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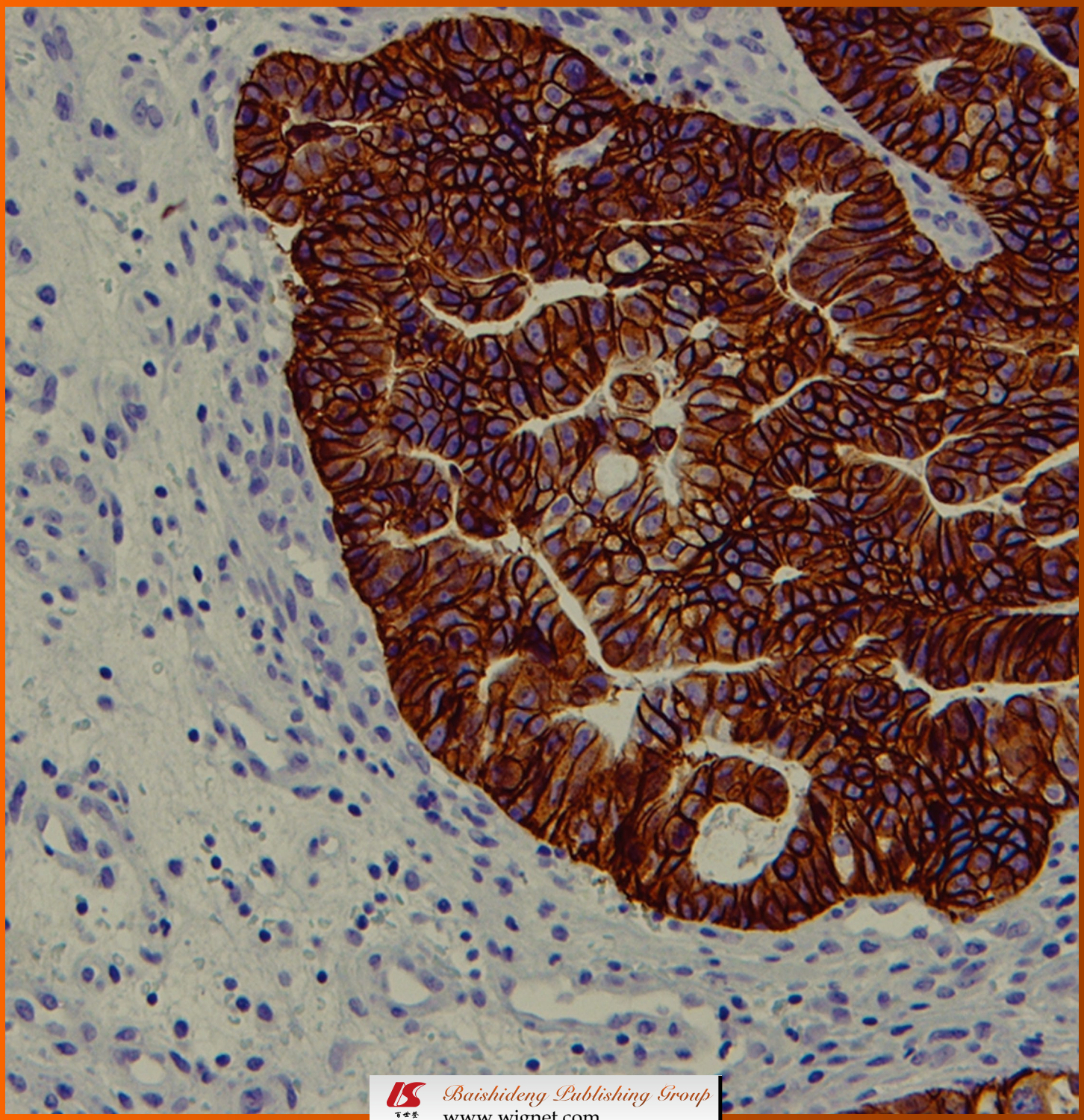

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EDITORIAL

Multiple cells of origin in cholangiocarcinoma underlie biological, epidemiological and clinical heterogeneity

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Abstract

Recent histological and molecular characterization of cholangiocarcinoma (CCA) highlights the heterogeneity of this cancer that may emerge at different sites of the biliary tree and with different macroscopic or morphological features. Furthermore, different stem cell niches have been recently described in the liver and biliary tree, suggesting this as the basis of the heterogeneity of intrahepatic (IH)- and extrahepatic (EH)-CCAs, which are two largely different tumors from both biological and epidemiological points of view. The complexity of the organization of the liver stem cell compartments could underlie the CCA clinical-pathological heterogeneity and the criticisms in classifying primitive liver tumors. These recent advances highlight a possible new classification of CCAs based on cells of origin and this responds to the need of generating homogenous diagnostic, prognostic and, hopefully, therapeutic categories of IH- and EH-CCAs.

Key words: Intrahepatic cholangiocarcinoma; Extrahepatic cholangiocarcinoma; Cholangiocarcinoma classification; Cholangiolocarcinoma; Cells of origin; Cancer stem cells; Peribiliary glands; Biliary tree stem/progenitor cells; Human hepatic stem cells; Risk factors; Targeted therapies

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INTRODUCTION

Cholangiocarcinoma (CCA) is an extremely heterogeneous cancer from a topographical, morphological, bio-

logical and clinical point of view[1-8]. The two main forms, intrahepatic (IH)- and extrahepatic (EH)-CCAs, showed, in the last decades, opposite epidemiological behavior, with incidence and mortality progressively increasing for the IH form but stable or slightly decreasing for the EH form[6-8]. This suggests different risk factors and, indeed, evidence exists that IH- and EH-CCAs may emerge from a different pathological background[8]. A large body of recent literature deals with the role of stem cells in carcinogenesis[9,10]. In this regard, different stem cell niches have been recently identified in the liver and biliary tree with new implications of the origin of primitive liver cancers[11-15]. The complexity of the organization of the liver stem cell compartments could underlie the CCA clinical-pathological heterogeneity and well justifies the difficulties in clinical-pathological classification of primitive liver tumors[16-18]. Another point of great consideration is the relationship between chronic liver damage and the development of primitive liver tumors. Indeed, the chronically injured liver and biliary tree could be considered a classic model of stem cell derived carcinogenesis where the activation and proliferation of the stem cell compartment in response to tissue injury represent the first step of the carcinogenetic process[19-21]. In light of these recent advances, histological and morphological classification of primitive liver cancer is currently under revision, taking into consideration the potential cells of origin[17,18]. Histological characterization of CCAs based on cell of origin responds to the need of generating homogenous diagnostic, prognostic and therapeutic categories or classes for IH- and EH-CCAs. The cells of origin of CCAs also represent the cell targets of the hepatic and biliary diseases associated with the development of CCAs and this could explain the association of determined hepatic and biliary pathologies with each category of CCA, other than the differences in terms of epidemiological, behavioral and risk factors.

IH AND EH STEM CELL NICHES

CCA arises from the lining epithelium and peribiliary glands (PBGs) of the IH and EH biliary tree and shows variable degree of differentiation[1-5]. It has been recently elucidated how stem cells are particularly prone to be involved in the carcinogenic process due to their particular biological features[9,10]. Stem cell niches have been firstly identified within the adult liver in the canals of Hering, remnants of the ductal plate of fetal and neonatal livers[11-13]. Human hepatic stem cells (hHpSCs) residing in the canals of Hering can differentiate into hepatocytes and cholangiocytes lining the small bile ducts, which in turn can give rise to tumors with a whole range of phenotypes, with varying hepatocellular and biliary differentiation characteristics[5]. More recently, additional stem cell niches have been identified in PBGs[14,15]. PBGs are mucin-producing glandular elements located in the wall of the EH and large IH bile duct. Within PBGs, stem/progenitor cell niche composed of multipotent stem/progenitor cells of endodermal origin (biliary tree stem/progenitor cells: BTSCs) has been described, which represent the only cells potentially underlying the mucin-producing cells lineage within the liver[14,15]. PBGs are distributed along the biliary tree starting intrahepatically at the level of septal-segmental bile ducts and ending at the hepato-pancreatic common duct near the duodenum. PBGs are particularly high in density at the level of the cystic duct, hilum and periampular region, sites where EH-CCAs typically emerge[14,15]. The IH PBGs are indistinguishable from the EH ones[22]. For decades, the heterogeneity of IH and EH bile ducts has been the object of extensive investigations and the embryological origin of the biliary tree furnishes the basis for this topic[23,24]. From an embryological point of view, indeed, the medium-large IH and the EH bile ducts recognize a unique origin and represent the result of the proliferation of the primitive endoderm at *porta hepatis*[23,24]. The interlobular bile ducts, in contrast, derive from SOX (SRY (sex determining region Y)-box) 9 positive progenitors following the reorganization of the ductal plate[23,25]. Septal ducts (medium size), segmental ducts, larger IH bile ducts and EH bile ducts share unique histological features characterized by a discrete duct with a well defined wall constituted of connective tissue supporting the lining epithelia[22]. Another unique feature joining the large IH bile ducts and the EH bile ducts is the presence in the duct wall of the PBGs[22]. Furthermore, the large segments of the biliary tree share with EH bile ducts similar characteristic expression of cell markers both in physiological and pathological conditions that largely differ with respect to those observed in the interlobular bile ducts[26]. Specifically, pancreatic α-amylase, trypsin and pancreatic lipase are expressed in biliary cells lining the PBGs in immature ducts in fetal livers and in mature large bile ducts in postnatal livers[26]. Differently, these phenotypical markers disappear quickly when hHpSCs derived lineage restrict towards mature hepatocyte or cholangiocyte fates (9-25 wk of gestation) and interestingly expression is not found in developing peripheral IH bile ducts[26]. Recently, we demonstrated[14,15] that PBGs are stem cell niches in human EH bile ducts and that the maturation lineage progresses from the stem cells located in the deeper part of the wall, within the PBGs, to mature cells lining the surface epithelia[15]. We also observed an increased mucin production with the maturation in the duct wall[15]. The individuation of a stem cell niche within the bile ducts[14,15] opens the possibility that BTSCs within PBGs and their descendent cells could be further considered as cells-of-origin of mucin-producing CCAs (Figure 1).

CANCER STEM CELLS AND CANCER CELLS OF ORIGIN: DEFINITIONS

The definition "cancer stem cell (CSC)" indicates the cellular subset within the tumor that uniquely sustains malignant growth. Differently, the term "cell-of-origin" defines the normal cell that acquires the first cancer-initiating

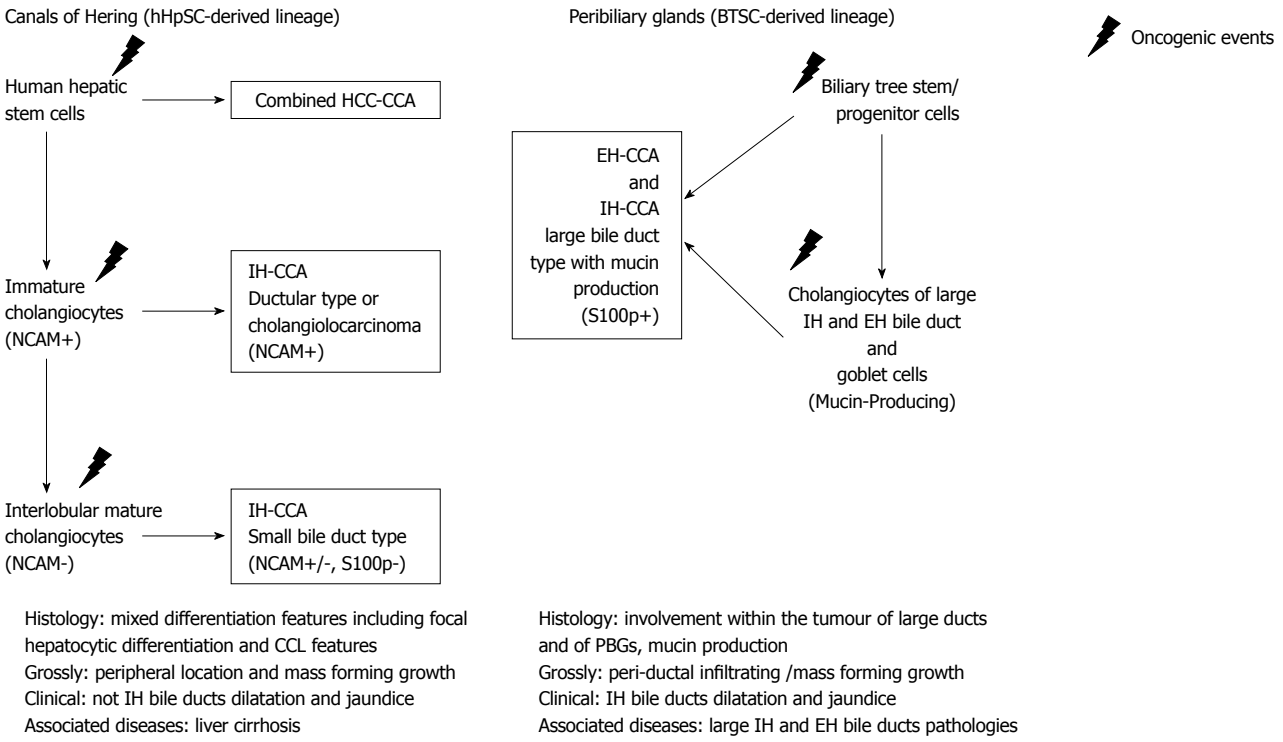

Figure 1 Schematic diagram of the cell-lineages-of-origin and relative cells-of-origin within and of the related cholangiocarcinoma subtypes. Cells belonging from human hepatic stem cell (hHpSC) lineage or from biliary tree stem/progenitor cell (BTSC) lineage are retained cells of origin of different intrahepatic (IH)- and extrahepatic (EH)-cholangiocarcinoma (CCA) subtypes recently described[17,18,58]. Histology, grossly, the main clinical features and the associated diseases of the CCAs arising within the two cell lineages are showed respectively. HCC: Hepatocarcinoma; CLC: Cholangiolocarcinoma.

mutation(s)[27]. Although the terms "cell-of-origin" and CSC have been used interchangeably, they are distinct concepts referring to cancer-initiating cells and cancer-propagating cells, respectively[27,28]. The cancer-initiating cell denotes the cell-of-origin. It is important to note that the cell-of-origin is not necessarily related to the CSC and its phenotype may be substantially different[27]. The cancer cell-of-origin has great importance in tumor cell fate and pathology; the activation of the same genetic/epigenetic mutation in different maturational phases within a cellular lineage of a given organ may have profound implication, either in malignant potential or in cancer morphology and phenotype (intratumoral heterogeneity)[29]. This is the case in a transgenic mouse model which showed how the mutation of *Hras* targeted to the hair follicle region (earlier cells within the lineage) highly predisposed mice to squamous carcinomas, whereas the targeting to interfollicular or suprabasal cells (more differentiated cells) resulted in papillomas with low malignant potential[30,31].

LIVER CANCER STEM CELLS AND NEW CANCER THERAPEUTIC TARGETS

Many years of investigations and daily clinical practice suggest an alternative model of carcinogenesis where only a subset of CSCs has the ability to proliferate extensively and form new tumors[9,10]. Signalling pathways associated with oncogenesis, including the Notch, Sonic hedgehog and Wnt signalling, play a major role in regulating stem cell self-renewal. The machinery for self-renewal is already activated in CSCs, thus fewer mutations may be required to maintain self-renewal than to activate it ectopically. Stem cells often persist for long periods of time, increasing the probability of mutations. CSCs tend to be more resistant to chemotherapeutics due to high levels of expression of multidrug resistance genes[9]. As far as liver is concerned, intermediate carcinoma may be a distinct type of primary liver carcinoma, morphologically and phenotypically intermediate between hepatocellular carcinoma (HCC) and CCA, which originates from transformed hepatic progenitor cells[32]. Moreover HCCs expressing biliary cell markers, such as keratin(K)7 and K19, have been demonstrated to carry a significantly poorer prognosis and have a higher recurrence rate after surgical resection and liver transplantation[5]. A number of cell surface markers have been proved to be useful for the isolation of CSC enriched fractions in liver malignancies, including CD133 (also known as Prominin-1), CD44, CD24, epithelial cell adhesion molecule (EpCAM), α-fetoprotein, Thy-1 and ATP-binding cassette B5, as well as Hoechst$_{33342}$ exclusion by the side population cells[28]. Indeed, recently, it has been described that a poor prognosis characterizes HCCs expressing stem markers such as EpCAM and CD133[33,34]. A correlation between the stage of hepatic differentiation and clinical manifestation, notably vascular invasion, metastatic spread and patient survival, was also established[10,33-35]. Primary liver tumors might arise from impairment of the normal liver differentiation program associated with excessive

Wnt/β-catenin signaling[10]. Recently, EpCAM was identified as a direct transcriptional target of Wnt/β-catenin signaling in HCC[36]. A number of EpCAM-regulated target genes have been identified, including c-myc and cyclins, and additional genes involved in cell growth and proliferation, cell cycle and cell death[10]. These findings indicate that expression of EpCAM is strongly linked with proliferation of stem cells and that cancer development from CSCs may occur after aberrant EpCAM re-expression. Recently, it has been demonstrated that the induction of terminal differentiation of HCC CSCs by using oncostatin M is associated with a marked reduction of the proliferative properties of the cells and with enhanced sensibility to chemotherapy[34]. Finally, a subset of highly chemoresistant and invasive HCC CSCs with aberrant expressions of IL-6 and the transcription factor Twist has been recently described. This subset of CSCs displays regulated let-7 and miR-181 miRNA family members, where modulation of both miRNA dependent pathways can impact significantly on their biology[35]. Thus, the modulation of aberrantly expressed miRNA in HCC CSCs may be a useful strategy to limit CSC differentiation and invasion or improve responses to cytotoxic therapies. In different cancers, recent studies addressed potential strategies of treatment based on selective target of specific CSCs[10]. Various therapeutic drugs that directly modulate CSCs have been examined *in vivo* and *in vitro*. However, CSCs clearly have a complex pathogenesis, with a considerable crosstalk and redundancy in signaling pathways, and hence targeting single molecules or pathways may have a limited benefit for treatment. Many of the key signaling molecules are shared by both CSCs and normal stem cells, which add further challenges for designing molecularly targeted strategies specific to CSCs. In addition to the direct control of CSCs, many other factors that are needed for the maintenance of CSCs, such as angiogenesis, vasculogenesis, invasion and migration, hypoxia, immune evasion, multiple drug resistance and radioresistance, should be taken into consideration when designing therapeutic strategies[10]. In CCA, these studies are only at the beginning and the heterogeneity of this cancer further hampers advancement. To this latter regard, obtaining clinical-pathological information capable of driving the diagnostic setting or the accurate realization of basic science studies pass through the mandatory acquisition of CCA tissue[37].

CCA CELLS OF ORIGIN AND NEW CCA CLASSIFICATION PROPOSALS

CCA is the primary malignancy of the biliary tract[38]. This cancer has been classified as either IH or EH, with the second-order bile ducts acting as the separation point[4]. Classically, EH-CCA has been divided into perihilar and distal CCA. According to the American Joint Cancer Committee/Union for International Cancer Control perihilar CCA is proximally separated from IH-CCA by the second-order bile ducts and distally separated from distal EH-CCA by the insertion of the cystic duct into the EH biliary tree[39]. CCA arises from the lining epithelium and peribiliary PBGs of the IH and EH biliary tree[18]. Recent studies further stressed the concept of CCA heterogeneity. The accurate comparison of lineage markers between normal and neoplastic cells can lead to individuate the cell-of-origin in different tumor subtypes arising within a given organ, even if tumor cells show phenotypical plasticity or dedifferentiate during neoplastic progression (Table 1). Therefore, lineage markers and molecular signatures of tumor cells may not precisely reflect the true cell-of-origin in normal tissue. The individuation of a stem cell niche within the bile ducts opens the possibility that BTSCs within PBGs could be further considered as cells-of-origin of mucin-producing CCA[14,15] (Figure 1). Indeed, BTSCs represent the only cells potentially underlying the mucin-producing cells lineage within the liver. Strict similarities between the pathologies of biliary tract and pancreas have been recently suggested[18]; in response to injury, pancreatic duct glands undergo a mucinous metaplasia and have been indicated as a possible cell of origin of pancreatic cancer[18]. An unresolved question regarding CCA is which cell have to be considered as cells-of-origin (Figure 1). The involvement of different cells-of-origin could underlie CCA heterogeneity[27]. The most primitive cells, stem cells, are candidates for targets of transformation because of their self-renewal and longevity, which would allow the sequential accumulation of genetic or epigenetic mutations[27]. Two stem cell niches have been described within the liver: the Ca-

Table 1 Phenotype markers of candidate cholangiocarcinoma cells of origin

Marker	Mature cholangiocytes	hHpSCs in canals of Hering	BTSC in peribiliary glands
Nanog, OCT4	-	-	+
CXCR4	-	-	+
FoxA ½	-	-	+
PDX1, NGN3	-	-	+
AFP	-	+	+
Sox 9/17	-	+	+
Prominin-1 (CD133)	-	+	+
EpCAM	+/-	+	+
NCAM	-	+	+
Thy	-	+	+
CK7/19	+	+	+
Secretin Receptor	+	-	-
γGT	+	+/-	+/-

Comparison of the phenotype among mature cholangiocytes, hepatic stem cells (hHpSCs) in canals of hering and biliary tree stem/progenitor cells (BTSC) in peribiliary glands. Mature cholangiocytes do not express markers of stem/progenitor cells. A complete study of the phenotype of cholangiocarcinoma considering these markers would indicate the probable cell of origin. AFP: α-fetoprotein; CD133: Prominin; CK: Cytokeratin; CXCR4: CXC-chemokine receptor 4; EpCAM: Epithelial cell adhesion molecule; FOXa2: Forkhead box a2; γGT: γ-glutamiltranspeptidasi; NCAM: Neural cell adhesion molecule; NGN3: Neurogenin 3; OCT4: Octamer-binding transcription factor 4 also known as POU5F1 (POU domain, class 5, transcription factor 1); PDX1: Pancreatic and duodenal homeobox 1; SOX: Sry-related HMG box.

nals of Hering containing hHpSCs[13] and IH PBGs composed of BTSCs[14,15]. Nakanuma *et al*[18] recently proposed a new classification of CCA taking into consideration the heterogeneity of hepatic stem/progenitor cells and the pathological similarities between biliary and pancreatic neoplasms. The authors classified IH-CCA into: (1) bile ductular type or cholangiolocarcinoma (CLC); (2) intraductal neoplasm type; (3) conventional (bile duct) type and; and (4) rare variants[18]. CLC is thought to originate from canals of Hering/bile ductules where hHpSCs are located. Komuta *et al*[17,40] showed that this subtype of CCA is mainly composed of CLC areas showing small monotonous and/or anastomosing glands, strongly positive for K7 and K19, with tumor boundary being characterized by a HCC-like trabecular area and with some cases expressing CCA areas with scarce mucin production. A comparison between CLC with K19-positive HCC and with combined HCC-CCA indicated a high homology[17,40]. The clear origin of CCL from hHpSCs or immediate descendent cells deserves high attention and the accurate histological observation of transitional zones within the tumor and the phenotype characterization are strongly recommended for a proper diagnosis. Following the maturation arrest theory, one could speculate that CCL represents the result of a carcinogenetic process involving cells within the lineage derived from the hHpSCs and that the differentiation grade of the tumor reflects the grade of maturation of the cells primarily involved in the carcinogenesis process (Figure 1). In this view, the CCAs arising from the interlobular bile duct (small bile duct type CCAs) could be considered a tumor arising from differentiated cells belonging to the hHpSC-derived lineage (Figure 1). The evidence that IH-CCA and EH-CCA may be dissimilar tumors is supported by the recent discovery that, *in vitro*, they express diverse cellular proteins and have different cellular shape, doubling time, chromosome karyotype and chemosensitivity[41]. Similarly, researchers from France showed that hilar CCAs express higher levels of MUC5AC (60% *vs* 22%), Akt2 (64% *vs* 36%), K8 (98% *vs* 82%), annexin (56% *vs* 44%) and less vascular epithelial growth factor (VEGF) (22% *vs* 78%) as compared to IH-CCAs[42]. Moreover, prognostic markers were differentially expressed, as hilar CCAs carried out stronger perineural invasion (83% *vs* 42%) than peripheral CCAs[42]. The different biological and molecular features strongly support the concept that IH-CCA and EH-CCA arise from different carcinogenetic processes and different cells-of-origin. Particularly relevant in the view of future clinical trials is the lower expression of VEGF in EH-CCA with respect to the IH-CCA, which could affect the response to anti-angiogenic based therapy. Relevant advantages in the way to a physio-pathological classification of the CCAs have been recently achieved by Komuta *et al*[17], who carried out a study aiming to investigate the CCA histological diversity in relationship to the heterogeneity of cholangiocytes lining the biliary tree: hilar mucin producing cells *vs* peripheral cuboidal ductular cells or hHpSCs. They investigated the clinical-pathological and molecular features of 79 resected CCAs and their relationship with hHpSCs and compared the spectrum of CCAs with respect to K19-positive or negative HCCs. According to this study, 52% of the IH-CCAs were pure mucin producing, whereas 48% showed mixed differentiation features, including focal hepatocytic differentiation and CCL features. CCAs with mixed features (mixed-CCAs) showed peripheral location, larger tumor size, less microvascular invasion, less lymph node involvement compared to pure mucin producing CCAs which showed perihilar location, smaller tumor size, more microvascular invasion and more lymph node involvement. S100p expression was seen only in pure mucin-producing CCAs, while NCAM expression was only present in mixed-CCAs and particularly in CLC. Molecular profiling showed high homology between mixed-CCAs and K19-positive HCCs (considered of hHpSCs origin). The authors concluded that mixed-CCAs and K19-positive HCCs have a similar molecular profile as the most peripheral ductules containing hHpSCs, while mucin producing CCAs have a similar profile to mucin producing large IH and EH bile ducts, possibly reflecting the different cells-of-origin[17]. Differences in clinical-pathological features between CCAs arising from small (interlobular bile ducts) or medium-large IH bile ducts are under investigations. Responding to the need for classifying IH-CCA in relationship to the hetereogenity of the small *vs* the medium-large IH bile ducts, recently Nakanuma *et al*[18] proposed to separately consider a small bile duct type (peripheral type) and a large bile duct type (perihilar type). The former is mainly described as a tubular or micropapillary adenocarcinoma while the latter involves the IH large bile ducts. In accordance with phenotypic differences between interlobular and medium-large bile ducts, Aishima *et al*[43] investigated 87 cases of IH-CCA smaller than 5 cm in diameter. They considered a hilar type IH-CCA, showing IH large bile duct involvement within the tumor, and a peripherla type IH-CCA contained preserved architecture of the portal triad. They demonstrated that the frequency of perineural invasion, lymph node metastasis, vascular invasion, IH metastasis and EH recurrence of IH-CCA from large ducts was significantly higher than that of IH-CCA from small ducts[43]. The survival of patients with IH-CCA from large ducts was worse than that of patients with IH-CCA from small ducts[43]. In our hypothesis, the clinical-pathological differences observed among CCAs arising from small bile ducts and large bile ducts reflect the different lineage of origin, with the former arising from cells of the hHpSC-derived lineage and the latter arising from BTSC-derived lineage (Table 1, Figure 1). Also, the multiple lineages of origin could determine differences in signaling pathways or epigenetic mechanisms associated with the early phase of tumor development in the course of the hepatic and biliary diseases. By considering the process of maturation from the two different stem cell niches (canals of Hering and PBGs), one could expect that some IH-CCAs originate from cells within the lineage starting in the canals of

Hering (hHpSC-derived lineage), while other IH-CCAs and the EH-CCAs could originate from cells within the lineage starting in the PBGs (BTSC-derived lineage) of the medium-large IH and EH bile ducts (Figure 1). The former could be constituted, on the basis of the grade of maturation of the cell-of-origin (maturation arrest), by combined HCC-CCA, CCL and CCA of the small bile ducts (interlobular), while the latter by CCA of the large bile ducts with variable degree of mucin production (Figure 1).

RISK FACTOR AND ASSOCIATED PATHOLOGIES: HOW THEY FIT WITH THE RECENT CLASSIFICATION OF CCAS BASED ON CELLS OF ORIGIN

Actually, the role of hHpSC in normal turnover of hepatocyte and cholangiocyte is debated[44,45]. In contrast, numerous evidences indicate the activation of resident stem cell compartment in the majority of acute and chronic liver diseases. In chronic hepatic diseases, hHpSCs highly proliferate and give rise to newly derived EpCAM positive hepatocytes in correlation with hepatocyte senescence[46,47]. More recently, an additional stem cell niche has been identified in the PBGs[14,15]. PBGs are particularly high in density at the level of cystic duct, hilum and periampular region, sites where CCAs typically emerge[48]. Within PBGs, stem cell niche has been recently described which is composed by multipotent stem/progenitor cells of endodermal origin (BTSCs) and potentially supplies the renewal of the surface epithelium of large IH bile duct and EH biliary tree[14,15]. During pathological conditions of large bile ducts PBG cells proliferate potentially underlie the increased turnover of mature cells. The existence of two different stem cell niches, the canals of Hering and the PBGs, involved in the cell turnover of IH and EH biliary tree in adult life and activated in pathological conditions, has been recently put in relationship with CCA clinical-pathological heterogeneity as well as with differences in risk factors between IH- and EH-CCA[8,18,49]. We recently revised the literature dealing with risk factors and pathologies associated with IH- and EH-CCA[8]. It is clearly evident from the literature that there are pathologies exclusively associated with IH-CCA or EH-CCA and pathologies associated with both. Choledochal cysts, cholangitis/primary sclerosing cholangitis (PSC), secondary biliary cirrhosis, choledocholithiasis, cholecystitis and liver flukes are pathological conditions primarily affecting large intra-hepatic bile ducts and/or extra-hepatic bile ducts. In keeping, these pathological conditions are risk factors for both IH- and EH-CCA. Differently, parenchymal liver diseases, including chronic viral and non-viral liver diseases and schistosomiasis, exclusively target interlobular bile ducts, bile ductules and the canals of Hering and, consistently, these pathologies are exclusively associated with development of IH-CCA. These pathologies are characterized by a strong ductular reaction, a phenomenon involving interlobular bile ducts, bile ductules and canals of Hering, which is currently considered the morphological expression of the activation of the stem/progenitor cell compartment aimed to repair liver injury[50]. From the other side, pathologies of the large IH and EH bile ducts, such as liver flukes, cholangitis, PSC, choledochal cysts, secondary biliary cirrhosis, choledocholithiasis, hepatholithiasis and cholecystitis, are characterized by the involvement of PBGs where cells proliferate and acquire the expression of stem cells and neuroendocrine markers (C-met, c-erbB-2, argirophil granules, chromogranin A)[51-54]. On the basis of these recent observations, we hypothesize that early cells within PBGs are the sites of origin of malignancies associated with chronic diseases or pathological conditions of the IH medium-large and EH bile ducts[8]. Differently, parenchymal liver diseases, including chronic viral and non-viral liver diseases and especially the liver cirrhosis, could be recognized as the associated diseases of the CCAs arising from the hHpSC derived lineage[8]. In complete agreement with this hypothesis, it has been recently demonstrated that viral hepatitis is associated with IH-CCA with cholangiolocellular differentiation and N-cadherin expression[55]. We strongly believe that a lineage based classification of the CCAs could reveal the real strength of association of determined hepatic or biliary diseases with each class of CCA or resolve the bias of the spurious associations. Further studies are needed to corroborate these hypotheses which could explain the large different epidemiological profile of IH- and EH-CCA[8,49].

NEW INSIGHTS INTO LIVER STEM CELLS ORGANIZATION AND CCA DEVELOPMENT

Although the role of hHpSC in normal turnover of hepatocyte and cholangiocyte is still debated[44,45], the role of the stem cells during hepatic and biliary development has been recently better elucidated. Specifically, it was shown that interlobular bile ducts, during the early phase of embryological development, derive from the differentiation of hepatoblasts located closely to the forming portal tract (ductal plate) and is driven by the expression of SOX9[25]. Recently, Carpentier *et al*[44] came to the innovative result that the cells of the canals of Hering would be in direct communication and hierarchically derived from cells originating from the ductal plate. Ductal plate derived lineage should supply the epithelium of the inter- and intralobular bile ducts and passing through the canals of Hering should give rise to the periportal hepatocytes. In this way, the development of the biliary tree and liver should proceed from the hilum to the periphery. Large IH bile ducts and EH bile ducts are very similar in terms of histology, cell phenotype and share common stem cells constituted by the BTSCs of the PBGs[14,15]. This is in keeping with their common embryological origin from a pancreatic-biliary progenitor [SOX17+/pancreatic and

duodenal homeobox 1(PDX1)+], representing the result of the organization of the proliferation of the primitive endoderm at the *porta hepatis*. Recently, we demonstrated that remnants of these multipotent stem cells deriving from ventral endoderm are still present in the adult biliary tree, especially within PBGs[14,15]. The phenotype of the cells lining the large IH and the EH bile ducts or the PBGs in adult and fetal life[15] and the recent insights supporting the hilum-to-periphery development of the biliary tree[25,44], suggest that cells of the forming large IH bile ducts and EH bile ducts are precursors of the ductal plate cells in the fetal life. The new insights into liver stem cells niches organization further complicate the picture in relationship to the clinical-pathological classification of the primary liver cancers. Indeed, according to the innovative explanation of the liver organogenesis, the classical organization of the hepatic parenchyma stem cell niche, the canals of Hering, and the cell differentiation hierarchy within, are under debate. On the basis of these recent advances and analyzing the phenotype of the hHpSCs and of BTSCs (Table 1), an emerging hypothesis is that the BTSCs are precursors of the hHpSCs. This new scenario opens further perspectives in CCA classification. Indeed, based on this concept, the CCAs arising from the BTSC-derived lineage should be composed of tumor cells with earlier and endodermal-like phenotype with respect to hHpSC-derived CCAs. In this view, the anatomical localization of the CCAs, other than reflecting a different cell-of-origin, could be associated with different prognostic CCA classes. Indeed, it has been already demonstrated by different groups how the EH-CCAs (mostly hilar CCAs)[17,42] and the IH-CCAs involving the large IH bile ducts are associated with the worst prognostic markers in comparison to the peripheral IH-CCAs involving the small bile ducts[17,42,43]. However, very recently, Andersen *et al*[56] showed that discrete homogenous molecular profiles of both hilar and peripheral-type CCAs were associated with different prognostic classes, suggesting that a similar molecular pathogenesis rather than the anatomical location defines the overall prognosis. However, IH-CCA could arise either from interlobular bile ducts/canals of Hering or from large IH bile ducts (segmental and septal), thus recognizing different cells-of-origin. Some of these cells-of-origin, the ones belonging to the BTSC-derived lineage, are the same for IH- and EH-CCA, while others, the ones derived from the hHpSCs, are specific for the IH-CCA (Figure 1). In our opinion, the different cells-of-origin potentially underlying the development of different IH-CCA subtypes should be taken into adequate consideration in defining prognostic classes of CCA (Figure 1). A gross classification based only on the anatomical localization and that considers all the IH-CCAs as a homogenous entity, does not reflect the complex biology of this cancer and could result in biases and criticisms.

CONCLUSION

The new scenario created by recent advances on liver stem cells suggests a physio-pathological classification of CCAs based on the cell-lineage-of-origin. Following the process of maturation from the two different stem cell niches, one could hypothesize that some IH-CCAs originate from cells within the hHpSC-derived lineage starting in the canals of Hering, while other IH-CCAs and the EH-CCAs could originate from the BTSC-derived lineage within the medium-large IH and EH bile ducts. The former could be classified on the basis of the grade of maturation of the cell-of-origin, in: (1) combined HCC-CCA (hHpSCs); (2) CCL or ductular type CCA (immature cholangiocytes); and (3) CCA of the small bile ducts or mixed-CCA (mature cholangiocytes of the interlobular bile ducts) (Figure 1). The latter could be classified in mucin-producing CCA of large bile ducts recognizing as cells-of-origin the ones within the BTSC-derived lineages (i.e., BTSCs in PBGs, cholangiocytes of large IH and EH bile ducts and goblet cells) (Figure 1). These observations are also supported by the similarities between the neoplastic pathologies of biliary tract and pancreas[57]. Indeed, most biliary and pancreatic neoplasias are of ductal lineage, characterized by tubule (gland), papillary structure formation and different degree of mucin production and expression of mucin-related glycoproteins[57]. Classification of CCAs based on cells-of-origin needs definitive cells markers able to distinguish the CCA subtypes and thus it remains a challenge for future studies[58]. Meanwhile, however, it can be noted that the available diagnostic tools (imaging, clinical, histology) can suggest the presumptive cell-lineage-of-origin of the single CCA. Indeed, CCAs of the small bile ducts or mixed-CCAs, the hHpSC-lineage derived CCAs, usually show a peripheral localization and a mass forming growing pattern, while IH-CCAs of the large bile ducts, the BTSC-lineage derived CCAs, usually show a peri-ductal infiltrating and/or mass forming growth pattern and are hilar or peri-hilar and usually associated with IH bile duct dilatation and jaundice. From a histological point of view, CCAs of the small bile ducts or mixed-CCAs showed mixed differentiation features, including focal hepatocytic differentiation, ductular features and NCAM expression, while differently IH-CCAs of the large bile ducts are characterized by the involvement within the tumor of large bile ducts and of PBGs, mucin production and S100p expression. Taking into consideration this tentative of classsification, risk factors and underlying pathologies associated with CCA development should be regarded in a new light. Parenchymal liver diseases, including chronic viral and non-viral liver diseases and liver cirrhosis, should be considered as risk factors for development of mixed-CCAs arising from the hHpSC-derived lineage, activated and expanded in the course of these pathologies. In contrast, chronic biliary diseases or pathologies and conditions affecting the IH medium-large and EH bile ducts are risk factors for CCAs of the large bile ducts since in these pathologies, stem cell niches located in the PBGs are activated. A physio-pathological classification of the CCAs according the cell-lineages-of-origin could have, in the

future, important clinical implications with the definition of different prognostic classes or specific therapeutic targets. Given the differences in biology and clinical-pathology[59], IH-CCA with mixed features (mixed-CCAs or small bile ducts type) and mucin producing IH-CCA (large bile ducts type) should be considered separately (Figure 1).

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BRIEF ARTICLE

Relationship between HER-2 overexpression and brain metastasis in esophageal cancer patients

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Abstract

AIM: To study if HER-2 overexpression by locally advanced esophageal cancers increase the chance of brain metastasis following esophagectomy.

METHODS: We retrospectively reviewed the medical records of esophageal cancer patients who underwent esophagectomy at University of Iowa Hospitals and Clinics between 2000 and 2010. Data analyzed consisted of demographic and clinical variables. The brain metastasis tissue was assayed for HER-2 overexpression utilizing the FDA approved DAKO Hercept Test®.

RESULTS: One hundred and forty two patients were reviewed. Median age was 64 years (36-86 years). Eighty eight patients (62%) received neoadjuvant chemoradiotherapy. Pathological complete and partial responses were achieved in 17 (19%) and 71 (81%) patients. Cancer relapsed in 43/142 (30%) patients. The brain was the first site of relapse in 9/43 patients (21%, 95% CI: 10%-36%). HER-2 immunohistochemistry testing of the brain metastasis tissue showed that 5/9 (56%) cases overexpressed HER-2 (3+ staining).

CONCLUSION: HER-2 overexpression might be associated with increased risk of brain metastasis in esophageal cancer patients following esophagectomy. Further studies will be required to validate this observation.

Key words: Esophageal neoplasm; Esophageal cancer; HER-2; Genes, erbB-2; Brain Neoplasms; Brain metastasis

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INTRODUCTION

Brain metastasis from locally advanced esophageal cancer as the first site of disease relapse following multimodality treatment that includes chemotherapy, radiation therapy and esophagectomy is rare[1,2]. The incidence rate of brain metastasis, thought to be around 1%-5%, is derived from case series and autopsy reports[3,4]. Although the treatment goal of locally advanced esophageal cancer is to cure the disease, there is a high rate of disease relapse, whether locally or as distant metastasis, with the majority of relapses occurring in the liver, abdomen, lungs and bone[1]. Urba *et al*[5], showed that 65% of patients treated with concurrent chemotherapy and radiation therapy then esophagectomy had distant metastases rather than local recurrence upon relapse.

Multiple clinical and pathological features have been identified as prognostic factors in patients who receive concurrent chemoradiotherapy and esophagectomy. Factors including pathological complete response (pCR) to neoadjuvant treatment[6,7], lower tumor grade and stage[8,9], and smaller tumor length[10] are associated with favorable outcomes. Other trials showed that larger tumors and perioperative chemotherapy or radiation therapy might be associated with a higher risk of subsequent brain metastases[11,12]. In breast cancer, other risk factors such as over expression of HER-2, a membrane bound tyrosine kinase, were shown to predispose to brain metastasis (hazard ratio: 4.23, $P = 0.0007$)[13,14].

HER-2 is over expressed in approximately 25% of esophageal cancers[15,16] and is associated with a worse prognosis[17]. HER-2 receptor status became more clinically relevant after the ToGA trial showed that targeting HER-2 positive gastric and gastroesophageal junction tumors with Trastuzumab (Herceptin), a recombinant humanized monoclonal antibody that inhibits HER-2 receptor, combined with chemotherapy improved survival in patients with metastatic disease[18]. To our knowledge, there has been no correlation identified between esophageal cancer HER-2 receptor positivity and risk of brain metastasis.

MATERIALS AND METHODS

A request to review the electronic medical records of esophageal cancer patients who underwent esophagectomy at University of Iowa Hospitals and Clinics was submitted to the Institutional Review Board (IRB) and approved (IRB identification number: 201012764). The requirement for consent was waived by the IRB. We identified the patients who had esophagectomy for esophageal cancer through the pathology department database. A total of 142 electronic medical charts of patients with locally advanced esophageal cancer who underwent esophagectomy at UIHC between January 2000 and September 2010 were reviewed. Patients characteristics collected include age, sex, smoking history, esophagectomy date, cancer stage, location in the esophagus, histology and grade, administration and response to neoadjuvant chemotherapy and radiation therapy, resection margins status, number of total and positive lymph nodes removed, cancer relapse, date and location of relapse and survival data. HER-2 overexpression was assayed on the brain metastasis tissue utilizing the FDA approved DAKO Hercept Test® with exact following of the technique as outlined in the product insert. Semi-quantitative interpretation was done in accordance with the parameters outlined for gastro-intestinal malignancies in the ToGA trial[18].

Statistical analysis

Kaplan-Meier curves were constructed for overall survival. To compare survival distributions for the patients who had complete or partial tumor response to neoadjuvant treatment, a log-rank test was used. Statistical analyses were performed using SAS (version 9.2).

RESULTS

Demographics and clinical data are presented in Table 1. Median age at diagnosis was 64 years (36-86 years). There were 124 males (87%) and 18 females (13%). The number of patients who smoked more than 10 pack-years was 87 (61.3%). There were 118 (83%) adenocarcinomas, 22 (15.5%) squamous cell carcinomas, 1 (0.7 %) small cell carcinoma and 1 (0.7 %) gastrointestinal stromal tumor. Regarding staging, 47/142 (33%) patients had stage T3N1M0 (AJCC 6th edition). The frequency of T classification was: T1: 18 (12.7%), T2: 19 (13.4%), T3: 76 (53.5%), T4: 2 (1.4%). The frequency of nodal classification was: N0: 49 (34.5%), N1: 65 (45.8 %), N2: 3 (2.1%). Neoadjuvant chemoradiotherapy was delivered for 88 patients (62%). Out of those, 17 (19 %) patients had pCR and 71 (81%) patients had pathological partial response (pPR).

Regarding survival, 65/142 patients (45%) were deceased at the time of analysis. Overall survival for all patients is shown in Figure 1. Of the patients who reached pCR following neoadjuvant chemotherapy and radiation therapy, 58% were alive at 36 mo (median survival not

Table 1 Characteristics of esophageal cancer patients who underwent esophagectomy

Characteristics	*n* (%)
Age on diagnosis of esophageal cancer (yr)	
Median	64
Range	36-86
Sex	
Male	124 (87.3)
Female	18 (12.7)
Smoking	
< 100 cigs/life	33 (23.2)
< 10 pack-year	9 (6.3)
> 10 pack-year	87 (61.3)
Unknown	13 (9.2)
Esophageal cancer type (path report)	
Adenocarcinoma	118 (83.1)
Squamous cell carcinoma	22 (15.5)
Small cell carcinoma	1 (0.7)
GIST	1 (0.7)
T classification	
T1	18 (12.7)
T2	19 (13.4)
T3	76 (53.5)
T4	2 (1.4)
Unknown	27 (19)
N classification	
N0	49 (34.5)
N1	65 (45.8)
N2	3 (2.1)
Unknown	25 (17.6)
Neoadjuvant treatment	
Neoadjuvant treatment	88 (62)
No neoadjuvant treatment	52 (36.6)
Unknown	2 (1.4)
Response to neoadjuvant treatment	
No residual tumor (complete response)	17 (12)
Residual tumor present (partial response)	71 (50)
No neoadjuvant treatment	52 (36.6)
Unknown	2 (1.4)
Tumor grade	
Well differentiated	4 (2.8)
Moderately differentiated	67 (47.2)
Poorly differentiated	61 (43)
Unknown	10 (7)
Disease relapse	
Yes	43 (30.3)
No	91 (64.1)
Unknown	8 (5.6)

GIST: Gastrointestinal stromal tumor.

Table 2 First site of esophageal cancer relapse following esophagectomy

Relapse site	*n* (%)
Brain	9 (21)
Peritoneum	3 (7)
Esophageal remnants, paraesophageal lymph nodes or mediastinum (locoregional relapse)	13 (30)
Lungs	8 (19)
Liver	6 (14)
Bone	4 (9)

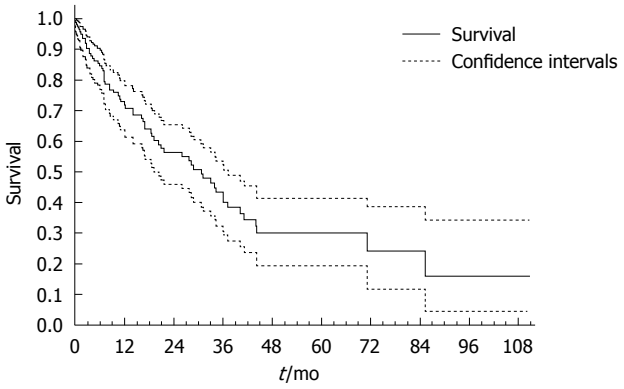

Figure 1 Overall survival for all patients.

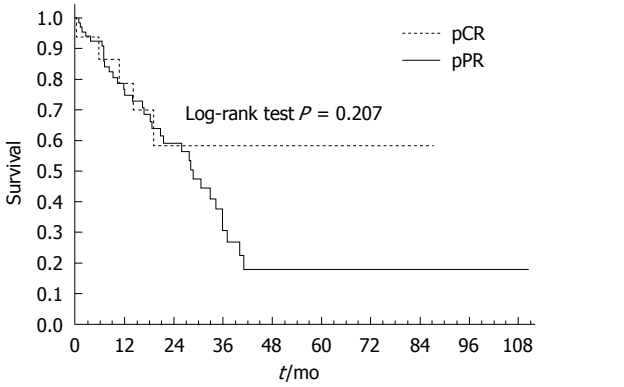

Figure 2 Overall survival for the patients who had pathological complete response or partial response. pCR: Pathological complete response; pPR: Pathological partial response.

reached). Median survival for the pPR patients was 28.8 mo (95% CI: 18.7-36.0). Although Figure 2 shows a survival difference for the patients who had pCR and pPR, this was not statistically significant ($P = 0.207$).

The total number of identified relapses was 43/142 (30.3%). Median follow up time was 11.8 mo (< 1-110 mo). Initial relapses occurred in the residual esophagus, para esophageal lymph nodes, mediastinum, liver, peritoneum, lungs, bone or brain. Frequencies of relapses at various sites are summarized in Table 2. There were 9/43 (21%) relapses in the brain (95% CI: 10%-36%) with the following characteristics: cancer stage T3N1M0 (7/9), neoadjuvant chemotherapy and radiation therapy (7/9), pCR (1/9), adenocarcinoma (7/9), squamous cell carcinoma (2/9).

HER-2 immunohistochemistry staining of the brain metastasis specimens showed that 5/9 specimens (56%) overexpressed HER-2 (3+ staining). The rest of the specimens (4/9) did not stain for HER-2 (0 staining). Figure 3 shows brain metastasis specimens with 3+ and 0 staining.

Treatment of brain relapses included surgical resection (2 patients), stereotactic radiosurgery (SRS) (1 patient), surgical resection followed by SRS to the tumor bed (3 patients), and whole brain radiation (3 patients). Survival following diagnosis of brain relapse ranged from < 1-22 mo. Two patients who had brain surgery and SRS lived longer than others (18 and 22 mo).

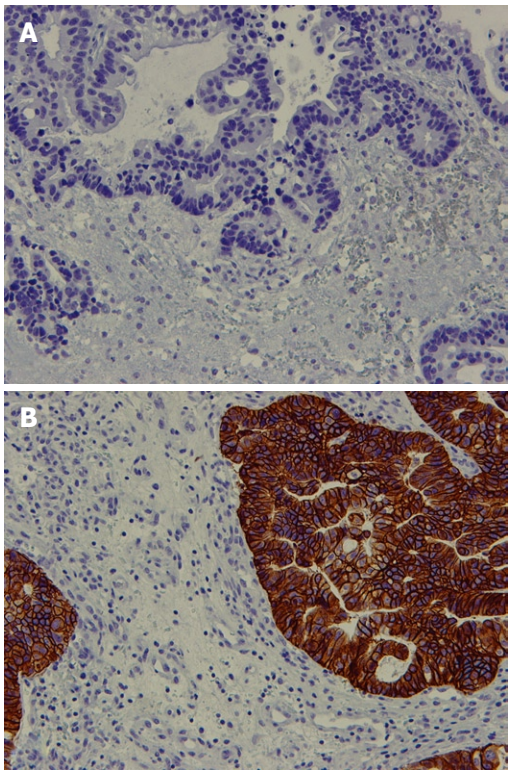

Figure 3 Brain metastasis staining for HER-2. A: 0 HER-2 staining; B: 3+ HER-2 staining.

DISCUSSION

Esophageal cancer is potentially a curable disease if diagnosed at an early stage but fatal when widely metastatic. The current standard of care of locally advanced esophageal cancer includes neoadjuvant concurrent chemotherapy and radiation therapy followed by esophagectomy[19,20]. Although significant advances have been made in achieving better quality of life and survival outcomes, it is estimated that only around 20% of the patients with local disease are alive 5 years following diagnosis[21,22].

Brain metastasis as the first site of disease relapse after esophagectomy for esophageal cancer is uncommon[3,4]. However, our study showed a higher frequency of brain relapses in locally advanced esophageal cancer patients who underwent esophagectomy compared to historical figures[1]. Recognizing the increased risk of brain metastasis in HER-2 positive breast cancer patients[13,14] and the known overexpression of HER-2 in esophageal cancers[23,24], we explored HER-2 expression status in the brain metastasis tissues obtained from esophageal cancer patients who underwent esophagectomy and relapsed in the brain. HER-2 was strongly positive in 56% of the cases which probably implies that HER-2 positivity in esophageal cancer predisposes to brain metastasis. Interestingly, in a phase Ⅰ/Ⅱ trial by Safran *et al*[25] testing Trastuzumab in HER-2 positive esophageal cancer patients, 3 out of the 10 relapses that occurred were in the central nervous systems (CNS).

Treatment of CNS metastasis, regardless of the primary cancer type, often includes surgery, radiation therapy or chemotherapy. Although surgical resection or SRS of a limited number of brain metastasis resulted in survival benefit in various cancers including esophageal cancer[26-28], chemotherapy treatment of CNS metastasis has been limited, primarily due to the blood brain barrier in addition to other factors[29,30]. Nevertheless, there have been recent advances in the chemotherapeutic management of CNS metastasis, whether parenchymal or leptomeningeal. Whereas Trastuzumab is known to be an effective treatment of metastatic HER-2 positive breast cancers, its CSF levels were reported to be low when administered intravenously[31]. Alternatively, intrathecal Trastuzumab showed encouraging results treating HER-2 positive breast cancer leptomeningeal metastasis[32,33]. Lapatinib, an oral HER-2 tyrosine kinase inhibitor that crosses the blood brain barrier, combined with Capecitabine resulted in partial and complete responses of brain metastasis from HER-2 positive breast cancers[34-37].

In summary, we noticed a high incidence of brain metastasis as the first site of cancer relapse in our series of locally advanced esophageal cancer patients who underwent esophagectomy. Additionally, we observed that HER-2 overexpression might be associated with increased risk of brain metastasis. The benefits of screening brain imaging in a selected population of HER-2 positive esophageal cancer patients before going through a major surgery such as esophagectomy and utilizing HER-2 directed therapy in case of brain relapse in that same subpopulation are potential considerations that deserve further exploration in future studies. Acknowledging the limitations of a retrospective study and the small sample size, our observations need to be replicated in a larger cohort.

COMMENTS

Background

The incidence of locoregional and advanced stage esophageal and gastro-esophageal junction adenocarcinoma is rising in the western world. In spite of the treatment advances, recurrence rate of the locoregional disease is still high. Recently, there has been mounting evidence that the incidence of esophageal cancer relapse into the brain is rising, but no definite etiology has been identified so far to explain this observation.

Research frontiers

HER-2 is a membrane tyrosine kinase that is over expressed in various cancers, including esophageal, breast and other cancers. It is well established that there is an association between HER-2 over expression and brain metastasis in breast cancer, but this correlation was not explored in esophageal cancer. In this study, the authors demonstrate that HER-2 over expressing locally advanced esophageal cancer patients might be prone to a higher incidence of brain relapse.

Innovations and breakthroughs

To our knowledge, this is the first study to suggest an association between esophageal cancer HER-2 status and the risk of brain metastasis. This finding is scientifically plausible given what we know about breast HER-2 over expression and brain metastasis. The test the authors used to examine the esophageal cancer HER-2 status (immunohistochemistry) is currently a standard and commonly used test in esophageal cancers as it has therapeutic implications. This broad application of HER-2 testing will definitely lead to identifying more patients who over express HER-2. Consequently, more robust studies with a larger sample size will be feasible to test the association between HER-2 over expression and brain relapse.

Applications

If subsequent larger studies support our observation of increasing risk of brain relapse from HER-2 overexpressing esophageal cancer, this will have various important implications. This subset of patients might benefit from screening brain imaging to rule our brain metastasis. This might decrease the number of futile esophagectomies which will be avoided if the patient is found to have brain metastasis before surgery. Additionally, there might be a role for biological agents, such as Trastuzumab or Lapatinib in the treatment of brain relapse from HER-2 overexpressing esophageal cancers.

Terminology

HER-2 is a membrane tyrosine kinase involved in signal transduction pathways that regulate cellular proliferation. Overexpression of HER-2 was identified in various cancers, such as esophageal, gastric and breast cancers. It correlates with an aggressive disease and worse prognosis in breast cancer. Antibodies that target HER-2, such as Trastuzumab, are available for clinical use and commonly utilized in breast cancer. Trastuzumab was also found to prolong survival in advanced stage gastric and gastroesophageal cancers when administered with cytotoxic chemotherapies.

Peer review

This paper presents an interesting topic about the relationship between HER-2 OVER expression and brain metastasis in esophageal cancer patients.

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BRIEF ARTICLE

Analysis of liver metastasis after resection for pancreatic ductal adenocarcinoma

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Abstract

AIM: To investigate the risk factors affecting the liver metastasis (LM) of pancreatic ductal adenocarcinoma (PDAC) after resection.

METHODS: We retrospectively analyzed 101 PDAC patients who underwent surgical resection at the Samsung Medical Center between January 2000 and December 2004. Forty one patients with LM were analyzed for the time of metastasis, prognostic factors affecting LM, and survival.

RESULTS: LM was found in 40.6%. The median time of the LM (n = 41) was 6.0 ± 4.6 mo and most LM occurred within 1 year. In univariate analysis, tumor size, preoperative carbohydrate antigen 19-9, and perineural invasion were factors affecting LM after resection. In multivariate analysis, tumor size was the most important factor for LM. In univariate analysis, tumor cell differentiation was significant to LM in low-risk groups.

CONCLUSION: LM after resection of PDAC occurs early and shows poor survival. Tumor size is the key indicator for LM after resection.

Key words: Pancreatic ductal adenocarcinoma; Liver metastasis; Recurrence

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INTRODUCTION

Pancreatic cancer is the fourth leading cause of death from cancer in the United States, 2006 and the fifth in South Korea[1,2]. Anatomical features including retroperitoneal location with proximity to the portal vein, celiac trunk, and superior mesenteric artery are associated with aggressive behavior of pancreatic ductal adenocarcinoma (PDAC). In many cases, patients present with PDAC which is already at an advanced stage at the time of diagnosis and unresectable. Pancreatectomy offers the only chance for long-term survival and is the single most important factor affecting patient outcome[3,4]. Even after curative radical surgery, the recurrence rate of PDAC is very high and high-volume centers report 5-year survival rates of only 10%-20%[3,5-7]. Postoperative adjuvant therapy, with the purpose of reducing hepatic metastasis and local recurrence, can influence survival gain[5]. Post-operative recurrence is categorized mainly by liver metastasis (LM),

peripancreatic or retroperitoneal recurrence, peritoneal seeding, and distant other organ metastasis. In this study, we analyzed LM after resection for PDAC.

MATERIALS AND METHODS

Between January 2000 and December 2004, 106 patients with PDAC underwent pancreatic resection with curative intent in the Department of Surgery, Samsung Medical Center, Seoul. Excluding for five patients who dropped out, 101 patients were enrolled. The clinical features 41 patients with LM and 60 patients without LM were compared. The average age was 58.6 years (range, 31-79 years) and the median follow-up period was 15.5 ± 17.4 mo (range, 3.3-81.4 mo). Before surgery, we evaluated the radiological tumor status using abdominal computed tomography (CT) with or without magnetic resonance imaging, but we did not performed positron emission tomography scans routinely.

Patients with cancer in the head, neck and uncinate process of the pancreas underwent pancraticoduodenectomy or pylorus-preserving pancreaticoduodenectomy (n = 70), and patients with cancer in the body or tail underwent distal pancreatectomy (n = 19). Total pancreatectomy was performed in twelve patients with severe pancreatitis combined with cancer or with tumors extending beyond the neck of the pancreas, delineated by the left border of the superior mesenteric vessels and into the body of the gland. Peripancreatic lymph nodes, hepatoduodenal nodes as well as the celiac axis and superior mesenteric lymph nodes were cleared in patients with head, neck and uncinate process cancer while aortocaval nodes were dissected in cases of enlargement. Follow-up study included routine laboratory tests, serum carbohydrate antigen 19-9 (CA 19-9), and abdominal CT in first month after surgery and every 3 mo thereafter. The time of recurrence or metastasis was defined initial occurrence time in CT and the site of recurrence or metastasis was defined from CT findings. We categorized the type of recurrence into LM, locoregional recurrence defined as a tumor confined at retroperitoneal margin and lymph nodes. Peritoneal dissemination and distant metastasis were also categorized. Tumor stage was defined according to the American Joint Cancer Committee (AJCC) criteria. Medical records were retrospectively reviewed to investigate radiological findings, pathological findings with T stage, tumor differentiation, lymph node or perineural invasion.

There was a lack of consensus on the indications and effectiveness of adjuvant therapy for resected PDAC, and a standard chemoradiation protocol has not been developed at our institute. The decision on whether adjuvant therapy was undertaken was made giving consideration to the age, compliance, economic status, and social activity of the patient. However, the majority of patients received adjuvant therapy protocols that consisted of 4000 to 5000 cGy of external beam radiation and gemcitabine or capecitabine based chemotherapy[6]. In this study, forty patients underwent concurrent chemoradiation therapy and ten patients underwent the alternatives of chemotherapy or radiation. For evaluating the clinical, pathological characteristics and survival with LM group, the patients were divided into two groups based on the occurrence of LM. Chi-square and Fisher exact tests were used for comparisons among the categorical variables. Survival analysis was performed using the Kaplan-Meier method. Univariate differences in survival among the subgroups were compared using the log-rank test. $P < 0.05$ was considered significant. SPSS 12.0 for Windows was used for all statistical analysis.

Table 1 Recurrence patterns of patients with liver metastasis (n = 41)

Recurrence patterns	n (%)
Liver metastasis only	28 (68.3)
Mixed	13 (31.7)
+ locoregional	6 (14.6)
+ peritoneal seeding	4 (9.8)
+ locoregional + peritoneal seeding	1 (2.4)
+ locoregional + seeding + lung[1] + bone[2]	1 (2.4)
+ lung[1]	1 (2.4)

[1]Lung = lung metastasis; [2]Bone = bone metastasis.

RESULTS

Analysis for patients with metastasis

Forty-one patients with LM comprised 28 solely with LM, and 13 patients who had additional metastases: retroperitoneal node and soft tissue metastases or peritoneal dissemination or lung or bone metastases (Table 1). Among 60 without LM, 40 patients showed various types of metastasis with locoregional recurrence, peritoneal dissemination, lung and bone metastasis, while 20 showed no evidence of recurrence or metastasis.

Timing of LM

The timing of LM after pancreatectomy was as follows; within 2 mo - 2 patients (4.9%), between 3 and 4 mo - 12 patients (29.3%), between 5 and 6 mo - 11 patients (26.8%), between 7 and 12 mo - 14 patients (34.1%), beyond 1 year - two patients had metastasis. LM occurred within 6 mo LM in 60.9 % of patients and within 1 year in 95.1% (39 patients). The median LM time was 6.0 ± 4.6 mo (Figure 1).

Factors affecting LM after pancreatic resection

Analysis using the *via* χ^2 test indicated that preoperative high level of CA 19-9, tumor size above 3cm, and perineural invasion of the tumor were significant clinical and pathological factors favouring LM in univariate analysis. Tumor location, cell differentiation, pancreatic resection margin involvement of the tumor, T stage (AJCC 6th), and lymph node involvement were not significant. Post operative adjuvant therapy including radiation did not

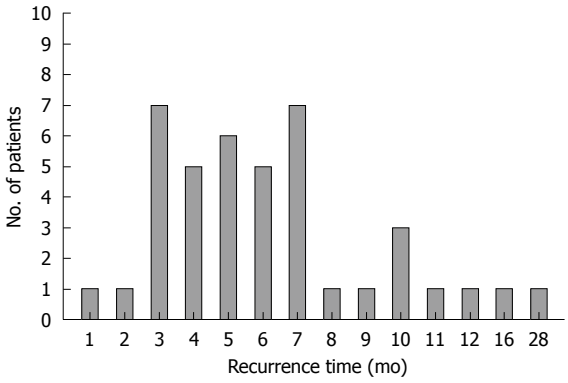

Figure 1 Time of liver metastasis in resected pancreatic ductal adenocarcinoma. The median time of the llive metastasis (n = 41) was 6.0 ± 4.6 mo. Almost liver metastasis occurred within 1 year.

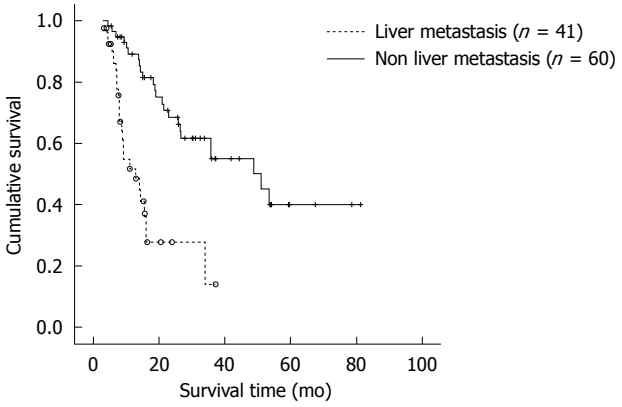

Figure 2 Comparison of overall survival according to liver metastasis. In patients without liver metastasis (n = 60), overall survival is better than those with liver metastasis (n = 41) (P < 0.001).

influence LM (Table 2). In multivariate analysis, preoperative CA 19-9 and tumor size were significant, but perineural invasion was not significant (Table 3).

Survival of patients with LM

The survival of 41 patients with LM and 60 without LM were compared. The median survival time with LM patients was 12.9 ± 3.2 mo, and the cumulative 1- and 3-year survival rates were 51.7% and 13.8%, respectively. In patients without LM, the median survival time was 48.8 ± 9.8 mo, the cumulative 1-, 3-, 5-year survival rates were 89.1%, 55.0% and 40.0% (P < 0.001) (Figure 2).

Pattern of LM with low risk patients

We investigated 22 patients with the low risk of LM (tumor size < 3 cm, preoperative normal CA 19-9 level); four patients with LM and eighteen without LM. Comparing clinical and pathological factors, univariate analysis indicated that poorly differentiated pancreatic tumors were more common in the LM group (Table 4).

DISCUSSION

Until recently, few clinical studies had been conducted on

Table 2 Factors influencing liver metastasis after pancreatectomy for pancreatic ductal adenocarcinoma

	Liver metastasis (n = 41)	Non-liver metastasis (n = 60)	P-value
Location			
Head	30	52	0.09
Body and tail	11	8	
Size (cm)			
< 3	23	45	0.04
⩾ 3	18	15	
Differentiation			
Well, moderate	29	49	0.08
Poor	12	11	
Perineural invasion			
Yes	28	30	0.04
No	13	30	
T-stage (AJCC, 6th)			
1-2	1	5	0.21
3-4	40	55	
N-stage			
N0	23	24	0.13
N1	18	36	
Resection margin			
Positive	3	6	0.46
Negative	38	54	
CA 19-9 (IU/mL)			
< 37	4	20	0.001
⩾ 37	28	20	
Adjuvant CTx			
Yes	14	26	0.41
No	27	34	
Adjuvant RTx			
Yes	16	29	0.32
No	25	31	

CTx: Chemotherapy; RTx: Radiotherapy; AJCC: American Joint Cancer Committee; CA 19-9: Carbohydrate antigen 19-9.

Table 3 Factors influencing liver metastasis after pancreatectomy for pancreatic ductal adenocarcinoma: multivariate analysis

	95% CI for Exp (B)			
	P-value	Odds ratio	Lower	Upper
Size (> 3 cm)	0.046	1.416	0.176	0.986
CA 19-9	0.013	0.204	0.058	0.713
Perineural invasion	0.059	2.228	0.969	5.123

CA 19-9: Carbohydrate antigen 19-9.

the recurrence of PDAC after pancreatic resection. The infrequency of study is influenced by the higher rate of recurrence and poorer survival rate after curative resection compared with another gastrointestinal cancers, and by the limited evidence of survival improvement after adjuvant treatment for PDAC. Surgical resection for PDAC is a unique treatment modality which is expected to curative. The investigation of surgical resection and research into adjuvant therapy are essential to achieve improvement in survival. For this reason, the evaluation of recurrence and metastasis of PDAC after resection is important.

Sperti *et al*[8] reported 89% patients with PDAC recur-

Table 4 Factors influencing liver metastasis after pancreatectomy for pancreatic ductal adenocarcinoma in patients without risk factors for liver metastasis

	Liver metastasis (n = 4)	Non-liver metastasis (n = 18)	P-value
Location			
Head	3	15	0.49
Body and tail	1	3	
Size (cm)			
< 2	3	6	0.19
⩾ 2	1	12	
Differentiation			
Clear, moderate	0	14	0.01
Poor	4	4	
Perineural invasion			
Yes	2	13	0.38
No	2	5	
T-stage (AJCC, 6th)			
1-2	0	2	0.23
3-4	4	16	
N-stage			
N0	4	11	0.19
N1	0	7	
Resection margin			
Positive	0	0	NA
Negative	4	18	

NA: Not available; AJCC: American Joint Cancer Committee.

rence after surgical resection. Local recurrence was 72%, and hepatic metastasis was 62%, over 22 years of study. Nitecki *et al*[9] reported 25% local recurrence and 37.5% hepatic metastasis. In a Korean study of PDAC recurrence in a single institute[10], 69% of recurrences occurred during the 12 mo after surgical resection. A 74.4% local recurrence included 51.2% of hepatic metastasis, while independent local recurrence and hepatic metastasis were 41% and 18.6%, respectively. In our investigation, over 16 mo of median follow up, 34.6% local recurrence and 34.6% independent LM occurred. Total LM occurred in 51 patients (50.6%). The recurrence mostly consisted of local recurrence and LM, with similar distribution of both recurrence patterns. Mixed LM with another type of recurrence pattern was dominant over independent LM. Several studies[11-13] have revealed that the prognosis in those with local recurrence is superior to those with distant metastasis including LM. Shibata *et al*[14] reported that mean survival time and actuarial 5-year disease-specific survival were significantly lower in cases of hepatic metastasis (13 mo, 0%) than in cases of local retroperitoneal recurrence (30 mo, 21%). In our report, the median survival time of 41 patients with hepatic metastasis was 12.9 mo and compared with 26.4 mo for patients without hepatic metastasis. These results are similar to those of a previous Japanese study. In particular, hepatic metastasis occur early after surgical resection and appear to have very poor prognosis. Sperti *et al*[8] reported that the median survival time with independent hepatic metastasis was 9 mo and with combined hepatic metastasis and local recurrence was no more than 6 mo.

Another report[11] showed that the median survival time of patients with hepatic metastasis was 6 mo and when hepatic metastasis in combined with local recurrence only 4 mo, Various investigations have shown few patients with over 1 year survival. Poor survival and prognoisis were influenced by very early recurrence within a year despite radical resection for PDAC[15,16].

In particular, Hishinuma *et al*[17] demonstrated that local recurrence occurs frequently, but is rarely a direct cause of death, and most patients died of metastatic disease according to 27 patients autopsies. Our series revealed that 60.9% of LM occur within 6 mo, and 95.1% LM within a year. It is not too much to say that LM of PDAC will almost certainly arise within a year.

Amikura suggested that the early development of liver metastases within 3 mo after pancreatic resection supports the hypothesis that occult microscopic liver metastases are frequently present at the time of resection[18]. A recent Japanese study reported that undifferentiated PDAC is independently associated with hepatic metastasis after pancreatic resection[14]. Our data showed no difference in terms of tumor cell differentiation between LM and other type of recurrence. In groups at low risk for LM, cell differentiation is a meaningful predictor for LM. In our study, tumor size and CA 19-9 levels are significant predictors for LM, Takamori *et al*[19] revealed the positive correlation between the expression of CA 19-9 and the hepatic metastatic potential of pancreatic cancer. The depth of portal vein wall invasion significantly alters survival after curative pancreatic resection combined with portal vein resection[20]. Previous studies have suggested that several molecules, including epidermal growth factor receptor, E-cadherin, and laminin *g*-chain, that are expressed at high levels in undifferentiated PDAC are associated with postoperative hepatic metastasis[21-23]. Such molecular changes may enhance the ability of pancreatic ductal carcinoma to metastasize to the liver[14]. Niedergethmann *et al*[24] reported that CTSB and CTSL rather than UICC stage, TNM classification, or tumor grading, are strong and independent prognostic markers in resectable pancreatic adenocarcinoma. Furthermore, CTSB is a predictor for early recurrence after curative resection. Seo *et al*[25] suggested that vascular endothelial growth factor expression seems to be an important predictor for both LM and poor prognosis in ductal pancreatic adenocarcinoma. Other study suggested that fibrotic focus reduced membranous β-catenin expression, and reduced cytoplasmic β-catenin expression were significantly associated with shorter LM-free survival[26,27]. These investigations suggest that cancer differentiation relating factors influence the hepatic metastasis of PDAC, and predict poor prognosis. We support cautiously the hypothesis that selective adjuvant chemotherapy may be possible using post operative LM prediction.

Although no standard post pancreatectomy adjuvant chemotherapy for PDAC has been established, several gemcitabine-based adjuvant therapies have been investigated since 2000. In one European ramdomized

controlled prospective study, postoperative gemcitabine significantly delayed the development of recurrent disease after complete resection of pancreatic cancer[28]. A Japanese study[29] reported similar results for patients with PDAC and LM. A number of papers have revealed that in patients with advanced PDAC, intra-arterial chemotherapy or chemotherapy *via* portal vein with systemic chemotherapy appeared to be effective against PDAC and LM[15,30-33]. Hepatectomy was applied in patients with LM in Germany, with between 9 and 24 mo of survival after hepatectomy reported[34]. Not only adjuvant local chemotherapy but also liver resection for LM were successful in achieving survival improvement after pancreatectomy with PDAC. The enthusiastic efforts of several researchers searching for molecular factors predicting LM may result in selective adjuvant therapy and improvement of survival in future.

In conclusion, LM after resection of PDAC occurs early and shows poor survival. Tumor size is the clearest indicator for LM after resection.

COMMENTS

Background

The prognosis of pancreatic ductal adenocarcinoma (PDAC) with liver metastasis (LM) is dismal even after curative pancreatectomy. However, prognostic factors for LM after PDAC resection are not well established.

Research frontiers

The authors retrospectively analyzed 101 PDAC patients who underwent surgical resection at the Samsung Medical Center between January 2000 and December 2004.

Innovations and breakthroughs

In univariate analysis, tumor size, preoperative carbohydrate antigen 19-9, and perineural invasion were factors affecting LM after resection. In multivariate analysis, tumor size was the most important factor for LM. In univariate analysis, tumor cell differentiation was significant to LM in low-risk groups. LM after resection of PDAC occurs early and shows poor survival. Tumor size is the key indicator for LM after resection.

Applications

To investigate prognostic factors for LM, the authors compared and analyzed the clinical and pathological factors between two groups, segmented according to LM.

Peer review

This report deals with very important problems and supports the understanding of the physician treating pancreatic cancer.

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CASE REPORT

A case of severe acalculous cholecystitis associated with sorafenib treatment for advanced hepatocellular carcinoma

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Abstract

Sorafenib, a multikinase inhibitor, is the first and only drug, which improves significantly the overall survival in patients with advanced hepatocellular carcinoma (HCC). However, many patients experience diverse side effects, some of them severe and unexpected. To date, acute acalculous cholecystitis has not been documented in association with a HCC patient treated with sorafenib. Here, we report the case of a 43-year-old woman with hepatitis C virus-related advanced HCC. She received sorafenib, and later complained of a sudden onset of severe right hypocondrial pain with rebound tenderness and muscle defense. Laboratory examination showed mild elevation of transaminases, biliary enzymes, bilirubin, inflammation markers, and a marked peripheral eosinophilia. Abdominal computed tomography (CT) revealed a swollen gallbladder with exudate associated with severe inflammation without stones or debris. Consequently, sorafenib treatment was stopped immediately, and steroid-pulse therapy was performed. Steroid therapy drastically improved all clinical manifestations along with normalization of CT findings, eosinophilia, and liver functions. In summary, we herein report a rare case of acute severe acalculous cholecystitis associated with sorafenib in the patient with advanced HCC.

Key words: Hepatocelluar carcinoma; Sorafenib; Acalculous cholecystitis

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INTRODUCTION

Hepatocellular carcinoma (HCC) is ranked the sixth most common tumor type worldwide, and because of its very poor prognosis, is the third most common cause of cancer death with an annual mortality of 600 000 patients[1]. Before the development of sorafenib, effective standard chemotherapy was unavailable. Sorafenib has anti-proliferative, anti-angiogenic, and anti-apoptotic effects by inhibiting multiple kinases such as RAF kinase, and vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, and VEGFR-3[2]. We previously reported that suppression of VEGF and VEGFR signaling significantly suppressed HCC growth in the animal model[3]. Accordingly, it has been shown that sorafenib significantly improved the overall survival in patients with advanced HCC in Western countries in the SHARP trial[4]. Furthermore, an Asia-Pacific trial has shown that it was also effective in the region[5]. Sorafenib is now recognized in many countries as one of the standard therapies for advanced HCC, and consequently medical treatment has changed dramatically. However, so far many types of diverse side effects have been reported, such as hand-foot skin reaction, gastrointestinal bleeding and arterial thromboembolism. Furthermore, additional unexpected effects include spleen infarction, acute pancreatitis and thyroiditis, which are rare in conventional chemotherapy[6-8]. To our knowledge, there is no report linking a case of acute cholecystitis with sorafenib treatment. Here, we report a case of acute acalculous cholecystitis along with a marked eosinophilia in an advanced HCC patient during the course of treatment with sorafenib.

CASE REPORT

A 43-year-old woman with hepatitis C virus (HCV)-related liver cirrhosis was admitted to our hospital to treat the advanced HCC. She had previously received transcatheter hepatic arterial chemoembolization (TACE) 3 times, and recently 2 cycles of hepatic artery infusion (HAI) chemotherapy to treat the multiple HCC. However, the presence of several new lesions within a few months after the treatment led to categorize the case as a progressive disease in agreement with RECIST criteria (Figure 1A). She was in a good state of health (ECOG PS 0) before the treatment. The absence of encephalopathy and ascites, and the normality of coagulation parameters (PT-INR 1.12) of bilirubin (0.7 mg/mL), and albumin (3.9 g/dL) led to classifying the patient into functional class Child-Pugh A. Blood chemistry tests showed a mild elevation of α-fetoprotein values (33.2 ng/mL), and a slight increase of aspartate aminotransferase (AST) (61 IU/L) and alanine aminotransferase (ALT) (49 IU/L). Treatment with sorafenib at 800 mg/d was started from the next admission. Although she showed several diverse effects such as diarrhea and hand-foot-skin reaction, which met the criteria of grade 1-2 of Common Terminology Criteria for Adverse Event v3.0 (CTCAE), these symptoms were manageable and did not interfere with the patient's daily activities.

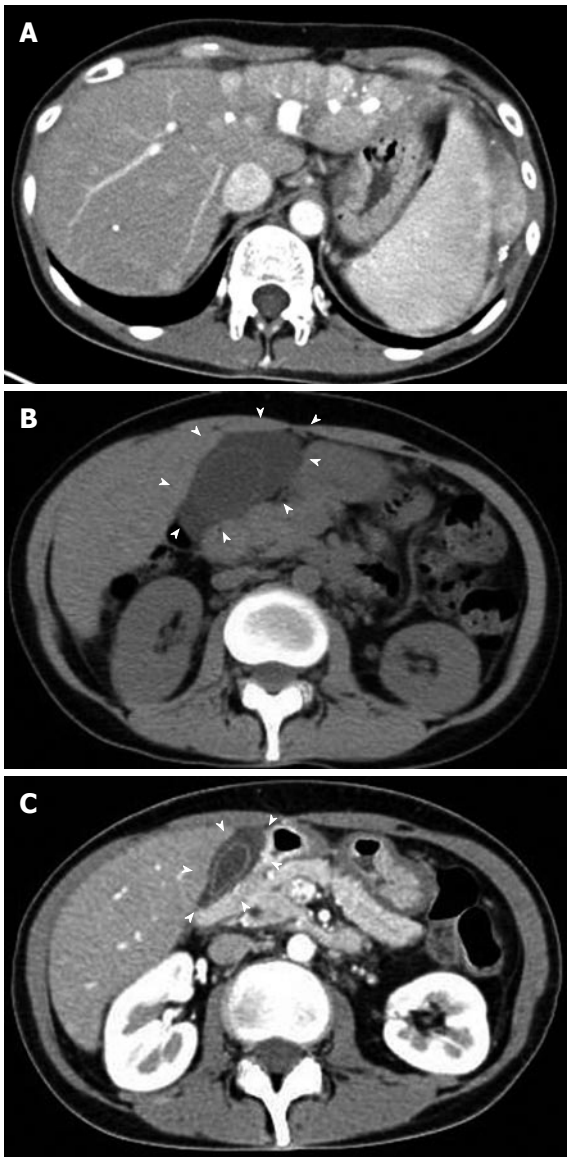

Figure 1 Abdominal computed tomography scan of the patient. A: Enhanced abdominal computed tomography (CT) scan showing the diffuse HCC which occupied whole left lobe and several new lesions within diameter 1 cm in right liver before the treatment with sorafenib. Triangle indicates the HCC lesion; B: Abdominal CT scan at the onset of acute cholecystitis during the treatment with sorafenib. The CT revealed the gallbladder swelling with exudate associated with severe inflammation without stones or debris (arrowheads); C: Follow-up abdominal CT scan at 5 d after treatment of acute cholecystitis. Gallbladder swelling was markedly improved with reduced ascites exudate (arrowheads).

At 27th day of sorafenib therapy, the patient complained of a sudden onset of severe right hypocondrial pain with rebound tenderness and muscle defense. Laboratory examination revealed mild elevation of transaminases (AST: 134 IU/L, ALT: 118 IU/L), biliary enzymes (γGTP: 78 IU/L, alkaline phosphatase: 503 IU/L), bilirubin (1.4 mg/ml), inflammation markers (WBC: 10 500/μL, CRP: 2.3 mg/dL) and a marked eosinophilia (eosinocyte 32.3%). Abdominal computed tomography (CT) revealed a swollen gallbladder with exudate associated with severe inflammation without stones or debris (Figure 1B). Unfortunately, in this case no other diagnostic image such

as MRCP, was performed at the same time. Sorafenib was immediately stopped, and steroid-pulse therapy was performed. Prednisolone (500 mg/d) for 3 d drastically improved all clinical manifestations along with normalization of CT findings, eosinophilia, and liver functions. Five days after treatment, the gallbladder swelling was markedly improved with reduced ascites exudate (Figure 1C). The patient was discharged from hospital 2-wk after treatment.

DISCUSSION

In this report, we describe a patient who developed acute acalculous cholecystitis during the course of sorafenib treatment along with a marked eosinophilia in an advanced HCC. The most common adverse effects of sorafenib consist of fatigue, as well as gastrointestinal side effects such as nausea and diarrhea, anorexia, weight loss, and skin toxicity such as hand-foot syndrome[4]. Most of these effects are tolerable, and we can manage these clinical symptoms since we have experienced them with conventional chemotherapeutic agents. However, unexpected sorafenib toxicities have also been reported including thrombotic events and splenic infarction[6]. To date, there is no report describing acute acalculous cholecystitis during the course of sorafenib treatment. The exact mechanism of this effect is unclear at this time. However, we postulate that eosinophilic cholecystitis could occur due to a marked peripheral blood eosinophilia. Eosinophilic cholecystitis is an infrequent form of cholecystitis[9,10]. In clinical practice, eosinophilic cholecystitis is usually unsuspected and is clinically indistinguishable from the predominant form of calculous cholecystitis[10,11]. Although the etiology of eosinophilic cholecystitis is still uncertain, the proposed causes include parasites, gallstones, and allergic hypersensitivity response to drugs such as phenytoin, erythromycin, cephalosporin, and herbal medications[12,13]. The condition sometimes shows a marked peripheral blood eosinophilia. Eosinophilic cholecystitis may develop with several diseases, such as eosinophilic gastroenteritis, eosinophilic pancreatitis, and idiopathic hypereosinophilic syndrome[14-16]. Unlike eosinophilic gastritis, most patients with eosinophilic cholecystitis have no history of allergy, similar to our case[17]. Peripheral hypereosinophilia is not a constant finding either, although the characteristic histologic feature of eosinophilic cholecystitis is transmural inflammatory infiltration of the gallbladder wall that is composed of more than 90% eosinophils[10]. In the current case, we did not have any histological evidence of eosinophilic cholecystitis since the patient did not undergo cholecystectomy. This is the main negative point of the final diagnosis of eosinophilic cholecystitis in our case. However, the patient exhibited a marked peripheral eosinophilia along with confirmation of acute cholecystitis by several imaging modalities such as CT. It has been reported that a marked peripheral eosinophilia mostly correlates with eosinophilic infiltration in the gallbladder wall, indicating that, at least, there was some infiltration of eosinophils in the gallbladder. Medical management of eosinophilic cholecystitis may depend on the severity and disease location. Considerable infiltration of the muscularis by eosinophils with vascular occlusion entails surgery, whereas involvement of the mucosa or adventitia without vascular changes responds well to steroids[18]. In this case, after termination of sorafenib and treatment with steroid, eosinophilia and all clinical manifestations drastically improved along with normalization of the imaging features.

Another possibility is the ischemic change of the gallbladder by sorafenib since ischemic heart disease has been reported in the SHARP trial[4]. It has been reported that gallbladder ischemia sometimes occurred after the treatment with TACE, especially along with embolization of the gallbladder artery[19]. However, we postulate that this was not the case in our patient. We performed selective TACE and HAI for the respective tumor lesion, and we did not inject the gelform and chemotherapeutic agent into a cholecystic artery in this patient. Furthermore the clinical course of this patient was not typical of manifestations of ischemic cholecystitis. In future, further examination of this type of patient is required to elucidate the exact mechanisms.

In conclusion, we report a rare case of acute cholecystitis along with a marked eosinophilia in a patient with advanced hepatocellular carcinoma during the course of sorafenib treatment. Since this compound can induce multiple adverse effects, which are uncommon using conventional chemotherapeutic agents, physicians should be aware and consider the possibility of clinical manifestations of acute cholecystitis when using sorafenib.

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CASE REPORT

Greater omentum gastrointestinal stromal tumor with *PDGFRA*-mutation and hemoperitoneum

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Abstract

Although gastrointestinal stromal tumor (GIST) occurs generally in the digestive tract, omental GIST is very rare. We report the first case of an adult greater omental GIST with a new platelet-derived growth factor receptor α gene (*PDGFRA*)-mutation with hemoperitoneum. A 43-year-old man was admitted to our hospital complaining of acute abdominal pain. Abdominal contrast-enhanced computed tomography revealed a huge mass in the right abdominal cavity, and a large accumulation of fluid in the pelvic cavity, suggesting hemoperitoneum. We diagnosed the rupture as an intra-abdominal tumor, and an emergency tumorectomy was performed with resection of the greater omentum. This tumor was located in the distal right side of the greater omentum, and showed no continuity with the gastric wall. The tumor occurred primarily in the greater omentum. The resected tumor was about 19 cm × 12 cm × 14 cm in diameter, and weighed 1529 g. Histologically, the tumor was composed of epithelioid-shaped cells with high cellularity, and was positive for CD117 and CD34, and negative for S-100, α-smooth muscle actin. The mitosis was 6/50 under high power field. This case showed exon 18 mutation of *PDGFRA* with 846 (Asp to Glu) substitution, 848 (Asn to Lys) substitution. This is the first report of this *PDGFRA* mutation in omental GIST, and this might play an important role in the tumorigenesis of this case. Based on these findings, the tumor was diagnosed as high risk GIST primarily occurring in the greater omentum. The patient was treated with imatinib at a dose of 400 mg/d as adjuvant chemotherapy, and has been followed up for 24 mo with no evidence of recurrence.

Key words: Gastrointestinal stromal tumor; Greater omentum; Hemoperitoneum; Platelet-derived growth factor receptor α gene; KIT

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs), while relatively

rare, are the most common mesenchymal tumors of the digestive tract and are believed to originate from the interstitial cells of Cajal (ICCs) or from their precursors in the gastrointestinal tract[1,2].

GISTs can occur anywhere in the gastrointestinal tract where ICCs are present, including the stomach (40%-60%), small intestine (30%-40%), anorectum (7%), colon, and esophagus, as well as in extra-gastrointestinal locations such as mesentery, omentum, and peritoneum[1,3]. Omental, mesenteric, and retroperitoneal tumors comprise less than 5%[4-9]. Tumors occurring in the greater omentum are very rare, and the diagnosis of such lesions is difficult. The incidence of primary GIST in the greater omentum has been reported to be less than 1%[10-12].

The majority of adult GIST cases (83.6%-88.2%) have activation mutations in the *KIT* gene, which codes for the KIT receptor tyrosine kinase. These mutations result in constitutive activation of the receptor, and subsequently cell survival and proliferation, in the absence of ligand binding. In addition, platelet-derived growth factor receptor α gene (*PDGFRA*) mutations account for a further 2.6%-4.7% of cases while the remaining 7.1%-13.8% are wild types for either receptor[13,14].

Here we report the first case of the greater omentum GIST with the new *PDGFRA*-mutation and hemoperitoneum.

CASE REPORT

A 43-year-old man was admitted to our hospital for acute abdominal pain. He had no past medical or surgical history, was taking no medications, and never had a previous colonoscopy or upper endoscopy. There was no family history of any gastrointestinal malignancies. His height was 173 cm, weight was 108 kg (BMI: 36). The only positive findings on examination were right lower abdominal pain, tenderness, and defense. Hematological examination found slight anemia with a hemoglobin level of 6.8 g/dL and high levels of C-reactive protein of 4.46 mg/dL. The levels of CEA, CA19-9, and AFP were within the normal ranges. A contrast-enhanced computed tomography (CT) scan of the abdomen and pelvis showed a huge mass in the right abdominal cavity. The interior was heterogeneous, with some high density area, but comprised mostly of low density regions which seemed to be a cystic component or interstitial mucous (Figure 1A and B). Moreover a large amount bloody ascites was found in the pelvic cavity, suggesting hemoperitoneum. We diagnosed the rupture as an intra-abdominal tumor, and an emergency tumorectomy was performed. This tumor was located in the distal right side of omentum. The disconnect was successfully ligated to the greater omentum mass insertion, and the tumor showed no continuity with the gastric wall. The tumor size was oval, 19 cm × 12 cm × 14 cm in diameter, and the weighed 1529 g. There was about 850 mL of bloody asictes in the abdominal cavity. On gross examination, the resected tumor was a dark-red, relatively hard mass, and mixed with partly bleeding blood clots. The cut surface of the tumor showed cystic degeneration, and focal hemorrhage (Figure 2A and B). The tumor occurred primarily in the greater omentum. Tumor invasion to adjacent organs, liver metastasis, peritoneal dissemination, and omental lymph node swelling were not observed. Haematoxylin and eosin (HE) staining and immunohistochemistry were carried out on paraffin wax sections of the formalin-fixed tissues[10]. HE staining showed that the tumor cells were composed of epithelioid-shaped cells with high cellularity (Figure 3A and B). The mitosis was 6/50 under high power field. Immunohistochemical staining showed that the tumor cells were positive for CD117 (Figure 3C), positive for CD34 (Figure 3D), and negative for S-100 and α-smooth muscle actin (α-SMA), consistent with a GIST. Therefore, these features strongly indicate clinical malignancy with abdominal hemorrhage, most likely GIST[4].

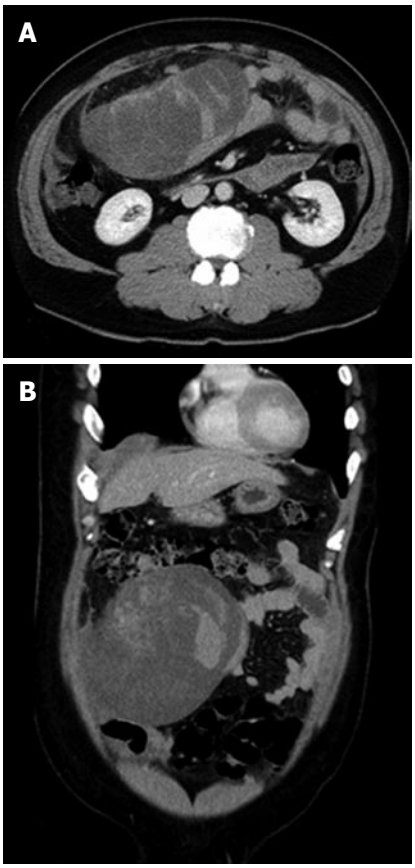

Figure 1 Contrast-enhanced axial (A) and coronal (B) abdominal computed tomography. A huge mass was seen in the right abdominal cavity showing internal heterogeneity, with some high density area, but comprised mostly of low density regions which seemed to be a cystic component or interstitial mucous. The high density area was not enhanced, thus hemorrhage was suggested. Moreover a large amount of bloody ascites was seen in the pelvic cavity.

Genomic DNA was extracted from the formalin-fixed, paraffin wax-embedded tissues using the QIAamp DNA Mini Kit (QIAGEN, Valencia, CA, USA), and Exon 9, 11, 13, 17 of *KIT* and exon 12, 14 or 18 of *PDGFRA*, were amplified using polymerase chain reac-

Table 1 Polymerase chain reaction primers used to analyze *c-kit* and *PDGFRA* gene exons

Gene	Exon	Forward primer	Reverse primer
c-kit	9	TTCCCTTTAGATGCTCTGCTTCT	CCTTTGTTGTTACCTTTAAATGC
	11	GAGTGCTCTAATGACTGAGA	AAAGGTGACATGGAAAGCCC
	13	GCTTGACATCAGTTTGCCAG	AAAGGCAGCTTGGACACGGCTTTA
	17	GTTTTCTTTTCTCCTCCAAC	TGCAGGACTGTCAAGCAGAG
PDGFRA	12	GGACTTTGGTAATTCACCAG	TGTAAAGTTGTGTGCAAGGG
	14	ACAGGAAGTTGGTAGCTCAG	TCACAACCACATGTGTCCAG
	18	ACCATGGATCAGCCAGTCTT	TGAAGGAGGATGAGCCTGACC

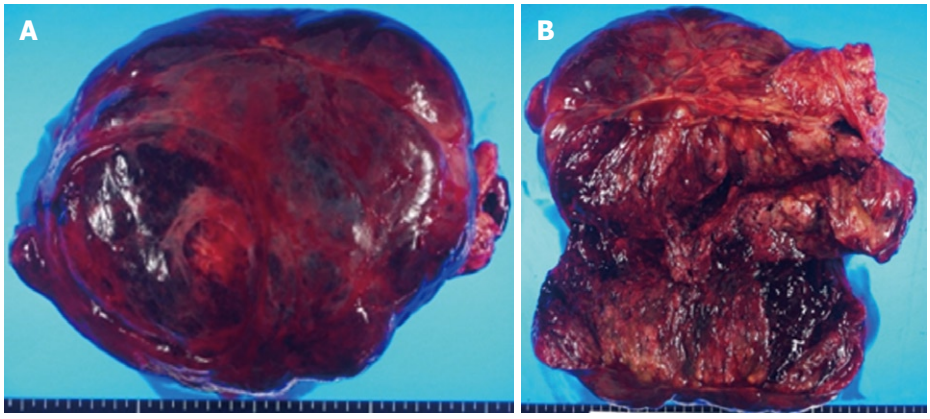

Figure 2 Gross appearance of the resected specimen. A: The tumor appeared as a dark-red, relatively hard mass mixed with partly bleeding blood clots; B: The cut surface of the tumor showed cystic degeneration, and focal hemorrhage.

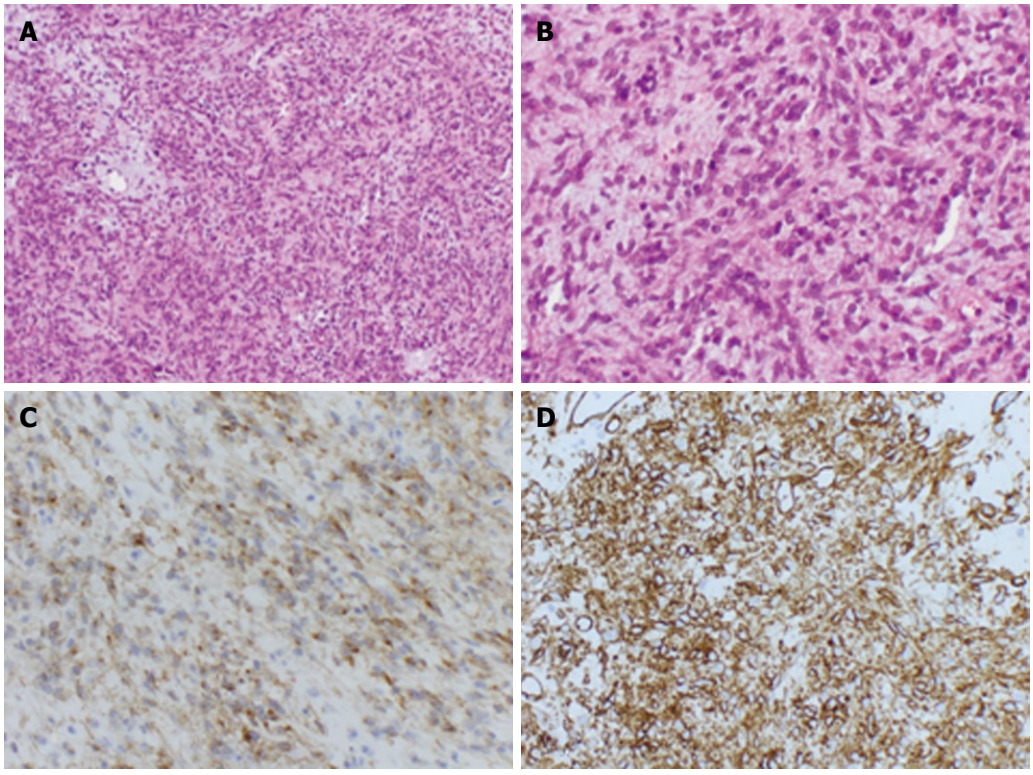

Figure 3 Histopathological findings of the resected specimen of the tumor. A and B: The tumors were characterized by epithelioid-shaped cells and showed high cellularity (HE staining, A: × 40, B: × 200); C: Immunostaining of CD117 (KIT) was positive; D: Immunostaining of CD34 was positive (C, D: × 200).

tion (PCR), as described previously[15] and PCR primers listed in Table 1. This analysis of extracted genomic DNA revealed no mutations of exons 9, 11, 13, 17 of *KIT* and exons 12 or 14 of *PDGFRA*. There was, how-

Table 2 Clinicopathologic findings in 11 cases of omental gastrointestinal stromal tumor

Case No.	Age (yr)/sex	Size (cm)	Mitosis/ 50HPF	Risk group	Cell type	Mutation	Follow up (mo)	Outcome	Ref.
1	73/F	4	3[1]	Low	Myxoid Ep	Exon18 del D842V	4	NED	[5]
2	52/M	> 20	4[1]	High	Ep	Exon18 D842_H845del	13	NED	[5]
3	49/F	17	1	3b	Ep	Exon18 D842_H845del	48	NED	[12]
4	65/M	20	2	3b	Myxoid Ep	Exon12 V561D	6	NED	[20]
5	64/M	15	115	6b	Sp	Exon12 polymorphism Q567P	NA	NED	[21]
6	62/F	11	3	3b	Ep	Exon 18 D842V	87	NED	[22]
7	41/M	19	0	3b	Ep	Exon 18 D842V	27	NED	[22]
8	69/M	8.5	1	3a	Ep	Exon18 del IMHD843-846	20	NED	[22]
9	54/F	20	18	6b	Ep	Exon 18 del DIMH842-845	15	DOD	[22]
10	59/M	33	1	3b	Ep	Exon 18 D842Y	2	DOD	[22]
11	43/M	19	6	6b	Ep	Exon18 D846E, N848K	24	NED	Our case

[1]MIB-1-labeling index (%). Tumors were divided into risk groups described previously[18,22]. Case 1 and 2 were graded as high, intermediate, or low risk as described previously[22]. Ep: Epithelioid; Sp: Spindle; NED: No evidence of disease; DOD: Die of disease; NA: Not available.

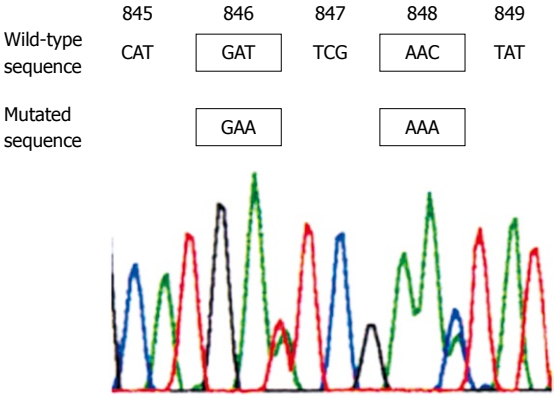

Figure 4 Representative sequencing results of omentum gastrointestinal stromal tumor. This case showed a codon 846 (Asp to Glu) substitution, and a codon 848 (Asn to Lys) substitution within exon 18 of *PDGFRA* gene.

ever, exon 18 mutation of *PDGFRA* with 846 (Asp to Glu) substitution and 848 (Asn to Lys) substitution (Figure 4). Informed consent for the present analysis was previously obtained. Based on these findings, the tumor was diagnosed as high risk GIST primarily occurring in the greater omentum. The patient was treated with imatinib at a dose of 400 mg/d as adjuvant chemotherapy, and has been followed up for 24 mo with no evidence of recurrence.

DISCUSSION

In general, GISTs are the most common mesenchymal tumors of the gastrointestinal tract, occurring mainly in stomach, and small and large intestine. They are considered to be derived from the ICCs[1], and the incidence of the primary GIST lesion in the greater omentum is very rare[10-12].

It has been reported that GIST in the mesentery and greater omentum, structures which lack ICCs, are derived from mesenchymal cells that are less differentiated than ICCs[16]. These may be ICC precursors straying into the abdominal cavity[1], or KIT-positive cells similar to ICCs immediately below mesothelial cells in the greater omentum[11] although the precise etiology remains to be clarified. The present case has shown KIT-positive and CD34 positive cells within specimens from the greater omentum. However, the meaning of this is uncertain.

It has previously been reported that omental GISTs are clinicopathologically heterogeneous[17,18]. Patients with solitary tumors usually show gastric GIST-like morphology and have a better prognosis than those with multiple tumors, whose tumors usually show small intestinal GIST-like histology. Omental GISTs unattached to the gastrointestinal tract often resemble gastric GISTs, suggesting that they may be gastric GISTs directly extending into, or parasitically attached to the omentum, whereas multiple omental GISTs more often resemble small intestinal GISTs, suggesting that they may be metastases or derived from this source. Most single omental GISTs are relatively indolent tumors compatible with long-term patient survival, despite large tumor size. The present case was a solitary omental GIST, suggesting overall similarity with gastric GISTs.

Recent studies have established that activating mutations in the *KIT* gene are present in up to 92% of GISTs. *PDGFRA* mutations account for a further 2.6%-4.7% of cases, while the remaining 7.1%-13.8% are WT for either receptor[13,14]. These gain-of-function mutations result in constitutive *KIT* or *PDGFRA* activation without ligand stimulation and are considered to be a cause of GISTs[18]. The respective oncoproteins exhibit constitutive tyrosine kinase activity and promote cell growth, and might play a central role in GIST pathogenesis[2,18,19]. Imatinib mesylate, a tyrosine kinase inhibitor known to inhibit the activities of BCR-ABL, KIT, and PDGFR, is currently being used for the treatment of both chronic myeloid leukemia and metastatic GIST. In Table 2 we summarize the collected data on *PDGFRA* mutation primarily from omental GIST case-reports (Table 2)[5,12,17,20-22]. In addition, Miettinen *et al*[18] reported *PDGFRA* mutations in 10 cases. There were exon 18 D842V substitutions in 6 cases, exon 18 deletions of 842-845 in 1 case, exon 18 deletions of 841-845 in 1 case, exon 12 substitution V561D in 1 case, and exon 12 deletion of 566-571 in 1

case. Of the 21 cases available for molecular study, 17 cases (81%) had *PDGFRA* gene mutations at exon 18 and 4 cases (19%) had *PDGFRA* gene mutations at exon 12. Only case 5 had both *PDGFRA*12 and *KIT*11 mutation. The majority of *KIT*-negative extra-gastrointestinal stromal omental tumors were characterized by epithelioid cell type, predominant *PDGFRA* mutation genotype, and showed low mitotic activity and a relatively favorable prognosis, despite a large tumor size[18,22]. However, as molecular genetic data has been reported in only a small number of omental GIST, further studies with a larger number of omental GIST cases will be needed. The present case showed exon 18 mutation of *PDGFRA* with 846 (Asp to Glu) substitution and 848 (Asn to Lys) substitution. This is the first report of this *PDGFRA* mutation in an omental GIST, and this might play an important role in the tumorigenesis of this case.

The mean diameter of omental GISTs has been reported to be about 15.35 cm[17] and was 19cm in the present case. Moreover, mitotic activity, cellularity and presence of necrosis have been found to be associated with worse outcomes. A high mitotic rate (> 5/50 HPF) and a high Ki-67 labeling index (> 10%) indicate a significantly poorer outcome[4]. In the present case, the large size, high mitotic counts and extensive hemorrhagic necrosis were malignant features, so the tumor was diagnosed as malignant GIST. Although peritoneal metastasis was not seen in the present case, we must pay attention to tumor recurrence because the tumor ruptured. *PDGFRA* may become a molecular therapeutic target of imatinib in at least some populations of omentum GIST. The preliminary clinical data and *in vitro* studies have demonstrated that GISTs with a *PDGFRA* D842V substitution were resistant to imatinib, but some populations of other *PDGFRA* mutants were sensitive[8,23-25]. Todoroki *et al*[20] and Kim *et al*[21] used STI-571 as adjuvant postoperative treatment. Because the *PDGFRA* genotype in this case might be sensitive to imatinib, the patient was treated with adjuvant chemotherapy imatinib at a dose of 400 mg/d before possible tumor recurrence was identified. This patient remains alive without disease 24 mo after surgery. We will carefully follow up with CT and expect to conduct further clinical investigation.

In conclusion, we have reported the first case of the greater omentum GIST with a new type of *PDGFRA*-mutation and hemoperitoneum. Both immunohistochemical evaluation and molecular analysis are necessary not only to confirm the diagnosis, but also to determine the therapeutic strategy. The existing data on greater omentum GIST is not sufficient to make a firm conclusion on the prognosis and survival. Further studies are necessary to distinguish between the *PDGFRA*-mutation and clinicopathologic factors or biologic behaviors.

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January 14-17, 2012
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Steamboat Springs, CO, United States

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EASL Monothematic Conference: IMLI - Immune Mediated Liver Injury
Birmingham, United Kingdom

January 19-21, 2012
American Society of Clinical Oncology 2012 Gastrointestinal Cancers Symposium
San Francisco, CA, United States

January 19-21, 2012
2012 Gastrointestinal Cancers Symposium
San Francisco, CA, United States

January 20-21, 2012
American Gastroenterological Association Clinical Congress of Gastroenterology and Hepatology
Miami Beach, FL, United States

February 2-4, 2012
2012 Genitourinary Cancers Symposium
San Francisco, CA, United States

February 6-8, 2012
Pediatric Cancer Translational Genomics
Phoenix, AZ, United States

February 8–10, 2012
The 84th Annual Meeting of Japanese Gastric Cancer Association
Osaka, Japan

February 10-11, 2012
Cancer Survivorship for Clinicians
Seattle, WA, United States

February 14-17, 2012
ASCO Multidisciplinary Cancer Management Course
Eldoret, Kenya

February 20-24, 2012
Word Conference on Colorectal Cancer
FL, United States

February 22-23, 2012
National Cancer Institute Annual Biospecimen Research Network Symposium: "Advancing Cancer Research Through Biospecimen Science"
Bethesda, MD, United States

February 22-25, 2012
30th German Cancer Congress
Berlin, Germany

February 24, 2012
ASCO-German Cancer Society Joint Symposium, German Cancer Congress
Berlin, Germany

February 24-27, 2012
Canadian Digestive Diseases Week 2012
Montreal, Canada

March 7-8, 2012
First International Gulf Joint Conference: Management of colon, breast, and lung cancer (Joint Symposium)
Dammam, Saudi Arabia

March 9-10, 2012
ESMO Conference on Sarcoma and GIST
Milan, Italy

March 10-11, 2012
Colorectal Polyps and Cancers: A Multidisciplinary Approach
Scottsdale, AZ, United States

March 17-21, 2012
Methods in Cancer Research Workshop (Advanced Cancer Course)
Al Asha, Saudi Arabia

March 22-24, 2012
The 1st St.Gallen EORTC Gastrointestinal Cancer Conference
St.Gallen, Switzerland

April 13-15, 2012
Asian Oncology Summit 2012
Singapore, Singapore

April 15-17, 2012
European Multidisciplinary Colorectal Cancer Congress 2012
Prague, Czech

April 18-20, 2012
The International Liver Congress 2012
Barcelona, Spain

April 19-21, 2012
Internal Medicine 2012
New Orleans, LA, United States

April 20–21, 2012
OOTR 8th Annual Conference - Organisation for Oncology and Translational Research
Kyoto, Japan

April 28, 2012
Issues in Pediatric Oncology
Kiev, Ukraine

May 19-22, 2012
Digestive Disease Week 2012
San Diego, CA, United States

June 18-21, 2012
Pancreatic Cancer: Progress and Challenges
Lake Tahoe, NV, United States

June 27-30, 2012
ESMO 14th World Congress on Gastrointestinal Cancer 2012
International Convention Center Of Barcelona,
Barcelona, Italy

July 1–5, 2012
10th World Congress of the International Hepato-Pancreato-Biliary Association
Paris, France

July 5-7, 2012
International Research Conference on Liver Cancer
Heidelberg, Germany

July 6-8, 2012
The 3rd Asia – Pacific Primary Liver Cancer Expert Meeting "A Bridge to a Consensus on HCC Management"
Shanghai, China

September 1-4, 2012
OESO 11th World Conference
Como, Italy

September 14-16, 2012
ILCA 2012 - Sixth Annual Conference of the International Liver Cancer Association
Berlin, Germany

September 21-22, 2012
Research Symposium, Inflammation and Cancer
Houston, TX, United States

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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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Conference paper

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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