the obstruction is usually supravaterian (above the junction with the bile ducts), and more than 60% of affected neonates have associated anomalies, such as congenital heart defects, tracheoesophageal fistula and aneuploidies [61,62].
Histologically, the annular tissue is identical to the normal pancreatic tissue. Thus, it is subject to the same pathological processes. Intermingling of pancreatic tissue with the duodenal wall muscles has been described [63].
AP generally represents an additional incidental finding at laparotomy for duodenal atresia. This anomaly may be discovered at prenatal US, which shows a classic double bubble sign (stomach and first duodenal segment dilated). After birth, the baby is evaluated with abdominal X-ray, which shows the same sign. Surgery is the treatment of choice and consists in a "Diamond shaped" duodenal-duodenal anastomosis.

Pancreatic Heterotopia

Pancreatic heterotopia/ectopia (PE), defined as the presence of pancreatic tissue outside its physiological location and without vascular or other anatomical connections to the native pancreas, is a frequent condition, largely occurring within the gastrointestinal tract [64]. It is widely accepted that most ectopic pancreatic rests, with the exception of pancreatic metaplasia in chronic atrophic gastritis, represent congenital heterotopias, rather than metaplasias [64].
In comparison to other congenital anomalies, PE, which occurs in similar rates among men and women, is a relatively frequent anomaly, having been identified in 2% to 15% of autopsy studies [65].
PE has been identified in various locations; however, it is most frequently encountered in the gastrointestinal tract, and particularly in the stomach, duodenum and the first part of the jejunum.
Little is known about the precise etiopathogenesis of PE. The most widely accepted theory postulates a misplacement of pancreatic tissue fragments during embryonic foregut rotation and fusion of central and dorsal pancreatic buds.
Clinically, most PE are asymptomatic. However, larger lesions, especially when located in the stomach, can cause epigastric pain, postprandial nausea and vomiting, weight loss, dyspepsia, malabsorption, bleeding, gastric outlet occlusion and intussusception, ruptured cysts and pseudocysts [66].
From a histopathological point of view, PE can be classified according to the Heinrich's Classification: type 1, characterized by acini ducts and endocrine islet cells; type 2, similar to type 1 but without islet cells; type 3, characterized by pancreatic ducts only [67].
Large heterotopias have been known to display intraepithelial pancreatic neoplasia [68]. While true neoplastic transformation appears to be exceedingly rare, other neoplasms such as ductal adenocarcinoma and neuroendocrine tumors have been described [69,70].
Islet cell adenomatous hyperplasia in PE with subsequent hyperinsulinism has been described as well [71,72].

Anomalous Pancreaticobiliary Junction (APBJ)

It is a rare congenital anomaly with an incidence of 1.5-3% of patients undergoing endoscopic retrograde cholangiopancreatography (ERCP); in this anomaly, the junction of the pancreatic and bile ducts are outside the duodenal wall, approximately 1-2 cm from the Oddi sphincter [3,73]. The precise etiopathogenesis has yet to be elucidated.
APBJ occurs with or without biliary dilatation and choledochal cyst in more than 90% of cases [74,75].
Due to the abnormal long channel and subsequent lack of control of the duodenal papillary sphincter on the pancreaticobiliary junction, regurgitation occurs, with subsequent development of pancreatitis, hepatitis, and ultimately biliary carcinoma [3,74].
Biliary carcinogenesis in these cases appears to be triggered by recurrent reflux and stasis of bile and pancreatic juices. Carcinoma of the gallbladder and of the biliary tract in the setting of non-dilated APBJ has been reported to be as high as 36.1% and 4%, respectively [76].
Numerous classification systems, based on type of confluence between the pancreatic and distal common bile ducts, have been proposed, none of which has been widely accepted.
The most recent classification system of the Japanese Study Group of Pancreaticobiliary Maljunction comprises four types: A) stenotic type, B) non-stenotic type, C) dilated channel type and D) complex type.
Histological and immunohistochemical studies in non-dilation APBJ have shown how the ventral and dorsal pancreatic buds fuse obliquely, instead of parallel, thus giving possibly rise to the long common channel [77].

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