[75] G. Jia, M. Kwon, H. L. Liang et al., "Chronic treatment with lisinopril decreases proliferative and apoptotic pathways in autosomal recessive polycystic kidney disease," *Pediatric Nephrology*, vol. 25, no. 6, pp. 1139–1146, 2010.

[76] F. Park, W. E. Sweeney Jr., G. Jia et al., "Chronic blockade of 20-HETE synthesis reduces polycystic kidney disease in an orthologous rat model of ARPKD," *American Journal of Physiology*, vol. 296, no. 3, pp. F575–F582, 2009.

[77] X. Wang, P. C. Harris, S. Somlo, D. Batlle, and V. E. Torres, "Effect of calcium-sensing receptor activation in models of autosomal recessive or dominant polycystic kidney disease," *Nephrology Dialysis Transplantation*, vol. 24, no. 2, pp. 526–534, 2009.

[78] Y. Sato, K. Harada, S. Furubo et al., "Inhibition of intrahepatic bile duct dilation of the polycystic kidney rat with a novel tyrosine kinase inhibitor gefitinib," *American Journal of Pathology*, vol. 169, no. 4, pp. 1238–1250, 2006.

[79] C. Renken, D. C. Fischer, G. Kundt, N. Gretz, and D. Haffner, "Inhibition of mTOR with sirolimus does not attenuate progression of liver and kidney disease in PCK rats," *Nephrology Dialysis Transplantation*, vol. 26, pp. 92–100, 2010.

Hindawi Publishing Corporation
International Journal of Hepatology
Volume 2012, Article ID 403954, 7 pages
doi:10.1155/2012/403954

Review Article

Pathological Features of New Animal Models for Primary Biliary Cirrhosis

Koichi Tsuneyama,[1] Yuki Moritoki,[2] Kentaro Kikuchi,[3] and Yasuni Nakanuma[4]

[1] *Department of Diagnostic Pathology, Graduate School of Medicine and Pharmaceutical Science, University of Toyama, 2630 Sugitani, Toyama 930-0194, Japan*
[2] *Department of Infection, Allergy, Clinical Immunology and Laboratory Medicine, Graduate School of Medicine, Akita University, Hondo, Akita 010-8543, Japan*
[3] *Fourth Department of Internal Medicine, Mizonokuchi Hospital, Teikyo University School of Medicine, Takatsu-ku, Kawasaki 213-8507, Japan*
[4] *Department of Human Pathology, Graduate School of Medicine, Kanazawa University, Kanazawa 920-8640, Japan*

Correspondence should be addressed to Koichi Tsuneyama, ktsune@med.u-toyama.ac.jp

Received 30 March 2011; Accepted 11 April 2011

Academic Editor: Alberto Quaglia

Primary biliary cirrhosis (PBC) is an autoimmune liver disease characterized by immune mediated biliary damage and frequent appearance of autoantibodies against mitochondrial enzymes. There is almost no useful animal model that is globally recognized and routinely used, however, several unique animal models manifested the characteristic clinical and pathological features of human PBC within the last 5 years. Herein, we compare the pathological features of previously reported and newly introduced novel animal models of PBC. Knowledge and understanding of the strengths and the limitations of each animal model have led to the development of promising therapies and novel tools to characterize these clinical conditions. Moreover, suitability of the model for the intended purpose should be confirmed by further research and analysis.

1. Introduction

Primary biliary cirrhosis (PBC) is an autoimmune disease of the liver that often develops in middle-aged women. Antimitochondrial antibodies (AMAs) appears in the serum of almost all cases of PBC while the occurrence of AMA is rare in other diseases. The major autoantigens recognized by AMA are identified as the E2 subunits of pyruvate dehydrogenase (PDC-E2), branched-chain 2-oxo acid dehydrogenase (BCOADC-E2), and 2-oxo-glutarate dehydrogenase (OGDC-E2) [1–3]. AMA or anti-PDC-E2 antibody is therefore an extremely useful diagnostic marker of PBC. Pathological destruction of interlobular bile ducts in the liver associated with lymphocytes and plasma cells is known as chronic nonsuppurative destructive cholangitis (CNSDC) and is considered the primary lesion of PBC, and eventually the interlobular bile ducts are destroyed, cholestasis occurs, bile ductules proliferate, and fibrosis develops as the disease advances. In some cases, an epithelioid granuloma is developed in the portal tract accompanied by varying degrees of eosinophilic infiltration [4–12]. PBC is considered a prototype of autoimmune diseases of the liver; it is responsible for both humoral (appearance of AMA/anti-PDC-E2 antibody) and cellular immunity (CNSDC, granuloma formation, etc.). An animal model of PBC that reflects both humoral and cellular immunological features is useful in elucidating the underlying pathophysiology of the disease or establishing an effective treatment. In addition, the characteristic pathophysiological findings of the disease such as the presence of related cytokines and chemokines, nature of inflammatory cells, extent of bile duct destruction, and granuloma formation are considered important aspects of the animal model of PBC. Moreover, ease of handling, the frequency with which relevant pathophysiology develops, and flexibility are important elements. The development of an animal model of PBC has been attempted at many research institutes over

a number of years; moreover, some animal models that show pathophysiological symptoms similar to those of PBC have been reported [12–22]. Currently, however, there is almost no useful animal model that is globally accepted and routinely used. Within the last 5 years, there have been also reports of several murine models that manifest the characteristic clinical features of human PBC. In this review, we compare the pathological features of previously reported animal models and a newly introduced novel animal model of PBC.

2. Previously Reported PBC Animal Models of PBC (up to 2005) (Table 2)

Attempts have been made to develop an animal model of PBC in many institutions. In 1989, Krams et al. immunized mice of various strains such as AKR/J, C3 H/J, and CBA/HeJ with recombinant polypeptides of dihydrolipoamide acetyltransferase, which is a constituent of the pyruvate dehydrogenase complex (PDC), and verified that an anti-PDC antibody appeared in each mouse strain although antibody titer levels varied among the strains. However, there were no signs of inflammation or bile duct lesions in the portal tract [13]. Krams et al. transferred lymphocytes from the peripheral blood of a PBC patient into severe combined immunodeficient (SCID) mice, which resulted in the appearance of AMA and anti-PDC-E2 antibodies, as well as marked lymphocytic infiltration around the interlobular bile ducts with slight morphological damage to the portal tract. This was a successful animal model from the perspective of humoral and cellular immunity [14]. However, this model was difficult to reproduce and was only moderately flexible; furthermore, it was not suitable for the analysis of pathological lesions. Masanaga et al. in 1998 used PDC to immunize A/J mice that were neonatally thymectomized, and they succeeded in inducing pathognomonic cholangitis/biliary damage. Although the bile duct lesion in this model was similar to that of human PBC, the appearance of AMA was not clearly described, and the removal of the thymus in the neonatal period posed as a technical difficulty [15, 16]. Tsuneyama et al. [17] and Ohba et al. [18] reported the presence of AMA in the serum of MRL/*lpr* mice, a model of autoimmune disease in which vasculitis, glomerular nephritis, arthritis, inflammation of the salivary glands, and interstitial pneumonia develop spontaneously in the same individual. Because inflammatory cell infiltrates and biliary damage in the portal tract similar to that seen in PBC also appeared in the liver of MRL/*lpr* mice, it was assumed that this mouse may serve as a model of PBC. However, the fact that only about 50% mice showed PBC-like features was a serious problem. The most widespread animal model of PBC is considered to be a graft versus host disease (GVHD) model [19–22]. Initiating the development of GVHD by transferring splenic immune cells from a donor mouse into a host mouse with major histocompatibility complex class-II antigens different from those of the donor leads to the appearance of an underlying autoimmune-like mechanism, such as hypergammaglobulinemia and the production of AMA. Furthermore, the initial pathological changes of PBC with similar associated findings appear in the liver. There have been several pathological analyses using the advantages of this animal model of PBC [19–22]. However, this model is now seldom used, due to its complexity and/or low flexibility.

3. Novel Animal Models of PBC (Since 2006) (Tables 3 and 4)

Several novel animal models of PBC have been reported since 2006. These can be roughly classified into spontaneous models, which employ genetic modifications seen in animals, and induced models immunized with xenobiotics whose structures are similar to that of PDC-E2.

Each of these new models shows autoantibodies characteristic of PBC, as well as the appearance of hepatic and bile duct lesions. Their profile also resembles that of PBC with respect to infiltrating inflammatory cells and the appearance of serum inflammatory cytokines. Furthermore, it is easy to establish experimental systems with these models, such as immune cell transfer and mating with other transgenic (Tg) and knockout (KO) mice. Therefore, they fulfill many of the requirements for a PBC animal model, as listed in Table 1, and are currently applied in various investigations of PBC worldwide. Although these animal models are currently considered among the most useful models of PBC, their pathophysiology needs further investigation because some models may show complications that are unusual in PBC, such as peritonitis or inflammatory bowel disease. The pathological features of each of these animal models are outlined below.

4. Spontaneous Models

4.1. The NOD.c3c4 Mouse. Nonobese diabetic (NOD) mice are a well-known model exhibiting susceptibility to the spontaneous development of autoimmune insulin-dependent diabetes mellitus (IDDM) [41]. Genetic loci associated with susceptibility to IDDM, as well as several insulin-dependent diabetes (Idd) loci and candidate genes, have been defined through the development of congenic mouse strains [42–44]. NOD mice are also prone to the development of other autoimmune syndromes in addition to IDDM [45]. In the NODc3c4 mouse model, the diabetes susceptibility genes on chromosomes 3 and 4 of the NOD mouse are replaced with the diabetes resistance genes of B6 and B10 mice, respectively. Although this helps in controlling the onset of diabetes in this mouse, autoimmune cholangitis and biliary dilatation similar to that seen in Caroli's disease appear. Serologically, AMA appears in 50–60% and antinuclear autoantibodies (ANA) in 80–90% of the animals. Immunohistochemical analysis demonstrated that the affected parts of the biliary epithelium are infiltrated with $CD3^+$, $CD4^+$, and $CD8^+$ T cells. Furthermore, treatment of NOD.c3c4 mice with monoclonal antibody to CD3 protects them from autoimmune biliary disease. NOD.c3c4-scid mice develop the disease after adoptive transfer of splenocytes or $CD4^+$ T cells, demonstrating a central role of T cells in pathogenesis of the disease in this model [23, 24]. Recently, aggregated lymphocytes surrounding the bile ducts resembling

Table 1: Requirements for the ideal animal model of PBC.

(i) Specific liver pathology (cellular immunity)
(1) Destruction of interlobular bile duct
(2) T-cell aggregation around the damaged bile ducts
(3) Epithelioid granuloma formation
(4) Fibrosis/cirrhosis
(ii) Specific autoantibodies (humoral immunity)
(1) Antimitochondrial autoantibodies (AMAs)
(2) Anti-PDC-E2 antibodies, anti-BCOADC-E2 antibodies, and anti-OGDC-E2 antibodies
(3) Antinuclear antibodies (ANAs)
(iii) Other immunological characters
(1) Increase in inflammatory cytokines
(2) Decrease in functional regulatory T cells
(3) Increase in natural killer T (NKT) cells
(iv) General versatility
(1) High reproducibility and disease frequency
(2) Simplicity of model production
(3) Long-term maintenance of disease
(4) Long lifespan without severe complicating disorders

Table 2: Representative PBC animal models reported up to 2005.

(1) PDC-immunized mice [13]
(2) Neonatally thymectomized mice with PDC immunization [15, 16]
(3) MRL/*lpr* mice [17, 18]
(4) GVHD model [19–22]

Table 3: Novel PBC animal models reported since 2006.

Spontaneous models
(1) NOD.c3c4 mice [23–25]
(2) Dominant negative TGF-β receptor II mice [26–31]
(3) IL-2 receptor $\alpha^{-/-}$ mice [32, 33]
(4) Scurfy mice [34]
(5) $Ae2_{a,b}^{-/-}$ mice [35]
Xenobiotic-immunized induced model
(1) 6-Bromohexanoate-immunized guinea pigs [36]
(2) 2-Octynoic acid-immunized mice [37–40]

the aggregations seen in Sjogren's syndrome, were observed in the salivary glands of this mouse [25]. Because Sjogren's syndrome is often seen as a complication in PBC patients, the pattern of inflammation seen in NOD.c3c4 mice has many similarities to those seen in PBC. However, the cyst-like dilatation of the affected bile duct that is characteristic of these mice is not seen in PBC patients at all. When the dilatation becomes marked, the biliary epithelium of NOD.c3c4 mice frequently exfoliates, and the exfoliated cells together with infiltrated histiocytes fill the lumen. If such dilatation becomes significant, neutrophil infiltration may be also observed resulting in a variable clinical picture such as cholangitis. Therefore, further pathological evaluation of this phenomenon is mandatory.

4.2. The Dominant Negative TGF-β Receptor II Mouse. Dominant negative TGF-β receptor II (dnTGF-βRII) mice overexpress the dominant negative form of TGF-β receptor type II under the control of the CD4 promoter [46]. Deficiency of TGF-β signaling results in various pleiotropic immunological abnormalities including colitis and relatively short lifespan [47–49]. dnTGF-βRII mice exhibit major serological and histological characteristics of human PBC, suggesting that the TGF-β signaling pathway is important in the pathogenesis of PBC. Serologically, AMA appears in 100% of these mice. The corresponding antigens include PDC-E2, BCOADC-E2, and OGDC-E2; these are the main autoantigens recognized by AMAs of PBC. Furthermore, hepatic lesions characteristic of PBC, such as lymphocytic infiltration, interlobular bile duct destruction, and granuloma formation in the portal tract, appear at high frequency. Various infiltrating cells are found in the portal tracts, including B cells, plasmacytoid dendritic cells, NK cells, and macrophages, in addition to $CD4^+$ and $CD8^+$ T cells. A particular characteristic is the increased ratio of $CD8^+$ T cells to $CD3^+$ T cells. This mouse strain presents mild inflammatory bowel disease and crypt abscesses similar to those of ulcerative colitis. Increased levels of inflammatory cytokines such as TNF-α, IFN-γ, IL-12p40, and IL-6 are also detected in the serum of these mice [26].

The dnTGF-βRII mouse is a spontaneous PBC model in which pathophysiological variations are minimum among individuals; furthermore, humoral and cellular immune responses appear to be reproducible and at high frequency. It has given rise to many models that are used for pathophysiological analysis. Yang et al. produced a model by transferring various fractions of splenocytes of dnTGF-βRII mice into Rag-$1^{-/-}$ mice. Their study revealed that PBC-like hepatic lesions were produced after the transfer of total splenic lymphocytes and that more severe hepatic lesions occurred after splenic $CD8^+$ T-cell transfer. On the other hand, PBC-like hepatic lesions did not appear, however the colitis worsened after splenic $CD4^+$ T-cell transfer. Currently, the $CD8^+$ T-cell transfer model shows maximum similarities to PBC, such as severe inflammatory cell infiltration, bile duct destruction, and granuloma formation in the portal tract [27]. A derived PBC model, produced by crossing dnTGF-βRII mice with a variety of genetically modified mice, is also used for pathological analysis. Moritoki et al. crossed dnTGF-βRII mice with mu-mutant mice ($Ig\mu^{-/-}$) to produce a B-cell-deficient model in order to study the role of B cells in the pathogenesis of PBC [28]. Chuang et al. studied NKT-cell commitment in a model produced by crossing dnTGF-βRII mice with $CD1d^{-/-}$ or $CD1d^{+/-}$ mice [29]. To investigate the roles of various cytokines, Yoshida et al. and Zhang et al. produced animal models by crossing dnTGF-βRII mice with IL12p40 KO and IFN-γ KO mice and by crossing dnTGF-βRII mice with IL-6 KO mice, respectively [30, 31]. Each of these derived models makes a considerable contribution to the pathological analysis of PBC. Interestingly, the grade of hepatic lesions in animal models produced by crossing

Table 4: Comparison of novel PBC animal models.

	Spontaneous models					Xenobiotic-immunized induced model	
	NOD.c3c4 mice	dnTGF-βRII mice	IL-2 R$\alpha^{-/-}$ mice	Scurfy mice	$Ae2_{a,b^{-/-}}$ mice	6-BH-immunized guinea pigs	2-OA-immunized mice
Advantages							
AMA	50–60%	100%	100%	100%	40–80%	100%	100%
Dominant AMA target protein	PDC-E2	PDC-E2	PDC-E2	PDC-E2	PDC-E2	PDC-E2	PDC-E2
Biliary damage	+	++	+–++	+–++	+–+++	+	+–++
Granuloma	+	+	– or +	–	?	++	++
Pro-inflammatory cytokines	+	+	+	+	+	+	+
Disadvantages	Biliary dilatation	moderate colitis	Severe colitis Severe hemolytic anemia	Short lifespan	Late onset	Late onset	peritonitis

does not vary greatly among individuals; moreover, it is easy to assign scores to different degrees of pathology for the purpose of evaluation. The dnTGF-βRII mouse model is now used in various analyses throughout the world, and it may be regarded as the most useful PBC animal model available at present. However, it is not totally satisfactory as a PBC model because the pathophysiological grade is not severe; furthermore, events that occur in the advanced stage of PBC, such as loss of the bile duct, cholestasis, and fibrosis, are rarely seen. Therefore, the pathophysiological model based on this mouse needs to be further developed.

4.3. The IL-2 Receptor $\alpha^{-/-}$ Mouse. IL-2 is critical for the development and peripheral expansion of $CD4^+$ $CD25^+$ Tregs that promote self-tolerance by *in vivo* suppression of T-cell responses [50, 51]. In IL-2 receptor $\alpha^{-/-}$ (IL-2R-$\alpha^{-/-}$) mice, the IL-2 signal, which is important in controlling the fate of mature T cells, is intercepted; these mice develop an inflammatory bowel disease and a lymphoproliferative autoimmune disease. Also, 25–50% mice develop severe hemolytic anemia at 8–20 weeks of age. It was reported that children with a genetic deficiency of IL-2R-α developed clinical manifestations similar to those of PBC [52]. Anti-PDC-E2 antibody is present in the serum of all IL-2R-$\alpha^{-/-}$ mice, and ANA is also present in the serum of 80% of these mice. There is profound lymphocytic infiltration in the portal tract and the interlobular bile duct is also damaged. $CD8^+$ T cells are predominant among the infiltrating lymphocytes, and $CD4^+$ T and B cells are also present in increased numbers. In addition, granulomas are formed, though in small numbers. Increased levels of inflammatory cytokines such as TNF-α, IFN-γ, IL-12p40, and IL-6 are present in the serum. The extent of inflammatory bowel disease is relatively severe and frequently associated with formation of crypt abscesses [32]. Using a derived model produced by crossing IL-2R-$\alpha^{-/-}$ mice with CD4 KO and CD8 KO mice, Hsu et al. showed that $CD8^+$ T cells participate in the pathogenesis of PBC [33]. The hepatic lesions of IL-2R-$\alpha^{-/-}$ mice are similar to those of PBC, though the complication of severe hemolytic anemia or colitis has not been evaluated. Moreover, the reduced lifespan of these mice makes it difficult to use them in various experiments, such as those involving mating; this is considered a limitation of this model.

4.4. The Scurfy Mouse. The Scurfy mouse is a mouse with loss of functional regulatory T cells caused by the *forkhead boxp3* (*Foxp3*) gene mutation. AMAs are present in all Scurfy mice at 3-4 weeks of age, and the portal tract shows moderate to marked lymphocytic infiltration and development of a severe interlobular bile duct lesion similar to PBC with high levels of cytokines such as TNF-α, IFN-γ, IL-6, IL-12, and IL-23 present in the serum and liver. However, Scurfy mice have an extremely short lifespan of about 4 weeks. This is a serious drawback with regard to its use in experiments [34].

4.5. $Ae2_{a,b^{-/-}}$ Mice. The anion exchanger (Ae)$2_{a,b}$-deficient mouse model was constructed by Salas et al. in Spain, based on a clinical investigation showing that *Ae2* gene expression was reduced in liver biopsy specimens and blood lymphocytes from patients with PBC [35]. $Ae2_{a,b^{-/-}}$ mice exhibit enhanced production of IL-12p70 and IFN-γ, an expanded $CD8^+$ T cell population, and a reduced number of Treg cells. Serum analysis by immunoblotting showed that 9 out of 11 $Ae2_{a,b^{-/-}}$ mice had AMAs. A histological study of liver sections from 11 $Ae2_{a,b^{-/-}}$ mice revealed mild to severe portal inflammation in 10 animals. Although the mechanism leading to the deficiency of *AE2* in the liver and blood mononuclear cells in human PBC is unclear, observations of $Ae2_{a,b^{-/-}}$ mice indicate a relationship between biliary epithelial dysfunction and the pathogenesis of PBC.

5. Immunity Induced by Xenobiotics in Mice

Not only genetic factors but also various environmental factors, such as bacterial infection and exposure to xenobiotics, are strongly implicated in the onset and development of PBC. Most importantly, prolonged exposure over an extended period of time to various xenobiotics with a structure similar to that of the inner lipoyl domain of PDC-E2 has attracted attention as a trigger for the development of PBC.

It has been revealed that two types of xenobiotics induce a pathophysiology that is very similar to that of PBC.

5.1. Guinea Pigs Immunized with 6-Bromohexanoate. 6-Bromohexanoate (6-BH) coupled with bovine serum albumin (BSA) has a structure similar to that of the inner lipoyl domain of PDC-E2 [53]. Increased levels of anti-PDC-E2 antibody, anti-BCOADC-E2 antibody, and anti-OGDC-E2 antibody appear in the serum of guinea pigs when they are immunized with BSA-coupled 6-BH. In addition, slight to moderate lymphocytic infiltration, interlobular bile duct irregularity, and granuloma formation in the portal tract are seen in the liver at an advanced age. Many vacuole-like lipid droplets are seen in the granulomas, and there are also aggregations of macrophages that phagocytoze lipids. Since these vacuolar changes are also seen in control animals to a slight extent, they may be related to immune reactions to foreign substances in the oil emulsion. The limitation of this animal model is the difficulty of use in some experiments because the extent of hepatic lesions is slight and lesions are slow in development, not appearing until 18 months after immunization [36].

5.2. Mice Immunized with 2-Octynoic Acid. 2-Octynoic acid (2-OA) is a xenobiotic widely used as a food additive and as a component of certain cosmetic products. 2-OA coupled to BSA has a structure similar to that of the inner lipoyl domain of PDC-E2 [54]. Wakabayashi et al. immunized C57BL/6 mice with BSA-coupled 2-OA and detected AMA and anti-PDC-E2 antibodies as well as increased serum levels of TNF-α and IFN-γ. Marked inflammatory cell infiltration and bile duct lesions in the portal tract frequently appeared, which were mainly associated with $CD8^+$ T cells [37]. Using the same methods, Wakabayashi et al. also succeeded in producing a PBC-like lesion in another mouse strain (nonobese diabetic (NOD) congenic strain 1101) [38]. This model is innovative because it induces PBC-like pathophysiology by administration of xenobiotics that may be related to the cause of PBC. As the reproducibility of this model is comparatively high and flexibility is also high, various pathophysiological analyses of this model are in progress in different countries' institutions [39, 40]. At present, however, the hepatic and bile duct lesions show many differences from those of PBC, and further evaluation of the model is needed. In the original immunization procedure used by Wakabayashi et al., BSA-coupled 2-OA was introduced into the abdominal cavity using complete Freund's adjuvant (*M. tuberculosis* in adjuvant oil), following which BSA-coupled 2-OA using incomplete Freund's adjuvant (adjuvant oil only) was administered every 2 weeks as a booster immunization. This model always developed peritonitis of various grades as an adverse effect. A preliminary experiment is necessary in order to check the extent to which peritonitis influences the development of pathological changes in the liver, particularly in that portion which is histologically evaluated. Moreover, a granuloma often appears in the portal tract or the hepatic parenchyma; this could be attributed to the complete Freund's adjuvant administered at the time of immunization. However, methods of immunization have improved; as a result, various modifications designed to induce more serious pathophysiology can be tested. Reports of studies using this model are eagerly awaited.

6. Conclusion

The pathophysiology of PBC involves both humoral and cell-mediated immunity, and it can be considered the prototype of autoimmune diseases of the liver. The production of a practical animal model of PBC has been a challenge for researchers interested in PBC and autoimmune diseases for many years. Although animal models based on a variety of mechanisms have been reported from many laboratories, the ideal animal model has still not been available. Recently, several PBC animal models based on different mechanisms were reported. While these newer animal models show the characteristic findings of PBC unlike earlier models, they still show different features from those of human PBC. Understanding the strengths and limitations of each animal model is required in order to match the model to the intended purpose; moreover, suitability of the model for the intended purpose should be confirmed by further research and analysis.

References

[1] P. S. Leung, D. T. Chuang, R. M. Wynn, S. Cha et al., "Autoantibodies to BCOADC-E2 in patients with primary biliary cirrhosis recognize a conformational epitope," *Hepatology*, vol. 22, no. 2, pp. 505–513, 1995.

[2] S. Moteki, P. S. Leung, E. R. Dickson et al., "Epitope mapping and reactivity of autoantibodies to the E2 component of 2-oxoglutarate dehydrogenase complex in primary biliary cirrhosis using recombinant 2-oxoglutarate dehydrogenase complex," *Hepatology*, vol. 23, no. 3, pp. 436–444, 1996.

[3] J. Van de Water, A. Ansari, T. Prindiville et al., "Heterogeneity of autoreactive T cell clones specific for the E2 component of the pyruvate dehydrogenase complex in primary biliary cirrhosis," *Journal of Experimental Medicine*, vol. 181, no. 2, pp. 723–733, 1995.

[4] M. E. Gershwin, A. A. Ansari, I. R. Mackay et al., "Primary biliary cirrhosis: an orchestrated immune response against epithelial cells," *Immunological Reviews*, vol. 174, pp. 210–225, 2000.

[5] H. Ishibashi, S. Shimoda, and M. E. Gershwin, "The immune response to mitochondrial autoantigens," *Seminars in Liver Disease*, vol. 25, no. 3, pp. 337–346, 2005.

[6] Y. H. Chuang, W. M. Ridgway, Y. Ueno, and M. E. Gershwin, "Animal models of primary biliary cirrhosis," *Clinics in Liver Disease*, vol. 12, no. 2, pp. 333–347, 2008.

[7] M. Folci, F. Meda, M. E. Gershwin, and C. Selmi, "Cutting-edge issues inprimary biliary cirrhosis," *Clinical Reviews in Allergy and Immunology*. In press.

[8] M. E. Gershwin and I. R. Mackay, "The causes of primary biliary cirrhosis: convenient and inconvenient truths," *Hepatology*, vol. 47, no. 2, pp. 737–745, 2008.

[9] P. S. Leung, R. L. Coppel, and M. E. Gershwin, "Etiology of primary biliary cirrhosis: the search for the culprit," *Seminars in Liver Disease*, vol. 25, no. 3, pp. 327–336, 2005.

[10] X. Liu, P. Invernizzi, Y. Lu et al., "Genome-wide meta-analyses identify three loci associated with primary biliary cirrhosis," *Nature Genetics*, vol. 42, pp. 658–660, 2010.

[11] A. Lleo, C. L. Bowlus, G. X. Yang et al., "Biliary apotopes and anti-mitochondrial antibodies activate innate immune responses in primary biliary cirrhosis," *Hepatology*, vol. 52, no. 3, pp. 987–998, 2010.

[12] S. Oertelt, R. Rieger, C. Selmi et al., "A sensitive bead assay for antimitochondrial antibodies: chipping away at AMA-negative primary biliary cirrhosis," *Hepatology*, vol. 45, no. 3, pp. 659–665, 2007.

[13] S. M. Krams, C. D. Surh, R. L. Coppel et al., "Immunization of experimental animals with dihydrolipoamide acetyltransferase, as a purified recombinant polypeptide, generates mitochondrial antibodies but not primary biliary cirrhosis," *Hepatology*, vol. 9, no. 3, pp. 411–416, 1989.

[14] S. M. Krams, K. Dorshkind, and M. E. Gershwin, "Generation of biliary lesions after transfer of human lymphocytes into severe combined immunodeficient (SCID) mice," *Journal of Experimental Medicine*, vol. 170, no. 6, pp. 1919–1930, 1989.

[15] T. Masanaga, Y. Watanabe, J. Van de Water et al., "Induction and persistence of immune-mediated cholangiohepatitis in neonatally thymectomized mice," *Clinical Immunology and Immunopathology*, vol. 89, no. 2, pp. 141–149, 1998.

[16] Y. Aisaka, Y. Watanabe, M. Kamiyasu et al., "Immune-mediated cholangiohepatitis in neonatally thymectomized mice: the role of T cells and analysis of T-cell receptor Vβ usage," *Journal of Autoimmunity*, vol. 14, no. 3, pp. 239–246, 2000.

[17] K. Tsuneyama, M. Nose, M. Nisihara et al., "Spontaneous occurrence of chronic non-suppurative destructive cholangitis and antimitochondrial autoantibodies in MRL/lpr mice: possible animal model for primary biliary cirrhosis," *Pathology International*, vol. 51, no. 6, pp. 418–424, 2001.

[18] K. Ohba, K. Omagari, K. Murase et al., "A possible mouse model for spontaneous cholangitis: serological and histological characteristics of MRL/lpr mice," *Pathology*, vol. 34, no. 3, pp. 250–256, 2002.

[19] T. Saitoh, M. Fujiwara, M. Nomoto et al., "Hepatic lesions induced by graft-versus-host reaction across MHC class II antigens: an implication for animal model of primary biliary cirrhosis," *Clinical Immunology and Immunopathology*, vol. 49, no. 1, pp. 166–172, 1988.

[20] T. Saitoh, Y. Ikarashi, S. Ito et al., "Depletion of CD8+ cells exacerbates organ-specific autoimmune diseases induced by CD4+ T cells in semiallogeneic hosts with MHC class II disparity," *Journal of Immunology*, vol. 145, no. 10, pp. 3268–3275, 1990.

[21] C. D. Howell, J. Li, and W. Chen, "Role of intercellular adhesion molecule-1 and lymphocyte function- associated antigen-1 during nonsuppurative destructive cholangitis in a mouse graft-versus-host disease model," *Hepatology*, vol. 29, no. 3, pp. 766–776, 1999.

[22] T. Wake, H. Takatsuka, Y. Seto et al., "Similarity between hepatic graft-versus-host disease and primary biliary cirrhosis," *Hematology*, vol. 7, no. 5, pp. 305–310, 2002.

[23] J. Irie, Y. Wu, L. S. Wicker et al., "NOD.c3c4 congenic mice develop autoimmune biliary disease that serologically and pathogenetically models human primary biliary cirrhosis," *Journal of Experimental Medicine*, vol. 203, no. 5, pp. 1209–1219, 2006.

[24] Y. Nakagome, Y. Ueno, T. Kogure et al., "Autoimmune cholangitis in NOD.c3c4 mice is associated with cholangiocyte-specific Fas antigen deficiency," *Journal of Autoimmunity*, vol. 29, no. 1, pp. 20–29, 2007.

[25] Y. Moritoki, M. Tsuda, K. Tsuneyama et al., "B cells promote hepatic inflammation, biliary cyst formation, and salivary gland inflammation in the NOD.c3c4 model of autoimmune cholangitis," *Cellular Immunology*, vol. 268, no. 1, pp. 16–23, 2011.

[26] S. Oertelt, Z. X. Lian, C. M. Cheng et al., "Anti-mitochondrial antibodies and primary biliary cirrhosis in TGF-βreceptor II dominant-negative mice," *Journal of Immunology*, vol. 177, no. 3, pp. 1655–1660, 2006.

[27] G. X. Yang, Z. X. Lian, Y. H. Chuang et al., "Adoptive transfer of CD8(+) T cells from transforming growth factor beta receptor type II (dominant negative form) induces autoimmune cholangitis in mice," *Hepatology*, vol. 47, no. 6, pp. 1974–1982, 2008.

[28] Y. Moritoki, W. Zhang, K. Tsuneyama et al., "B cells suppress the inflammatory response in a mouse model of primary biliary cirrhosis," *Gastroenterology*, vol. 136, no. 3, pp. 1037–1047, 2009.

[29] Y. H. Chuang, Z. X. Lian, G. X. Yang et al., "Natural killer T cells exacerbate liver injury in a transforming growth factor β receptor II dominant-negative mouse model of primary biliary cirrhosis," *Hepatology*, vol. 47, no. 2, pp. 571–580, 2008.

[30] K. Yoshida, G. X. Yang, W. Zhang et al., "Deletion of interleukin-12p40 suppresses autoimmune cholangitis in dominant negative transforming growth factor β receptor type II mice," *Hepatology*, vol. 50, no. 5, pp. 1494–1500, 2009.

[31] W. Zhang, M. Tsuda, G. X. Yang et al., "Deletion of interleukin-6 in mice with the dominant negative form of transforming growth factor β receptor II improves colitis but exacerbates autoimmune cholangitis," *Hepatology*, vol. 52, no. 1, pp. 215–222, 2010.

[32] K. Wakabayashi, Z. X. Lian, Y. Moritoki et al., "IL-2 receptor α(−/−) mice and the development of primary biliary cirrhosis," *Hepatology*, vol. 44, no. 5, pp. 1240–1249, 2006.

[33] W. Hsu, W. Zhang, K. Tsuneyama et al., "Differential mechanisms in the pathogenesis of autoimmune cholangitis versus inflammatory bowel disease in interleukin-2Rα(-/-) mice," *Hepatology*, vol. 49, no. 1, pp. 133–140, 2009.

[34] W. Zhang, R. Sharma, S. T. Ju et al., "Deficiency in regulatory T cells results in development of antimitochondrial antibodies and autoimmune cholangitis," *Hepatology*, vol. 49, no. 2, pp. 545–552, 2009.

[35] J. T. Salas, J. M. Banales, S. Sarvide et al., "Ae2-deficient mice develop antimitochondrial antibodies and other features resembling primary biliary cirrhosis," *Gastroenterology*, vol. 134, no. 5, pp. 1482–1493, 2008.

[36] P. S. Leung, O. Park, K. Tsuneyama et al., "Induction of primary biliary cirrhosis in guinea pigs following chemical xenobiotic immunization," *Journal of Immunology*, vol. 179, no. 4, pp. 2651–2657, 2007.

[37] K. Wakabayashi, Z. X. Lian, P. S. Leung et al., "Loss of tolerance in C57BL/6 mice to the autoantigen E2 subunit of pyruvate dehydrogenase by a xenobiotic with ensuing biliary ductular disease," *Hepatology*, vol. 48, no. 2, pp. 531–540, 2008.

[38] K. Wakabayashi, K. Yoshida, P. S. C. Leung et al., "Induction of autoimmune cholangitis in non-obese diabetic (NOD).1101 mice following a chemical xenobiotic immunization," *Clinical and Experimental Immunology*, vol. 155, no. 3, pp. 577–586, 2009.

[39] A. Dhirapong, A. Lleo, G. X. Yang et al., "B cell depletion therapy exacerbates murine primary biliary cirrhosis," *Hepatology*, vol. 53, no. 2, pp. 527–535, 2011.

[40] S. J. Wu, Y. H. Yang, K. Tsuneyama et al., "Innate immunity and PBC: activated invariant NKT cells exacerbate murine autoimmune cholangitis and fibrosis," *Hepatology*, vol. 53, no. 3, pp. 915–925, 2011.

[41] H. Kikutani and S. Makino, "The murine autoimmune diabetes model: NOD and related strains," *Advances in Immunology*, vol. 51, pp. 285–322, 1992.

[42] Y. G. Chen, F. Scheuplein, M. A. Osborne, S. W. Tsaih, H. D. Chapman, and D. V. Serreze, "Idd9/11 genetic locus regulates diabetogenic activity of CD4 T-cells in nonobese diabetic (NOD) mice," *Diabetes*, vol. 57, no. 12, pp. 3273–3280, 2008.

[43] C. J. Fox, A. D. Paterson, S. M. Mortin-Toth, and J. S. Danska, "Two genetic loci regulate T cell-dependent islet inflammation and drive autoimmune diabetes pathogenesis," *American Journal of Human Genetics*, vol. 67, no. 1, pp. 67–81, 2000.

[44] H. I. Fraser, C. A. Dendrou, B. Healy et al., "Nonobese diabetic congenic strain analysis of autoimmune diabetes reveals genetic complexity of the Idd18 locus and identifies Vav3 as a candidate gene," *The Journal of Immunology*, vol. 184, no. 9, pp. 5075–5084, 2010.

[45] C. A. Aoki, A. T. Borchers, W. M. Ridgway, C. L. Keen, A. A. Ansari, and M. E. Gershwin, "NOD mice and autoimmunity," *Autoimmunity Reviews*, vol. 4, no. 6, pp. 373–379, 2005.

[46] L. Gorelik and R. A. Flavell, "Abrogation of TGFβ signaling in T cells leads to spontaneous T cell differentiation and autoimmune disease," *Immunity*, vol. 12, no. 2, pp. 171–181, 2000.

[47] E. C. Ebert, A. Panja, K. M. Das et al., "Patients with inflammatory bowel disease may have a transforming growth factor-β-, interleukin (IL)-2- or IL-10-deficient state induced by intrinsic neutralizing antibodies," *Clinical and Experimental Immunology*, vol. 155, no. 1, pp. 65–71, 2009.

[48] J. M. Kel, M. J. Girard-Madoux, B. Reizis, and B. E. Clausen, "TGF-β is required to maintain the pool of immature Langerhans cells in the epidermis," *The Journal of Immunology*, vol. 185, no. 6, pp. 3248–3255, 2010.

[49] S. Perruche, P. Zhang, T. Maruyama, J. A. Bluestone, P. Saas, and W. Chen, "Lethal effect of CD3-specific antibody in mice deficient in TGF-β1 by uncontrolled flu-like syndrome," *Journal of Immunology*, vol. 183, no. 2, pp. 953–961, 2009.

[50] J. H. Buckner, "Mechanisms of impaired regulation by CD4(+)CD25(+)FOXP3(+) regulatory T cells in human autoimmune diseases," *Nature Reviews Immunology*, vol. 10, pp. 849–859, 2010.

[51] T. R. Malek and I. Castro, "Interleukin-2 receptor signaling: at the interface between tolerance and immunity," *Immunity*, vol. 33, no. 2, Article ID 20732639, pp. 153–165, 2010.

[52] C. A. Aoki, C. M. Roifman, Z. X. Lian et al., "IL-2 receptor alpha deficiency and features of primary biliary cirrhosis," *Journal of Autoimmunity*, vol. 27, no. 1, pp. 50–53, 2006.

[53] P. S. Leung, C. Quan, O. Park et al., "Immunization with a xenobiotic 6-bromohexanoate bovine serum albumin conjugate induces antimitochondrial antibodies," *Journal of Immunology*, vol. 170, no. 10, pp. 5326–5332, 2003.

[54] K. Amano, P. S. Leung, R. Rieger et al., "Chemical xenobiotics and mitochondrial autoantigens in primary biliary cirrhosis: identification of antibodies against a common environmental, cosmetic, and food additive, 2-octynoic acid," *Journal of Immunology*, vol. 174, no. 9, pp. 5874–5883, 2005.

胆と膵 Vol. 32 (12) p. 1331～1338, 2011

胆管内腫瘍の組織分類とそのエビデンス

佐藤　保則[1)]・中沼　安二[1)]

要約：WHOによる消化器腫瘍分類が10年ぶりに改訂され，胆管内腫瘍では胆管上皮層内腫瘍（biliary intraepithelial neoplasia：BilIN）と胆管内乳頭状腫瘍（intraductal papillary neoplasm［IPN］of the bile duct）の二つの分類が新たに採用された。それぞれ，膵管内腫瘍であるpancreatic intraepithelial neoplasia（PanIN）とintraductal papillary mucinous neoplasm（IPMN）に相同性を示す胆管内腫瘍である。新WHO分類においてBilINとIPN of the bile ductはともにprecursor lesions of invasive neoplasiaとされ，胆道癌の多段階発癌のプロセスにおける前癌病変としての位置づけが明確にされた。BilINとIPN分類の導入により，胆道系腫瘍の病理病態がより理解しやすくなったが，その一方で分類上のいくつかの問題点も残されている。また，分子病理学的な側面からの解析も行われつつあり，これらの分類がWHO分類に採用されたことで研究面でも広く活用され，病態解析がさらに進行することが期待される。

Key words：胆管内腫瘍，BilIN，IPNB，WHO腫瘍分類

はじめに

消化器腫瘍分類に関して，2010年10月にWHOの下部組織であるIARC（国際がん研究機関）が発行するWHO腫瘍分類が「WHO Classification of Tumors of the Digestive System（4th edition）」として出版された。前版（2000年）から10年目の改訂であり，胆膵腫瘍組織分類に関してもいくつかの概念が導入され，改変が行われた。胆管内腫瘍では胆管上皮層内腫瘍（biliary intraepithelial neoplasia，BilIN）と胆管内乳頭状腫瘍（intraductal papillary neoplasm［IPN］of the bile duct）が新たに採用された。

2010年WHO腫瘍分類（以下WHO分類）において，胆道系腫瘍はUICC/AJCC（7th edition）による胆道系の分類に沿って乳頭部腫瘍（第5章）と肝臓・肝内胆管腫瘍（第10章），胆嚢・肝外胆管腫瘍（第11章）の各章に記載がなされている。本稿では胆管内腫瘍として主に肝門部から肝外胆管でみられるBilIN，IPNを中心に解説し，最後にわれわれが近年報告した胆管内管状腫瘍の概念を紹介する。

Evidence-based Histological Classification of Intraductal Neoplasm of the Bile Duct
Yasunori Sato et al
1）金沢大学大学院医学系研究科形態機能病理学
（〒920-8640 金沢市宝町13-1）

Ⅰ．BilIN

1．位置づけ

BilINは胆管上皮層内異型病変の分類であり，上皮の異型度によりBilIN-1からBilIN-3に分類される[1)]。これは膵臓のpancreatic intraepithelial neoplasia（PanIN）分類との対比を想定している。当初は肝内結石症で観察される胆管上皮層内異型病変を対象として検討が行われたが，現在は肝内結石症に限らず，原発性硬化性胆管炎などの慢性胆管上皮傷害を基盤とする胆管癌発生の多段階発癌プロセスに含まれる前癌・早期癌病変とみなされている[2)]。また，アルコール性肝障害や慢性C型肝炎を背景とする胆管癌の発生に関与するという指摘もある[3)]。

WHO分類では第1章で診断用語の解説が行われており，この中でBilINはIPNとともにprecursor lesions of invasive neoplasiaとして位置づけられる[4)]。

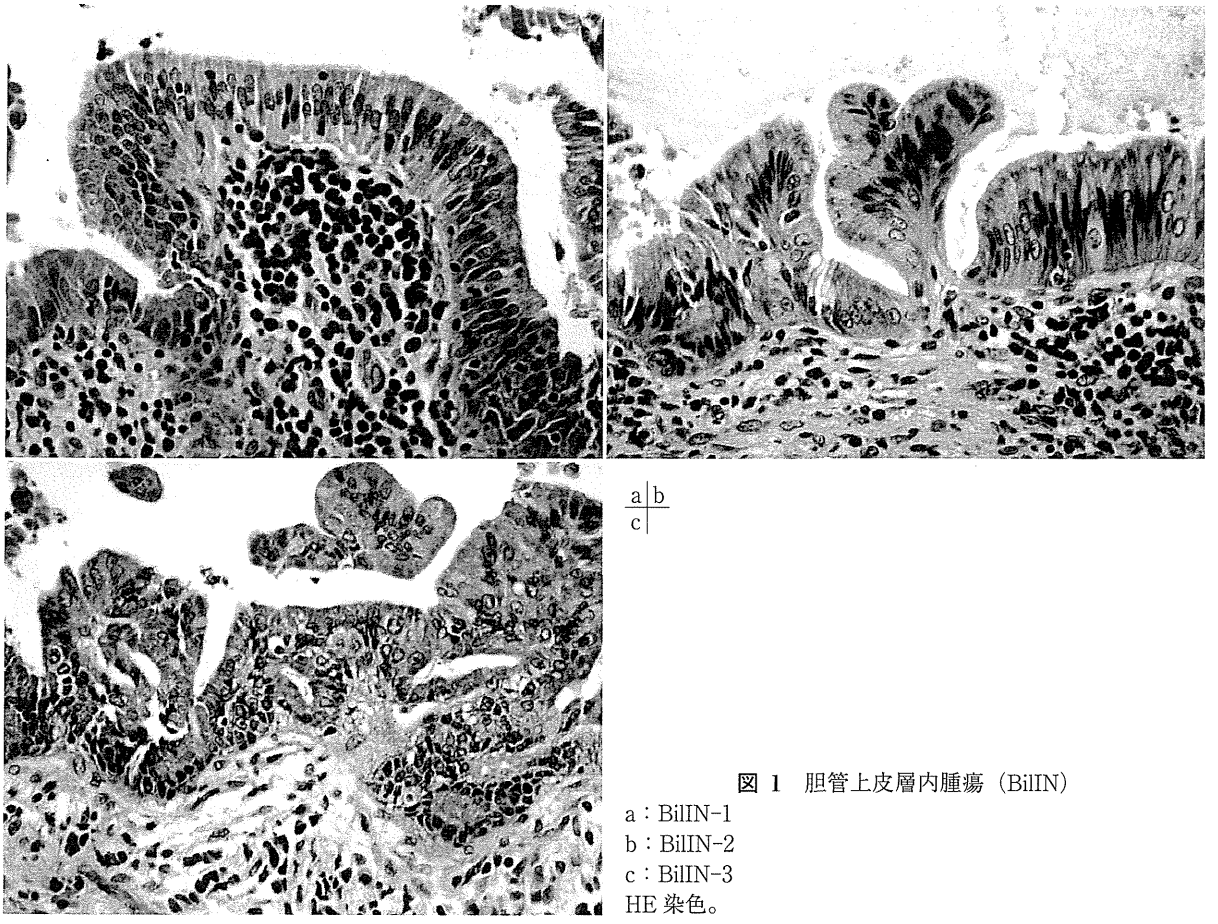


図 1 胆管上皮層内腫瘍（BilIN）
a：BilIN-1
b：BilIN-2
c：BilIN-3
HE 染色。

なお，前版（第3版）の WHO 分類でも precursor lesions として biliary intraepithelial neoplasia（dysplasia）が取り上げられていたが，今回の改訂で BilIN という用語が正式に採用された。BilIN-1 は low-grade，BilIN-2 は intermediate-grade，BiiIN-3 は high-grade lesion に相当する[5]。通常，わが国において BilIN-3 は上皮内癌と同等の扱いだが，WHO 分類では BilIN-3 は胆道系の premalignant lesions の一つに位置づけられ，上皮内癌を包括する概念とされている。

2．病理形態

①形態学的特徴

BilIN は肉眼や画像で検出できない顕微鏡的病変で，主に肝門部の大型胆管や肝外胆管に認められる。病理組織学的に以下のように特徴づけられる[1]。

BilIN-1（図 1a）：胆管上皮細胞の核の多層化，核の大小不同，核のクロマチンの増加を認める。

BilIN-2（図 1b）：核や細胞の大小不同がさらに強くなり，核の管腔縁までの迫り出し，細胞の極性の乱れがみられる。

BilIN-3（図 1c）：細胞の極性の乱れがさらに高度となり，細胞学的，構造的に癌と診断される。間質浸潤は認めない。

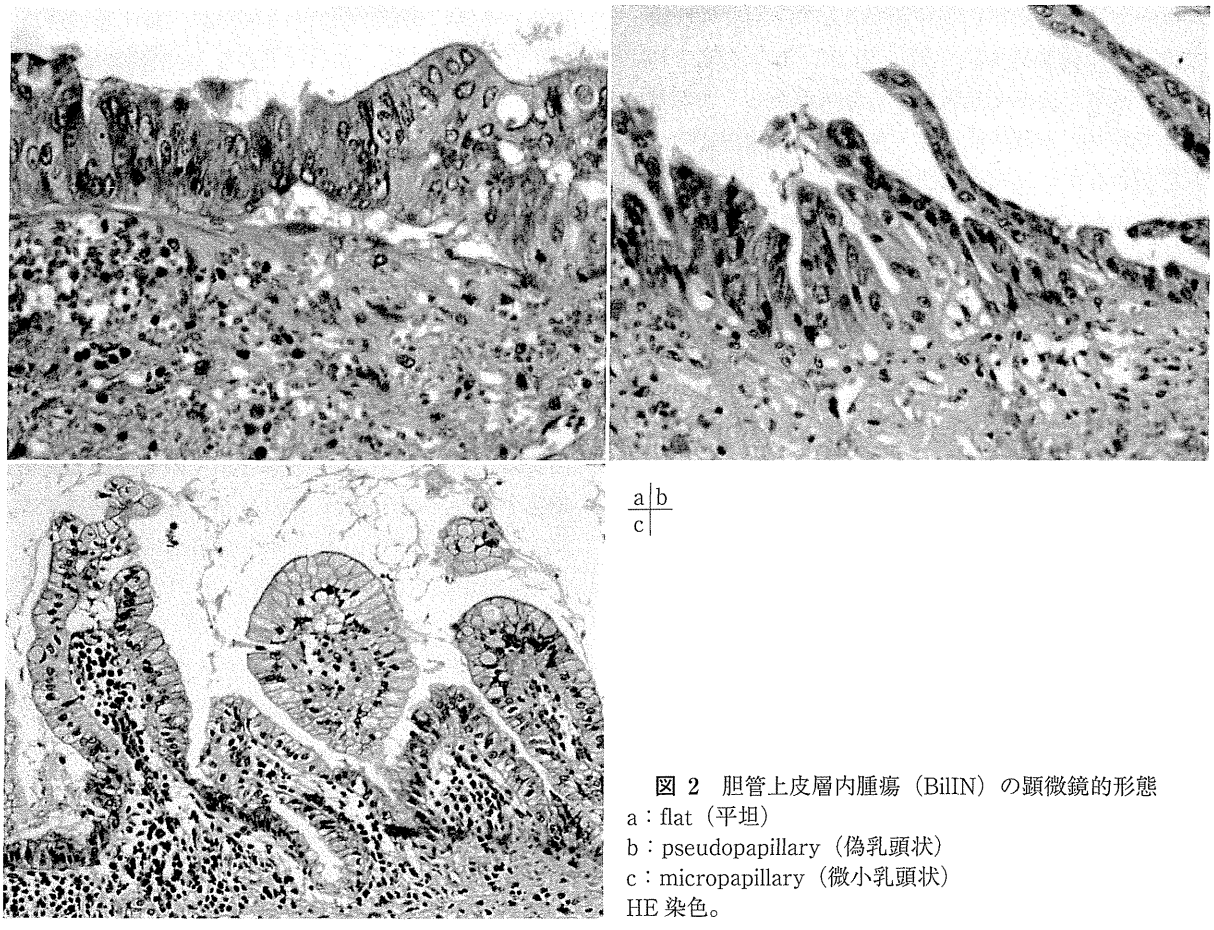
これらの組織所見のうち，実際の病理診断に際して BilIN-1 は核の多層化，BilIN-2 は核の迫り出し，BilIN-3 は細胞極性の乱れがあることを特に重要視している。

BilIN は肉眼では平坦な病変であるが，顕微鏡的に flat（平坦），pseudopapillary（偽乳頭状：血管結合織の芯のない微小乳頭状病変），micropapillary（微小乳頭状：血管結合織の芯を伴う微小乳頭状病変）の三つの形態を呈しうる（図 2）。これらの顕微鏡的形態は一つの症例内でさまざまな程度に混在して認められるが，flat と pseudopapillary の形態の出現頻度が micropapillary より高率である。

BilIN には胆道固有の上皮だけはなく，gastric type や intestinal type の細胞形質を示すものがしばしば観察される（図 3）。BilIN でのこうした化生上皮の出現頻度は特に gastric type（foveolar metaplasia）が高率である。なお，oncocytic type の化生を示す BilIN は通常みられない。

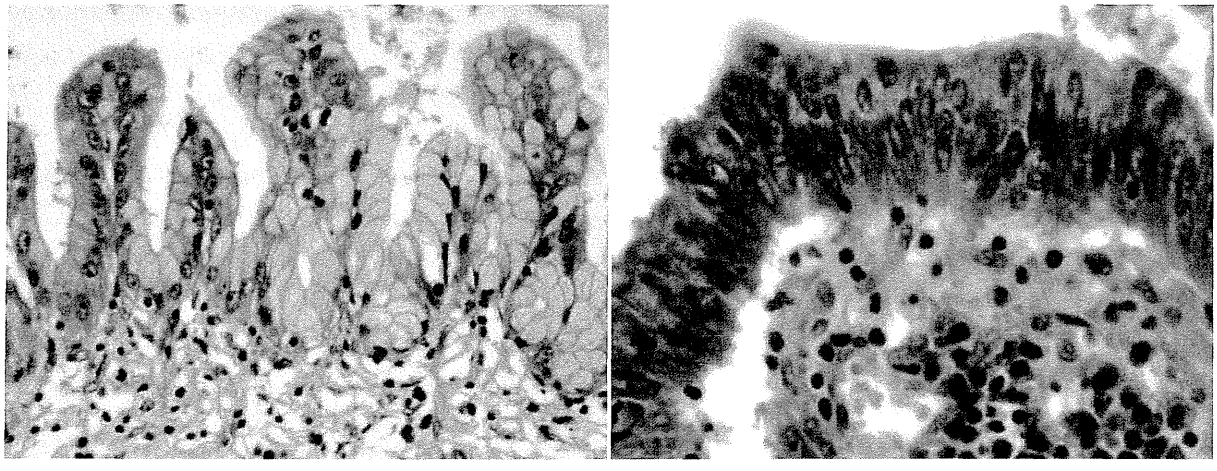
粘液形質の検討では，BilIN の多くは MUC2 陰性，MUC5AC 陽性を示し，foveolar type の形質を示すことが多い[6]。

BilIN はしばしば胆管周囲付属腺にも認められる。



a|b
c|

図 2 胆管上皮層内腫瘍（BilIN）の顕微鏡的形態
a：flat（平坦）
b：pseudopapillary（偽乳頭状）
c：micropapillary（微小乳頭状）
HE 染色。



a|b

図 3 胆管上皮層内腫瘍（BilIN）にみられる化生
a：foveolar metaplasia
b：intestinal metaplasia
HE 染色。

近年，胆管周囲付属腺の壁内腺に類似する膵管腺（pancreatic duct gland）が，主膵管やその主な分枝に存在することが報告されているが，この膵管腺に化生やPanIN類似の病変が発生しうるとされており，胆管付属腺にみられる異型上皮病変の発生機序を考察する上で興味深い[7]。

②広範囲進展

一般にBilINは肝門部大型胆管や肝外胆管の限局した範囲内に領域性に出現する。顕微鏡下ではその領域内で非連続性，多発性の病変を形成しているようにみえることもしばしば経験される。

通常，BilINは末梢側の小型胆管には出現しないが，

アルコール性肝硬変やC型肝硬変などの非胆汁性肝硬変では，小葉間胆管や細胆管にBilIN，もしくはそれと同等の異型上皮病変が多発する症例があることが報告されており，末梢型胆管癌の前癌・早期癌病変の一つと推測されている（図4）[8,9]。

胆道癌における上皮内癌の出現様式の一つとして，癌の表層進展がある[10]。概念的にBilINは多段階発癌の過程を反映し，膵管のPanINに対応する病変である。一方，胆道癌の表層進展は浸潤性膵管癌の主膵管内進展，いわゆるcancerizationに近い概念と思われる。

顕微鏡下で観察した場合，胆管壁に浸潤性の腺癌がみられ，浸潤癌に近接する胆管の上皮層内に上皮内癌が存在し，これが正常胆管上皮との間に明瞭なフロントを形成している場合，癌の表層進展の可能性がある（図5）。浸潤癌を合併した肝内結石症を対象としたわれわれの検討では，こうした上皮内癌の出現様式が約40％の症例に観察され，一部の症例では上皮内癌が肝内胆管のかなり広い範囲に進展していた。

このようにBilINと胆道癌の表層進展は本質的に異なるものと考えられるが，実際の病理組織では両者の区別が困難なことも多い。

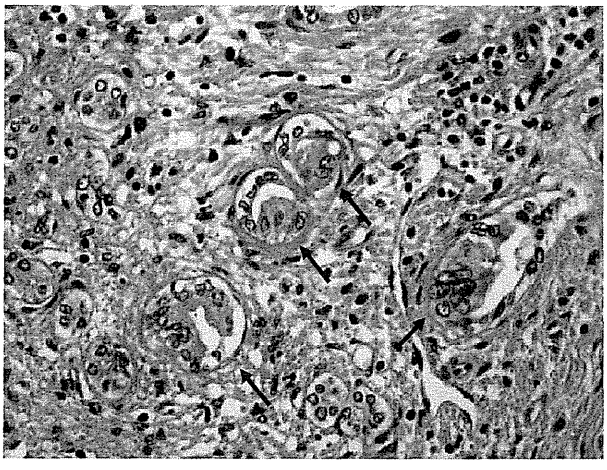


図 4　細胆管内の異型上皮病変（矢印）
C型肝硬変症例。HE染色。

3．分子病理学

BilINの異型度が高くなるに従い，p21やcyclin D1といった細胞周期関連分子の発現が亢進し，細胞外マトリックス分解酵素の発現増加が浸潤癌への移行に関与する[11~13]。細胞接着や形態維持に関与するE-cadherinやβ-catenin，あるいはSMAD4の発現は低下傾向を示す。p53蛋白の発現はBilINの異型度とともに増加するが，その頻度はBilIN-3でも10％程度であり決して高率ではない[12]。同様に頻度は高くないが，BilINの中にKRAS変異を示すものがあることがわかっている。熱ショックタンパク質（heat shock protein，HSP）であるHSP27やHSP70は高異型度のBilINや浸潤癌で発現が亢進しており，腫瘍細胞のアポトーシス抵抗性への関与が示唆される。

BilIN-1では癌抑制遺伝子p16（INK4a）の発現がしばしばみられるが，異型度の進展とともに発現が低下し，浸潤癌ではほとんどみられない。逆に，ポリコーム蛋白EZH2は異型度とともに発現が低下し，EZH2の過剰発現がp16（INK4a）プロモーターのメチル化を誘導し，これがp16（INK4a）の発現低下を来す機序が明らかとなっている[14]。BilINの異型度はHE染色標本で判定されるが，病理組織診断の観点から，p16（INK4a）とEZH2の免疫染色における染色パターンは，BilINの異型度をより客観的に判定する一助となる可能性がある。

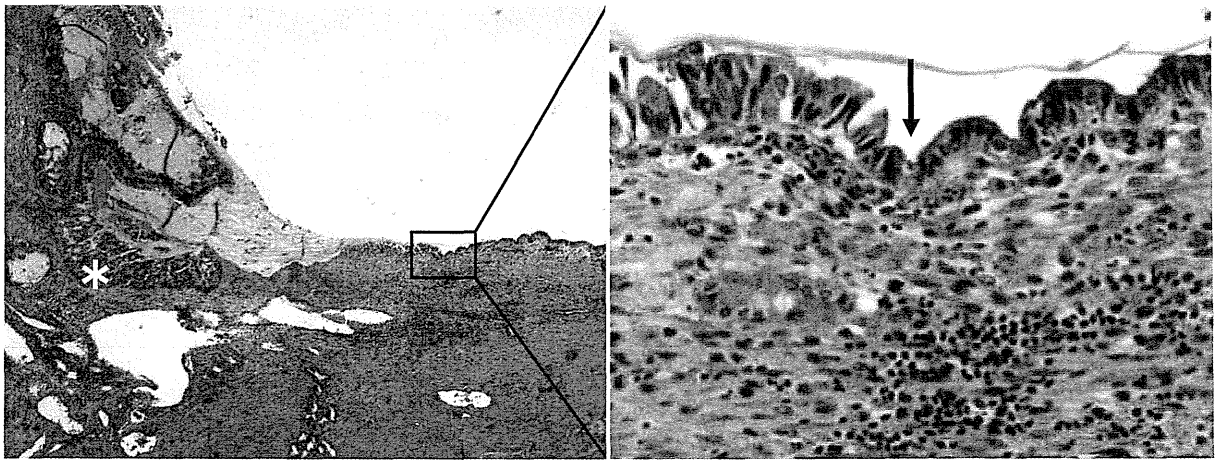


図 5　胆道癌の表層進展
浸潤癌（＊）に近接する胆管の上皮層内に上皮内癌が存在し，これが正常胆管上皮との間にフロント（矢印）を形成している。HE染色。

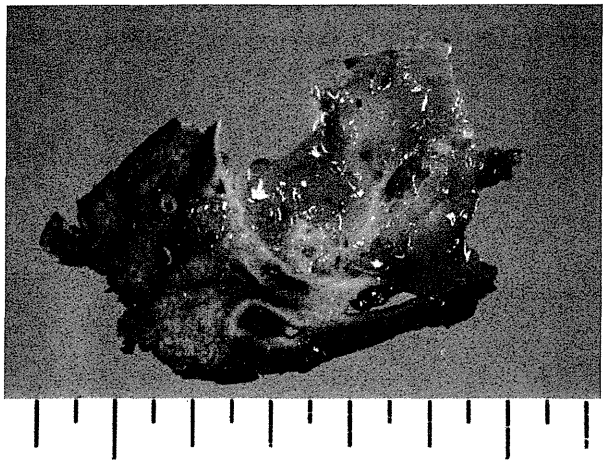


図 6 胆管内乳頭状腫瘍（IPNB），肉眼像

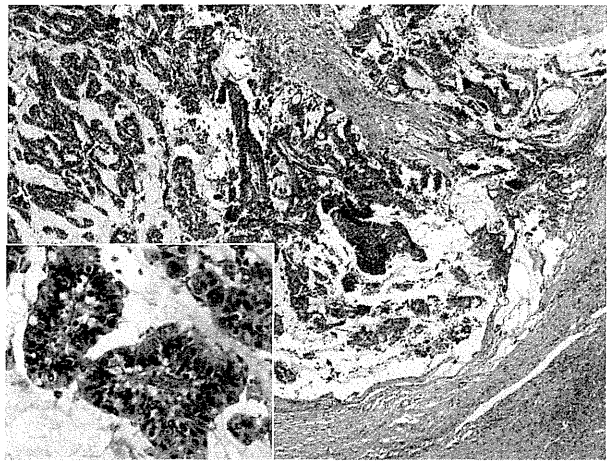


図 7 胆管内乳頭状腫瘍（IPNB），病理組織像
インセットは拡大像。HE 染色。

4．問題点

BilIN 分類が再現性をもって広く使用される上での問題点の一つが反応性異型・過形成の取り扱いである。BilIN-1 と診断される病変の中に反応性異型・過形成が含まれる可能性があり，反応性と腫瘍性の鑑別は HE 染色標本のみでは必ずしも容易ではない。鑑別を可能にする遺伝子異常の解析や新規染色マーカーの探索が望まれる。利便性の向上には，膵臓（PanIN）で行われているように BilIN-1 を BilIN-1A と-1B に細分化することが有効かもしれない。また，化生上皮の評価，あるいは背景に高度の炎症を伴う場合に BilIN 分類を適用する基準を示すことが今後の課題としてあげられる。

Ⅱ．IPN of the bile duct

1．位置づけ

BilIN 分類と同様，IPNB も膵管内腫瘍との対比から，膵臓（特に主膵管）に発生する intraductal papillary mucinous neoplasm（IPMN）との相同性に基づく疾患概念である[15]。WHO 分類では IPN with low-or intermediate grade intraepithelial neoplasia および IPN with high-grade intraepithelial neoplasia が premalignant lesions であり，IPN with an associated invasive carcinoma が malignant という位置づけである[5]。なお，本病変は WHO 分類では IPN of the bile duct もしくは IPBN（intraductal papillary biliary neoplasm）と略称されているが，ここでは従来から広く用いられてきた IPNB という略語を使用する。

IPNB には papilloma や papillomatosis として報告されている病変，あるいは現行の胆道癌取扱い規約（第5版）の胆道癌・乳頭型，原発性肝癌取扱い規約（第5版補訂版）の肝内胆管癌・胆管内発育型の一部が包括されうる。

2．病理形態

① 形態学的特徴

肉眼的に拡張した胆管内に乳頭状腫瘍を形成する（図 6）。低乳頭状で微細な不整粘膜を呈する症例もある。粘液の過剰産生は約 1/3 の症例でみられる。

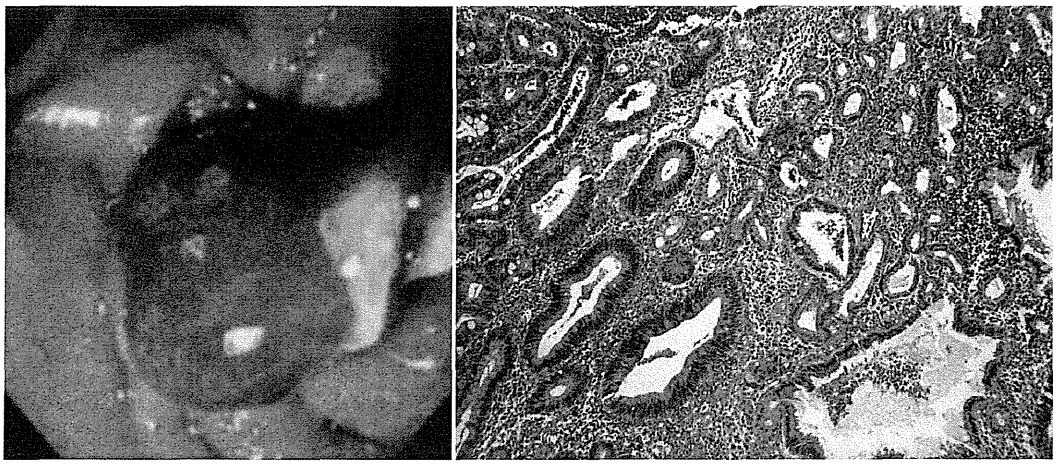
組織学的に血管結合織の芯を伴う異型胆管上皮の乳頭状増殖を特徴とする（図 7）。IPNB の病巣周囲の肉眼的に平坦にみえる胆管粘膜にも，主病巣から連続して異型上皮が進展していることもしばしば経験される。膵 IPMN と同様，上皮の細胞形質は pancreatobiliary，gastric，intestinal，oncocytic type の 4 型に分類される。Pancreatobiliary type，次いで intestinal type が多く，膵 IPMN と比較すると gastric type の頻度が低い。免疫染色では MUC2 や CK20 などの intesitinal type の形質の発現が高率にみられる[16]。

浸潤部の組織型は管状腺癌と粘液癌の形態をとることが多く，intestinal type で粘液癌が好発することは膵 IPMN と同様である。浸潤部の組織型が術後の予後に影響し，粘液癌合併例に比較して管状腺癌合併例はリンパ節転移の頻度が高く予後が悪い[17]。

② Cystic variant

胆管の嚢胞状拡張を示す IPNB があり，cystic variant として知られている[18]。Mucinous cystic neoplasm（MCN）との鑑別が問題となる病変であり，卵巣様間質の存在や胆管との非交通性，女性であれば MCN，卵巣様間質の欠如と胆管との交通性は IPNB を支持するが，これらの所見は絶対的なものではない[19]。

IPNB は主膵管型の IPMN に相同性を示す病変とみなされるが，分枝型 IPMN に相当する胆道系病変は未



a|b

図 8 胆管内管状腫瘍（ITN）
a：肉眼像
b：病理組織像。HE 染色。

だ不明確である。IPNB の cystic variant や MCN，上皮の増殖性変化の目立つ胆管周囲嚢胞にそうした病変が含まれている可能性がある。また，胆管周囲付属腺に由来する IPNB の報告例もあり，これも分枝型 IPNB に相当する可能性が指摘されている[20]。

3．分子病理学

IPNB の分子異常については少数の報告があるのみである。KRAS 変異は約 30％程度と低く，マクロサテライト不安定性は 10％程度でみられる[21,22]。β-catenin の核内発現増強や p53 蛋白の発現異常，SMAD4 の発現低下もみられるが，異常の検出頻度は高くなく，いずれも症例の半数以下である[12]。

4．問題点

胆道系の腫瘍分類に膵腫瘍の分類を適用すると，その病態病理が理解しやすいが[23]，IPNB 分類には粘液産生の多寡は基準として加えられていない。この点は粘液の過剰産生を特徴とする主膵管型 IPMN と大きく異なっている。近年，粘液を過剰産生する IPNB は膵 IPMN によく類似するが，粘液非産生性の IPNB はそれとは異なる hetetogeneous な性質を示すことが指摘されている[24]。

WHO 分類では膵管内腫瘍として膵管内管状乳頭腫瘍（intraductal tubulopapillary neoplasm，ITPN）の概念が新たに導入されたが，ITPN は乏液性の病変である。今後，膵腫瘍の分類を胆道系にさらに適用していく場合，粘液産生の観点も加えて胆管 IPNB と膵 ITPN との異同を検証し，IPNB の疾患単位としてのスペクトルムを明確にする必要がある。

Ⅲ．胆管内管状腫瘍

胆管内管状腫瘍（intraductal tubular neoplasm，ITN）は稀な病変と考えられ，その概念も一般的ではないが，最近われわれは総胆管に発生した管状腺管からなる腫瘍を経験し，それを膵 ITN の胆道系カウンターパートとして報告した[25]。

自験例は，肉眼上は表面平滑な有茎性ポリープ（径 10 mm 大）（図 8a）で，組織学的に異型性に乏しい管状腺管（pyloric gland adenoma に類似：図 8b の右側）と異型性の高度な管状腺管（腸型の tubular adenoma に類似：図 8b の左側）の混在からなる病変であった。一部に上皮内癌に相当する部位を認めたが，間質浸潤はなかった。部分像として adenomyoma と鑑別を要する腺管成分を認めたが，平滑筋線維の増生はなかった。こうした組織所見から膵 ITN に類似した胆道系腫瘍を考えた。

最近，膵 ITPN に相当する胆道系病変についての報告や，胆管周囲嚢胞に由来する ITPN の症例報告もなされている[26,27]。このように膵腫瘍の疾患分類が確立されるにつれ，それに相同性を示す胆道系病変が潜在的に存在することが明らかになりつつある。

ま と め

2010 年に改訂された WHO 分類に基づき，胆管内腫瘍として BilIN と IPNB を中心に概説した。これらの概念の導入により，胆道系腫瘍の病理病態がより理解しやすくなったが，一方で今後明らかにしていくべき問題点もいくつか残されている。分子病理学的な側面

からの解析も行われつつあり，WHO分類に採用されたことでBilIN，IPNB分類が研究面でも広く活用され，病態解析がさらに進行することが期待される。

参考文献

1) Zen Y, Aishima S, Ajioka Y, et al. : Proposal of histological criteria for intraepithelial atypical/ proliferative biliary epithelial lesions of the bile duct in hepatolithiasis with respect to cholangiocarcinoma : preliminary report based on interobserver agreement. Pathol Int **55** : 180-188, 2005.
2) Zen Y, Adsay NV, Bardadin K, et al. : Biliary intraepithelial neoplasia : an international interobserver agreement study and proposal for diagnostic criteria. Mod Pathol **20** : 701-709, 2007.
3) Wu TT, Levy M, Correa AM, et al. : Biliary intraepithelial neoplasia in patients without chronic biliary disease : analysis of liver explants with alcoholic cirrhosis, hepatitis C infection, and noncirrhotic liver diseases. Cancer **115** : 4564-4575, 2009.
4) Odze RD, van Krieken JH, Riddell RH, et al. : Premalignant lesions of the digestive system. WHO Classification of Tumors of the Digestive System, Eds : Bosman FT, Carneiro F, Hruban RH, et al., 4th Edition, 10-12, IARC Press, Lyon, 2010.
5) Nakanuma Y, Tsui WMS, Curado MP, et al. : Intrahepatic cholangiocarcinoma. WHO Classification of Tumors of the Digestive System, Eds : Bosman FT, Carneiro F, Hruban RH, et al., 4th Edition, 217-224, IARC Press, Lyon, 2010.
6) Zen Y, Sasaki M, Fujii T, et al. : Different expression patterns of mucin core proteins and cytokeratins during intrahepatic cholangiocarcinogenesis from biliary intraepithelial neoplasia and intraductal papillary neoplasm of the bile duct-an immunohistochemical study of 110 cases of hepatolithiasis. J Hepatol **44** : 350-358, 2006.
7) Strobel O, Rosow DE, Rakhlin EY, et al. : Pancreatic duct glands are distinct ductal compartments that react to chronic injury and mediate Shh-induced metaplasia. Gastroenterology **138** : 1166-1177, 2010.
8) Aishima S, Nishihara Y, Tsujita T, et al. : Biliary neoplasia with extensive intraductal spread associated with liver cirrhosis : a hithero unreported variant of biliary intraepithelial neoplasia. Hum Pathol **39** : 939-947, 2008.
9) Rougemont AL, Genevay M, McKee TA, et al. : Extensive biliary intraepithelial neoplasia (BilIN) and multifocal early intrahepatic cholangiocarcinoma in non-biliary cirrhosis. Virchows Arch **456** : 711-717, 2010.
10) Nakanishi Y, Zen Y, Kawakami H, et al. : Extrahepatic bile duct carcinoma with extensive intraepithelial spread : a Clinicopathological study of 21 cases. Mod Pathol **21** : 807-816, 2008.
11) Nakanuma Y, Sasaki M, Sato Y, et al. : Multistep carcinogenesis of perihilar cholangiocarcinoma arising in the intrahepatic large bile duct. World J Hepatol **1** : 35-42, 2009.
12) Nakanishi Y, Zen Y, Kondo S, et al. : Expression of cell cycle-related molecules in biliary premalignant lesions : biliary intraepithelial neoplasia and biliary intraductal papillary neoplasm. Hum Pathol **39** : 1153-1161, 2008.
13) Itatsu K, Zen Y, Ohira S, et al. : Immunohistochemical analysis of the progression of flat and papillary preneoplastic lesions in intrahepatic cholangiocarcinogenesis in hepatolithiasis. Liver Int **27** : 1174-1184, 2007.
14) Sasaki M, Yamaguchi J, Itatsu K, et al. : Over-expression of polycomb group protein EZH2 relates to decreased expression of p16 INK4a in cholangiocarcinogenesis in hepatolithiasis. J Pathol **215** : 175-183, 2008.
15) Zen Y, Fujii T, Itatsu K, et al. : Biliary papillary tumors share pathological features with intraductal papillary mucinous neoplasm of the pancreas. Hepatology **44** : 1333-1343, 2006.
16) Nakanuma Y, Zen Y, Harada K, et al. : Tumorigenesis and phenotypic characteristics of mucin-producing bile duct tumors : an immunohistochemical approach. J Hepatobiliary Pancreat Sci **17** : 211-222, 2010.
17) Nanashima A, Kinoshita N, Nakanuma Y, et al. : Clinicopathological features of 'intraductal papillary neoplasm of the bile duct' and patient outcome after surgical resection. Hepatogastroenterology **55** : 1167-1173, 2008.
18) Zen Y, Fujii T, Itatsu K, et al. : Biliary cystic tumors with bile duct communication : a cystic variant of intraductal papillary neoplasm of the bile duct. Mod Pathol **19** : 1243-1254, 2006.
19) Zen Y, Pedica F, Patcha VR, et al. : Mucinous cystic neoplasms of the liver : a clinicopathological study and comparison with intraductal papillary neoplasm of the bile duct. Mod Pathol **24** : 1079-1089, 2011.
20) Nakanishi Y, Zen Y, Hirano S, et al. : Intraductal oncocytic papillary neoplasm of the bile duct : the first case of peribiliary gland origin. J Hepatobiliary Pancreat Surg **16** : 869-873, 2009.
21) Abraham SC, Lee JH, Hruban RH, et al. : Molecular and immunohistochemical analysis of intraductal papillary neoplasms of the biliary tract. Hum Pathol **34** : 902-910, 2003.
22) Abraham SC, Lee JH, Boitnott JK, et al. : Microsatellite instability in intraductal papillary neoplasms of the biliary tract. Mod Pathol **15** : 1309-1317, 2002.
23) Nakanuma Y : A novel approach to biliary tract

pathology based on similarities to pancreatic counterparts : is the biliary tract an incomplete pancreas? Pathol Int **60** : 419-429, 2010.
24) Ohtsuka M, Kimura F, Shimizu H, et al. : Similarities and differences between intraductal papillary tumors of the bile duct with and without macroscopically visible mucin secretion. Am J Surg Pathol **35** : 512-521, 2011.
25) Sato Y, Osaka H, Harada K, et al. : Intraductal tubular neoplasm of the common bile duct. Pathol Int **60** : 516-519, 2010.
26) Park HJ, Jang KT, Heo JS, et al. : A potential case of intraductal tubulopapillary neoplasms of the bile duct. Pathol Int **60** : 630-635, 2010.
27) Zen Y, Amarapurkar AD, Portmann BC : Intraductal tubulopapillary neoplasm of the bile duct : potential origin from peribiliary cysts. Hum Pathol 2011. (in press)

*　　*　　*

臨牀消化器内科 2011 Vol.26 No.13

特集 肝門部～肝内胆管癌

1

肝門部～肝内胆管癌の病理

中沼 安二* 佐々木素子* 佐藤 保則*
原田 憲一* 池田 博子**

Key words: 肝管癌，肝門部胆管癌，胆管内乳頭状腫瘍，肝内胆管癌，肝粘液嚢胞性腫瘍

要 旨

肝門部胆管癌および肝内胆管癌を解剖学的部位に従い解説した．胆道癌に分類される肝門部胆管癌と肝内胆管癌に分類される傍肝門型の肝内胆管癌は肉眼像，組織像が類似しており，鑑別が困難な症例がみられ，傍肝門型胆管癌に含めて分類するのも一つの選択肢と考えられる．また，肝外胆管と肝内大型胆管の内腔に乳頭状に発育する腫瘍は胆管内乳頭状腫瘍(IPNB)と呼称され，胆管内腔の拡張を伴い，肝胆の粘液嚢胞性腫瘍(MCN)との鑑別が必要である．MCNでは，卵巣様の間質を伴うのが特徴であり，エストロゲン受容体，プロゲステロン受容体を発現する．末梢型の肝内胆管癌(胆管細胞癌)は，腫瘤形成型の肉眼像を示すことが多い．

はじめに

胆管癌(cholangiocarcinoma)は胆管被覆上皮(cholangiocyte)あるいは胆管周囲付属腺(peribiliary glands)に由来する，あるいは形態が類似する悪性腫瘍で，細胆管，肝内外胆管系，それに乳頭部に発生する[1)~3)]．最近の臨床病理的な話題として，肝門部胆管癌(hilar cholangiocarcinoma)の範囲や定義の見直し，さらに傍肝門型胆管癌(perihilar cholangiocarcinoma)の導入が検討されている[4)]．また，胆管系の内腔に乳頭状の増殖形態を示す胆管内乳頭状腫瘍(intraductal papillary neoplasm of bile duct；IPNB)[5),6)]と，従来から知られている胆管嚢胞腺腫/嚢胞腺癌〔2010年WHO改訂[1)]では，肝粘液嚢胞性腫瘍(mucinous cystic neoplasm；MCN)と呼ぶ〕との異同も注目されている．

本稿では，肝門部胆管癌，肝内胆管癌，それにIPNBおよびMCNの病理を概説する．肝内胆管癌に関しては，傍肝門型と末梢型の肝内胆管癌に分けて述べる．また，一般的な胆管癌(胆管壁や周囲に結節性，浸潤性の形態を示す)と肝内胆管癌の胆管内発育型および胆道癌の乳頭型とを一応区別し，後2者はIPNB，MCNの項で記載する．また，胆管系を「胆道癌取扱い規約」に従い解剖学的に分類し(**図1**)[2)]，さらに肝内胆管系を肝内大型胆管，隔壁胆管，小葉間胆管に亜分類する[7)]．肝内大型胆管，肝門部胆管，肝外胆管には胆管周囲付属腺が分布する[7),8)]．

*金沢大学大学院医学系研究科形態機能病理学
**金沢大学附属病院病理部
(〒920-8640 石川県金沢市宝町13-1)

0911-601X/11/JCOPY

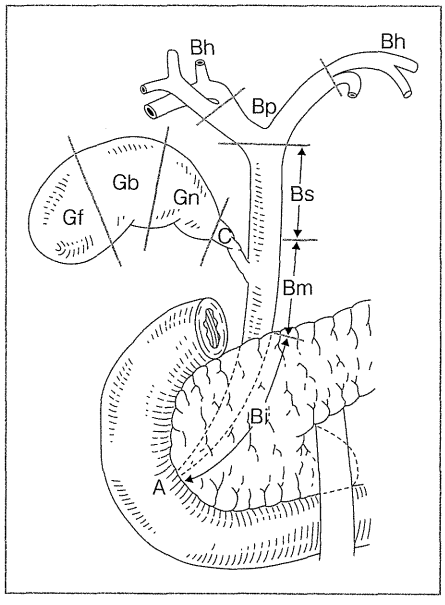


図1　胆管系の区分

Bh：肝内胆管，Bp：肝門部胆管(左右肝管，肝管合流部)，Bs：上部胆管，Bm：中部胆管，Bi：下部胆管，C：胆嚢管，Gn：胆嚢頸部，Gb：胆嚢体部，Gf：胆嚢底部

〔日本胆道外科研究会 編：外科・病理 胆道癌取扱い規約(第5版)．金原出版，2003[2]，p.3より引用〕

Ⅰ．肝門部～肝内胆管癌(傍肝門型)

この項のポイント

- 肝門部胆管癌と傍肝門型の肝内胆管癌の病理像(肉眼，組織)は類似している．

肝門部胆管癌(狭義)は，肝門部胆管(左右肝管および肝管合流部)に発生あるいは主座をもつ癌腫であり，癌腫の主座が上部胆管(Bs)または肝内胆管(Bh)のものは除くとされている[2]．肝内胆管癌(intrahepatic cholangiocarcinoma；ICC)は，左右肝管の肝側の肝内胆管とその分枝に発生する癌腫であり，肝門部に近い肝内大型胆管に発生する肝門型の肝内胆管癌(hilar ICC)〔あるいは傍肝門型肝内胆管癌(perihilar ICC)〕と肝内小型胆管あるいは細胆管から発生する末梢型肝内胆管癌(peripheral ICC，胆管細胞癌)に分ける場合がある[1]．しかし，進行例では肝門部胆管癌と肝門型肝内胆管癌や上部胆管癌との区別がしばしば困難であり，上部胆管(Bs)または肝内胆管(Bh)の癌腫を含める広義の肝門部胆管癌なる名称も用いられることがある[2]．さらに国際的には，外科的な治療法を重視し，総肝管，肝門部胆管，さらに左右肝管の第二次分枝までの癌腫を広くperihilar cholangiocarcinoma(傍肝門型胆管癌)として扱うことが提唱されている[4]．

1．肉眼像

肝門部胆管癌(狭義)の肉眼像の多くは，結節型(nodular type)および平坦型(flat type)に分類される(「胆道癌取扱い規約」)[2]．一方，肝内大型胆管に発生する傍肝門型の肝内胆管癌の多くは胆管浸潤型(periductal infiltrating type)に分類される(「原発性肝癌取扱い規約」)[3]．いずれも線維増生の多い腫瘍で，白色あるいは灰白色を呈する．結節型は，比較的境界が明瞭であるが，被膜形成はない．平坦型と胆管浸潤型は類似しており，浸潤性の増殖を示すことが多い(**図2**)．事実，これら癌腫の進行例では，肝門部胆管癌(狭義)なのか，傍肝門型肝内胆管癌なのかの鑑別は不可能なことが少なくない．榊野らは，一つの臓器というべき胆管系を無理に肝内と肝外に分け，規約を別々に規定したことが混乱の要因となっているとしている[9]．傍肝門型の肝内胆管癌と肝門部胆管癌(狭義)は類似の病理像を示すので，これらの癌腫を傍肝門胆管癌として扱うことも一つの選択肢と思われる[4]．

なお，発生学的には，肝内胆管・胆道系は胎生4週頃に原始腸管の前腸内胚葉十二指腸領域から発生する肝の原基〔肝嚢(hepatic diverticulum)〕に由来する．肝嚢は二つの成分，すなわち，肝細胞索を形成する部分(頭側方向に増殖)と肝外胆道系になる部分(尾側方向に増殖)

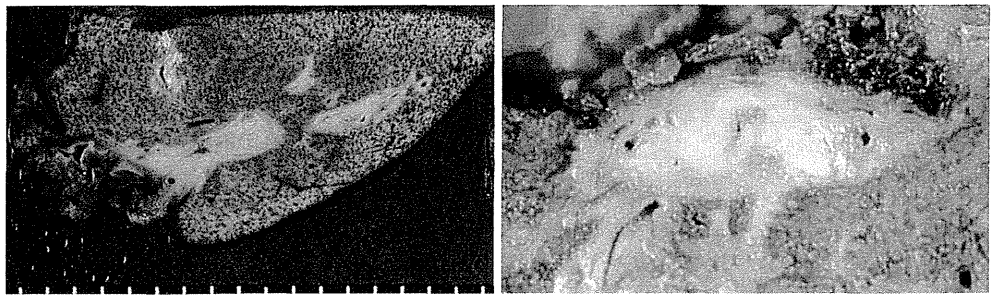


図2　胆管癌の肉眼型
a：傍肝門型の胆管癌で，胆管周囲浸潤型と判断される．
b：肝門部胆管癌で結節浸潤型と判断される．

に分かれる．肝内胆管は肝細胞索を構成する原始肝細胞に由来する胆管板から派生する．したがって，胆道癌と肝内胆管癌は発生する胆管上皮が解剖・発生学的には異なっていると思われる[8]が，完成した癌あるいは前癌病変に，現在のところ，本質的な差異は見出されていない．将来的に，肝門部胆管癌(胆道癌)と傍肝門型の肝内胆管癌の両者を一般の検査室レベルで区別できれば，肝門部，傍肝門部に発生する胆管癌の病態解析が大きく進展すると思われる．

2．組織像

一般的な腺癌(adenocarcinoma)と，特殊な癌腫に分類される．腺癌は，管状あるいは乳頭状の形態が主であり，多くの症例では，高分化型，中分化型であり，豊富な線維増生を伴う症例が多い[1),10)]．索状あるいは充実性の増殖を示す例もある．これらの例では，線維性間質の乏しい例もあり，肝細胞癌との鑑別が問題となる．癌巣の主座となっている，あるいは原発と考えられる腫瘍性胆管，あるいはこれに隣接する胆管では，胆管内面に微小乳頭状あるいは平坦な高分化な腺癌をみることが多く(粘膜病変)，胆管壁へ浸潤している像(胆管壁浸潤病変)を同時にみる(**図3**)．腫瘍部胆管が腫瘍内に埋もれている場合でも，線維染色(弾力線維染色を含める)などで原発胆管あるいは隣接胆管を同定することが，病理診断学的に必要である．特殊な癌腫として，扁平上皮癌，腺扁平上皮癌，内分泌癌などが知られているが，まれである[1),10)]．胆管周囲への浸潤，血管やリンパ管内への侵入がみられ，さらに神経周囲への浸潤がみられる．とくに，神経周囲に浸潤する例では，浸潤腺癌の内腔が拡張し，原発巣と紛らわしいことがあり，注意が必要である．

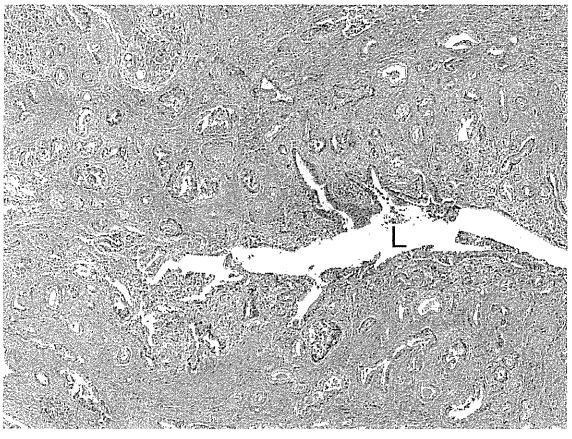


図3　原発部に近いと考えられる癌性の肝内大型胆管
粘膜病変と胆管壁浸潤病変をみる．
L：狭窄した胆管内腔．HE 染色．

Ⅱ．末梢型の肝内胆管癌(胆管細胞癌)

この項のポイント

- 末梢型の肝内胆管癌は，腫瘤形成性の増殖像を示し，傍肝門型の肝内胆管癌とはその病理像が異なる．

「原発性肝癌取扱い規約」では，肝内胆管癌の肉眼像を腫瘤形成型(mass forming type)，胆管浸潤型(periductal infiltrating type)，胆管内発育型(intraductal growth type)の3型に大きく分類している[3]．この分類は現在，WHOの肝内胆管癌の分類にも用いられている[1]．

1．肉眼像

末梢型肝内胆管癌は腫瘤形成型を呈する例が多い．肝実質内にみられる肝内に白色～灰白色，充実性の腫瘤で，境界は比較的明瞭である(**図4**)．進行例では肝内で多発性，癒合性の腫瘍結節を形成する．線維性の明瞭な被膜形成はみられない．肝臓の被膜直下に存在する腫瘤は，癌腫を形成する．中心部に高度の線維化あるいは硝子化を見る例が少なくない．また，中心部に壊死を示す例もある．傍肝門型の肝内胆管癌とは肉眼像が異なる．

2．組織像

傍肝門型の肝内胆管癌と同じく，腺癌と特殊な癌腫に分類される．腺癌は，高分化型あるいは中分化型であり，豊富な線維増生を伴う症例が多い．しかし，線維増生の乏しい症例も少なくない．肝内小型胆管を管腔に沿って浸潤する像が少なくない[1),10)]．

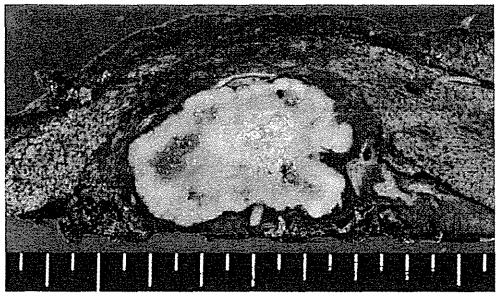


図4　腫瘤形成型の肝内胆管癌

Ⅲ．IPNBおよびMCN

この項のポイント

- IPNBとMCNは類似した肉眼像を示すが，MCNの間質は卵巣様であり，プロゲステロンやエストロゲン受容体を発現する．

1．IPNB

従来より，頻度は低いが，肝内外の大型胆管内腔で乳頭状に発育する腫瘍が知られている．胆道癌の乳頭型と肝内胆管癌の胆管内発育型が代表的であり，これらは相互に類似している．これら症例の病理形態像が膵管内乳頭粘液性腫瘍(IPMN)に類似しており，IPNBと呼ぶことが提唱されている(**図5**)[1),5),6),11)]．腫瘍性胆管はしばしば拡張しており，乳頭状の増殖を示す高分化型腺癌あるいは腫瘍性胆管上皮〔ディスプラジア，境界病変(borderline malignancy)〕の増殖があり，大量の粘液の産生・分泌がみられることが少なくない．現在，「胆道癌取扱い規約」[2)]に記載されている胆道癌の乳頭型，胆管乳頭腫(症)(papilloma，papillomatosis)として報告されている病変，さらに「原発性肝癌取扱い規約」[3)]で定義されている肝内胆管癌の胆管内発育型も，IPNBとの関連性で再分類できる．

胆管内乳頭状腺癌(乳頭型胆道癌および胆管内発育型肝内胆管癌)：肝内外の胆管内腔に乳頭状に増殖する高分化型腺癌であり，間質は狭い線維性の血管線維性芯である．

胆管乳頭腫(症)：肝内外の胆管内腔での胆管上皮の乳頭状増殖で特徴づけられ，狭い線維性間質を伴う．胆管内腔の拡張を伴うことが多い．境界病変あるいはlow grade malignancyとの意見が多い．

胆管の嚢状拡張を示す胆管腫瘍：胆管内腔の嚢