

Liver biopsy interpretation in the differential diagnosis of autoimmune liver disease in children

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Abstract

Autoimmune liver disease (AILD) represents a group of complex inflammatory liver diseases, all characterized by an aberrant autoreactivity against hepatocytes and/or biliary structures. AILD may be subclassified into four major diseases: autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), and autoimmune cholangitis (AIC). Recently a new entity frequently associated with autoimmune pancreatitis and defined IgG4-related cholangitis (IgG4-RC), has been added to the spectrum of AILD. The most frequent autoimmune liver diseases of the AILD spectrum occurring in children and in young adults are AIH and PSC, overlap syndrome between AIH and PSC, also

defined as autoimmune sclerosing cholangitis (ASC), representing a frequent finding in pediatric patients. Here, the morphological findings that may help liver pathologists in the differential diagnosis of AILD in pediatric patients are reviewed, underlying the frequency in liver biopsy interpretation of complex cases in which a precise diagnosis may remain controversial, due to overlap of hepatocytic and bile duct cell lesions. Among the multiple morphological changes typical of AILD, the detection of an high number of plasma cell clusters in the portal and periportal regions is generally considered one of the main clue for the diagnosis of AIH. The recent report in a 13-year old boy of IgG4-associated cholangitis, induces pathologists when detecting a huge number of plasmacells, to consider the differential diagnosis between AIH and IgG4-RC.

Keywords

Autoimmune liver disease, IgG4-related disease, autoimmune sclerosing cholangitis, children, autoimmune hepatitis.

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Introduction

Autoimmune liver disease (AILD) represents a group of complex inflammatory liver diseases, all characterized by an aberrant autoreactivity against hepatocytes and/or biliary structures, occurring in genetically susceptible individuals, resulting from the interaction between environment and the genetic background of the host [1]. AILD may be subclassified into four major diseases: autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), and autoimmune cholangitis (AIC). Recently a new entity frequently associated

with autoimmune pancreatitis and defined IgG4-related cholangitis (IgG4-RC), has been added to the spectrum of AILD [2] (**Fig. 1**). The borders among the autoimmune diseases included within the AILD spectrum are not sharp: each of these entities may show overlapping clinical, laboratory and histological features and, on occasion, one entity may transform into another, suggesting that they may be considered part of a spectrum of one complex liver disease [3]. The most frequent autoimmune liver diseases of the AILD spectrum occurring in children and in young adults are AIH [4] and PSC [5], overlap syndrome between AIH and PSC, also defined as autoimmune sclerosing cholangitis (ASC), representing a frequent finding in pediatric patients (**Fig. 2**) [6, 7]. On the contrary, PBC should be considered an

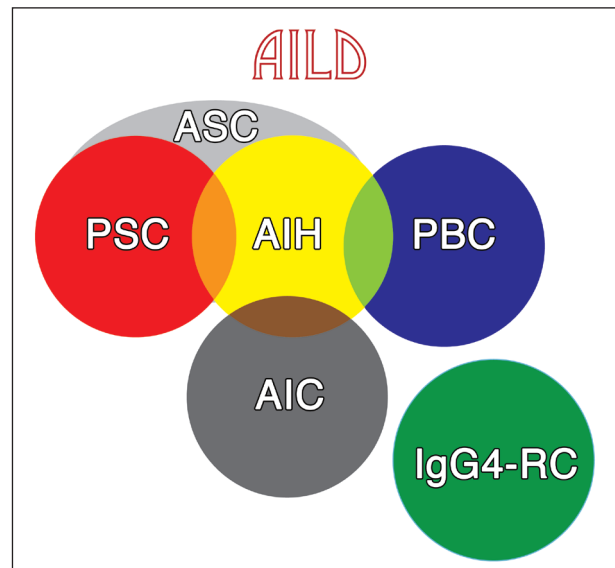


Figure 1. AILD subclassification into four major diseases: autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), autoimmune cholangitis (AIC) and the new entity IgG4-related cholangitis (IgG4-RC).

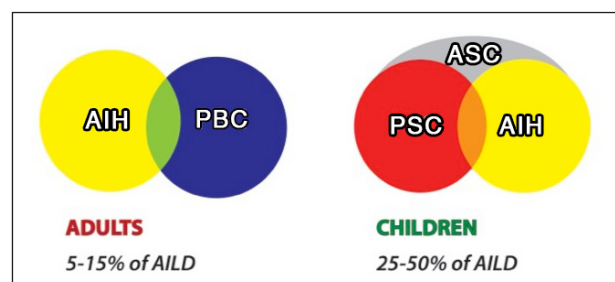


Figure 2. The most frequent autoimmune liver diseases of the AILD spectrum occurring in children and in young adults: AIH, PSC and overlap syndrome.

autoimmune disease restricted to adult patients, only very rare cases having been documented in pediatric patients [8, 9].

Here we will focus on the morphological findings that may help pathologists in the differential diagnosis of AILD in pediatric patients, underlying the frequency in liver biopsy interpretation of complex cases in which a precise diagnosis may remain controversial, due to overlap of hepatocytic and bile duct cell lesions. We will try to give an answer to the following questions frequently emerging during liver biopsy interpretation:

- a. Which morphological lesions are indicative of AILD?
- b. May immunohistochemistry help in AILD diagnosis?
- c. Which lesions are specific or characteristic of each single entity included in the AILD spectrum?

A) Which morphological lesions are indicative of AILD?

Portal tracts represent the liver district mainly affected in AILD. As a consequence, the pathologist should focus on the sequential examination at intermediate/high power of all portal tracts, in order to evidence the elementary lesions that might induce to consider the diagnostic hypothesis of AILD in a needle liver biopsy performed in a child. The most important elementary lesions that could help in the diagnosis of autoimmune liver disease will be here summarized, and their occurrence and diagnostic significance in pediatric patients will be underlined.

1. Bile duct cell vacuolization. Portal tracts may show sometimes a normal architecture. The presence of small clear vacuoles in the cytoplasm of bile duct cells, often associated with irregularities in the shape and staining of nuclei, may represent the unique pathological change, whose presence should induce to hypothesize the presence of a biliary disease (Fig. 3).
2. Lymphocytic cholangitis. The presence of small lymphocytes on the inner side of the basal membrane encircling bile ducts is considered a certain sign of an inflammatory destructive process of intrahepatic bile

ducts (Fig. 4). Lymphocytic cholangitis is typically found in primary biliary cirrhosis as well as in autoimmune cholangitis. Its presence has been also reported in about 10% of autoimmune hepatitis. This elementary lesion sometimes may be easily identified in liver biopsy (Fig. 5a), whereas in other occasions its identification in an inflamed portal tract may be difficult, requiring an accurate scanning of the affected portal tract (Fig. 5b).

3. Periductal lymphocytic aggregates, also known as lymphocytic nodules, are a certain sign of a destructive autoimmune process targeting the biliary tract. Remnants of the bile duct cells undergoing apoptosis may be occasionally detected in the center of the lymphoid aggregate (Fig. 6).

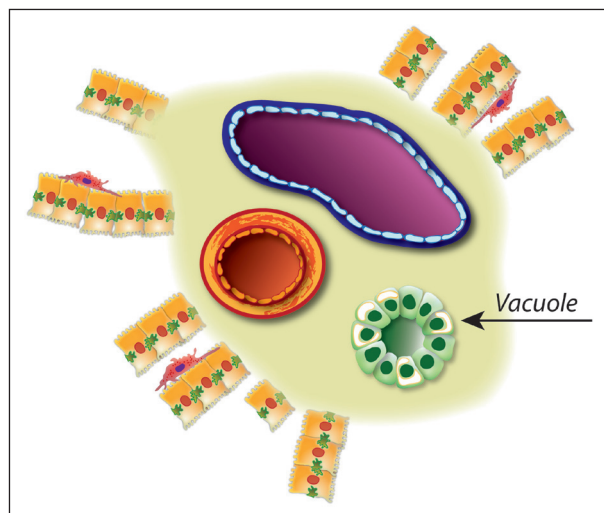


Figure 3. Bile duct cell vacuolization.

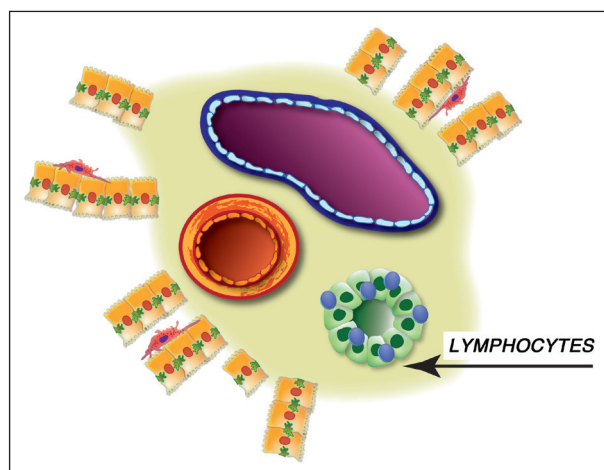
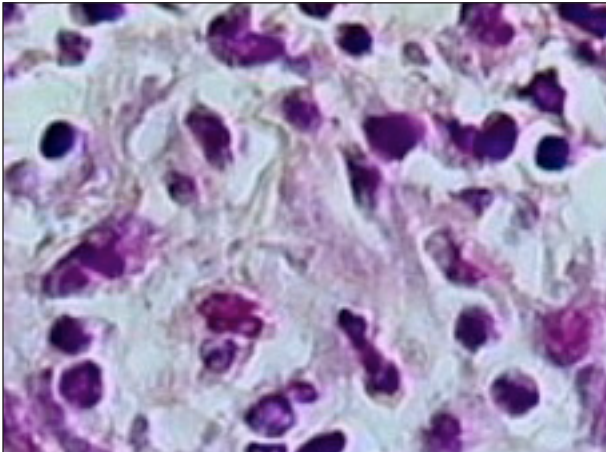


Figure 4. Lymphocytic cholangitis.

4. Ductular metaplasia of periportal hepatocytes is characterized by the expression of “biliary” cytokeratins (CKs) 7 and 19 by periportal hepatocytes, still bearing an hepatocellular phenotype. It is an early marker of chronic cholestatic disease (Fig. 7).

A.



B.

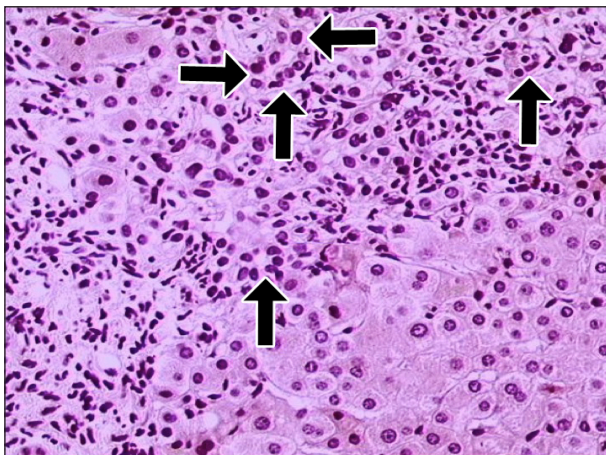


Figure 5. Lymphocytic cholangitis easily identified in liver biopsy (A), occasionally it may be difficult (B).

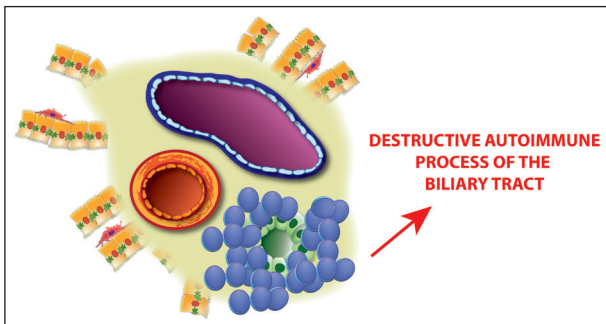


Figure 6. Periductal lymphocytic aggregates (lymphocytic nodules) and remnants of the bile duct cells occasionally detected in the center of the lymphoid aggregate.

5. Biliary interface activity. Previously known as biliary piecemeal necrosis, it refers to the disruption of the periportal limiting plate by proliferating biliary cells. This elementary lesion is related to the activation of stem/progenitor cells at the periphery of portal tracts, and may represent the main clue for the diagnosis of a disorder of the biliary tree (Fig. 8). It should be differentiated from lymphocytic piecemeal necrosis: proliferating biliary cells show an oval nucleus with clear chromatin, and a large cytoplasm. Immunoreactivity for CK7 may help in identifying proliferating biliary cells (Fig. 9).

6. Periductal concentric fibrosis. The onion-skin type of periductal concentric fibrosis, when

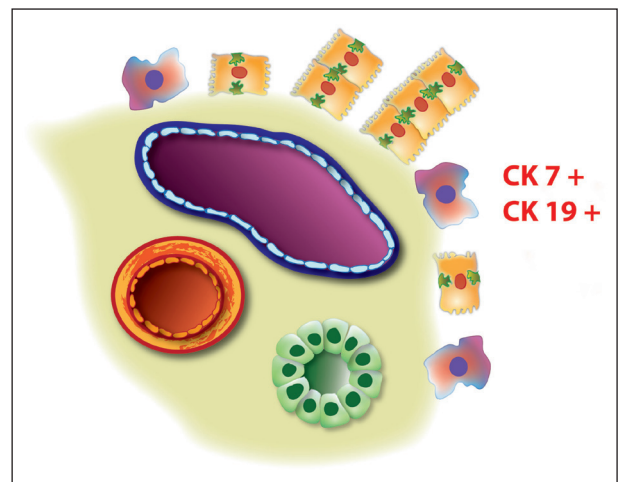


Figure 7. Ductular metaplasia of periportal hepatocytes characterized by the expression of “biliary” CKs 7 and 19 by periportal hepatocytes, still bearing an hepatocellular phenotype.

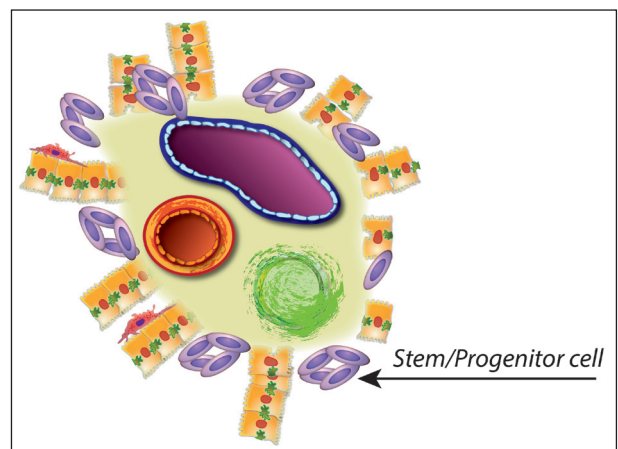


Figure 8. Biliary interface activity (biliary piecemeal necrosis) related to the activation of stem/progenitor cells at the periphery of portal tracts.

associated with fibro-obliterative cholangitis, is a common feature of PSC (**Fig. 10**). It is mainly observed around medium-sized and large bile ducts (**Fig. 11**).

7. Ductopenia. The absence of the septal duct in more than 50% of portal tracts is a certain sign of an ongoing destructive process of the intrahepatic bile ducts. It appears as roundish blocks of connective tissue, remembering a tombstone, located in close proximity of a branch of the hepatic artery, giving rise to the typical sign of “unaccompanied arteries” (**Fig. 12**). This lesion is considered a certain sign of an chronic ongoing destructive process of the biliary tract.
8. Portal epithelioid cell granuloma. The occurrence of a granuloma formed by large epithelioid cells with large cytoplasm surrounding remnants of a necrotic bile duct is highly indicative of a destructive process of intrahepatic bile ducts (**Fig. 13**). Moreover, this lesion is considered characteristic of primary biliary cirrhosis, being also detected in autoimmune cholangitis.
9. Plasma cell clusters. Interface hepatitis with predominant plasma cells extending from portal tracts towards periportal parenchyma, often encircling suffering hepatocytes, is one of the typical pathological changes highly suggestive for the diagnosis of autoimmune hepatitis (**Fig. 14**). Plasma cell clusters may be also found in primary biliary cirrhosis, and in recent years they have been reported in IgG4-related cholangitis [10]. In cases in which on H&E-stained sections the

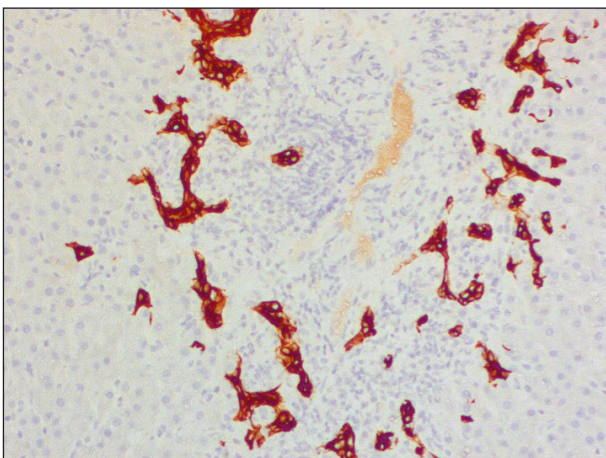


Figure 9. Proliferating biliary cells with an oval nucleus and a large cytoplasm, easily identified by immunoreactivity for CK7.

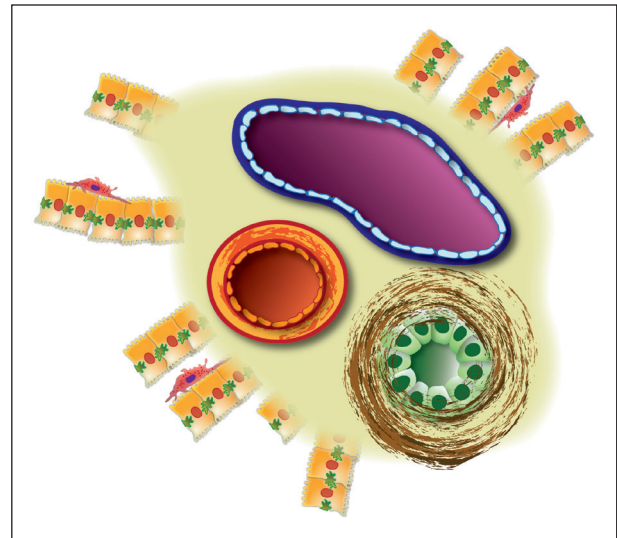


Figure 10. Schematic representation of periductal concentric fibrosis (onion-skin type).

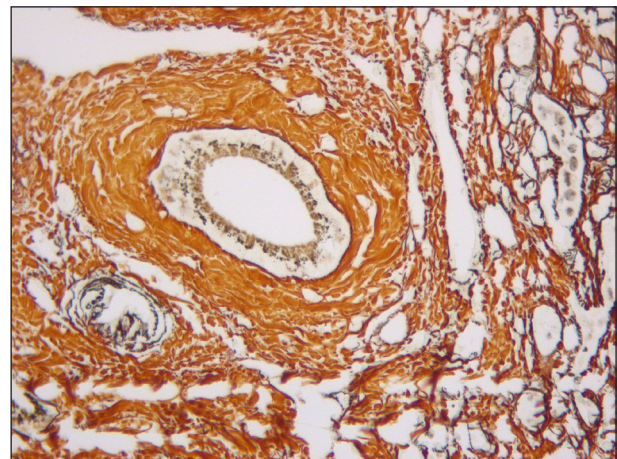


Figure 11. Histological picture of periductal concentric fibrosis (onion-skin type).

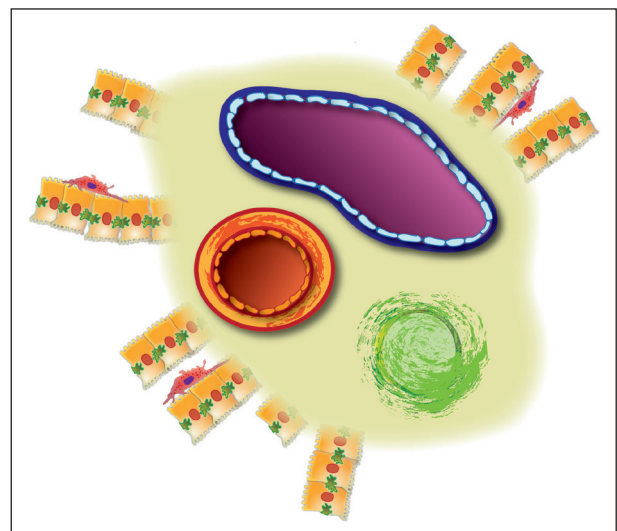


Figure 12. Ductopenia: roundish blocks of connective tissue (tombstone).

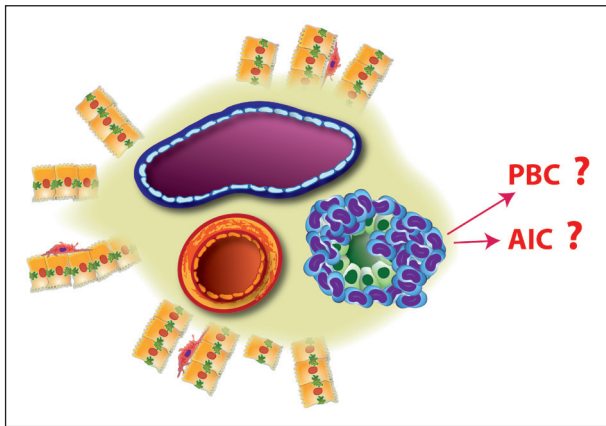


Figure 13. Portal epithelioid cell granuloma: large epithelioid cells with large cytoplasm surrounding remnants of a necrotic bile duct, highly indicative of a destructive process of intrahepatic bile ducts, such as PBC and AIC.

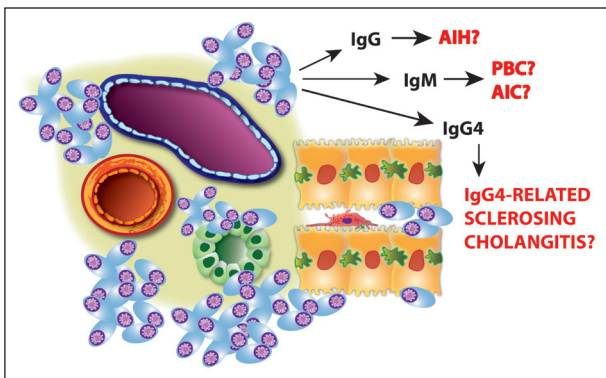


Figure 14. Plasma cell clusters as one of the typical pathological changes highly suggestive for the diagnosis of AIH that should be considered in the differential diagnosis with PBC, AIC and IgG4-RSC.

identification of plasma cells is not certain, immunohistochemistry for CD138 may be helpful, revealing the real amount of plasma cell infiltrate in portal tracts (Fig. 15).

10. Bilirubinostasis. This lesion should not be considered to be diagnostic for AILD, appearing only late in the natural history of autoimmune cholangitis and autoimmune hepatitis. Bilirubin storage, in the cirrhotic stage, may affect several liver compartments, including hepatocytes, bile canaliculi, and Kupffer cells (Fig. 16).
11. Centrilobular injury. The presence of necro-inflammatory lesions in terminal (centrolobular) veins, with polymorphonucleates surrounding the terminal vein, associated with swelling, detachment and apoptosis of the endothelial

layer, are frequently seen in AIH, but not in autoimmune cholangitis (Fig. 17).

12. Multinucleated giant cells. They are closely associated with AIH. May be detected in all acinar zones, have a large diameter reaching 30-40 micron, and show 4 or more nuclei (Fig. 18).

All these data taken together, clearly show that pathologists have several tools for the diagnosis of AILD: some of them are indicative for an immune attack against hepatocytes, and thus suggestive for the diagnosis of autoimmune hepatitis (Fig. 19); others indicate bile duct cells as the main target of autoimmunity, thus suggesting the diagnosis of vanishing bile duct disease; finally, others elementary lesions may be found both in AIH and autoimmune cholangitis, and simply indicate the presence of an autoimmune process targeting liver cells.

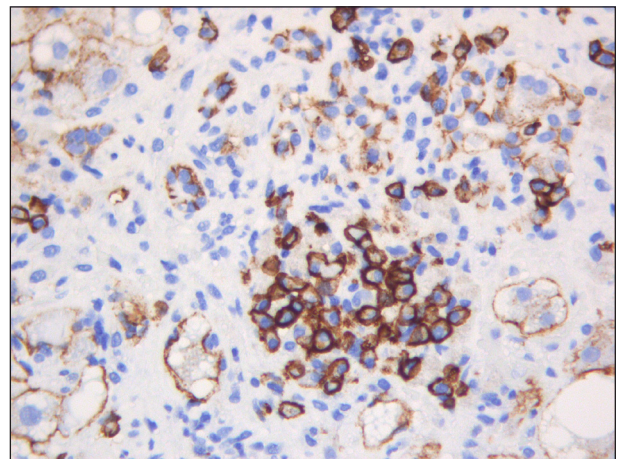


Figure 15. Immunohistochemistry for CD138 helpful in revealing the real amount of plasma cell infiltrate in portal tracts.

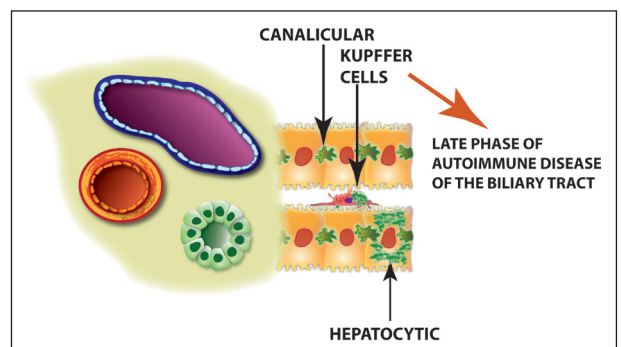


Figure 16. Bilirubinostasis may affect including hepatocytes, bile canaliculi, and Kupffer cells and appears only in late in the natural history of autoimmune cholangitis and autoimmune hepatitis.

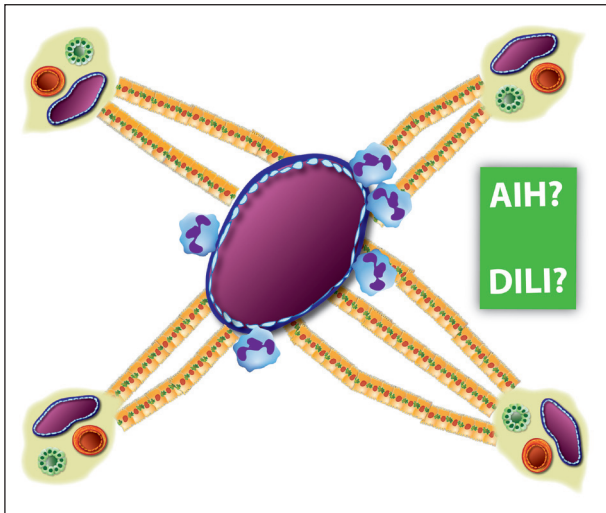


Figure 17. Centrilobular injury: necro-inflammatory lesions in terminal (centrolobular) veins, with polymorphonucleates surrounding the terminal vein, frequently seen in AIH, but not in autoimmune cholangitis.

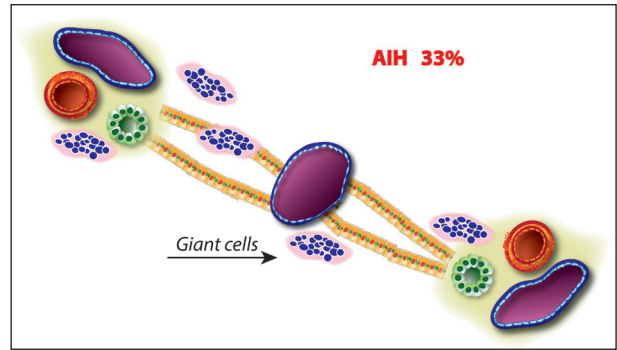


Figure 18. Centrilobular injury: necro-inflammatory lesions in terminal (centrolobular) veins, with polymorphonucleates surrounding the terminal vein, frequently seen in AIH, but not in autoimmune cholangitis.

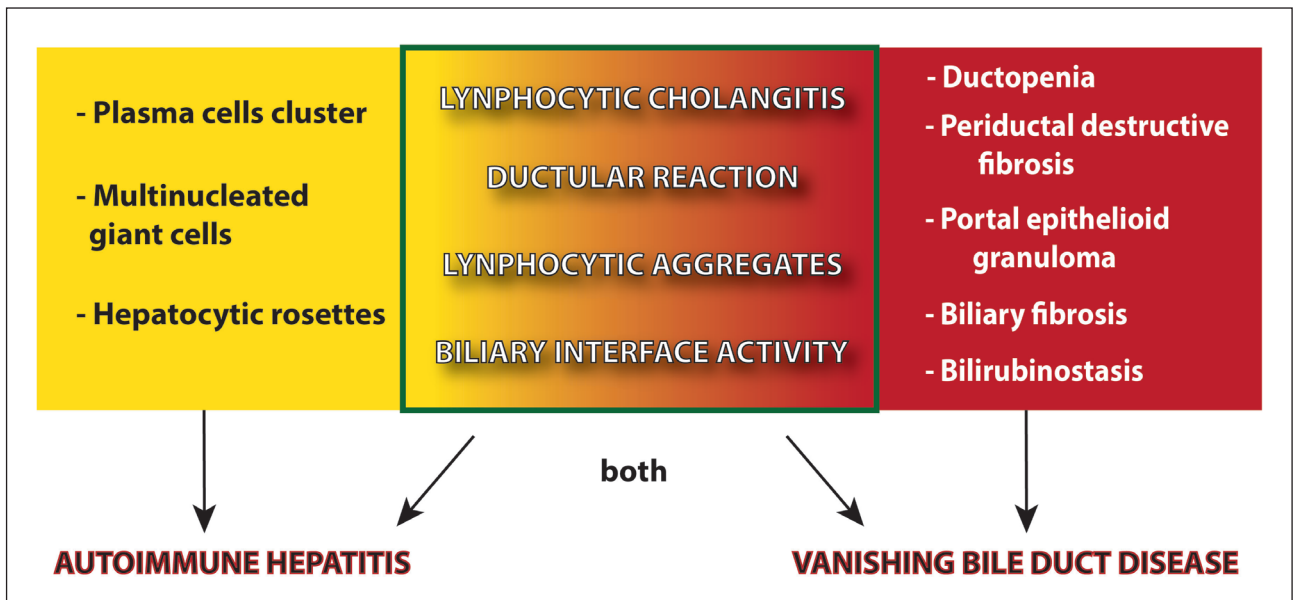


Figure 19. AILD morphological tools.

B) May immunohistochemistry help in the identification of a destructive process of the biliary tract?

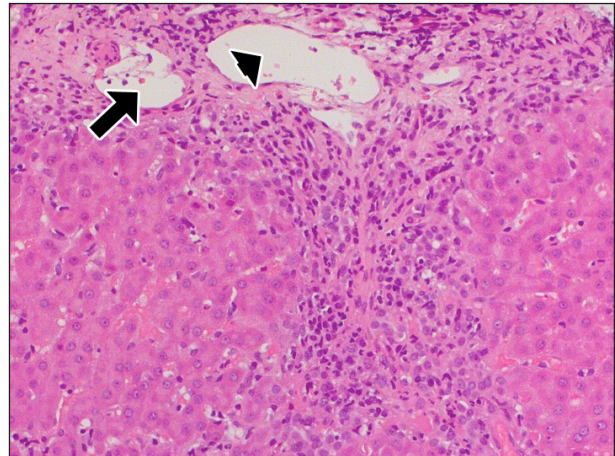
In some liver biopsies, and in particular in some portal tracts of children affected by autoimmune liver disease targeting hepatocytes or bile ducts or both, the identification of typical elementary lesions suggesting this pathological entities may be not immediately evident at H&E-stained sections. A strong inflammatory infiltrate extending from the inflamed portal tracts and obscuring the portal structures may be misleading,

forcing the pathologist towards a general diagnosis of “active hepatitis”, and giving very few useful data to clinicians or alternatively giving them a misleading information. In these cases, according with our experience, immunohistochemistry may be very useful for diagnostic purposes, revealing the involvement of the biliary structures that, at a first look, was completely missed. Ductular reaction with proliferation of single biliary cells, and neoductulogenesis at the periphery of portal tracts may be not clearly seen on H&E-stained sections, but they represent a certain sign that something is going wrong in the biliary

compartment. In particular, at the eyes of a surgical pathologist with a limited experience of liver biopsy interpretation in this peculiar field of liver disease, the presence of proliferating scarcely differentiated biliary cells, even when giving rise to ductal-plate-like images, may be overlooked. In order to avoid the possibility of missing a diagnosis of AILD and, in particular, of an autoimmune destructive pathology affecting the biliary tract, immunohistochemistry for CK7 may represent a useful tool for revealing the presence of biliary interface activity, the main clue for the diagnosis of a disorder of the intrahepatic bile ducts [11]. Here we will show some example of the ability of this simple technique, introduced in clinical practice by Valeer Desmet and Peter Van Eyken in the 80s of the previous century, and that represents nowadays one of the best stains in the interpretation of needle liver biopsy and in the diagnosis of vanishing bile duct disease [12, 13].

In **Fig. 20A**, a portal tract with a diffuse inflammation extending from the limits of the portal tract towards the surrounding parenchyma is seen. In this portal tract, the main pathological sign is the absence (or better the lack of evidence) of the septal bile duct. The hepatic artery (arrow) and of portal vein (arrowhead) are seen. In this case, only based on H&E-stained sections, we could simply say that lacking of evidence of the septal duct might induce to better analyze all portal tracts, in order to exclude ductopenia. CK7 immunohistochemistry of the same portal tract (**Fig. 20B**) reveals a tremendous periportal ductular reaction at the interface between portal tract and hepatocytes, an elementary lesions that represents the main clue for the diagnosis of a disorder of intrahepatic bile ducts. Several cell types are involved in this regenerative process of biliary cells at the periphery of this portal tract: we can see liver stem cells (arrowheads), appearing as single cells with an oval nucleus; newly formed ductules, without clear evidence of a lumen, proliferating and trying to form a new biliary network (short arrow; and finally newly formed ductules that encircle an area of connective tissue, giving rise to structures resembling the ductal plates (long arrow) physiologically present in the human fetal liver during development. Moreover, in the central area of the postal tract immunostained for CK7 the a newly formed small duct without lumen is seen, in the absence of the septal bile duct. Taken together, these data obtained by immunostaining the liver biopsy

A.



B.

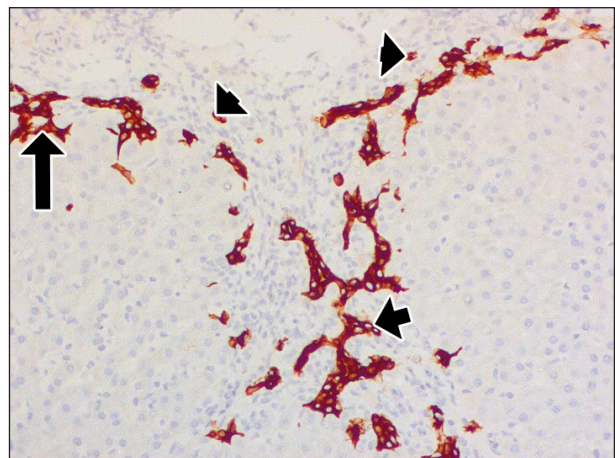


Figure 20. A. Portal tract with a diffuse inflammation extending from the limits of the portal tract towards the surrounding parenchyma and absence of septal duct; arrow: hepatic artery, arrowhead: portal vein; **B.** CK7 immunohistochemistry of the same portal tract reveals a tremendous periportal ductular reaction at the interface between portal tract and hepatocytes, including liver stem cells (arrowheads), appearing as single cells with an oval nucleus; newly formed ductules, without clear evidence of a lumen, proliferating and trying to form a new biliary network (short arrow); and newly formed ductules that encircle an area of connective tissue, giving rise to structures resembling the ductal plates (long arrow).

with antibodies against CK7 clearly indicate the presence of a destructive process of biliary structures, followed by the proliferation of liver stem/progenitor cells with activation of fetal programs typical of the developmental phase of the ductal plate.

Fig. 21A shows two typical bridging septa, extending from a portal tract (up-center) towards other vascular structures (bottom right and left). The bridging septua are characterized by

piecemeal necrosis of the periseptal limiting plate, a finding that is suggestive for activity of the hepatitis, compatible for viral or drug-induced or metabolic (Wilson's disease) liver disease. At examination of H&E-stained sections, such a picture does not contain any significant sign of involvement of the biliary tract. The same portal tract immunostained for CK7 (**Fig. 21B**) reveals a tremendous proliferation of biliary cells at the border of both bridging septa, clearly showing that the irregularity of the periseptal limiting plate is not due to inflammatory cells, but to isolated progenitor cells showing a biliary phenotype (arrowheads) and to biliary cells arranged in cords without lumen (short arrows) occasionally originating ductal plate structures (long arrow). Such an immunohistochemical picture clearly indicates an important involvement of the biliary compartment, aiding in the diagnosis of a destructive process of the bile ducts.

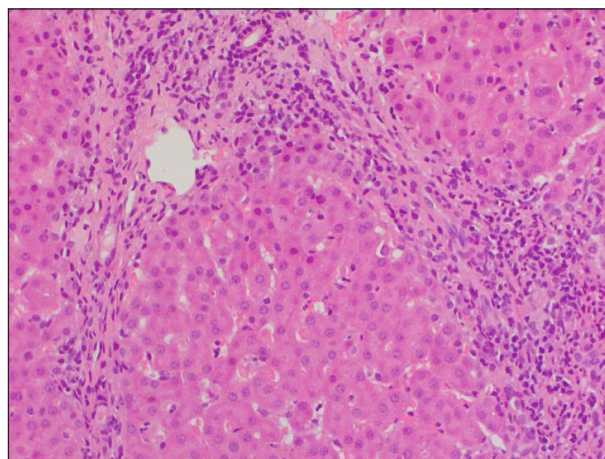
The two examples here reported clearly show that immunohistochemistry for "biliary type" cytokeratins may help in the diagnosis of autoimmune cholangitis, and suggest the use of CK7 immunostaining as a routine method to apply to every liver biopsy taken from pediatric patients, in order to avoid misleading diagnoses due to the inability of routine staining to evidence biliary reaction.

C) Which lesion is specific or characteristic of each disease within the AILD spectrum?

When during the analysis of liver biopsy we reach the evidence of an autoimmune process targeted to liver cells, the first question regards the identification of the exact target of autoimmunity: is it represented by hepatocytes, suggesting AIH, or by bile duct cells, suggesting a cholangitis, or by both hepatocytes and biliary cells, suggesting an overlap syndrome? (**Fig. 22**).

As stated before, the detection of an high number of plasma cells and in particular of plasma cell clusters in the portal and periportal regions is generally considered one of the main clue for the diagnosis of AIH. The recent report in a 13-year old boy of IgG4-associated cholangitis [14], should induce pathologists when detecting a huge number of plasmacells, to consider the differential diagnosis between AIH and IgG4-related cholangitis (IgG4-RC). The typical lesion of IgG4-related disease is the association of a lymphoplasmocytic sclerosing cholangitis with

A.



B.

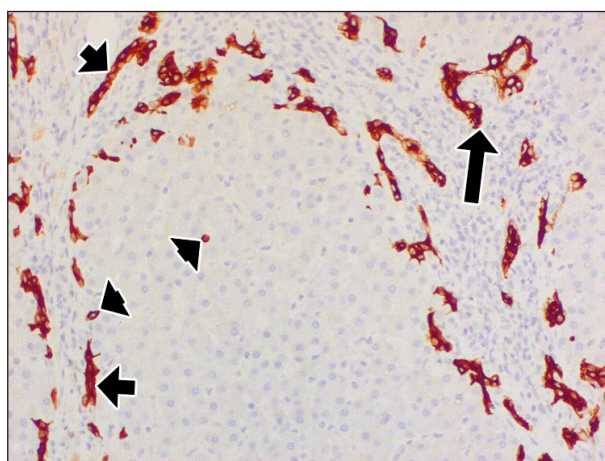


Figure 21. A. two typical bridging septa, extending from a portal tract (up-center) towards other vascular structures (bottom right and left), characterized by piecemeal necrosis of the periseptal limiting plate, without any significant sign of involvement of the biliary tract; B. the same portal tract immunostained for CK7 reveals a tremendous proliferation of biliary cells at the border of both bridging septa, clearly showing that the irregularity of the periseptal limiting plate is not due to inflammatory cells, but to isolated progenitor cells showing a biliary phenotype (arrowheads) and to biliary cells arranged in cords without lumen (short arrows) occasionally originating ductal plate structures (long arrow).

autoimmune pancreatitis, an association that is at the origin of the definition of pancreatocholangitis [15]. The unified nomenclature as IgG4-related disease (IgG4-RD) has been recently proposed [16]. Other than pancreas and the biliary tract, other common sites of involvement in IgG4-RD are salivary glands, orbit, lymph nodes, but any organ can be involved in this multi-system disease, often characterized by the emergence of pseudotumors in different organs [17]. IgG4 disease affecting the

biliary tree may exhibit multiple morphological changes: sclerosing cholangitis characterized by segmental fibrosis of the bile duct wall associated with extensive inflammation, mainly localized at the liver hilum and at extrahepatic bile ducts (**Fig. 23**). Variable histological changes may be encountered when a needle liver biopsy is taken in these patients (**Fig. 24**). Portal tracts may be normal, in cases in which the pathological process is restricted to the parahilar liver regions. More frequently, the finding of a strong plasmocytic infiltrate may represent the diagnostic clue, with more than 50 IgG4-positive plasmacells per high power field and with a ratio IgG4/IgG plasmacells superior to 40% [10]. These strict criteria are due to the fact that IgG4-positive plasmacells are not specific of this disease, being

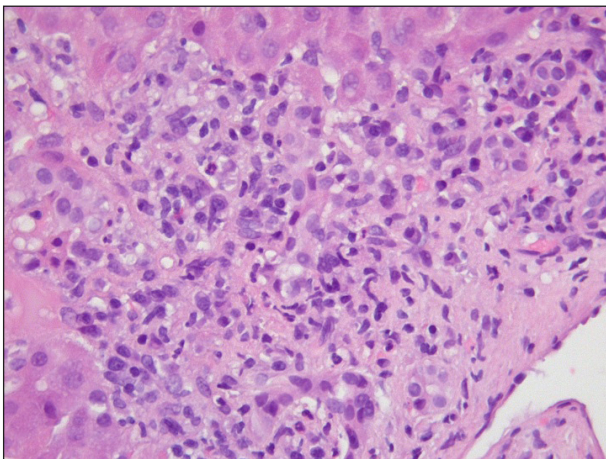


Figure 22. Identification of the exact target of autoimmunity: hepatocytes, suggesting AIH, bile duct cells, suggesting a cholangitis, or by both hepatocytes and biliary cells, suggesting an overlap syndrome.

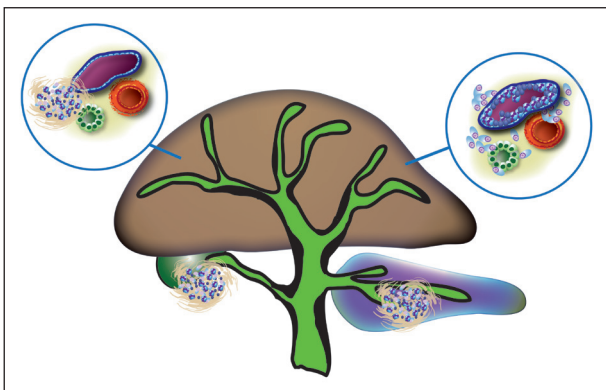


Figure 23. Multiple morphological changes of IgG4 disease: sclerosing cholangitis characterized by segmental fibrosis of the bile duct wall, extensive inflammation, mainly localized at the liver hilum and at extrahepatic bile ducts.

encountered in liver biopsy in AIH as well as in other hepatitis. Another typical feature in liver biopsy of patients with IgG4-RD is obliterative phlebitis, characterized by an intense inflammatory infiltrate involving the wall of small portal veins, ending with the obliteration of the lumen. Finally, periportal small inflammatory nodules, consisting of inflammatory cells, including plasmacells and eosinophils intermingled with fibroblasts and myofibroblasts, sometimes represent a typical lesion of IgG4-RD [18].

IgG4-RD should be always considered in the differential diagnosis when many plasmacell clusters are present in portal tracts and in the periportal areas. Pathological features less likely representing IgG4-RD are: 1) periductal onion-like concentric destructive fibrosis: this lesion is typical of PSC and, particularly in children, it may be observed in ASC, the overlap syndrome between AIH and PSC that is diagnosed in about 50% of pediatric patients with AIH [7]. PSC is strictly associated in children with a particular form of idiopathic bowel disease, showing features not typical of ulcerative colitis neither of Chron's disease [5]; 2) ductopenia, a typical lesion of PBC and PSC, that has never been reported in IgG4-RD; 3) portal epithelioid granulomas involving a bile duct, a lesion typical of PBC and of AIC, has never been described in IgG4-RD; 4) few IgG4-positive plasmacells, when their number does not reach ten cells per high power field, excludes the diagnosis of IgG4-RD, being detected in the majority of AILD (**Fig. 25**).

Liver biopsy may have a significant role in the differential diagnosis between IgG4-related sclerosing cholangitis and a new form of sclerosing cholangiopathy recently described in pediatric patients: sclerosing cholangitis with granulocyte epithelial lesion (GEL), characterized by a low number of plasmacells and by the a predominance in the portal infiltrate of polymorphonucleates surrounding and infiltrating damaged bile ducts. In a recent retrospective study carried out on 103 children with a previous diagnosis of ASC, reevaluation of liver biopsies evidenced the presence of GEL in 4 cases (4%), all characterized at cholangiogram by diffuse stricturing of bile ducts indistinguishable from that seen in patients with IgG4-RD, underlying the importance of considering such an entity in the differential diagnosis of sclerosing cholangitis in childhood, in view of its excellent response to immunosuppressive treatment [19].

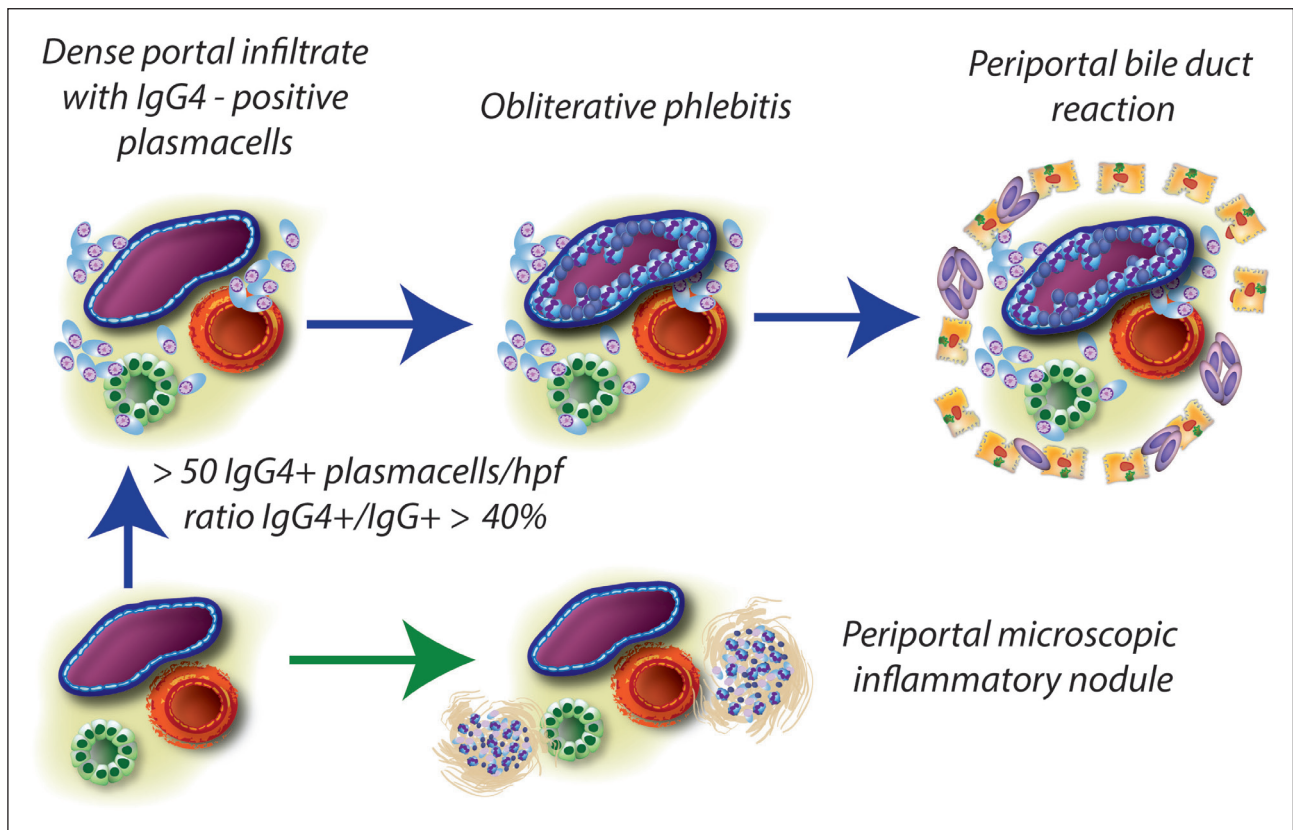


Figure 24. Morphological feature of portal tracts in IgG4-RSC: normal, strong plasmocytic infiltrate (more than 50 IgG4-positive plasmacells HPF and IgG4/IgG ratio superior to 40%), obliterative phlebitis, periportal bile duct reaction, periportal microscopic inflammatory nodule.

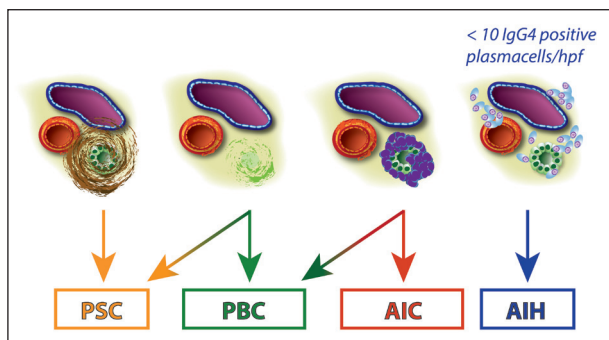


Figure 25. Schematic features less likely to represent IgG4-RDS: 1) periductal onion-like concentric destructive fibrosis; 2) ductopenia; 3) portal epithelioid granulomas; 4) few IgG4-positive plasmacells.

Conclusions

In conclusion, liver biopsy interpretation in children affected by autoimmune liver disease may be very useful for a precise definition of the disease, particularly in cases in which the autoimmune process is targeted towards both hepatocytes and bile duct cells, with overlap between different pathological entities at ckinical, laboratory and eventually at histological level. The complexity

of the differential diagnosis between the multiple diseases you may find within the spectrum of AILD asks for the formation of expert pathologists in the interpretation of liver disease, and for the dialogue between pathologists, radiologists, and clinicians in order to reach a definitive diagnosis and the best therapy for affected children. Many are the peculiarities of autoimmune liver disease in children, as compared with adults, that should be taken into consideration in clinical practice [20]: the rarity in childhood of PBC; the rarity of IgG4-RD, that putatively might also related to the scarcity of knowledge of this “new” entity by pediatricians; the strict association between AIH and PSC (autoimmune sclerosing cholangitis); the frequent association between PSC and IBD in children; the reported possible evolution restricted to children from AIH to ASC over the years [21].

A finding rarely reported in the literature, but frequently discussed in debates on the histopathology of AILD in children, is the possibility that the inflammatory portal infiltrate may be very low in patients with certain clinical and laboratory signs of autoimmune disease. This finding represents, at the best of our knowledge,

a peculiar finding of AIH in children, that should be taken in consideration by liver pathologists, in order to not exclude the diagnosis of AILD, but simply describe the “mute” histological pattern in these complex cases.

Finally, according to data collected by Kings College hospital in London, a marked increase in the yearly prevalence of AILD in childhood should be taken in account by pediatricians: whereas in the 1990s AILD was diagnosed in 2.3% of children older than 4 months admitted to this hospital, in the 2000s their incidence rised to about 12% [6, 7]. This increase induces to consider the diagnosis of AILD, and particularly of ASC, i. e. the association of AIH with PSC, in the differential diagnosis of liver disease presenting in children, by asking magnetic resonance cholangiography in all children presenting with autoimmune features.

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Declaration of interest

The Authors declare that there is no conflict of interest.

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