IFN・Ribを併用して治療を行った．DFPPはカテーテル穿刺や管理に伴う合併症や血漿交換に伴う副作用が10～30%報告されているが[11]，今回の12例はいずれもDFPPに伴う合併症や副作用は認められずPEG IFN・Ribを併用でき，DFPP併用PEG IFN・Ribの安全性が確認されたと考えられる．

HCVが血漿交換で除去されることは，1999年Mantinらのクリオグロブリン症とC型肝炎合併例[13]やMarsonらの家族性高コレステロール血症とC型肝炎合併例[14]やRarmratnamらのHIVとC型肝炎合併例[15]で報告されていた．2007年Fujiwaraら[11]の検討により30nmの孔径を有する膜型血漿成分分離機カスケードフロー(EC-50W；旭化成クラレメディカル社)が完成されGenotype 1b・高ウイルス量の難治性C型慢性肝炎に対し血漿交換が臨床導入されるにいたった．これを用いてC型慢性肝炎患者にDFPPを行うと，二次膜出口のHCV RNA量は99.98%以上とほぼ完全に除去されるが，除去しても2時間以内に急速にHCVが再び産生されることが問題であった．そこでDFPP後直ちにPEG IFNを注射しRib内服を開始することにした．初回DFPP前後での1回DFPPのHCV除去効率をHCV core抗原値の変化で見ると平均25.9%であった(Table 2, b-c/b)．これはFujiwraら[11]の報告でのHCV RNAを用いた一回のHCV除去率26.1%とほぼ一致した．DFPPを5回繰り返した全ての効果を初回前と5回目DFPP後でHCV RNA量の変化で見ると，平均1.8 Log IU/ml(Table 2, a-d)約2Log IU/mlの減少であり報告と同等であった．Response-guided therapy[10]ではHCV RNA量が12週以内に2Log IU/ml低下することが効果判定の目安となっており，DFPP前後の2週間以内に同等のHCV減量を獲得できたこととなる．しかし，2Log IU/ml以下の低下例が7例あり，1Log IU/ml以下も3例存在した．2Log IU/ml以下であってもCase1と7の2例は最終的にSVRになっておりDFPPによるHCV減量効果だけでは治療予測はできなかった．

Enomoto[4]らは，ISDRの変異数が多いほどC型慢性肝炎のIFN治療でSVR率が高くなり，坂本ら[16]はPEG IFN・Rib療法ではISDR変異数0または1（ISDR0～1）の症例のSVR率は40%であるのに対し，2個以上の変異では81%の高いSVR率が得られたと報告している．Akutaらは PEG IFN・Rib治療でHCV core領域のaa70およびaa91 mutant例ではNRが有意に多く[5]，両者wild例ではSVRが多い[17]と報告している．DFPP前後でのHCV RNA減量は，IFN治療が効き易いとされるISDR変異2個以上2例では－1.5 LogIU/ml, ISDR 0～1かつCDMでない6例では－2.3 LogIU/ml，PEG IFN・RibでもNRが多いとされるISDR0～1かつCDM 4例では－1.4 LogIU/mlであり，ISDRとcore変異別に見てもDFPPの効果に差を認めなかった（Table 3）．一方，前IFN別でのDFPP前後でのHCV RNA減量は，IFN単独3例では－2.7 LogIU/mlだったのに対し，IFNα 2b・Rib 2例では－1.9 LogIU/ml，PEG IFN・Rib 7例では－1.4 LogIU/mlであり，有意に前治療IFN単独例でのDFPPの効果が高かった（Table 4）．今回の検討ではDFPP効果がISDRやcore変異よりも前IFNの種類に影響されたが理由は不明である．症例を増やしてさらに検討が必要である．

12例中2例がDFPP後に血球減少でPEG IFN・Ribを中止したが，継続できた10例の効果はRVR2例(16.7%)，EVR2例(16.7%)，LVR2例(16.7%)，最終的にはSVR5例（41.7%）であった．これは，2010年Kanekoらが報告[18]したDFPP＋IFN併用の成績RVR 14.9%，EVR 57.5%比し不良であった．しかし，前治療IFNがNR例に限ればRVR 12.9%，EVR 41.9%，さらに前治療PEG IFN・Ribに限ればRel例で各々7.4%，63.0%，NR例で5.4%，18.9%と低下すると報告している．その理由の一つとして，前治療非治癒という条件はGenotype 1b・高ウイルス量C型慢性肝炎の中でもさらに難治例を囲い込む可能性があることと思われる．我々の12例でもISDR 0～1が10例(83.3%)，core aa 70か91何れか変異を認めるのが8例（66.7%）と非常に難治な集団であった（Table 1）．先に述べたようにISDRやCoreの変異はDFPPの効果には直接影響しなかったが，最終治療結果だけ見ればSVR率はISDR ≧2で2/2(100%)に対しISDR0～1では3/10(30.0%)と低く，坂本ら[16]の報告の傾向と一致する．Coreの変異を組み合わせるとSVR率はISDR0～1かつCDM以外で2/6(33.3%)，Akutaらの報告[5]でも最も難治と予想されるISDR0～1かつCDMで1/4（25.0%）と最も低かった(Table 3)．ISDR0～1かつCDMで唯一SVRとなったCase3は前治療IFN単独無効例であり，DFPPでHCV RNAは2.8Log IU/ml低下した後にPEG IFN・RibでEVRを示し，DFPPとPEG IFN・Ribの組み合わせが奏功したと考えられた症例であった．一方，2009年Tanakaら[6]によりPEG IFN・Rib治療における現在のところ最強の宿主側因子であるIL28Bが発見され，IL28B MajorではSVR率が高く，Minorでは低いと報告されている．今回の12例にL28B Minor症例が多数

含まれていた可能性があり今後検討していきたい.

McHutchison[7]らはPEG IFNとRibのAdherence 80%以上がSVR率を向上させる条件に挙げているが, 前回治療がRibとの併用療法であった9例の前回のPEG IFNのAdherenceは平均86.3%, Ribは平均87.8%であり十分な投与量を確保できていたと考えられる. 前治療ではCase7とCase12で一旦HCV RNA陰性となったが最終的にRelとなり, それ以外の7例は一度もHCV RNA陰性が得られないNRであった. これらに今回はDFPPを併用してPEG IFN・Ribを行ったが, 前治療でRelであった2例のみがSVRとなった. この2例は前回と今回のPEG IFN・Rib投与期間およびAdherenceがほぼ同じにも関わらず, HCV RNA陰性化時期がCase 7では12週から5週に, Case12は8週から4週に早まっておりDFPPを併用した効果であると考えられた. しかし, 他の前治療NR症例ではCase9でLVRとなったものの最終的にRelとなりSVRは獲得できなかった. 以上, 前治療PEG IFN・Rib-NRでISDR0～1かつCore mutant症例ではDFPPを併用してPEG IFN・Ribで再治療しても今のところSVRとなった例はなくさらに症例を積み重ねて検討すべきと思われた.

Genotype 1b・高ウイルス量の難治性C型慢性肝炎に対してはPEG IFN・Ribにプロテアーゼ阻害剤Telaprevirを加えた3剤併用療法[19]が近々臨床応用される予定だが, 貧血などの副作用などが報告されている. DFPP併用PEG IFN・Rib療法は安全性が高く, 新規治療以外の再治療では, SVRが期待できる前治療IFN単独NR症例やPEG IFN・Rib併用Rel症例に於いては適応を検討しても良いのではないかと考えられた.

結　語

DFPP併用PEG IFN・Rib療法は安全性が高くHCV RNA量を早期に約2 Log IU/ml低下させる可能性を持つ優れた治療法である. 以前IFNを行ったがSVRが得られなかったGenotype 1b・高ウイルス量の難治性C型慢性肝炎に対し, DFPP併用PEG IFN・Rib療法を再治療として行う場合は前治療IFN単独NR症例やPEG IFN・Rib併用Rel症例に於いてはSVRが期待できると考えられた. さらに症例を増やして検討していきたい.

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Double filtration plasmapheresis and peginterferon plus ribavirin combination therapy for chronic hepatitis C patients with genotype 1b and high viral load not cured by previous interferon therapy

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Twelve chronic hepatitis C patients (six men and six women; average age 60.3 years) with genotype 1b and high viral load who were not cured by previous interferon (IFN) therapy received double filtration plasmapheresis (DFPP) and peginterferon plus ribavirin (PEG IFN・Rib) combination therapy. In the previous IFN therapy, there were three non-responders (NR) to IFN monotherapy, two NRs to IFNα2b・Rib, two relapsers (Rel) and five NRs to PEG IFNα2b・Rib. Viral load reduction by DFPP was 1.8±1.2 (range: 0.1-4.8) log IU/m*l*. The mutations of the interferon sensitivity determining region (ISDR) and HCV core amino acid (aa) did not affect the viral load reduction by DFPP. The viral load reduction rate of NRs to a previous IFN monotherapy was significantly higher than that of the patients who previously received Rib combination therapy ($p<0.05$). Three (100%) of the patients who previously received IFN monotherapy showed a sustained viral response (SVR). The patients who previously received IFNα2b・Rib did not become HCV RNA-negative. Among the patients who previously received PEG IFNα2b・Rib, two Rels showed SVR but five NRs did not showed SVR. Two Rels became HCV RNA-negative after the present treatment at an earlier stage than the previous PEG IFNα2b・Rib. Finally, five of all the patients (41.7%) and two of 9 (22.2%) who previously received Rib combination therapy showed SVR. The rates of patients showing SVR in the cases of ISDR mutation≧2, ISDR mutation of 0 or 1 and either a core aa70 or aa91 mutant, ISDR mutation of 0 or 1 and both a core aa70 and aa91 mutant were 2/2 (100%), 2/6 (33%) and 1/4 (25%), respectively. The indication of DFPP + PEG IFN・Rib for the retreatment of chronic hepatitis C of genotype 1 and a high viral load was suggested for NRs to a previous IFN monotherapy or Rels to a previous PEG IFN・Rib.

Key words: chronic hepatitis C double filtration plasmapheresis peginterferon plus ribavirin therapy viral mutation

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報告

発症2カ月で慢性肝炎の組織像を呈しインターフェロンで治癒したHBV Genotype A急性肝炎の1例

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要旨 症例は34歳男性．2009年9月，HIV検診にてHBs抗原陽性で紹介となったが，HBV DNAのみ陽性でIgM HBc抗体・HBc抗体共に陰性・HIVも陰性であった．2009年11月，入院となりAST 754IU/ml，ALT 1486IU/ml，HBs抗原92997S/N，HBe抗原1272S/CO，HBe抗体0％INH，IgMHBc抗体28S/CO·HBc抗体4.41S/CO，HBV DNA8.6Logコピー/mlよりB型急性肝炎と診断した．GenotypeはA型であった．肝生検で慢性肝炎と診断されたため，天然型インターフェロンαを開始し24週間継続した．2010年3月HBs抗原は陰性化，4月HBs抗体が陽性化した．若年層を中心に蔓延する恐れのあるHBV genotype A急性肝炎に対し慢性化が危惧される場合にはインターフェロンを選択の一つに考慮してもよいと思われた．

キーワード　急性肝炎，B型肝炎，Genotype A，慢性肝炎，インターフェロン

はじめに

最近，従来日本には認められなかったHBV genotype A急性肝炎の発症が増加しており，国際交流の増加や性生活の多様化と深く関連しているといわれている[1)2)]．また，HBV genotype Aはほかのgenotypeよりも慢性化しやすいことも報告されており[3)4)]，わが国においてHBV genotype A感染者が蔓延しやすいことが危惧されているが，慢性化を予防する治療法の検討はなされていない．今回，発症から2カ月でHBV genotype Aの急性肝炎と診断されたが，肝生検で慢性肝炎の組織像を呈していたためインターフェロンを投与したところB型肝炎は治癒した1症例を経験したので，若干の文献的考察を加えて報告する．

症　例

症例：34歳男性．
主訴：全身倦怠感
既往歴：特記なし

毎年職場で健康診断を受けているが，肝機能検査

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（平成23年3月3日受付，平成23年7月10日受理）
Administration of Interferon for Chronic Hepatitis Resulting from Acute HBV Genotype A Infection
Noboru Hirashima, Masanao Uraoka*, Asako Kamiya*, Misaki Yokoi*, Masayuki Saitoh*, Dai tamaki*, Yoshimitu-Ryuuge*, Hisanori Watanabe*, Yuusuke Hibino*, Masaaki Shimada*, Tomoyuki Tsuzuki* and Hiroaki Iwase*, NHO Higashi Nagoya Hospital, *NHO Nagoya Medical Center
Key Words: acute hepatitis, hepatitis B, genotype A, chronic hepatitis, Interferon

表1　入院時血液生化学検査

末梢血						ウイルスマーカー		
WBC	4500	/mm^3	ALP	290	IU/L	HBs antigen	92996.92	S/N
Neut	44.6	%	LDH	486	IU/L	HBe antigen	1272.71	S/CO
Lymph	40.4	%	γ-GTP	442	IU/L	HBe antibody	0	%INH
RBC	528	10^4/mm^3	BUN	10	mg/dl	HBc antibody	4.41	S/CO
Hb	14.8	g/dl	Cre	0.78	mg/dl	IgM-HBc antibody	28	S/CO
Hct	44.8	%	T-Chol	121	mg/dl	HBV DNA	8.6	Log copies/ml
Plt	18.8	10^4/mm^3	TG	132	mg/dl	HCV antibody	(−)	
凝固			T-Bill	1.40	mg/dl	HIV antibody	(−)	
APTT	28.4	sec	Glu	135	mg/dl			
PT%	104	%	CRP	0.18	μg/dl	Genotype	A	
生化学			Na	144	mEq/L			
TP	7.1	g/dl	K	3.8	mEq/L			
Alb	4.2	g/dl	Cl	108	mEq/L			
AST	754	IU/L						
ALT	1486	IU/L	AFP	6	ng/ml			

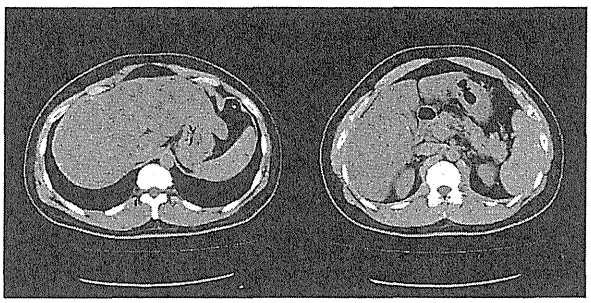

図1　入院時CT検査
入院時のCTは肝腫大と脂肪肝を認めた

を含め異常を指摘されたことはない
家族歴：特記なし
生活歴：喫煙・飲酒せず
独身で男性女性ともに複数回性交渉あるが，特定のパートナーはいない．
現病歴：2009年9月，HIV検診でHBs抗原92S/Nと陽性を指摘されて紹介となった．外来初診時9月16日はAST 101IU/ml，ALT 169IU/ml，HBs抗原102S/N，HBe抗　原36.5S/CO，HBe抗　体0，IgM HBc抗体・HBc抗体ともに陰性，HBV DNA7.1 Logコピー/mlであった．HIVは陰性であった．2009年11月，肝障害の増悪で入院となった．
入院時現症：身長165cm，体重71kg，血圧112/78 mmHg，脈拍62/min・整，意識清明，貧血・黄疸なし，肝脾触知せず，腹水・浮腫なし，神経学的に異常なし．
入院後経過：2009年11月10日入院時，AST 754IU/ml，ALT 1486IU/ml，HBs抗原92997S/N，HBe抗原1272S/CO，HBe抗体0%INH，IgM HBc抗体28 S/CO·HBc抗体4.41S/CO，HBV DNA8.6Logコピー/mlでありB型急性肝炎と診断した．GenotypeはA型であった（表1）．腹部CTは肝腫大を認め，肝のCT値は42と低下していた（図1）．11月12日，肝生検を実施したところ，門脈域に線維化をともなう慢性炎症細胞浸潤を認め，慢性肝炎（F2A2）と診断された．中等度の脂肪沈着も認められたが，肝細胞の脂肪化，肝細胞の水腫状変性（ballooning），マロリー体を認めず，好中球を含む炎症細胞浸潤，線維化がzone3において高度ではないため非アルコール性脂肪肝炎（NASH）は否定的であった（図2）．以上より，ウイルス性肝炎像と診断した．11月17日，AST 230IU/ml，ALT 784IU/mlと低下していることを確認して，患者に説明を行い同意を得て天然型インターフェロンα（スミフェロン®）を600万単位2週間連日投与開始した．投与後の12月1日にAST 450IU/ml，ALT 649IU/mlまで再上昇したがその後低下した．開始後2日間の発熱と軽度の全身倦怠感を認めた．
退院後外来経過：インターフェロンαは300万単位週3回に減量して退院とし，2010年4月30日まで開始からTotal24週間投与した．2010年3月5日HBs抗原は陰性化し，4月30日にはHBs抗体が陽性化しAST，ALTも正常化した（図3）．

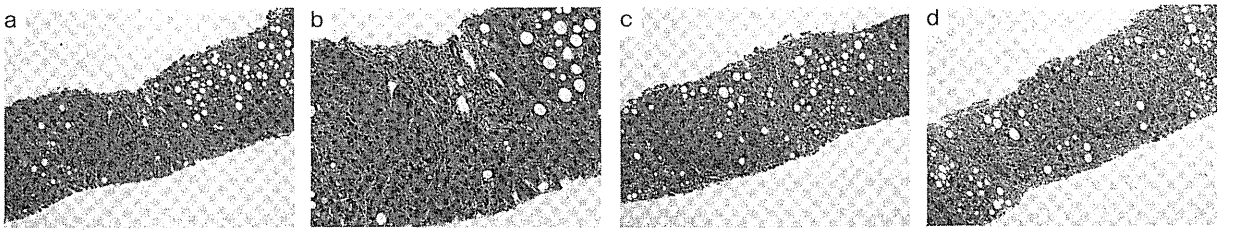

図2　肝生検

a：HE 染色（100倍）　b：HE 染色（200倍）　c：HE 染色（100倍）　d：アザン染色（100倍）

門脈域にリンパ球を含んだ炎症細胞浸潤を認め限界板の破壊を認める．線維が門脈域外に拡大し慢性肝炎（F2A2）と診断された．中等度の脂肪沈着も認められたが，肝細胞の脂肪化，肝細胞の水腫状変性（ballooning），マロリー体を認めず，好中球を含む炎症細胞浸潤，線維化が zone 3 において高度ではないため非アルコール性脂肪肝炎（NASH）は否定的であった．

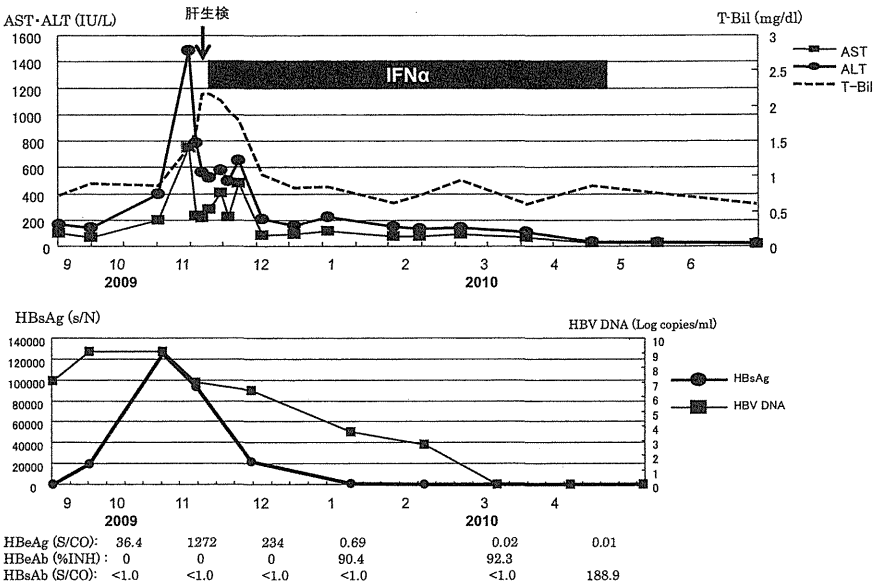

図3　臨床経過

インターフェロンαを24週間投与して肝機能は正常化し HBs 抗体が出現した．

考　　案

HBV genotype A は従来，日本には存在しないタイプであったが，最近増加傾向を示している[1)-4)]．B 型急性肝炎は genotype 別に特徴的な臨床経過を示すことが知られている[2)3)]．HBV genotype A 急性肝炎は若年男性が大多数を占め，その多くが性行為を有し，血清学的にはビリルビン値が高く，HBe 抗原値と HBV DNA 量が高値であることが特徴的である[2)]．さらに問題となるのは，重症化と慢性化の確率が高いことである[5)6)]．重症化が推測される HBV genotype A 急性肝炎に対しラミブジン投与を行って軽快した報告が散見される[7)-11)]．B 型急性肝炎に対するラミブジンの保険適応は認められていないが，重症化・劇症化例でその有効性が示されている[8)-10)]．しかし，慢性化する可能性が高い症例の特徴を考察することは今のところできず，どのような症例にいつ投与開始すべきか一定の基準は確立されていない．

HBV genotype A 急性肝炎に対し，影山ら[8)]は慢性化と劇症化の2症例・和久井ら[9)]は慢性化の1症例・土屋ら[10)]は劇症化の1症例にラミブジン投与後 HBs 抗体が出現してラミブジンを中止することができたと述べているが，大森ら[11)]は多数例の検討を行い重症化のためラミブジン投与した HBV genotype A 急性肝炎15例中4例で HBV 感染が6カ月以上持続して慢性化したと報告している．急性肝炎に対して肝生検を施行することは一般臨床ではまれ

であるが，HBV genotype A急性肝炎の慢性化報告もあるためわれわれは肝生検を行った．和久井ら[9]の報告では感染後6カ月以上経過してから肝生検を行って慢性肝炎の診断を得ている．われわれの症例はIgM HBc抗体が陰性から陽性になったHBV感染確認後2カ月の時点の肝生検で，門脈域に線維化と炎症細胞浸潤を認め慢性肝炎（F2A2）と診断された．病理学教科書[12][13]には急性肝炎では門脈域に線維化は認められないとされるので病理学的には慢性肝炎と診断される．慢性肝炎は6カ月以上AST，ALTの異常が続くことと定義されているが，発生2カ月で慢性肝炎の組織像を示したことはB型急性肝炎の早期から病理組織学的には慢性肝炎に移行する可能性があることを示している．また，毎年の健康診断で肝機能検査を含め異常を指摘されたことはないことから，以前から慢性肝炎が存在したとは考えにくかった．

通常のB型急性肝炎は自然経過で治癒することが多い．感染が持続する場合でも感染期間が短い場合でも早期にインターフェロンを投与すれば奏功する可能性が高いと考えられる．Suzuki[3]らはHBV genotype Aの急性からの慢性化7症例に対しラミブジン単独治療を2症例，インターフェロン単独治療を2症例，ラミブジン＋インターフェロン併用治療を2症例に行い，インターフェロン単独治療の1症例のみにHBs抗原の消失をみたと報告している．大森ら[11]はHBV genotype Aの急性からの慢性化4例中インターフェロン併用2例でHBs抗体の出現をみたが，2例はHBs抗原陽性が続き初めにラミブジンで治療を開始した症例であったと報告している．ラミブジン投与が慢性化に関与していたのかははっきりしないが，ラミブジンだけでは慢性化を阻止できておらず，また，ラミブジンを開始していったん慢性化するとラミブジンを中止することが難しくなる．本症例は急性肝炎であり治療介入をしなくても自然経過で軽快した可能性は否定できない．しかし，発生2カ月で慢性肝炎の組織像を呈したため慢性化を危惧して治療介入に踏みきった．34歳と若年であることもありラミブジンやエンテカビルの核酸アナログではなくインターフェロンを選択した．HBV genotype A急性肝炎に対するラミブジン投与例でキャリアー化している報告がある以上，核酸アナログを第一選択薬として投与するのは問題があると考えたからである．インターフェロンを24週間投与後，HBs抗体が陽性化したためB型肝炎は軽快したと判断した．HBV genotype Aは他のGenotypeよりもインターフェロンの感受性が高いというErhardtら[14]のドイツの報告も認められる．Oritoら[15]はB型慢性肝炎720人のうち1.7%が・松浦ら[16]はB型慢性肝炎1,271人のうち3.5%がGenotype Aであったと報告し，わが国では既にHBV genotype Aキャリアーが存在している可能性が高く若年層に蔓延する恐れも指摘されている．ラミブジンで治療開始例に慢性化したためにラミブジンを止めることができなくなった症例が存在している以上，とくに若年層のHBV genotype A急性肝炎で慢性化が危惧される場合にはインターフェロン投与を検討してもよいのではないかと考えられた．

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Administration of interferon for chronic hepatitis resulting from acute HBV genotype A infection

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Abstract：On November 9, 2009, a 34-year-old male was admitted to our hospital for the treatment of HBs antigen-positive hepatopathy. He was positive for HBV DNA, but negative for IgM HBc antibody, HBc antibody and HIV antibody. On December 10, laboratory test showed following: the increase in transaminase levels(AST 754 IU/ml and ALT 1486 IU/ml), HBs antigen 92997 S/N, HBe antigen 1272 S/CO, HBe antibody 0 % INH, IgM HBc antibody 28 S/CO, HBc antibody 4.41 S/CO and HBV DNA 8.6 Log copies/ml. Liver biopsy revealed chronic hepatitis. The HBV genotype was type A. Therefore, we concluded that his HB virus-related acute hepatitis was already chronic. Interferon α at 600 MU/day was administrated for 2 weeks and continued at 300 MU twice for 22 weeks, 24 weeks in total.He became negative for HBs antigen in March 2010 and positive for HBs antibody in April 2010. We considered that the administration of interferon might be effective for acute HBV genotype A infection to prevent it from being a chronic condition.

Prevalence of type 2 diabetes mellitus in Japanese patients with hepatocellular carcinoma

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Abstract. The possibility has been raised in a number of cohort and case-control studies that diabetes mellitus (DM) may increase the risk of liver cancer, as well as that of cancer at other sites. To verify this possibility, we conducted a retrospective cohort study to determine the prevalence of type 2 DM in Japanese patients with hepatocellular carcinoma (HCC). A total of 1,251 patients with HCC, diagnosed at two major liver centers in the Nagasaki area, were consecutively recruited and categorized according to the etiology of HCC into four groups: HCC-B, HCC-C, HCC-BC and HCC-nonBC cases. Type 2 DM was diagnosed on the basis of standard criteria. The prevalence rate of HCC-nonBC and HCC-C was significantly higher than that of HCC-B, while the prevalence rate of HCC-nonBC was significantly higher than that of HCC-C. The prevalence of type 2 DM in HCC-B, HCC-C and HCC-nonBC patients under 66 years of age was 11, 31 and 32%, respectively, vs. 24, 22 and 40%, respectively, in patients over 66 years of age. In patients over 66 years of age, the prevalence of type 2 DM in HCC-B and HCC-nonBC cases was increased, whereas the prevalence of type 2 DM in HCC-C cases was significantly decreased. Our findings indicate that the effects of the interaction between type 2 DM and HCV increase the prevalence of HCC.

Introduction

Of the three leading causes of death in Japan – malignant neoplasms, cardiovascular diseases and cerebrovascular diseases – malignant neoplasms have been the leading cause of death in Japan since 1981. For the last 30 years, liver cancer has been the third leading cause of death by malignant neoplasms in men and, during the past decade, has ranked fifth in women (1-3). Hepatocellular carcinoma (HCC) accounts for 85-90% of cases of primary liver cancer, and chronic hepatitis B and C infections are the main cause of HCC. However, the prevalence of HCC in Japan in the liver of patients that are both hepatitis B surface antigen (HBsAg)- and hepatitis C virus (HCV)-RNA-negative has been increasing over the last 12 years (4).

Epidemiological findings have recently been reported proposing a link between type 2 diabetes mellitus (DM) and cancer in various organs (5,6). The possibility that DM may increase the risk of liver cancer, as well as cancer at other sites, has been raised in a number of cohorts and case-control studies (7-10). We carried out this retrospective study to determine the prevalence of type 2 DM in Japanese patients with HCC.

Patients and methods

Patients. A total of 1,251 patients with HCC diagnosed between January 1991 and December 2005 at the liver disease centers of the National Nagasaki Medical Center and Nagasaki University Hospital were consecutively recruited for this study. Informed consent was obtained from all patients. The diagnosis of HCC was based on the elevation of serum α-fetoprotein or des-γ-carboxy prothrombin levels, characteristic image findings obtained using ultrasonography, computerized tomography, magnetic resonance imaging and hepatic angiography, and/or histological diagnosis using tumor biopsy samples.

Etiology of HCC. The HCC cases were categorized according to etiology into four groups: HCC-B, hepatitis B virus surface antigen (HBsAg)-positive and hepatitis C virus (HCV)-RNA-negative; HCC-C, HCV-RNA-positive and HBsAg-negative; HCC-BC, both HBsAg- and HCV-RNA-positive; and HCC-nonBC, both HBsAg- and HCV-RNA-negative. A diagnosis of chronic HCV infection was based on the presence of both serum anti-HCV antibody and HCV-RNA detected by polymerase chain reaction (PCR), while a diagnosis of chronic hepatitis B virus (HBV) infection was based on the presence of HBsAg.

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Key words: hepatitis virus, hepatocellular carcinoma, diabetes mellitus

Table I. Characteristics of the HCC patients.

	HCC-B	HCC-C	HCC-BC	HCC-nonBC	Total
No.	248	809	29	165	1,251
Gender					
Male	191	566	19	121	897
Female	57	243	10	44	354
Ratio (male/female)	3.4	2.3	1.9	2.8	2.5
Age (IQR), in years	57 (15)	67 (9)	65 (12)	67 (14)	66 (11)
<66	190	341	17	71	619
≥66	58	468	12	94	632
Child-Pugh grade					
A	95	70	80	67	412
B	111	213	240	292	1,134
C	8	8	9	11	46

Gender: HCC-B vs. HCC-C, p=0.031. Age: HCC-B vs. HCC-C, p<0.001; HCC-B vs. HCC-BC, p=0.022; HCC-B vs. HCC-nonBC, p<0.0001; HCC-C vs. HCC-BC, p=0.004; HCC-BC vs. HCC-nonBC, p=0.009. IQR, interquartile range.

Diagnosis of type 2 DM. Type 2 DM was diagnosed on the basis of the presence of hyperglycemia (≥200 mg/dl) in at least two postabsorptive samples, overt glycosuria, or both; or active treatment with insulin, oral hypoglycemic agents, or both. No consideration was given to minor alterations in glucose metabolism, such as impaired glucose tolerance based on an oral glucose tolerance test, in accordanc with World Health Organization criteria.

Statistical analysis. Data were analyzed by the Mann-Whitney U test for continuous ordinal data, and by the χ^2 test with Yates' correction and Fisher's exact test for associations between two qualitative variables. $p<0.05$ was considered statistically significant. Data analysis was performed with SPSS version 16.0 for Windows.

Results

Clinical features of the studied patients. As shown in Table I, of the 1,251 patients with HCC, 20% (248/1,251) were diagnosed with HCC-B, whereas 65% (809/1,251) had HCC-C and an additional 2% (29/1,251) had HCC associated with both viruses. In the remaining 165 patients (13%), no association was found between HCC and either of the viruses. Analyzing the patients with HCC by category revealed the male/female ratio in HCC-B, HCC-C, HCC-BC and HCC-nonBC to be 3.4, 2.3, 1.9 and 2.8, respectively. The male/female ratio in HCC-C was less than that in HCC-B. In addition, the median age of patients diagnosed with HCC-B, HCC-C, HCC-BC and HCC-nonBC was 57, 67, 65 and 67 years, respectively. The median age of patients diagnosed with HCC-B was significantly lower than that of the patients with other types of HCC. Among the patients with HCC, 25% (310/1,251) had type 2 DM, 3% (34/1,251) HCC-B, 16% (209/1,251) HCC-C, 1% (6/1,251) HCC-BC and 5% (61/1,251) HCC-nonBC.

Prevalence of type 2 DM by stratification according to etiology in patients with HCC. Cohorts of patients with HCC were divided according to etiology. Fig. 1 shows that the prevalence rate of type 2 DM in HCC-B, HCC-C, HCC-BC and HCC-nonBC was 14% (34/248), 26% (209/809), 37% (61/165) and 21% (6/29), respectively. The prevalence rate of HCC-nonBC and HCC-C was significantly higher than that of HCC-B (HCC-B vs. HCC-nonBC, p≤0.001; HCC-B vs. HCC-C, p≤0.001), while the prevalence rate of HCC-nonBC was significantly higher than that of HCC-C (HCC-C vs. HCC-nonBC, p=0.003).

The prevalence rate of type 2 DM was 25% in patients under 66 years of age (154/619) and 25% in patients over 66 years of age (156/632). Fig. 2 shows the age distribution of the prevalence rate for type 2 DM in HCC-B, HCC-C and HCC-nonBC cases. The prevalence rate of type 2 DM in HCC-B, HCC-C and HCC-nonBC was 11% (20/190), 31% (107/341) and 32% (23/71), respectively, in patients under 66 years of age, vs. 24% (14/58), 22% (102/468) and 40% (38/94), respectively, for those over 66 years of age. The prevalence rate of type 2 DM in HCC-B and HCC-nonBC patients over 66 years of age was increased, whereas that of HCC-C was significantly decreased.

Discussion

A nationwide health survey regarding the prevalence of DM in the general Japanese population conducted in 2006 indicated that the prevalence of DM in Japan was 12%. However, the prevalence rate of type 2 DM is higher in patients with HCC than in the general Japanese population. In this two major liver center-based cohort study designed to examine the prevalence of type 2 DM in HCC patients, 25% of patients with HCC had type 2 DM. Previous studies have suggested that DM is a potential risk factor for HCC (10-13). Inoue *et al* prospectively

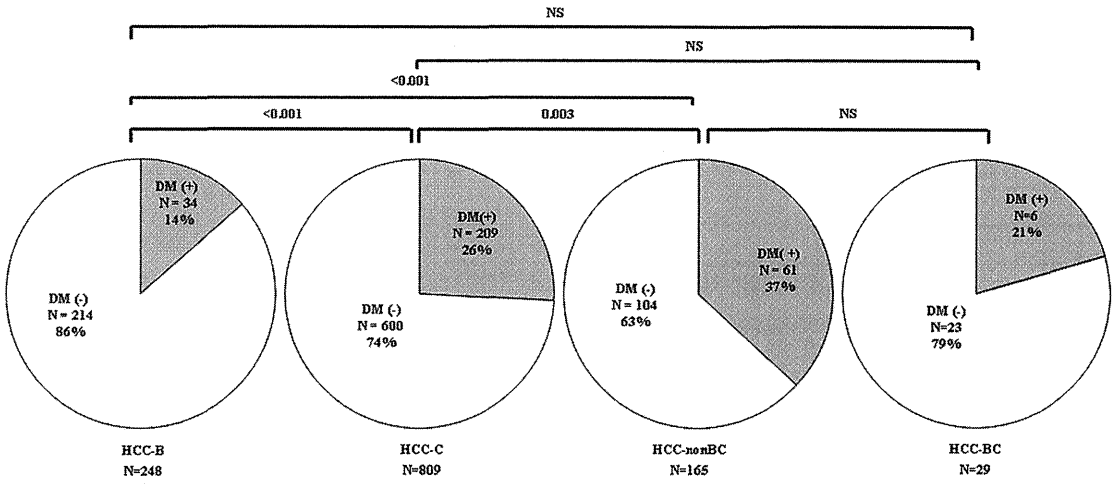

Figure 1. Prevalence rate of type 2 DM in HCC-B, HCC-C, HCC-BC and HCC-nonBC.

examined the association between a history of DM and the subsequent risk of cancer in a Japan Public Health Center-based prospective study, and found an increased risk of liver cancer in DM patients (12).

The present study found that the prevalence of type 2 DM was significantly higher in HCC-nonBC than in HCC-B and HCC-C patients. In particular, type 2 DM persisted in patients without chronic hepatitis virus infections; type 2 DM in these individuals may explain a relevant proportion of the observed cases of HCC. Previous studies have suggested that diabetes and/or non-alcoholic fatty liver disease account for at least a portion of these 'idiopathic' cases (14-16). Findings from the present study support the hypothesis that the presence of DM alone accounts for approximately 37% of cases of HCC-nonBC.

Investigations into the possible biological mechanisms of the association between type 2 DM and HCC-nonBC have been site-specific. However, these associations may be the result of metabolic and hormonal aberrations associated with type 2 DM, and common biological mechanisms may be at least partially associated with insulin and insulin-like growth factors (IGFs) (17).

The most obvious change in diabetic patients is reduced insulin sensitivity with compensatory hyperinsulinemia and elevated levels of IGF-1, which may in turn stimulate cell proliferation in the liver (18,19). At the same time, insulin activates the IGF-1 receptor, which is known to have a growth-promoting effect, including the modulation of cell cycle progression. Excess insulin may also indirectly affect the development of cancer by down-regulating the level of IGF-binding protein 1, which increases the level and bioavailability of total circulating IGF-1. Obesity and physical inactivity also cause hyperinsulinemia, and are thus also ultimately associated with cancer (17-20).

A survey of HCC-nonBC conducted between 1995 and 2003 in Japan by the Inuyama Hepatitis Research Group found that individuals with HCC-nonBC accounted for 9.3% of the general population (2). In the present study, we found the percentage of HCC-nonBC to be 14.1% in the Nagasaki area. Furthermore, the number and proportion of HCC-nonBC

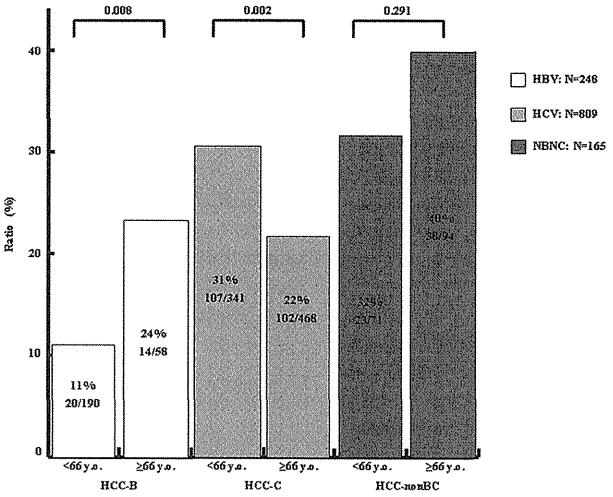

Figure 2. Age distribution for the prevalence rate of type 2 DM in HCC-B, HCC-C and HCC-nonBC.

cases gradually increased from 1981 to 2005 (4). According to an epidemiological study on DM by Nakano *et al*, the number of patients with DM has been gradually increasing since the development of an automotive society and the Westernization of the Japanese diet (21). Since the prevalence of DM increases with age, the proportion of individuals with DM aged 60 or above has exceeded two-thirds of the estimated total number of patients in Japan (7.40 million in 2002), which has a rapidly aging society (21). In other words, the number of individuals with type 2 DM is increasing in Japan, and these individuals are at high risk for HCC. Thus, the number of HCC-nonBC cases will increase in the next decade in Japan.

Approximately 60% of liver cancer cases in Japan are anti-HCV-positive (4). An experimental study revealed that HCV infection itself induces insulin resistance through the disturbance of the insulin intracellular signaling pathway by the hepatitis virus core protein (22). Liver fat deposition may contribute to insulin resistance, which in turn leads to a loss of the restraining effect of insulin on the production of glucose

by hepatocytes, thereby causing diabetes (23). Steatosis occurs more frequently in patients with chronic HCV infection than in those with chronic HBV infection; this may explain the increased risk of DM among HCV patients (24). Although we proposed possible explanations for the correlation between HCV infection and the prevalence rate of type 2 DM in patients in this study, it is also possible that the mechanism is multifactorial. A previous study identified chronic hepatitis B as having no relationship to DM, and on the basis of the results of this study, we arrive at the same conclusion (25,26).

Several studies have indicated that the progression from chronic hepatitis to cirrhosis and HCC is accelerated by dual HCV infection (11,27). The strong effect of DM on HCC in the absence of hepatitis infection suggests that, in addition to the hepatitis C causal pathway, HCC is mediated through the reduction of IGF-1 factors or IGF binding protein-3, caused by hyperinsulinemia. This in turn stimulates the proliferation of cancer cells, as demonstrated by Lagiou *et al* (28). In the present study, the prevalence rate of DM in patients with HCC-C was significantly higher in patients older than 66 years of age. Our findings demonstrate that the effects of the interaction between DM and HCV further the incidence of HCC.

In conclusion, the prevalence of HCC-nonBC and HCC-C was significantly higher than that of HCC-B, while the prevalence of HCC-nonBC was significantly higher than that of HCC-C. In patients over 66 years of age, the prevalence of type 2 DM in HCC-B and HCC-nonBC cases was increased, whereas the prevalence of type 2 DM in HCC-C cases was significantly decreased. Our findings indicate that the interaction between type 2 DM and HCV increases the prevalence of HCC.

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The incidence of hepatocellular carcinoma associated with hepatitis C infection decreased in Kyushu area

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Summary

Background: The incidence of hepatocellular carcinoma (HCC) in Japan has still been increasing. The aim of the present study was to analyze the epidemiological trend of HCC in the western area of Japan, Kyushu.

Material/Methods: A total of 10,010 patients with HCC diagnosed between 1996 and 2008 in the Liver Cancer study group of Kyushu (LCSK), were recruited for this study. Cohorts of patients with HCC were categorized into five year intervals. The etiology of HCC was categorized to four groups as follows; B: HBsAg positive, HCV-RNA negative, C: HCV-RNA positive, HBsAg negative, B+C: both of HBsAg and HCV-RNA positive, non-BC: both of HBsAg and HCV-RNA negative.

Results: B was 14.8% (1,485 of 10,010), whereas 68.1% (6,819 of 10,010) had C, and 1.4% (140 of 10,010) had HCC associated with both viruses. The remaining 1,566 patients (15.6%) did not associate with both viruses. Cohorts of patients with HCC were divided into six-year intervals (1996–2001 and 2002–2007). The ratio of C cases decreased from 73.1% in 1996–2001 to 64.9% in 2002-2007. On the other hand, B and -nonBC cases increased significantly from 13.9% and 11.3% in 1996-2001 to 16.2% and 17.6% in 2002-2007, respectively.

Conclusions: The incidence of hepatocellular carcinoma associated with hepatitis C infection decreased after 2001 in Kyushu area. This change was due to the increase in the number and proportion of the HCC not only nonBC patients but also B patients.

key words: hepatitis virus • hepatocellular carcinoma • Japan

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Background

The three leading causes of death in Japan are malignancy neoplasms, cardiovascular diseases, and cerebrovascular diseases. Since 1981, malignant neoplasms have been the leading cause of death in Japan. For the last 30 years, liver cancer has been the third leading cause of death from malignant neoplasms in men. In women, liver cancer has ranked fifth during the past decade [1]. Hepatocellular carcinoma (HCC) accounts for 85% to 90% of primary liver cancers[2] and the age-adjusted HCC mortality rate has increased in recent decades in Japan [3]. Similarly, a trend of increasing rates of HCC has been reported from several developed countries in North America, Europe and Asia [4,5]. HCC often develops in patients with liver cirrhosis caused by hepatitis B virus (HBV), hepatitis C virus (HCV), excessive alcohol consumption, or nonalcoholic fatty liver disease. Of the hepatitis viruses which cause HCC, HCV is predominant in Japan [6–9].

Although the age-adjusted incidence of HCC has increased in Japan, sequential changes in etiology of HCC patients between 2001 and 2008 are not fully understood [10]. To clarify factors affecting epidemiological changes in Japanese HCC patients, especially the recent trend of HCC, we analyzed the epidemiological trend of HCC in the western area of Japan, Kyushu area.

Material and Methods

Patients

A total of 10,010 patients with HCC diagnosed between 1996 and 2008 in the Liver Cancer study group of Kyushu (LCSK), were recruited for this study. The diagnosis of HCC was based on AFP levels and imaging techniques including ultrasonography (USG), computerized tomography (CT), magnetic resonance imaging (MRI), hepatic angiography (HAG), and/or tumor biopsy. The diagnostic criteria for HCC were either a confirmative tumor biopsy or elevated AFP (>20 ng/mL) and neovascularization in HAG and/or CT.

Etiology of HCC

A diagnosis of chronic HCV infection was based on the presence of HCV-RNA detected by polymerase chain reaction (PCR), whereas diagnosis of chronic HBV infection was based on the presence of hepatitis B surface antigen (HBsAg). The etiology of HCC was categorized to four groups as follows; **B:** HBsAg positive, HCV-RNA negative, **C:** HCV-RNA positive, HBsAg negative, **B+C**: both of HBsAg and HCV-RNA positive, **nonBC:** both of HBsAg and HCV-RNA negative.

Statistical analysis

The data were analyzed by the Mann-Whitney test for the continuous ordinal data, the x2 test with Yates' correction and the Fisher exact test for the association between two qualitative variables. The standard deviation was calculated based on the binomial model for the response proportion. P<0.05 was considered statistically significant.

Results

Clinical features of the studied patients

A total of 10,010 patients with HCC were diagnosed at our study group from 1996 to 2008. Table 1 show that the proportion of patients diagnosed with **B** was 14.8% (1,485 of 10,010), whereas 68.1% (6,819 of 10,010) had **C**, and an additional 1.4% (140 of 10,010) had HCC associated with both viruses. The remaining 1,566 patients (15.6%) did not associate with both viruses. In analysis of patients in HCC by category, the median age of patients at diagnosis of **B** was 57 years old significant younger than other types HCC(**C: 69, nonBC: 70,.B+C 65 years old)**.

As shown in Figures 1 and 2, the number and ratio of **B** cases remained unchanged from1996 to 2001 and thereafter increased and plateaued, whereas **C** rapidly increased from 1996 to 2000 and thereafter decreased and plateaued. In addition, the number and ratio of the **nonBC** cases has increased continued gradually and continued in this study period.

Change of etiology in patients with HCC during the period 1996–2007 with 6-years intervals

Cohorts of patients with HCC were divided into six-year intervals (1996–2001 and 2002–2007). Table 2 show that the incident rate of **C** decreased significantly from 73.1% in 1996-2001 to 64.9% in 2002-2007 (1996–2001 vs. 2002–2007, p=<0.001). On the other hand, the incident rate of **B** and **-nonBC** increased significantly from 13.9% and 11.3% in 1996-2001 to 16.2% and 17.6% in 2002-2007, respectively. Not only the incident rate but also number of **B** and **-nonBC** became larger in same 6 years periods.

Table 3 shows that male/female ratio of **C** and **-nonBC** decreased significantly from 2.2 and 4.0 in 1996-2001 to 1.8 and 2.7 in 2002-2007, respectively (p<0.001). The ratio became clearly smaller, indicates an increase in female patients with **C** and **nonBC.** On the other hand, the male/female ratio of **B** patients did not significantly change during the period. The median age at diagnosis of **B, C,** and **nonBC** in six-year intervals were significant increase from 56 to 58, from 67 to 71 and from 68 to 71 years of age during the period.

Discussion

Our study was the twenty-three major liver center-based study designed to examine the sequential change in the background of HCC patients during the past 13 years, 1996–2008. More than 80% of our patients had chronic HBV or HCV infections. During this observation period, the number and proportion of HCC-C reached a peak in 2000 and thereafter decreased and became stabilized. Previous studies from Japan reported that the proportion of the HCC patients with HCV infection had been increased and reached a plateau in the period of 1981–2001 [1,3,10–12]. However, in our study, the number and proportion of the HCC patients with HCV infection cases decreased in 2001–2008. The reason may be explained as follows; interferon therapy for chronic hepatitis C may have been associated with a decreased incidence of HCC [13–17]. Oral supplementation with a oral branched-chain amino acids has been useful in the prevention HCC [18]. Finally, the chronically HCV-infected

Table 1. The characteristic of HCC patients during the period of 1996–2008.

Age (y.o.)	B		C		nonB		B+C		Total
	Male	Female	Male	Female	Male	Female	Male	Female	
0–	1	0	0	1	0	0	0	0	**2**
10–	4	1	0	0	0	2	0	0	**7**
20–	6	2	1	0	1	1	0	0	**11**
30–	31	5	4	0	11	3	2	0	**56**
40–	204	22	130	12	32	15	12	0	**427**
50–	507	66	728	145	167	32	31	6	**1,682**
60–	287	118	1836	741	411	102	35	13	**3,543**
70–	140	64	1775	947	483	133	22	14	**3,578**
80–	9	18	271	214	97	65	1	4	**679**
90–	0	0	9	5	9	2	0	0	**58**
Total	**1,189**	**296**	**4,754**	**2,065**	**1,211**	**355**	**103**	**37**	**10,010**
	1,485 (4.8%)		6,819 (68.1%)		1,566 (15.6%)		140 (1.4%)		
Median	57	63	67	70	68	70	61	68	**67**
	57		69		70		65		
Mean	56	64	68	71	69	71	62	68	**67**
	58		68		68		63		
Range	1–87	14–89	27–94	0–93	28–96	17–90	36–82	55–82	**0–96**
	1–89		0–94		17–96		36–82		

Age: B vs. C $p \leq 0.001$; B vs. B+C $p \leq 0.001$; B vs. nonBC $p \leq 0.001$; C vs. BC $p \leq 0.001$; C vs. nonBC $p=0.043$; BC vs. nonB+C $p \leq 0.001$. IQR – interquartile range; SD – standard deviation.

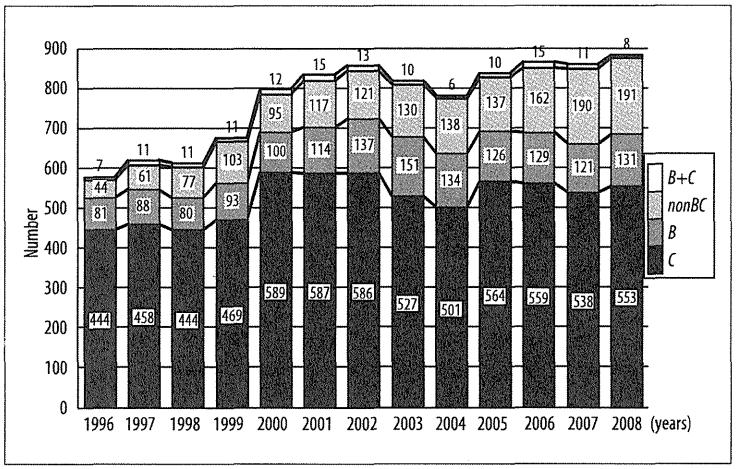

Figure 1. Sequential changes in the number of HCC patients categorized by etiology during the period 1996–2008.

population is aging in Japan. Yoshizawa et al. reported that age-specific prevalence for the presence of HCVAb among ~300,000 voluntary blood donors from Hiroshima in 1999 clearly increased with the age, reaching the highest proportion of 7% in individuals who were more than 70 years old [10,19]. In this study, the median age of the HCC patients with HCV infection steadily increased from 67 to 71 years of age during the studied period. In a word, HCV infected people become older with years in Japan and they were regarded as a high risk for HCC.

The prevalence rate of HBV in Kyushu area has been reported to be higher than other area in Japan [1]. In Kyushu area, 95% of patients with chronic HBV infection had HBV genotype C except for Okinawa [20]. HBV genotype C is thought to be associated with higher incidence of HCC

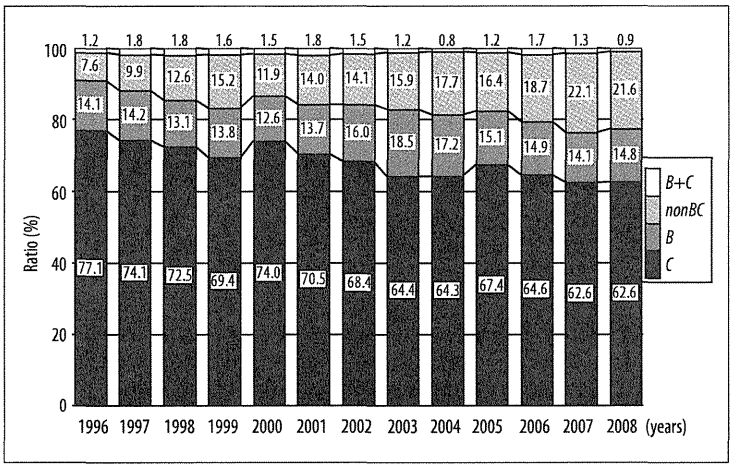

Figure 2. Sequential changes in the ratio of HCC patients categorized by etiology during the period 1996–2008.

Table 2. Change of etiology in patients with HCC during the period 1996–2007 with 6-years intervals.

Period		1996–2001	2002–2007	P value
Number		3,023	4,173	
Sex	Male	2,162	2,849	
	Female	861	1,324	
Ratio (male/female)		2.5	2.2	0.003
Age (y.o.) (IQR)		66 (14)	69 (12)	<0.001
Hepatitis virus (%)	B	13.9	16.2	
	C	73.1	64.9	
	B+C	1.7	1.3	
	nonBC	11.3	17.6	0.001

QR – interquartile range.

Table 3. The median age and male/female ratio of HCC patients during the period of 1996–2007.

Period		1996–2001	2002–2007	P value
B				
Age (y.o.) (IQR)		56 (14)	58 (15)	0.001
Sex	Male	331	519	
	Female	88	157	
Ratio (male/female)		3.8	3.3	0.391
C				
Age (y.o.) (IQR)		67 (9)	71 (11)	<0.001
Sex	Male	1,524	1,753	
	Female	687	955	
Ratio (male/female)		2.2	1.8	0.002
nonBC				
Age (y.o.) (IQR)		68 (12)	71 (13)	<0.001
Sex	Male	273	534	
	Female	69	201	
Ratio (male/female)		4.0	2.7	0.012

QR – interquartile range.

compared with other HBV genotypes [21]. In the present study, the incident rate of HCC patients with HBV infection became larger in this study period. To explain this change, we must consider from two viewpoints. The one is that the number of patients with HCC caused by HCV infection decreased, the other is that the proportion of chronic HBV infected patients who have reached the age of developing HCC is relatively high as described below.

Nationwide health survey for HBsAg in the over 40 years of age population had been done between 2002 and 2006 in Japan. This survey reports indicated that the average HBsAg prevalence was 1.2% in the total Japanese population patients with chronic HBV infection [10] and the age-specific prevalence of HBsAg was higher in the group aged between 50 (1.4%) and 55 years (1.5%). In the HCC patients with HBV genotype C, the mean age was 55 years in Japan [20]. This overlap between age-specific prevalence and hepatocellular carcinogenic age would be associated with the increase of HCC patients with HBV infection. Nucleoside analogue reverse transcriptase inhibitor (NARTI) therapy effectively reduces the incidence of HCC in chronic hepatitis B patients [22,23]. However, Interferon therapy for chronic hepatitis C started from 1992, whereas NARTI therapy for HBV started from 2000 in Japan [24,25]. Hence, HBV associated HCC will probably decrease in Japan during the next 10 to 20 years.

The survey of HCC patients associated with nonBC infection in Japan was conducted by Inuyama Hepatitis Research Group from 1995 to 2003. The ratio of HCC patients with nonBC accounted 9.3% [1]. In the present study, the ratio of HCC patients with nonBC was 14.1%. Furthermore, the number and the proportion of HCC patients with nonBC have been gradually increasing in the periods. The current two studies account for the increase in number and proportion of HCC patients with nonBC. First, Lai et al. reported

that type 2 diabetes increases the risk of developing HCC in those who are HCV negative or have a high level of total cholesterol [26]. Second, Nakano et al. reported that epidemiological studies on diabetes mellitus revealed that the number of patients with diabetes mellitus is gradually increasing in Japan along with development of car society and westernization of food intake. Since prevalence of diabetes mellitus increases with aging, proportion of individuals with diabetes mellitus aged over 60 has exceeded two-third of estimated total number of patients (7.40 million in 2002) in Japan where aging of society is rapidly progressing [27]. In a word, the number of type 2 diabetes people is increasing in Japan and they were regarded as a high risk for HCC. Then, the number and the proportion of HCC patients with nonBC have been increased recent twelve years in Japan.

It is known that 2 to 4 decades of chronic HCV infection are required to develop cirrhosis and subsequent HCC [28–31]. The number of HCC cases has increased in Japan, because individuals infected with HCV during the past have grown old and have reached the cancer-bearing age. The prevalence of HCV infection in young Japanese individuals is low and the incidence of HCVAb is very low because of preventative actions against HCV infection such as the screening of blood products for HCV and the use of sterile medical equipment [32]. Additionally, we showed that the number and proportion of patients with HCC-C cases decreased, whereas the number and ratio of HCC-nonBC steadily increased during the studied period. These findings may be expected that the incidence of HCC patients with nonBC in Japan may continue to increase even after the consequence of the HCV epidemic level off, a country that is far advanced with regard to HCC patients with HCV infection, in the near future.

Conclusions

In summary, HCC patients had increased from 1996 to 2000 and this increase was originated from HCC patients with HCV infection. The number and proportion of HCC patients with HCV infection reached a peak in 2000 and thereafter decreased and became stabilized. The incidence of hepatocellular carcinoma associated with hepatitis C infection decreased after 2001 in Kyushu area. This change was due to the increase in the number and proportion of the HCC not only nonBC patients but also B patients.

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Original Article

Data mining reveals complex interactions of risk factors and clinical feature profiling associated with the staging of non-hepatitis B virus/non-hepatitis C virus-related hepatocellular carcinoma

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Aim: Non-hepatitis B virus/non-hepatitis C virus-related hepatocellular carcinoma (NBNC-HCC) is often detected at an advanced stage, and the pathology associated with the staging of NBNC-HCC remains unclear. Data mining is a set of statistical techniques which uncovers interactions and meaningful patterns of factors from a large data collection. The aims of this study were to reveal complex interactions of the risk factors and clinical feature profiling associated with the staging of NBNC-HCC using data mining techniques.

Methods: A database was created from 663 patients with NBNC-HCC at 20 institutions. The Milan criteria were used as staging of HCC. Complex associations of variables and clinical feature profiling with the Milan criteria were analyzed by graphical modeling and decision tree algorithm methods, respectively.

Results: Graphical modeling identified six factors independently associated with the Milan criteria: diagnostic year of HCC; diagnosis of liver cirrhosis; serum aspartate aminotransferase (AST); alanine aminotransferase (ALT); α-fetoprotein (AFP); and des-γ-carboxy prothrombin (DCP) levels. The decision trees were created with five variables to classify six groups of patients. Sixty-nine percent of the patients were

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within the Milan criteria, when patients showed an AFP level of 200 ng/mL or less, diagnosis of liver cirrhosis and an AST level of less than 93 IU/mL. On the other hand, 18% of the patients were within the Milan criteria, when patients showed an AFP level of more than 200 ng/mL and ALT level of 20 IU/mL or more.

Conclusion: Data mining disclosed complex interactions of the risk factors and clinical feature profiling associated with the staging of NBNC-HCC.

Key words: data mining, disease progression, hepatoma, non-viral hepatitis, tumor marker

INTRODUCTION

HEPATOCELLULAR CARCINOMA (HCC) is the fifth most common cancer and the third most common cause of cancer-related deaths worldwide.[1–3] Chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) is a risk factor for HCC. Recent developments in the management of patients with viral hepatitis have resulted in early detection of HCC and improvement of prognosis.[4–8]

The number of patients with non-HBV/non-HCV-related HCC (NBNC-HCC) has been increasing, and NBNC-HCC now accounts for 12–16% of all the HCC cases in Japan.[8,9] A variety of factors are involved in the development and progression of this cancer including age, sex, alcoholic liver disease and diabetes mellitus.[10–12] Therefore, neither early detection nor improved prognosis has been achieved in NBNC-HCC.[6] Radical treatment is applicable to patients with NBNC-HCC who meet the Milan criteria;[13] however, this cancer is often detected at an advanced stage. For earlier detection, it is important to understand the complex interactions of the risk factors and clinical feature profiling associated with the Milan criteria, a staging system for NBNC-HCC.

Data mining, a set of statistical techniques, uncovers meaningful patterns and interactions of variables from a large data collection even when there is no a priori hypothesis imposed.[13] Graphical modeling is an exploratory multivariate analysis of data mining that reveals complex associations between variables.[14] This analysis assumes that the response variable is influenced by multiple factors.[15] Therefore, different from results of univariate analysis, an association between a risk factor and an outcome variable may disappear or appear because of the effects of another set of variables known as "confounding factors".[16,17] Furthermore, its findings are visualized as a graph, which provides an idea of how variables interact and denotes the conditional independence structure between random variables.[15] Therefore, graphical modeling is now identified as a new approach to model clinical data.[18]

Decision tree making is another exploratory technique of data mining that represents a series of rules for classification by identifying priorities.[19–21] It is an explicit, quantitative and systematic approach to decision-making under conditions of uncertainty and allows clinicians to choose an option that maximizes the net benefit to the patient.[22] Recently, decision trees were used to reveal the clinical feature profiling for staging of pancreatic cancer[23] and ovarian cancer.[24] However, decision trees have never been applied to identify the clinical feature profiling associated with the staging of NBNC-HCC.

The aims of this study were to reveal complex interactions of the risk factors and clinical feature profiling associated with the staging of NBNC-HCC using data mining techniques.

METHODS

Patient database

BETWEEN 1995 AND 2006, a total of 10 133 patients were diagnosed with HCC at 23 institutions located in Kyushu, a high morbidity area of HCC in Japan. Among them, 1363 patients were diagnosed with NBNC-HCC according to the negative results of both serum hepatitis B surface antigen and serum anti-HCV antibody or HCV RNA.

In order to examine the clinical variables associated with the staging of NBNC-HCC, a database of 663 patients with NBNC-HCC at 20 institutions was created on the basis of the following variables: diagnostic year of HCC; age; sex; family history of liver disease; past history of blood transfusion; alcohol intake; diagnosis of liver cirrhosis; diagnosis of liver disease; diagnosis of diabetes mellitus; serum aspartate aminotransferase (AST) level; serum alanine aminotransferase (ALT) level; serum α-fetoprotein (AFP) level; serum des-γ-carboxy prothrombin (DCP) level; size of HCC; and number of HCC.

For practical use, alcohol intake, serum AFP level and serum DCP level were categorized as follows. Alcohol intake: none; 60 g/day or less; 60–100 g/day; or more than 100 g/day. AFP level: 20 ng/mL or less; 20–200 ng/mL; or more than 200 ng/mL. DCP level: 40 mAU/mL or less; 40–100 mAU/mL; or more than 100 mAU/mL.