会長講演 自己免疫性肝疾患 ―温故知新―

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自己免疫性肝疾患には肝細胞障害を主体とする自己免疫性肝炎と胆管細胞障害による胆汁うっ滞を特徴とする原発性胆汁性肝硬変がよく知られている。これらはめずらしい疾患と思われていたが、今やまれなものとはいえない。われわれの教室において最近3年間に診療した慢性肝疾患の3大成因はC型、B型、ついで自己免疫性肝疾患である。この背景には肝疾患の診断法の確立と普及に加え、肝疾患における疾病構造の変遷もあげられよう。

最近の傾向の1つとして、本疾患は無症候性で診断され、とくに原発性胆汁性肝硬変にいたっては90%が無症候性である。また自己免疫性肝疾患の10-15%には、原発性硬化性胆管炎やいわゆる自己免疫性胆管炎、また肝炎ウイルスやいずれかの自己免疫性肝疾患をoverlapした症例などが認められる。治療に関しては、薬剤を上手に使い患者の予後は良くなった。その中でよりウルソデオキシコール酸は原発性胆汁性肝硬変の予後を望まされた。しかしわが国の自己免疫性肝疾患のnatural historyの詳細は不明で、根治的療法といえるものはない。また、長期生存した自己免疫性肝疾患から肝細胞癌が発症し、これらの対応に迫られているのが現状といえる。

自己免疫性肝疾患は自己免疫機序によって発症し、その引き金としてウイルス感染、薬剤、その他環境因子が関与し、特定の遺伝的素因のために病態が成立することは以前から指摘されてきた。しかし免疫学の革命的進歩にもかかわらず、その本体はいまなお不明な点が多い。

最近アポトーシスという概念が登場し、これは免疫寛容の維持のみならず正常組織の破壊にも関わり、自己免疫疾患の発症に強く関与することが明らかとなった。

自己免疫性肝炎に関する我々の研究では、肝細胞内浸潤リンパ球の大半はCD45RO陽性T細胞(メモリーT細胞)であり、細胞表面にCD95/CD95 Ligand (Fas/Fas L)を発現しており、CD8よりCD4細胞が生き残っている。そして活性化 helper T細胞はIL-2, IFN- γ また TNF- α / β など炎症性サイトカインを分泌する。また活動期には肝細胞内にはCo-stimulatory moleculeであるCD80やCD86陽性細胞が著明に集簇し、これらは肝臓における抗原提示能の異常、またアナジュー状態の解除を示す。これら細胞のligandであるCD28陽性の細胞、とくにCD28陽性CD8細胞が末梢血リンパ球では著減しており、これら細胞は肝臓内に呼び込まれて特異的なCTLとして働いているものと思われる。

本症の活動期においては、アポトーシスの回避に働くと考えられるbcl-2遺伝子産物を発現したリンパ球が末梢血ならびに肝細胞内に高率に存在し、この多くはCD4陽性でIFN- γ 産生細胞(Th1細胞)であった。また、AST、ALT値との相関も認められ、これらbcl-2陽性Th1型細胞がアポトーシスを回避して存在し、CTLを活性化し、本症の病態形成に関与する可能性がある。

一方、末梢血中にもbcl-2陽性CD19細胞(B細胞)が健康正常人に比し高率で、これは自己抗原反応性B細胞クローンの増大を示唆し、自己免疫性肝疾患における抗原産生に関与するにちがいない。自己抗体の対応抗原としてクロマチン、ヒストン、UI-RNP、SS-A/Ro、サイトスケルトン、サイトケラチンなどが特徴的であり、この多くはアポトーシスに陥った細胞に由来すると思われる。B細胞の自己抗体産生はT細胞によって調節されるので、自己免疫性肝疾患はT細胞異常に基づく疾患といえよう。

自己免疫性肝疾患の本体に迫るためにはアポトーシスとその異常の解析が重要であり、そして細胞障害機序を明らかにし、また副作用の少ない有効な治療法を確立することが今後に残された課題である。

招待講演 FRONTIERS OF AUTOIMMUNE HEPATITIS.Edward L. Krawitt, M.D., Professor of Medicine,
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Despite the recent advances in basic and clinical science applicable to autoimmune liver disease and the treatment thereof, many questions remain unanswered. Although of unknown etiology, the pathogenesis of autoimmune hepatitis is believed to be based at least in part on aberrant autoreactivity. The exact relationship between the genes which may predispose to occurrence and/or severity of disease and environmental agents capable of triggering a cirrhosis-producing autoimmune pathogenic process are not clearly defined. Future studies will be directed at examining the immunoglobulin supergene family, triggering agents including viruses and drugs, the T-cell receptor, relevant antigens, circulating antibodies and the mechanisms underlying humoral and cell-mediated aspects of the immunopathogenesis. The fruits of this research may permit distinction among autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis and overlap syndromes based on information other than the characteristic histologic, clinical and immunologic features, which we presently use for classification. Despite its striking heterogeneity and our incomplete understanding of its pathogenesis, autoimmune hepatitis is, in general, a glucocorticosteroid-responsive condition, although often steroid-sparing with azathioprine is required. Nevertheless, treatment failures occur and toxicity can be a significant problem. Possible future pre- or post-transplant treatment approaches may include newer immunosuppressants, T cell vaccines, blocking peptides, lymphokines and monoclonal antibodies.

招待講演 PRIMARY SCLEROSING CHOLANGITIS: ADVANCES IN DIAGNOSIS, ETIOPATHOGENESIS, AND TREATMENT. RH Wiesner, Mayo Clinic and Mayo Foundation, Rochester, MN (USA).

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease most likely related to autoimmune damage of the biliary tree. PSC is frequently associated with inflammatory bowel disease, most commonly chronic ulcerative colitis, and the presence of the HLA DR3 haplotype is often found, which is frequently associated with autoimmune conditions. PSC usually begins insidiously with the finding of a cholestatic biochemical profile, which later progresses to symptoms of fatigue, pruritus, and in the end-stage, jaundice and complications of portal hypertension. The disease usually progresses over a period of 12-20 years. Histologic evolution of PSC results in irreversible damage to the bile ducts, which ultimately leads to cholestasis, fibrosis, cirrhosis, and premature death from liver failure unless liver transplantation is performed. The histologic finding of the presence of fibrous obliterative cholangitis is nearly pathognomonic of the disease in a patient with chronic ulcerative colitis. Long-term follow up of PSC patients reveals a high incidence of colon cancer in patients with chronic ulcerative colitis and a high incidence of cholangiocarcinoma, which increases with disease duration. Both of these complications seem to be related to the chronic inflammatory state involved in these two organs. A number of medical (including ursodeoxycholic acid therapy), endoscopic, and surgical therapies have been evaluated for the treatment of PSC. However, to date, no therapy achieves a complete clinical, biochemical, or histologic remission. Radiologic or endoscopic intervention is indicated for those patients who have increasing jaundice or in those who have recurrent bouts of cholangitis. However, until the etiopathogenesis of PSC is better defined, effective therapy is unlikely to be found. Thus, liver transplantation, in which excellent results have been achieved, continues to be an important therapeutic intervention for the management of patients with end-stage PSC.

1. Primary sclerosing cholangitis
2. Chronic ulcerative colitis

招待講演

New insights into the etiopathogenesis of autoimmune liver diseases.

Michael P. Manns, Medical School of Hannover, Germany

Antinuclear antibodies (ANA) are very heterogeneous in autoimmune hepatitis. F-actin is the most significant cytoskeleton antigen while CYP 2D6 is the most important microsomal autoantigen. It is the main target of LKM-1 antibodies in autoimmune hepatitis type 2 and in some patients with chronic hepatitis C. Several linear and conformational epitopes have been identified. One linear epitope with sequence homology with the IE 175 protein of HSV-1 is almost exclusively recognized by autoimmune hepatitis sera. A new conformational epitope has been characterized lately that is common to both autoimmune and chronic hepatitis C sera. Liver infiltrating T lymphocytes were shown to recognize CYP2D6 which is expressed on the surface of the hepatocyte membrane. UDP-glucuronosyltransferases are targets for LKM-3 antibodies in hepatitis D and some patients with autoimmune hepatitis. The cytosolic SLA and LC-1 antigens have been cloned recently and await further molecular characterization. Immunogenetic studies have shown that HLA A1-B8-DRB1*0301 and HLA DRB1*4 alleles are associated with autoimmune hepatitis. They determine clinical course and treatment response rather than disease susceptibility. The autoimmune polyendocrine syndrome type 1 (APS-1) - a genetically determined multiorgan autoimmune disorder - is caused by mutations of the AIRE-1 gene which encodes a transcription factor expressed in thymus and other organs. Adrenal, gonadal, parathyroid, skin and liver are among the most significant organ manifestations. In adrenal insufficiency these patients' microsomal antibodies are directed against CYP c21, c17 and scc which all are involved in adrenal steroid synthesis. Four liver expressed CYP proteins have been identified as autoantigens in the APS-1 syndrome of which CYP 1A2 is closely associated with liver disease. The APS-1 syndrome gives new insights into the etiopathogenesis of autoimmune liver diseases.