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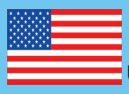

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Contents

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EDITORIAL

Regulation and deregulation of cholesterol homeostasis: The liver as a metabolic "power station"

Laura Trapani, Marco Segatto, Valentina Pallottini

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Author contributions: Trapani R wrote the paragraphs: Cholesterol metabolism deregulation and age related hypercholesterolemia; Segatto M wrote the paragraphs: Pharmacological treatment of hypercholesterolemia and Novel hypocholesterolemic strategies: future perspectives; and Pallottini V coordinated all the work and wrote the paragraphs: Introduction, liver cholesterol metabolism and conclusion.

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Abstract

Cholesterol plays several structural and metabolic roles that are vital for human biology. It spreads along the entire plasma membrane of the cell, modulating fluidity and concentrating in specialized sphingolipid-rich domains called rafts and caveolae. Cholesterol is also a substrate for steroid hormones. However, too much cholesterol can lead to pathological pictures such as atherosclerosis, which is a consequence of the accumulation of cholesterol into the cells of the artery wall. The liver is considered to be the metabolic power station of mammalians, where cholesterol homeostasis relies on an intricate network of cellular processes whose deregulations can lead to several life-threatening pathologies, such as familial and age-related hypercholesterolemia. Cholesterol homeostasis maintenance is carried out by: biosynthesis, *via* 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGR) activity; uptake, through low density lipoprotein receptors (LDLr); lipoprotein release in the blood; storage by esterification; and degradation and conversion into bile acids. Both HMGR and LDLr are transcribed as a function of cellular sterol amount by a family of transcription factors called sterol regulatory element binding proteins that are responsible for the maintenance of cholesterol homeostasis through an intricate mechanism of regulation. Cholesterol obtained by hepatic *de novo* synthesis can be esterified and incorporated into apolipoprotein B-100-containing very low density lipoproteins, which are then secreted into the bloodstream for transport to peripheral tissues. Moreover, dietary cholesterol is transferred from the intestine to the liver by high density lipoproteins (HDLs); all HDL particles are internalized in the liver, interacting with the hepatic scavenger receptor (SR-B1). Here we provide an updated overview of liver cholesterol metabolism regulation and deregulation and the causes of cholesterol metabolism-related diseases. Moreover, current pharmacological treatment and novel hypocholesterolemic strategies will also be introduced.

Key words: Cholesterol; 3-hydroxy-3-methylglutaryl coenzyme A reductase; Hypercholesterolemia; Low density lipoprotein receptors; Liver

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INTRODUCTION

Cholesterol plays several structural and metabolic roles that are vital for human biology. Although cholesterol

spreads along the entire plasma membrane of the cell where it modulates fluidity, it also concentrates in specialized sphingolipid-rich domains called rafts and caveolae[1]. In addition, cholesterol is a substrate for steroid hormones[2]. Too much cholesterol in cells, however, can lead to pathological consequences. This is particularly true for cells of the artery wall, where accumulation of cholesterol initiates atherosclerotic cardiovascular disease[3]. Therefore, the body relies on a complex homeostatic network to modulate the availability of cholesterol for tissues. This network operates on both the cellular level, mainly in the liver, and within the plasma compartment[4].

This paper reviews the present knowledge of cholesterol metabolism, homeostasis, deregulation and related pathologies. Moreover, standard and alternative therapeutic targets will also be discussed.

LIVER CHOLESTEROL METABOLISM

Cholesterol is both synthesized by cells and taken in with food intake. The liver is the principal site for cholesterol homeostasis maintenance carried out in many mechanisms, such as biosynthesis, *via* 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGR, E.C. 1.1.1.34) activity, uptake through low density lipoprotein receptors (LDLr), lipoprotein release in the blood, storage by esterification and degradation and conversion into bile acids[5]. The major precursor of cholesterol synthesis is acetyl-CoA which gives rise to hydroxyl methylglutaryl-CoA (HMG-CoA). The rate limiting step in the cholesterol biosynthetic pathway is the conversion of HMG-CoA to mevalonic acid (MVA) by HMGR[6].

The MVA biosynthetic pathway is a sequel of complex reactions that, besides cholesterol, produces several biomolecules involved in RNA transcription (isopentenyl tRNAs), protein N-glycosylation (dolichol), protein prenylation (farnesyl and geranylgeranyl moieties) and mitochondrial electron transport (ubiquinone), all indispensable for cell survival[7].

In addition to being synthesized, cholesterol can also be taken up through a classic example of receptor-mediated endocytosis by hepatocytes. LDLr plays an important role in cholesterol homeostasis since it binds plasma LDL particles, thus lowering plasma cholesterol levels[8]. This receptor was first discovered in cultured human fibroblasts. Later on, genetically and immunologically identical receptors were also identified in the liver[9].

LDLr and other proteins involved in cholesterol metabolism regulation, such as HMGR, are transcribed as a function of cellular sterol amount by a family of transcription factors called sterol regulatory element binding proteins (SREBPs). Once synthesised, SREBPs are associated with the endoplasmic reticulum (ER) membrane where they remain transcriptionally inactive. In the ER, the SREBP C-terminus interacts with the cargo protein SCAP (SREBP cleavage activating protein) which functions as a sterol sensor[6]. In sterol-deprived cells, SCAP binds SREBPs and escorts them from the ER to the Golgi apparatus where SREBPs are proteolytically processed to yield active fragments that enter the nucleus and induce the expression of their target genes (e.g., *LDLr, HMGR*). On the other hand, when intracellular sterol content increases, SCAP binds the insulin induced gene protein, which keeps the SCAP/SREBP complex into the ER, thus blocking the transcription of cholesterogenic genes[6]. This intricate mechanism of regulation is at the root of cholesterol homeostasis maintenance.

The cholesterol pool obtained from *de novo* synthesis by hepatocytes can be enzymatically esterified by Acyl-CoA- cholesterol Acyl transferase and incorporated into apolipoprotein B (apoB)-100-containing very low density lipoproteins (VLDL), which are then secreted into the bloodstream for transport to peripheral tissues[10]. Cholesterol synthesis in the peripheral tissues also contributes to the hepatic cholesterol pool through the transfer of cholesterol to the liver in a process mediated by high density lipoprotein (HDL) particles (known as reverse cholesterol transport). Dietary cholesterol is also transferred from the intestine to the liver by HDL; all HDL particles are internalized in the liver, interacting with the hepatic scavenger receptor (SR-B1)[10].

Once in the hepatocyte, cholesterol delivered by HDL particles may be utilized for hepatic cholesterol needs, converted into bile acids, or excreted into bile and eliminated through the feces[11].

CHOLESTEROL METABOLISM DEREGULATIONS

Familial hypercholesterolemia (FH), defined as the heritable occurrence of severe hypercholesterolemia with cholesterol deposits in tendons and premature heart disease, is caused by mutations in at least four genes whose products are involved in sterol and lipoprotein pathways: the LDLr, apoB, proprotein convertase subtilisin/kexin 9 (PCSK9) and the autosomal recessive hypercholesterolemia (ARH) adaptor protein. All of these disorders have a defective clearance of LDL in common, principally in the liver, within a complex system of lipid and lipoprotein metabolism and regulation[12].

Familial hypercholesterolemia

The primary causative defects in approximately 85% of FH cases are mutations or deletions in the liver plasma membrane LDLr. Over 1000 different mutations in the LDLr gene on the distal short arm of chromosome 19 (p13.1-p13.3) have been described to date[12], such as large rearrangements, premature stop codons, single amino acid substitutions, mutations in the promoter region that affect gene transcription, and mutations that affect splicing of the pre-messenger RNA (pre-mRNA)[12].

LDLr is a cell-surface glycoprotein that specifically binds extra-cellular lipoprotein particles containing apoB100 such as LDL with high affinity. The receptor: lipoprotein complex is then internalized by endocytosis

via clathrin-coated pits involving the specific clathrin adaptor ARH, and delivered first to early and then to late endosomes, where the acidic environment promotes dissociation of the receptor and the lipoprotein. The receptor recycles to the cell surface while the lipoprotein is degraded in lysosomes to release free cholesterol that regulates transcription of the LDL-receptor gene and genes involved in cholesterol biosynthesis[13] .

Owing to mutations in both alleles of the LDLr locus, homozygous LDLr-associated FH patients present markedly elevated total serum cholesterol (> 500 mg/dL, 13 mmol/L) and LDL-cholesterol levels (LDL-C, > 450 mg/dL, 11.7 mmol/L). The deposition of insoluble cholesterol causes xanthomata on the tendons of the hands and feet and cutaneous planar and corneal arcus in early life. Atheroma of the aortic root and valve can lead to myocardial infarction (MI) and sudden death before the age of 30 years.

Heterozygous patients typically have a lower serum cholesterol level (250-450 mg/dL or 6.5-11.6 mmol/L) and LDL-C (200-400 mg/dL or 5.2-10.4 mmol/L) with positive age correlation. They develop the above clinical features at a less accelerated rate but if untreated most suffer a severe MI and often sudden death or other cardiovascular events in the fourth or fifth decade of life[12].

Autosomal recessive hypercholesterolemia

The recessive rather than dominant pattern of inheritance of severe hypercholesterolemia is referred to as ARH. In patients suffering from ARH, LDLs cannot be taken up into cells, even although the LDL-receptor protein is produced normally. Instead, recessive null mutations in LDLRAP1 (or ARH) are observed[14].

The LDLRAP1 protein seems to work as an accessory adaptor protein which interacts with LDLr, enabling the receptor to engage with clathrin coated pit machinery for endocytosis. The phenotype in ARH is similar to that of patients with homozygous FH but is somewhat milder in terms of serum total cholesterol and LDL cholesterol levels[13].

Mutation in PCSK9

Mutations in *PCSK9*, a gene that encodes a putative protease subtilisin/kexin type 9 (PCSK9), were observed to cosegregate with severe hypercholesterolemia in a number of families in several countries. PCSK9 undergoes intra-cellular autocleavage and the cleaved protein is then secreted from the hepatocyte, together with the cleaved fragment that remains tightly associated. Once in the circulation, PCSK9 binds with high affinity to the extracellular region of the LDLr and is internalized with the receptor. With the acidic pH of the late endosome, the affinity of PCSK9 for the LDLr increases and the complex fails to dissociate. This has the apparent result of directing the LDLr to the lysosome for degradation, thereby preventing it from recycling normally to the cell surface for further rounds of LDL uptake[14].

Some patients suffering from hypercholesterolemia show PCSK9 gain of function mutations: the explanation for the gain of function variants that cause FH seems to be simply that they have a much higher binding affinity for the LDLr, especially at acid pH[13].

Familial ligand-defective apolipoprotein B

In the 1980s, a reduced LDL turnover in some hypercholesterolemic patients without any mutation in *LDLr* gene was described; a single amino-acid substitution of Arg3500 with glutamine in *apoB* gene in its proposed LDLr –binding domain was found to cause FH in those patients. The penetrance of the mutant apoB allele is not 100%, thus patients with familial ligand-defective apoB have less severe phenotypes than FH patients with LDLr mutations[15,16]. This mutant apoB allele is common in Europe, where 2%-5% of hypercholesterolemic patients are homozygous for the defective allele.

Despite extensive research, only one other mutation of the *apoB* gene has been found that affects its receptor-binding function: a substitution of Arg3500 with tryptophan. This mutation is rare in Europe but is relatively common in the Chinese population[17].

Other candidate genes

Variants in genes involved in cholesterol metabolism, such as *CYP7A1*, *SREBP-2* and *SCAP,* have been found in patients with FH[18], even although the evidence that these variants cause the phenotype is not strong[14].

AGE-RELATED HYPERCHOLESTEROLEMIA

Recent findings have shown that increased plasma cholesterol levels and hepatic cholesterol synthesis are accompanied by full activation of HMGR in the liver of aged rats, where the mitochondria produce significantly higher levels of superoxide ions and the ability of cells to remove the deleterious surplus of free radicals is strongly reduced, thus leading to a rise in intracellular ROS content[7].

According to the free radical theory of aging, the age-related deregulation of HMGR is accounted for by the increase of reactive oxygen species (ROS) levels that induce the dephosphorylation and the consequent full activation of HMGR[4].

Moreover, while many studies have established that susceptibility to coronary artery disease (CAD) increases with age, little is known about the mechanisms underlying the increased incidence of CAD in postmenopausal women compared to men of the same age.

Studies carried out on the liver of 12 mo old estropausal rats whose estrogen levels are decreased, showed that the animals have higher levels of plasma cholesterol, increased activation of HMGR, and decreased LDLr membrane exposure than 3 mo old female rats. These changes result in a reduction of cholesterol uptake and an increase of cholesterol synthesis, supporting the correlation between hypercholesterolemia, aging and estropause.

Table 1 Summary of the different causes of hypercholesterolemia

Disease	Cause	References
LDL r-related familial hypercholesterolemia	Over 1000 different mutations in *LDLr* gene	[12,13]
PCSK9-related hypercholesterolemia	Mutations in *PCSK9* gene	[13,14]
Other mutation-related hypercholesterolemia	Mutations in *CYP7A1, SREBP-2, SCAP* genes	[14,18]
Autosomal recessive hypercholesterolemia	Recessive null mutations in *LDLRAP1* gene	[13,14]
Familial ligand-defective apolipoprotein B	Mutations in *apoB* gene	[15-17]
Age-related hypercholesterolemia	Increased activation of HMGR	[4,19,20]

LDLr: Low density lipoprotein receptors; PCSK9: Proprotein convertase subtilisin/kexin 9; HMGR: 3-hydroxy-3-methylglutaryl-CoA reductase.

Increased activation of HMGR does not depend on an increase in ROS, as seen in aged-matched male rats[19,20].

Different types of hypercholesterolemia are summarized in Table 1.

PHARMACOLOGICAL TREATMENT OF HYPERCHOLESTEROLEMIA

Statins

As described above, the decrease of intracellular cholesterol leads to a homoeostatic response which induces the up-regulation of cell-surface receptors that bind atherogenic lipoproteins, which are taken up into cells and degraded. Thus, the reduction of hepatic cholesterol synthesis *via* HMGR inhibition is an attractive approach for the treatment of dyslipidemia.

Statins, strong HMGR inhibitors, are widely used in therapies against hypercholesterolemia and they are available or in late-stage clinical development. Statin treatment strongly reduces MVA production and, as a consequence, hepatic cholesterol biosynthesis. Although these drugs are generally well tolerated, statins can lead to several side effects, the most frequent is myopathy. Statin-associated myopathy is characterized by a wide spectrum of symptoms, ranging from myalgia up to life-threatening rhabdomyolysis[21,22]. These adverse effects could be ascribable to the decrease of some HMGR end-products such as prenyls or ubiquinone[23].

Niacin

Nicotinic acid (niacin) has long been used for the treatment of cholesterol disorders and CAD. Recently, new findings have provided new insights into the molecular mechanisms by which this compound is able to regulate lipid metabolism. For instance, niacin pharmacological doses reduce apoB100-containing lipoproteins. The liver is the most important organ for the synthesis and the secretion of apoB100, its associated lipids and, subsequently, lipoprotein particles[24]. Thus, the hepatic apoB100 processing plays a pivotal role in the modulation of apoB100-rich lipoprotein secretion. It has been demonstrated that niacin increases the intracellular apoB100 degradation and in turn reduces its secretion in HepG2 cell line[25]. This mechanism of action is at the root of the lower plasma atherogenic lipoprotein levels observed in hyperlipidemic patients who have undergone niacin pharmacological treatment[26].

In addition to the intestine, the liver is the major organ for the synthesis and secretion of apoAI and HDL particles. Studies on plasma HDL turnover showed that niacin decreases the fractional catabolic rate of HDL-apoA without altering apoA biosynthesis. In particular, this effect is due to a niacin-dependent inhibition of HDL-apoAI uptake, as demonstrated in HepG2 cells[27]. This mechanism, by which niacin reduces HDL-apoAI catabolism, is responsible for the increase of HDL half-life, thereby enhancing cholesterol efflux and reverse cholesterol transport[24]. Although effective in plasma cholesterol lowering at pharmacological doses, niacin is responsible for a wide range of side effects. The most common is the onset of cutaneous flushes that result from the prostaglandin D2-mediated vasodilatation of small subcutaneous blood vessels. Several gastrointestinal adverse effects, such as nausea, vomiting, dyspepsia and abdominal pain, can also occur. However, the most severe niacin-induced toxicity is hepatotoxicity, which is accompanied by an increase in hepatic transaminase levels[28].

Fibrates

Several studies have shown that fibrate therapies can lead to an overall benefit on plasma cholesterol levels. Fibrates exert their primary effects on the regulation of cholesterol levels by activating peroxisome proliferator-activated receptor alpha (PPARα), which modulates several target genes involved in lipid metabolism[29]. Besides triglycerides (TG) reduction by the decrease of both hepatic apoC Ⅱ and apoC Ⅲ[30,31], the fundamental hypocholesterolemic action of fibrates is the promotion of apoAI and apoA Ⅱ biosynthesis in the liver, which are the main apolipoproteins present in HDL[32]. Fibrates, modifying HDL metabolism, are able to regulate the reverse cholesterol transport pathway. Specifically, these PPARα agonists increase pre-β1-HDL levels in patients with metabolic syndrome, induce the activity of adenosine triphosphate-binding cassette transporter (ABCA1) and decrease total plasma cholesteryl ester transfer protein activity[33]. Fenofibrate also reduces apoB100 levels as a result of reduced hepatic synthesis and secretion of TG, not by a direct influence on apoB100 production. Moreover, fibrates have shown the ability to reduce cholesterol biosynthesis

through HMGR inhibition and by increasing cholesterol excretion into bile[34]. Despite the efficacy of the class of these compounds in modulating cholesterol metabolism, fibrate therapy has at times been discontinued because of adverse effects, such as myopathy, cholelithiasis and venous thrombosis[35].

NOVEL HYPOCHOLESTEROLEMIC STRATEGIES: FUTURE PERSPECTIVES

Non-statin enzyme inhibitors

Owing to the side effects of statin treatment, new molecules for the prevention of hypercholesterolemia should be considered. In particular, the development of new compounds that are able to inhibit cholesterol synthesis by blocking enzymes downstream of HMGR are interesting (Figure 1). Indeed, cholesterol-lowering agents targeting enzymes below the farnesyl pyrophosphate branch point of the cholesterol biosynthetic pathway might offer the possibility of removing the adverse effects of statins and be beneficial to patients suspected to be at risk of muscular damage.

Squalene synthase (SQS) is one of the most known enzymes of the MVA pathway since it catalyzes the first committed step of the *de novo* cholesterol biosynthesis. Inhibitors of this enzyme could be good candidates to be hypocholesterolemic drugs. Indeed, SQS inhibitors reduce plasma LDL levels and, as a consequence, increase the hepatic expression and membrane exposure of LDLr, as reported for statins[36]. Furthermore, since SQS, unlike HMGR, is not the major regulatory enzyme of the cholesterol biosynthetic pathway, it is less subject to feedback regulation. This important feature limits the induction of upstream and downstream enzymes of the MVA pathway that could participate to increase the rate of atherogenic lipoprotein production[37]. The compound EP2306 is one of the most promising SQS inhibitors in hypercholesterolemia treatment if it is considered that 2 mg/kg EP2306 significantly reduces total cholesterol and atherosclerotic lesions in a cholesterol-fed rabbits. Moreover, treatment with EP2306 does not affect liver transaminases or induce any histopathological change in several organs[38], thus indicating that this SQS inhibitor could prevent atherosclerosis-related disorders without inducing side effects.

Squalene epoxidase (SQLE), is a FAD containing enzyme located in the endoplasmatic reticulum catalyzing the epoxidation of squalene and producing 2,3-oxidosqualene[39,41]. Only recently, SQLE inhibitors have received attention as drugs for hypercholesterolemia since they have been extensively investigated for their antifungal properties over the past decades. FR194738 appears to be the most promising potent inhibitor of SQLE. Indeed, it inhibits hepatic SQLE activity and, as a consequence, cholesterol biosynthesis, without increasing HMGR activity by feedback regulation[42].

Oxidosqualene cyclase (OSC) is a monotopic integral membrane protein associated with ER that catalyzes the conversion of 2,3-monoepoxysqualene to lanosterol[43]. Several OSC inhibitors have been reported to show *in vitro* and *in vivo* potency, exerting deep lipid-lowering effects[44]. Furthermore, OSC downregulation stimulates HMGR degradation. OSC inhibition does not induce the overexpression of HMGR because of an indirect and negative feedback regulatory mechanism involving the production of 24(S),25-epoxycholesterol. This negative feedback potentiates synergistically the primary inhibitory effect with an indirect inhibition of HMGR[45,46]. The treatment with OSC inhibitors is not associated with the development of the range of severe side effects that are commonly reported for statins.

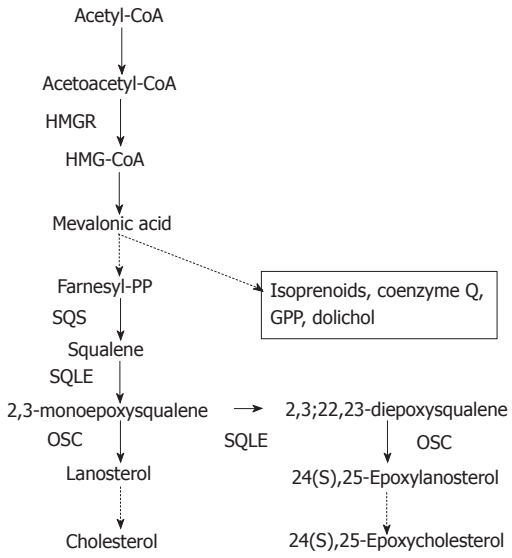

Figure 1 The principal steps of cholesterol biosynthetic pathway. MGR: 3-hydroxy-3-methylglutaryl-CoA reductase; SQS: Squalene synthase; SQLE: Squalene epoxidase; OSC: Oxidosqualene cyclase; GPP: Geranyl pyrophosphate.

Microsomal triglyceride transport protein inhibitors

Microsomal Triglyceride Transport Protein (MTP) is an endosomal protein, mainly expressed in gut and liver, which catalyzes the assembly of cholesterol, triglycerides and apoB to form VLDL or chylomicrons. Given the importance of this protein in atherogenic lipoprotein production, MTP inhibitors are good candidates to lower plasma cholesterol levels. Indeed, MTP inhibitors block fat intestinal absorption and reduce hepatic secretion of VLDL[47]. Phase 2 clinical trials have shown that MTP inhibitor AEGR-733 monotherapy led to a significant dose-dependent decrease in LDL cholesterol. On the other hand, MTP treatment can also cause hepatic steatosis, elevated transaminase plasma levels and other gastrointestinal side effects[47].

ApoB100 antisense oligonucleotides

Antisense Oligonucleotides (ASOs) are single-stranded DNA sequences that correspond to a specific mRNA.

ASOs, binding to mRNA by Watson-Crick hybridation, are able to induce the degradation of specific mRNAs. ApoB100 appears to be a good target for ASO therapy. Moreover, as far as we know, ASO is the only oral small molecule able to inhibit this protein production in the liver[48]. Phase 2 clinical trials demonstrated that the second-generation ASO apoB100 (mipomersen) induces a significant dose-response decrease in LDL cholesterol and apoB100 levels[49]. A LDL reduction ranging from 30% to 50% has been also reached in small trials but dose limitations have to be taken into account because of transaminase elevation and injection site reactions[47].

PCSK9 inhibition

As described above, PCSK9 plays a major regulatory role in cholesterol homeostasis. Given the important function of PCSK9 in regulating cholesterol plasma levels, pharmacological strategies that result in the inhibition of PCSK9 biosynthesis or in the inhibition of the binding of this protein to the LDLr could be useful in hypercholesterolemia treatment. Chan *et al* demonstrated that infusion of a humanized murine monoclonal antibody that binds to PCSK9, thus preventing LDLr internalization and the subsequent degradation, is able to reduce LDL levels by 80% at 10 d. Moreover, new studies have demonstrated that the decrease in hepatic PCSK9 production through ASOs administration is associated with lower circulating LDL levels[50].

Antioxidants

Mevalonate pathway deregulation by ROS clearly suggests that antioxidant compounds could play a significant role in restoring HMGR activity. For instance, ω-3 fatty acids completely prevented the ROS-induced age-related hypercholesterolemia in 24 mo old rats by exerting a powerful reduction of hepatic intracellular ROS[19].

Other antioxidants, such as naringenin and tocochromanols, have shown the ability, not only to block the ROS-induced HMGR activation, but also to modulate the hepatic enzyme protein levels independently from their antioxidant activity[51].

In addition, it was recently demonstrated in the HepG2 hepatocarcinoma cell line that a novel synthetic 4-methylcoumarin (4-methylesculetin) led to the reduction of a ROS-induced HMGR activation state through the increase of the enzyme phosphorylation. Moreover this compound modulates the protein amount of HMGR, affecting the enzyme long-term regulation[52].

CONCLUSION

Cholesterol homeostasis results from the network of complex processes mainly occurring in the liver. It is plain that even an impairment in one of the factors involved in cholesterol metabolism can cause deep alterations and, in turn, diseases such as FH and age-related hypercholesterolemia.

Considering that plasma cholesterol increase is the main cause of cardiovascular disease, cholesterol biosynthesis *via* HMGR and uptake *via* LDLr were the targets of hypercholesterolemia treatment: thus statins, able to inhibit intracellular cholesterol synthesis and, as a consequence, to increase LDLr membrane exposure, have been considered the golden standard against hypercholesterolemia. Nevertheless, since disruption of cholesterol homeostasis can be ascribable to other factors in addition to HMGR and LDLr deregulation, the current editorial highlights how hypercholesterolemia treatment should be supported by a specific diagnosis and, in turn, adapted to the identified causes of plasma cholesterol increase.

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CASE REPORT

Hepatocellular carcinoma and focal nodular hyperplasia of the liver in a glycogen storage disease patient

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Abstract

Glycogen storage disease type Ia (GSD-Ia; also called von Gierke disease) is an autosomal recessive disorder of carbohydrate metabolism caused by glucose-6-phosphatase deficiency. There have been many reports describing hepatic tumors in GSD patients; however, most of these reports were of hepatocellular adenomas, whereas there are only few reports describing focal nodular hyperplasia (FNH) or hepatocellular carcinoma (HCC). We report a case with GSD-Ia who had undergone a partial resection of the liver for FNH at 18 years of age and in whom moderately differentiated HCC had developed. Preoperative imaging studies, including ultrasonography, dynamic computer tomography (CT) and magnetic resonance imaging, revealed benign and malignant features. In particular, fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT revealed the atypical findings that FDG accumulated at high levels in the non-tumorous hepatic parenchyma and low levels in the tumor. Right hemihepatectomy was performed. During the perioperative period, high-dose glucose and sodium bicarbonate were administered to control metabolic acidosis. He had multiple recurrences of HCC at 10 mo after surgery and was followed-up with transcatheter arterial chemoembolization. The tumor was already highly advanced when it was found by chance; therefore, a careful follow-up should be mandatory for GSD-I patients as they are at a high risk for HCC, similar to hepatitis patients.

Key words: Glycogen storage disease type Ia; Hepatocellular carcinoma; Focal nodular hyperplasia; Hepatectomy; Metachronous

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INTRODUCTION

Glycogen storage disease type Ia (GSD-Ia; also called von Gierke disease) is an autosomal recessive disorder of carbohydrate metabolism caused by glucose-6-phosphatase deficiency[1]. The incidence of GSD-I is 1 in 100 000 to 1 in 300 000 live births[2]. Clinical manifestations of this disease include abdominal distension due to

hepatomegaly, rounded doll-like face, growth retardation, hypoglycemia during fasting leading to lactic acidosis, and a bleeding tendency due to impaired platelet agglutinability[2]. While it has been reported that hepatic tumors develop in GSD-Ia patients, the majority of these tumors are not malignant but are usually benign, e.g., hepatocellular adenoma (HCA)[3]. Although focal nodular hyperplasia (FNH) or hepatocellular carcinoma (HCC) can develop in GSD patients, it is a rare event, occurring at a much lower rate than HCA[4]. We report herein a case with GSD-Ia in whom FNH and HCC developed metachronously.

CASE REPORT

A 39 year old man with GSD-Ia, diagnosed with a liver biopsy by laparotomy at 1 year of age, was referred to our institute. He had developed metabolic acidosis after he had caught a cold and was transferred to hospital by ambulance, where a hepatic tumor was found on computer tomography (CT). He previously underwent a partial resection of the liver for a tumor in segment 4, resulting in FNH at 18 years of age (Figure 1). The patient had never smoked and seldom drank. His height was 153 cm and his weight was 36.6 kg due to the growth retardation of GSD-Ia. He had a typical doll-like face.

On physical examination, the bulbar conjunctiva showed no icterus. The liver was palpable 8 cm below the costal arch, while the spleen was not palpable. Laboratory workup revealed elevated levels of serum aspartate aminotransferase (65 IU/L; normal, 13-33 IU/L), alanine aminotransferase (88 IU/L; normal, 8-42 IU/L) and gamma-glutamyl transferase (127 IU/L; normal, 0-75 IU/L). Serum total bilirubin, total protein, albumin and prothrombin time were within normal limits. The levels of total cholesterol (279 mg/dL; normal, 128-219 mg/dL), triglyceride (830 mg/dL; normal, 30-149 mg/dL) and uric acid (8.1 mg/dL; normal, 3.6-7.0 mg/dL) were elevated. Blood urea nitrogen (28.8 mg/dL; normal, 8.0-22.0 mg/dL) and creatinine (1.83 mg/dL; normal, 0.6-1.1 mg/dL) levels were also elevated. Fasting blood glucose was 64 mg/dL (normal, 70-109 mg/dL). Serum alpha-fetoprotein was undetectable but protein induced by vitamin K absence or antagonist-Ⅱ was elevated at 139 mAU/mL (normal, 0-30 mAU/mL). The patient had lactic acidosis on blood gas analysis (pH: 7.229; $PaCO_2$: 25.2 mmHg; HCO_3^-: 10.2 mmol/L; Base excess: -15.9 mmol/L; Lactate: 7.3 mmol/L).

Ultrasonography (US) showed a heterogeneous echoic mass with a capsule of 10 cm in diameter in the right lobe. The tumor was accompanied with many daughter nodules around the capsule. Contrast-enhanced US with perfluorobutane microbubbles showed a highly enhanced mass in the early phase, whereas a washout effect was not obvious in the Kupffer phase (Figure 2). A dynamic CT scan showed a high-density tumor measuring 10 cm in diameter in the early phase and an iso-low-density tumor in the late phase. It had a capsule and septums, leading to the preoperative diagnosis of HCA. On the other hand, it had daughter nodules and the capsule was partially torn, suggestive of malignancy (Figure 3). Magnetic resonance imaging (MRI) showed a low-intensity tumor in T1-weighted images (WI) and a slightly high-intensity tumor in T2WI. Superparamagnetic iron oxide-enhanced MRI revealed the low uptake of Resovist, which was suggestive of HCC (Figure 4). Fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT showed a high accumulation of FDG with a maximum standardized uptake value (SUVmax) of 4.2 in the non-tumorous hepatic parenchyma and a relatively low uptake of FDG with a SUVmax of 2.7 in the tumor (Figure 5).

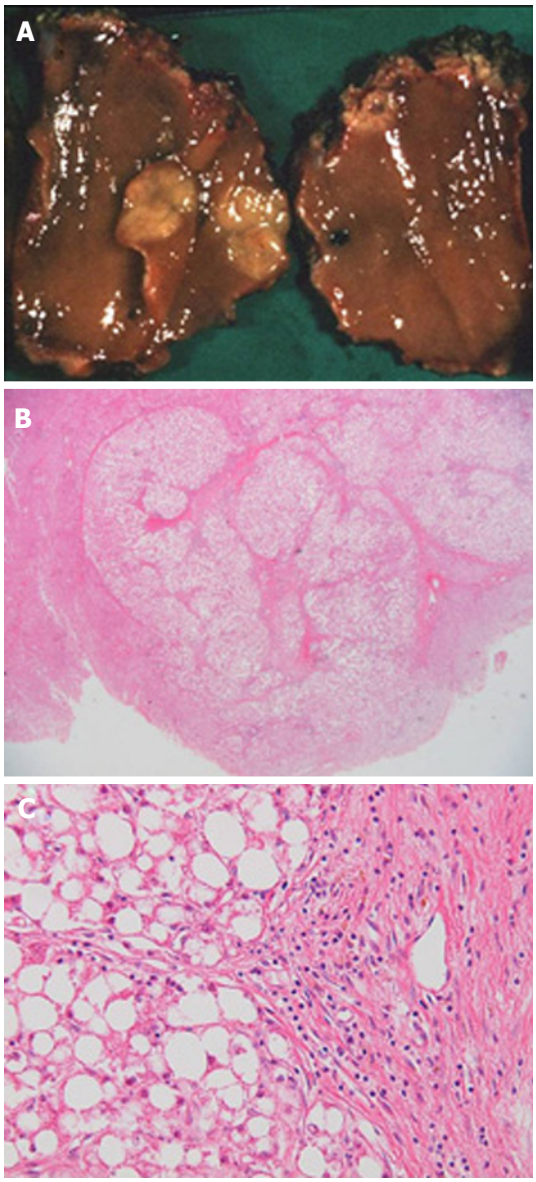

Figure 1 Initial surgery for focal nodular hyperplasia at the age of 18 years. A: Resected specimen; B: A central scar and fibrous partition in the nodule [hematoxylin and eosin stain (HE × 4)]; C: Markedly vacuolated cells, without atypical cells, in the nodule and central vein in the central scar (HE × 400).

The patient underwent a right hemihepatectomy without diagnostic confirmation of the giant hepatic tumor. During the perioperative period, high-dose glucose and sodium bicarbonate were administered to control the metabolic acidosis, as described previously[5]. The postop-

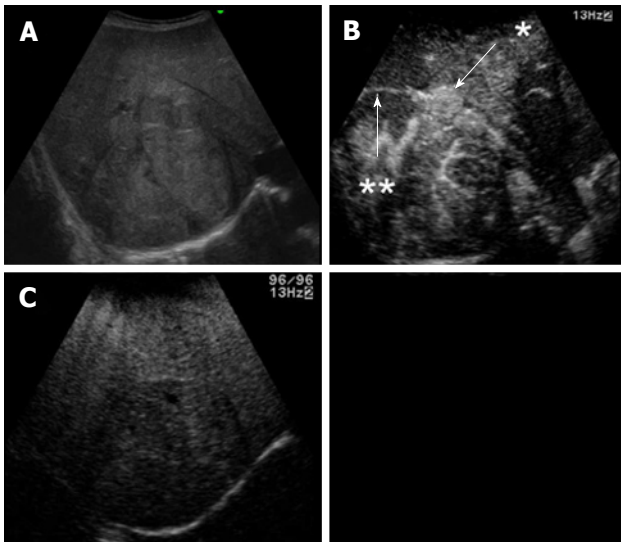

Figure 2 Ultrasonography. A: A heterogeneous echoic mass with a capsule of 10 cm in diameter; B: The tumor with many satellite nodules (arrow, star) around the capsule (arrow, double star) was highly enhanced in the early phase with the perflubutane microbubble contrast agent; C: The wash-out effect was not obvious in the Kupffer phase, which was an atypical finding inconsistent with hepatocellular carcinoma.

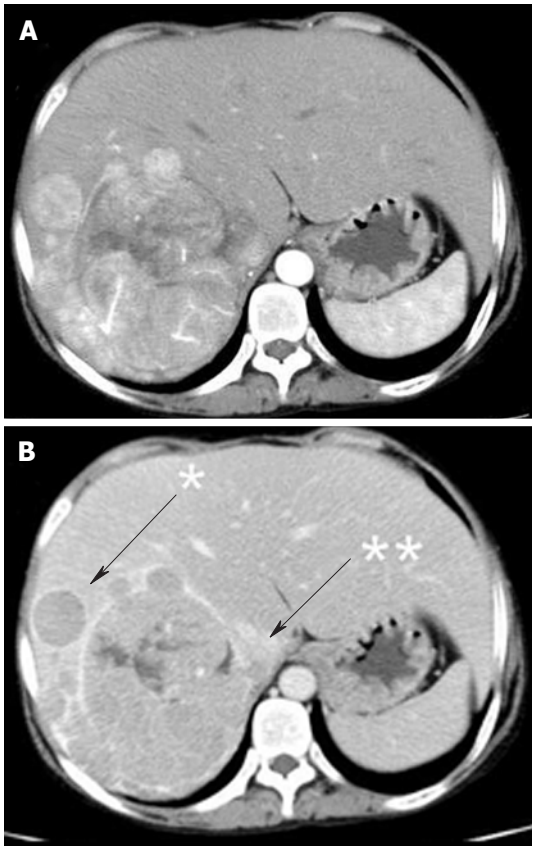

Figure 3 Dynamic computer tomography. A: A highly-enhanced tumor measuring 10 cm in the early phase; B: An iso- to low-density tumor in the late phase. It had satellite nodules (arrow, star) and a partially torn capsule (arrow, double star).

erative course was uneventful and he left the hospital on postoperative day 14.

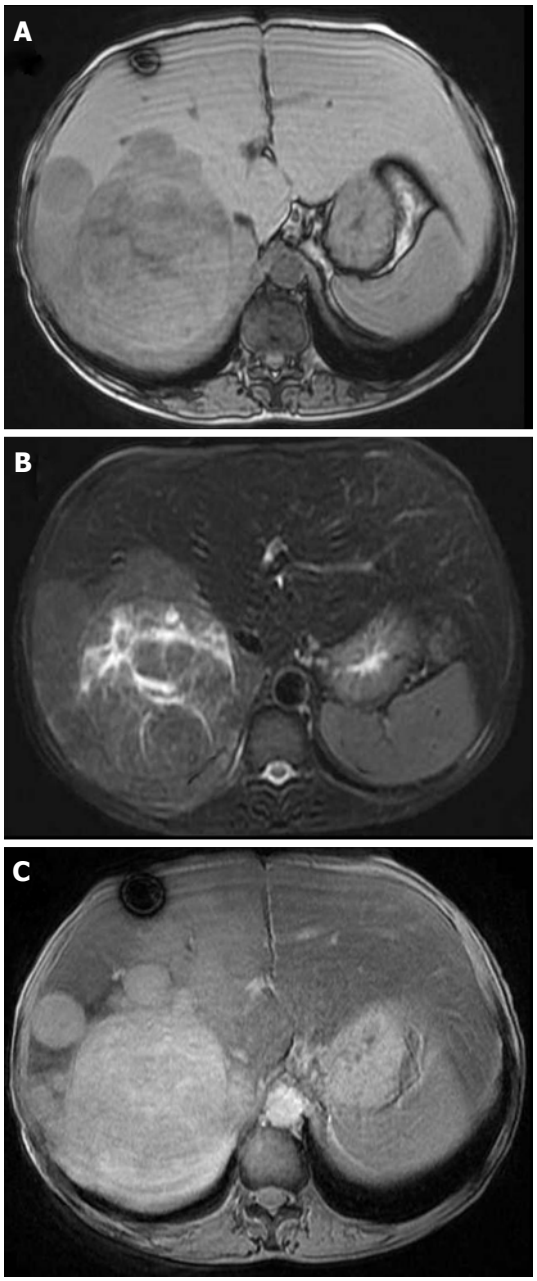

Figure 4 Magnetic resonance imaging. A: A low-intensity tumor in a T1WI; B: A high-intensity tumor in a T2WI; C: A tumor with low enhancement after resovist administration.

The weight of the resected specimen was 1914 g. The tumor was 100 mm in diameter with multiple satellite nodules. The main tumor contained septums and hemorrhagic regions. It also contained a capsule with some extracapsular invasion. Microscopic examination revealed that the tumor cells were swollen and polygonal with large round or irregular nuclei with rough chromatin aggregations, obvious nucleoli and mitoses. Multinucleated tumor cells were also found and many blood lakes had formed in the tumor. These findings resulted in the diagnosis of moderately differentiated HCC with intrahepatic metastases, whereas no adenomatous components were observed in the tumor. In the non-tumorous liver

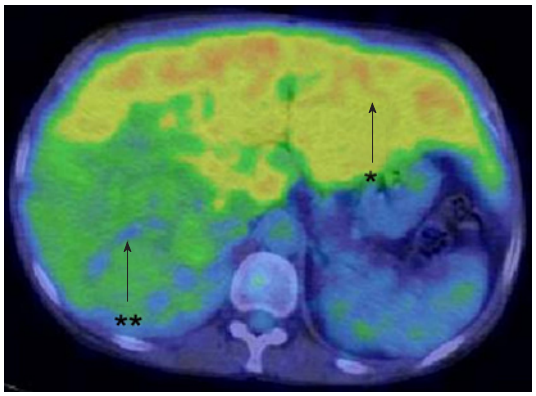

Figure 5 Fluorodeoxyglucose-positron emission tomography/computer tomography. High levels of FDG accumulation with a SUVmax of 4.2 in the non-tumorous liver (arrow, star) and relatively low uptake of FDG with a SUVmax of 2.7 in the tumor (arrow, double star). **FDG: Fluorodeoxyglucose-positron** emission tomography.

parenchyma, cells with a clear cytoplasm were positive for periodic acid-Schiff (PAS) staining; this finding was consistent with that of GSD (Figure 6).

The present case had multiple recurrences of HCC that were beyond the Milan criteria at approximately 10 mo after surgery. He was followed-up with transcatheter arterial chemoembolization.

DISCUSSION

GSD-Ia is an autosomal recessive disorder caused by glucose-6-phosphatase deficiency in the liver, kidneys and intestinal mucosa. The disease is characterized by the impaired conversion of glucose from glucose-6-phosphate in the liver, resulting in fasting hypoglycemia and lactic acidosis[1,2]. In the present case, the development of hypoglycemia and lactic acidosis led to the opportunity to use imaging studies for the diagnosis of a hepatic tumor.

Although US, CT, MRI and CT combined with arterial portography and hepatic arteriography are generally considered to be effective for the diagnosis of HCC, preoperative diagnosis was difficult in this case. Each imaging study revealed benign and malignant features. Moreover, FDG-PET/CT revealed the very interesting findings that FDG accumulated at high levels in the non-tumorous hepatic parenchyma and at low levels in the tumor. As GSD-I is characterized by glucose-6-phosphatase deficiency, it was hypothesized that the FDG ingested by hepatic cells was phosphorylated by hexokinase to FDG-6-phosphate, which accumulated in non-tumorous cells without dephosphorylation by glucose-6-phosphatase.

Liver tumors are common in GSD-I, the majority of which are HCAs[3]. Talente *et al*[3] described that 27 of 37 (73%) GSD-Ia patients had HCAs detected by US. Meanwhile, the concomitant occurrence of other tumor types is rare. Sumimoto *et al*[4] described 22 GSD-I cases with liver tumors and reported HCA, HCC, FNH and hepatoblastoma in 16, 3, 2 and 1 patients, respectively. To the best of our knowledge, there are no reports describing a case of GSD-I with FNH and HCC.

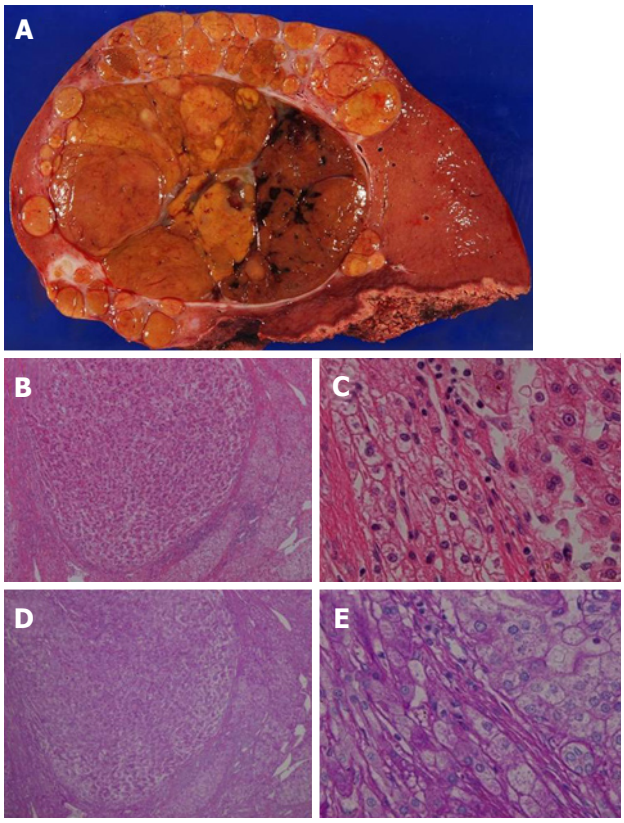

Figure 6 Giant tumor in the right lobe. A: Resected specimen showed a giant tumor of 10 cm in diameter on the cut surface. The tumor contained septums and hemorrhagic regions; B: hematoxylin and eosin stain **(HE) staining** revealed the capsule with some extracapsular invasions **(HE × 4); C: Histology** of the tumor revealed moderately differentiated hepatocellular carcinoma with intrahepatic metastases, whereas no adenomatous components were observed (HE × 400); D: Cells with enlarged clear endoplasmic reticula were observed in the non-tumorous region **[periodic acid-Schiff (PAS) stain × 4]. E: PAS staining** revealed a PAS-positive area in accordance with a clear area (PAS × 400).

Some authors have reported malignant formations from adenomas in GSD-I patients[6,7]. Bianchi summarized 10 cases of HCC in GSD-I patients reported in the literature and observed that the transition from HCA into HCC occurred in 50% of these cases[6]. The pathogenesis of HCC formation in GSD-I is not well understood. Some authors have described hypothetical causes, including the accumulation of abnormal metabolites in hepatic cells acting as carcinogens[8] and proliferative or neoplastic changes in hepatic cells caused by long-term hypoglycemia-induced chronic hormonal stimulation (e.g., low insulin and high glucagon levels)[7]. For these reasons, once GSD-I is diagnosed, it is necessary to maintain normal blood glucose levels to prevent HCC. In fact, in some cases of GSD-I with adenoma, regression of adenoma after nutrition therapy has been reported[6,9]. In our case, it was not obvious whether HCC developed from an adenoma since the patient was not followed-up after his initial surgery for FNH and there were no components of HCA in the resected specimen upon microscopic evaluation.

With regard to liver tumors in GSD-I patients, surgery might be indicated for HCC or even adenoma if it is likely to cause bleeding or complaints of compression[10]. When it is difficult to control metabolic acidosis in GSD-I patients, a liver transplantation could be performed[11,12]. As the present case had only 1 episode of acidosis and the tumor was so large that it did not meet the Milan criteria, hepatectomy and not liver transplantation was indicated.

Concerning perioperative management, hypoglycemia and lactic acidosis are common problems for GSD patients. Although glycogenolysis and glycogenesis are normal in these patients, the release of free glucose from the liver into the blood is greatly impaired. Since glycolysis of glucose 6-phosphate is intact or even intensified under hormonal counter regulation, similar to a fasting state, the production of pyruvate and lactate is increased[13]. Therefore, high-dose glucose and sodium bicarbonate were administered, as reported previously[5], resulting in the prevention of severe perioperative hypoglycemia and acidosis (data not shown).

Unfortunately, this patient was not followed-up well and over 20 years had passed since his initial operation for FNH. The tumor was already highly advanced when it was found by chance; therefore, careful follow-up should be mandatory for GSD patients as they are at a high risk of developing HCC, similar to hepatitis patients[14].

In conclusion, we report a very rare case of FNH and HCC that developed metachronously in a patient with GSD-Ia.

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CASE REPORT

Acute hepatitis secondary to parenteral amiodarone does not preclude subsequent oral therapy

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Abstract

Amiodarone chlorhydrate is a diiodated benzofuran derivative used to treat cardiac rhythm abnormalities. Hepatotoxicity is a relatively uncommon side effect of amiodarone and symptomatic hepatic dysfunction occurs in less than 1% to 3% of patients taking amiodarone. We report here on an unusual case of amiodarone-induced hepatotoxicity. A 29 year old woman with normal liver function was given amiodarone intravenously to treat her atrial fibrillation. She developed acute toxic hepatitis after 24 h. The intravenous form of amiodarone was immediately avoided and replaced by the oral form, using conventional loading doses as soon as the deranged liver function tests had normalized, without recurrence of the hepatitis. These observations show that the occurrence of acute hepatic impairment with intravenous amiodarone does not necessarily preclude the use of this drug by mouth and the necessity of monitoring the hepatic function of patients treated with amiodarone.

Key words: Amiodarone; Hepatitis; Toxic hepatitis; Polyoxenethylated sorbitan ester

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INTRODUCTION

Amiodarone is an iodine-rich drug that is highly effective and widely used as an antiarrhythmic agent for the treatment of symptomatic supraventricular and ventricular tachyarrhythmias[1]. Amiodarone is associated with many adverse effects that involve different organs. Although these side effects are generally mild, 10% to 15% of patients require withdrawal of the drug as a result of toxicity. The most prominent adverse effects during long-term therapy include thyroid dysfunction, corneal microdeposits and pulmonary and hepatic toxicity. Transient rises in hepatic enzyme activity have been reported in 40% of patients who received the antiarrhythmic agent amiodarone. Asymptomatic elevation of serum aminotransferases occurs in 25% of those patients who are treated with amiodarone. Micronodular cirrhosis that was clearly due to amiodarone therapy has been confirmed in 12 cases[2]. However, the prevalence of severe liver injury has been estimated at only 1% to 3%[3]. We describe here a case of amiodarone-induced acute toxic hepatitis after treatment with 400 mg of intravenous amiodarone for one day.

CASE REPORT

A 29 year old woman was admitted to our department complaining of palpitations. She had no risk factors for cardiovascular disease. She did not consume alcohol or tobacco. She was taking no medication. She presented with a six day history of permanent palpitations, without chest pain or disturbance of consciousness. Initial examination revealed a conscious anicteric patient. The respiratory rate was 18 breaths per minute, oxygen saturation was 94% (while she was breathing ambient air), pulse was irregular with an apical rate of 180 beats/minute, blood pressure 95/60 mmHg, temperature 37.5 °C, distal extremities were hot and her weight was 32 kg. The cardiovascular examination found no signs of right heart failure. Peripheral pulses were present and symmetrical. The initial cardiac auscultation was normal. The pleuropulmonary examination showed no lung crepitations. Biologically, the full blood count was normal, C-reactive protein 10.3 mg/dL, creatinine 70 micromol/L, urea 50 mg/dL and lactate dehydrogenase 263 IU/L. The liver function, including transaminases, gamma-GT, alkaline phosphatase and prothrombin level, was normal. Thyroid stimulating hormone was 4.4 U/mL with a normal free T4. An admission electrocardiogram confirmed atrial fibrillation with a fast ventricular response rate (200 beats/minute) with left ventricular hypertrophy. The chest xray found cardiomegaly. Echocardiography showed left ventricular dilatation with severe mitral regurgitation and pulmonary hypertension. Initial treatment with the ultimate intention of establishing sinus rhythm included 1.5 g of intravenous amiodarone, heparin and diuretics. One day after admission, she had reverted to sinus rhythm but repeat liver function tests revealed markedly elevated transaminases (ALT = 1050 UI/L). Gamma-glutamyl transferase (GGT) and alkaline phosphatase were respectively 56 U/L and 200 U/L, bilirubin was normal. An ultrasound examination of the liver was normal; hepatic echogenicity was homogeneous without dysmorphism and there were no bile duct abnormalities. The serology of viral hepatitis (A, B and C) and anti-tissue antibodies (antinuclear antibodies, anti-smooth muscle and antimitochondrial antibodies) were negative. Total creatinine kinase was normal. A diagnosis of acute toxic hepatitis secondary to amiodarone injection was made. So intravenous amiodarone was immediately avoided after 24 h and replaced by the oral form, using conventional loading doses (200 mg three times daily), without any derangement of liver function (Figure 1). The patient was discharged home on enalapril, furosemide, amiodarone and warfarin. Two months later, she remained in sinus rhythm on the same medications and her liver function, including transaminases, GGT and alkaline *phosphatase,* was normal. The patient was proposed for surgical treatment (mitral replacement).

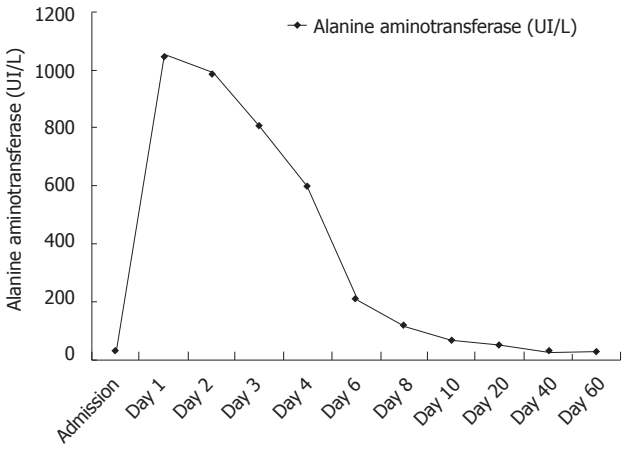

Figure 1 Evolution of liver function.

DISCUSSION

Amiodarone is an iodinated benzofurane derivative which is used in a wide variety of cardiac arrhythmias resistant to other treatments. It has a long half life and may be administered either orally or intravenously[4]. The drug has many extracardiac side effects. Severe acute hepatitis immediately after intravenous amiodarone has been reported[5-7]. In order to obtain stable solutions of amiodarone for intravenous use, the drug is dissolved in a mixture of polysorbate 80 (polyoxenethylated sorbitan ester) and a small amount of benzyl alcohol. Polysorbate 80 has been implicated in the E-ferol syndrome which has been described in infants. The E-ferol syndrome is characterised by hepatomegaly, splenomegaly, cholestatic jaundice, renal failure and thrombocytopenia. It is associated with the use of an intravenous preparation of vitamin E, E-ferol, which contains polysorbate 80 and polysorbate 20. The liver histology in this syndrome shows kupffer cell exfoliation, centrilobular accumulation of cellular debris and panlobular congestion, especially in central areas. The polysorbates are deemed responsible for these changes. The clinical features of the E-ferol syndrome show noticeable similarities to those found in cases of liver toxicity due to amiodarone[8,9]. This suggests that the hepatic insult may be a function of the diluent rather than the amiodarone[10,11]. This important distinction would not contraindicate oral amiodarone and was originally suggested by Rhodes *et al*[8,12] and others. Although this particular adverse reaction of intravenous amiodarone is rare[5], it remains important because of the popularity of amiodarone for the treatment of severe life threatening cardiac arrhythmias. In the present case, oral amiodarone was administered as soon as the deranged liver function tests had normalized, without recurrence of the hepatitis. This supports the concept that acute hepatitis complicating intravenous amiodarone is related mainly to the diluents. On this basis, we suggest amiodarone can be safely administered by the oral route even in patients who develop hepatitis with the intravenous loading, provided that liver function and renal parameters must be closely monitored.

This observation supports the concept that acute hepatitis complicating intravenous amiodarone is related to the diluent rather than the drug. Indeed, amiodarone

can be safely administered by the oral route, even in patients who develop hepatitis with the intravenous preparation, provided hepatic function is closely monitored.

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ESGE - Workshop on Advanced Endoscopy with Live Demonstrations
Vienna, Austria

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San Diego, CA, United States

April 18-22, 2012
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Organization as author

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Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

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Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
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