Dear Mr.Dalle,

Thank you for providing us the opportunity to review your manuscript titled, "Two cases of diabetes mellitus patients with cholangioma found by rapid progress of hyperglycemia and acute liver dysfunction", (ABCDY_1) for publication in your target journal, *PLOS ONE*.

This study describes sudden and simultaneous worsening of glycemic control and acute liver dysfunction (biliary obstruction) suggestive of extrahepatic cholangiocarcinoma (ECC). Overall the manuscript provides interesting information; however, it suffers from lack of enough background, rationale and take-home messages for the readers to understand the novelty of the study.

To improve chances of a positive review by the target journal, we recommend the authors to please address the following major comments:

1. Please include informed consent statement in the manuscript.
2. The methods and results need to be revisited for completeness and accuracy.
3. The findings should be appropriately discussed in the context of previous literature.
4. Please clearly describe the main methods, results, and conclusions in the abstract.

Further detailed comments can be found in the manuscript file. Comments are structured into focus areas and recommended actions.

- Focus areas are potential gaps that might be raised by journal peer reviewers.
- Recommended actions are solutions recommended by our expert to fix these problems. Please follow the recommended actions and make the suggested revisions.

We strongly recommend that you incorporate the suggested revisions. Please note that your revised manuscript will be returned to the same expert for confirmation of service pack progression.

We are truly committed to supporting you throughout your publication journey and will offer resubmission at no additional charge if the manuscript is rejected with major revisions that could have been identified in this service.

Next steps for you

- For service pack assignments: To proceed with the next step of your service pack, please make the suggested revisions and send us the revised manuscript.

Thank you for choosing Editage as your publication partner! We're happy to address any questions you may have on the report.

Best regards,
Editage

Two cases of diabetes mellitus patients with cholangioma found by rapid progress of hyperglycemia and acute liver dysfunction

no1 abstract and introduction

A sudden association of hyperglycemia and liver dysfunction revealed cholangiocarcinoma.

Abstract

Objective:

To report two cases that the sudden liver dysfuction and hyperglycemia were simultaneously observed.

The liver dysfunction was due to extra hepatic cholangiocarcinoma(ECC).

The relationship between diabetes mellitus (DM) and ECC might be suspected.

Methods:

The clinical manifestation and laboratory ,radiology and pathologic findings are presented.

Some literatures involving ECC and DM are referred

Result:

Case 1

A 59-year-old woman with a history of DM and slight apoplexy was referred to my clinic for follow-up.

After 2 years , simultaneous emergence of liver dysfunction and hyperglycemia were observed.

Lab data and ultrasonography disclosed the dilatation of bile duct.

Case 2

A 68-year-old woman presented with dull headache.

Routine examinations revealed hypertension,DM and dyslipidemia which were controlled soon by a stable dose of medicines.

After 4 years , a sudden rise in blood glucose level and liver dysfunction were found at the sametime.

Lab data and ultrasonography revealed the obstruction of bile duct.

Both case 1 and case 2 were referred to the special hospital for gastroenterology for further examination and pancreatoduodenectomy,

Pathologic findings :case 1 was adenocarcinoma (tub 1-tub 2) , pT3a, pN1, pStage II B .

case 2 was the collision cancer and partially mixed (tub 1 and neuroendocrine), pT3a, pN 0, pStage II A

This is a rather rare case of the collision cancer in common duct.

Commented [A1]: Focus area: The title is not clearly understandable and does not convey the study's intent.
Recommended action: Please consider rephrasing to: "Two cases of diabetes mellitus patients with cholangioma causing worsening of glycemic control and acute liver dysfunction"

Commented [A2]: Focus area: Is this the running title?
Recommended action: Please change the sub-heading to "Running title".

Commented [A3]: Focus area: This is abstract is too long for a case report. Please note that most journals allow abstracts to be max. 100-200 words for case reports.
Recommended action: Please remove the methods section since this is a case report.

Commented [A4]: Focus area: This section is not understandable and not required.
Recommended action: Please delete this section.

Commented [A5]: Please mention the city, country of the clinic. Please do not use personal pronouns.

Commented [A6]: Focus area: This statement is unclear to the readers.
Recommended action: Please be more specific and define what lab data were collected.

Conclusion:
The sudden concomitant of hyperglycemia and liver dysfunction due to ECC were observed , after both case 1 and case 2 were followed up as DM type 2 for2 years and 4 years , respectively. During these years the abnormal subjective and objective symptoms were not found.
The cause of ECC may be metabolic factors which made the epithelium of the bile ducts proliferated.
To the best of our knowledge, this is the first case report that the sudden hyperglycemia and liver dysfunction
due to ECC was observed, and the histology of ECC revealed the collision cancer in common duct.(case 2)

Introduction
The cause-and-effect relationship between DM and pancreas carcinoma had been discussed by many reports.(1)(2)
But the report of ECC with DM are not usually found.(3)(4)(5)(5)(6)(7)
D B Costa etc reported"hyperglycemic emergency with ECC"and speculated that"some factor(or factors)produced by tumor had a role in the metabolic decompensation"(8)
Our cases had the deterioration of DM and liver function simultaneously although metabolic factors were strong.
The same speculation (DB Costa) could not be ruled out in our cases, also.

no2 case 1
A-59-year-old woman was referred to my clinic for outpaient follow-up of 1.essential hypertension 2.dyslipidemia 3.apoplexy seguela on Mar 26,2012 with prescription amlodipine(5mg/day),pitavastatin(1mg/day) and clopidogrel(25mg/day)
The patient had a past history of apoplexy on Apr.27.2007(hypothalamus infarction) and DM (HbA1c7.9% on admission day was normalized below 6% within 2 months without any medications)
There is no family history of diabetes and cancer.
On physical examination
Her weight was 61.0kg and height was 154.2cm yielding a body mass index of 25.6 kg/m2
Blood pressure of 130/70 mmHg
Urinalysis showed trace positive for glucose protein(-) urobilinogen normal plus , pH 5 ketone(-)
Apr 4th 2012 75g OGTT(oral glucose tolerance test) was performed and showed IGT pattern.(HOMA-IR: 2.04)
Voglibose 0.6mg/day was prescribed for preventing DM and hypertension according to STOP-NIDDM study.(27)

Commented [A7]: Focus area: The conclusion section of abstracts should not exceed 1-2 sentences. This is too long.
Recommended action: Please reduce this section and present the main findings and interpretation in 2-3 sentences.

Commented [A8]: Focus area: The introductions is too short and does not provide background and rationale for the study.
Recommended action: This section would benefit from an expansion to include what is known in the current literature and why these cases are unique.

Commented [A9]: Focus area: These references have not been discussed in the introduction.
Recommended action: More discussion is needed about what is unique about these two cases. What additional information is being added to the field of based on these case reports?

Commented [A10]: Focus area: The introduction is abrupt and does not relate to the study results
Recommended action: Please mention what is known about the relation between DM and ECC and how this study is unique. Please mention what you are presenting in this case report.

Commented [A11]: Focus area: Most journal mandate case reports to include informed consent from participants.
Recommended action: Please include informed consent statement before the reference section.

Commented [A12]: Focus area: The format for case presentation is incorrect and does not follow most journal guidelines.
Recommended action: Please divide the case presentations into 3 distinct paragraphs, symptoms, diagnosis, treatment, and outcome.
Please do not use sub-headings as they are usually not allowed for case reports.

A lipid profil was normal .

Thereafter HbA1c level showed 6.0—7.0percent from 2013 to July 2014
On Sep.24 2014, HbA1c 7.5% slightly raised but liver function was normal (AST 21 U/L ALT 31 U/L γ-GTP 27 U/L)
On May 24 2015 HbA1c sharply raised 8.9 percent and fasting plasma glucose level of 200 mg/dl
Liver function test was abnormal (AST 39 U/L ALT 233 U/L γ-GTP 730 U/L)
On Jun.21 2015 AST 163 U/L ALT 454 U/L γ-GTP 3078 U/L total Bilirubin 2.4mg/dl serum amylase 72U/L
CEA 7.8 ug/ml CA19-9 2879 U/ml
Hepatitis B antigen and C antibody(3rd) were negative.
Ultrasonography demonstrated a dilated intra and extra hepatic bile duct and common bile duct.
However she had no subjective symptoms(thirst, polyuria, fatigue or weightloss) and gall stone (-).
For further evaluation including liver function, detecting the cause of obstructive jaundice, she was referred to the special hospital for gastroenterology.

CT (Computed tomography)of the abdomen revealed a 2.4x2.1cm mass at the end of dilated common duct.
Pancreas duct was normal range. No abnormality was found in SMA,SMV and PV.
Tumor or enlargement in liver was not detected.
MRI (magnetic resonance image)and ERCP (endoscopic retrograde cholangiopancreatography) showed
a dilated biliary duct with obstruction at the lower bile duct.
Endoscopy was performed to observe duodenum, the ampulla of Vater and intra bile duct and also to get biopsy specimen.
Biopsy specimen from lower common duct showed adenocarcinoma and from upper bile duct was negative for malignant involvement.

Pathological diagnosis
A tumor(16x15mm)at the distal bile duct was adenocarcinoma(tub1—tub2)which invaded to pancreas and duodenum, but did not do Aorta abdomen.
LN meta(+) There were no cancer cell at the resection margins (duodenum and pancreas) of operation.
Atypical cell was not found at gallbladder with thickened wall.

no3Case 2

Commented [A13]: Focus area: The presentation of this result is not clear
Recommended action: This would read better by documenting the "rise" in the lipid profile over time compared to baseline values. For clarity. it would help to perhaps have a chart showing the changes in values.

Commented [A14]: Focus area: Several imaging investigations (USG, CT, MRI, ERCP, endoscopy) were performed in the case. Were they all performed around the same time?
Recommended action: Please present the findings as timeline from the time of initial checkup instead of actual dates.

Commented [A15]: Focus area: The description lacks sufficient information on treatment and outcomes.
Recommended action: Please provide details on how the case was treated, and how the patient performed after treatment. Journals require several specific pieces of information in a case report, as outlined in the CARE checklist. Please make sure the relevant information on those topics are included in the case report.

Commented [A16]: Focus area: The presentation of this is too long. Recommended action: Please reduce and present only the main findings relevant to the study.

A-68-year- old woman presented with dull headache at the occipital region on Apr.21st.2010.
On physical examination,
Her blood pressure(BP) was 200/100mmHg, her height was 151.8 cm and weight was 63.0 kg yielding a body mass index of 27.3 kg/m2
Urinalysis showed trace positive for glucose, protein (-) ketone (-) urobilinogen normal positive pH 6
The 1.5-hour postprandial plasma glucose level(PG) was 285 mg/dl, hemoglobin A1c(Hb-A1c) 7.8%
She denied thirst, polyuria, polydipsia and diabetes history herself and her family.

After 1 week, 75gOGTT disclosed a diabetic curve because of the lack of insulin secretion. (HOMA-RI: 2.16 reference calculation because of FPG:175mg/dl > 140mg/dl)
Glymepirido(1mg/day) was prescribed with amlodipine (2.5mg/day losartan potassium)(50mg/day) hydrochrolomathiazide(2.5mg/day) for hypertension.

After 2 months, lab data showed FPG(fasting plasma glucose level) 118 mg/dl ,Hb-A1c 6.5%, BP 126/70 mmHg
weight 61.0 kg but dyslipidemia (TC 306 mg/dl,HDL-C 45mg/dl,LDL-C 219 mg/dl,TG 209 mg/dl) was found
and rosuvastatin calcium (2.5mg/day) was added to her prescription.

After 4 months, FPG 102mg/dl, Hb-A1c 5.5% TC 191mg/dl HDL-C 50mg/dl LDL-C 107 mg/dl TG 169mg/dl
BP 138/70 mmHg, weight 64.0kg
Thereafter laboratory data had been stable for 4 years

Jan. 4th 2014 FPG 137 mg/dl,Hb-A1c 6.3% TC 235mg/dl HDL-C 47mg/dl LDL-C 143mg/dl TG 222mg/dl
AST 18U/L ALT 15U/L γ—GTP 21U/L wight 68 kg (BMI 29.5)
The liver function was still within normal range but the glucose metabolism showed a rising tendency.

Nov. 5th 2014. FPG 155mg/dl. Hb-A1c 6.9% AST 20 U/L ALT 54 U/L γ-GTP 255U/L
weight 67.5 kg .
The lab data of ALT and γ-GTP indicated abnormal as well as glucose metabolism.

Feb.4th 2015
The both hyperglycemia and abnormal liver function were remarkable together.
FPG 216mg/dl Hb-A1c 7.2 % T.Bili 4.0 mg/dl ALP 1377 U/L AST 271 U/L ALT 503 U/L γ-GTP 1635 U/L
Serum amylase 68 U/L

Commented [A17]: Focus area: Presenting the lab results by date is distracting and hard to follow. Recommended action: The manuscript would read better if presented in narrative form. Instead of specific dates, it may help to present changes in measurements as a timeline (days from initial presentation).

Especially liver function data and tumor marker(Ca19-9 86 U/ml) suspected
the obstruction of bile duct by cancer. HBsAg(-) HCV antibody (3rd)(-)
The dilation of common bile duct by ultrasonography also confirmed the obstruction of the bile duct, gall stone(-).

She was referred to the special hospital for gastroenterology in order to detect the cause of bile duct obstruction.

CT of the abdomen revealed a 2.9x2.3 cm mass at the lower common bile duct which was similar region to case1.
The tumor or enlargement was not found in liver, gall bladder and spleen.
Portal vein and SMV appeared normal.

Pathological diagnosis
pT3a pN0 pStage II A
At the proximal, intra ductal tubular neoplasia was main and was transformed to neuroendocrine carcinoma (NEC)
on the ampulla of Vater (Ab). At the distal, both tub1 and NEC were invasive to nearby organs.
Especially NEC invaded to pancreas.
The border between tub 1 and NEC was clear (collision-like) but partially mixed.
Mixed carcinoma which originated in a common precursor cell differentiates in two directions, is considered (9)(10)(11)
The resection margins as well as the lymph nods were negative for tumor extension.

Immunohistochemically,
In tub 1 component, epithelial marker (AE1/AE3・CAM 5.2・CK20) was strong positive and CK7 was slight positive.
Neuroendocrine carcinoma cells was stained positive for AE1 / AE3・CAM 5.2 , slightly positive for CK7・CK 20 .
and strongly positive for Synaptophysin・Chromogranin・CD 56.
The result of Ki-67/MIB1 stain was positive (30~40 %) : neuroendocrine carcinoma which correspond with NET G3, small cell carcinoma.

no4 Discussion

There are many meta analysis reports about “The relationship diabetes mellitus and the risk of cancer morbidity”
DM patients have the more risk in hepatoma, pancreas ca, colon ca breast ca and bladder ca as compared with
non DM patients (12)(13)(14)

Commented [A18]: Focus area: Does this heading signify a diagnosis? This is not clear.
Recommended action: Please describe this heading. It is hard to understand if this diagnosis was established. In that case, why have you made it as a heading? Please review and revise.

Commented [A19]: Focus area: Details about the treatment are missing.
Recommended action: Please provide details on how the case was treated, and how the patient performed after treatment.

Commented [A20]: Focus area: Please note that currently you have 12 figures which might be too many for a case report. Please note that most journals limit the number of figures for case reports. Please note that you have not cited any figures in the report.
Recommended action: Please cite the figures against the relevant portions of the text and reduce the figures by combining or deleting some figures.

Commented [A21]: Focus area: The discussion is presently too long for a case report and does not provide the main essence of the findings
Recommended action: Please mention how this case report advances literature about diagnosis and management of rare cancers.

The association between pancreas carcinoma and diabetes has been discussed.
(1)(2)(15)
The pathophysiologic process have been discussed for long time.
On one hand, the rising risk of pancreas carcinoma by DM,
1. Insulin resistance (insulin by itself activates the MAPK)
2. IGF-1 (insulin decreases the IGF-1 binding protein and increase free IGF which accelerate the cell proliferation and inhibit the apoptosis (16)

On the other , the change of diabetic conditions by pancreas cancer.
The cancer produces the exacerbation factors of DM. One of the factors is adrenomedullin which inhibits insulin secretion from the pancreas β cell.(17)

Liver keeps a stable plasma glucose level in conjunction with adipose tissue and muscles.
Hepatic uptake, glycogen synthesis and hepatic output (glyconeogenesis) are controlled by hormonal signals,
metabolite (including lactate, enzyme: glucokinase etc) (18)
Several organs in abdomen are connecting to liver via portal vein.
Cancer products in pancreas ca, colon ca, stomach ca etc may reach to liver and contribute to the liver dysfunction
which effect the glucose metabolism in liver.

Pancreas carcinoma and extra hepatic cholangiocarcinoma have certain similar pathologic features.(19)
There was the etiologic study about extra hepatic cholangiocarcinoma.(3)
Obesity (> 27 kg/m2) had 2 times of the hazard ratio of ECC as compared with patients(<23kg/m2) in Japan.(6)
Patients(BMI>30kg/m2) had 1.5 times the risk of CC when compared with those (BMI,25kg/m2) in the United Kingdom.(7)
There were some reports of the molecular mechanism about biliary carcinogenesis and growth.
First the chronic inflammation by cholestasis occur, next growth factors and cytokines are activated (20)(21)(22)
and then proliferative signaling are transmitted.

The case report of the relationship DM and cholangiocarcinoma is rare.
D B Costa reported A-85-year-old woman with BMI 21.3 kg/m2 was admitted due to hyperglycemic crisis(DKA).
She had no prior history of glucose intolerant or diabetes. After emergency therapy,
CT(computed tomography of the abdomen) revealed a 1.3-cm rounded mass in the region of the head of pancreas.
He concluded the importance of considering the precise ”cause” of a patient’s diabetes when the presentation

Commented [A22]: Focus area: The sentence about adrenomedullin is important but incomplete.
Recommended action: The paragraph should be expanded to discuss why this is important in the pathogenesis of the current case.

Commented [A23]: Focus area: This statement needs citation
Recommended action: Please provide reference.

Commented [A24]: Focus area: The discussion lacks information on the rarity and novelty of the study.
Recommended action: It would help to explain what is unique about these cases in the introduction-ie the rarity of the association between cholangiocarcinoma and diabetes.

is atypical, as it was in this older, lean patient without recognized risk factors for diabetes.(8)

Our two cases had the history of DM, BMI>25 kg/m2, no weight loss, hypertension, dyslipidemia. (so-called metabolic factors) which may cause the chronic inflammation in bile duct and lead to ECC.
The liver dysfunction due to ECC (including the regurgitation of bile and tumor-secreted products) disturbs
the smooth function of these systems.
Especially in Case 1, if the detection of these lab data were delayed ,
the hyperglycemic crisis might happen as D B Costa case.

In case 2, tumor was found at the lower common bile duct (as same as case 1)
But the histology showed the collision cancer (tub 1 and neuroendocrine: NEC) and partially mixed carcinoma.(9)(10)(23)(24)
This is rare case of the collision cancer in common duct
Functioning pancreatic neuroendocrine tumors can hypersecrete substances.
Such as glucagon, insulin, gastrin, vasoactive intestinal peptide (VIP) and somatostatin resulting in a characteristic clinical syndrome
If glucagon is overproduced, DM may happen(low possibility)(25)(26)
It is thought the collision cancer in the common bile duct is rather rare case,
and it's ECC caused a sudden association of liver dysfunction and hyper glycemia.

Thus, FPG and Hb-A1c raised with liver dysfunction simultaneously mighty be alarm of the malignancy existence.

Acknowledgement must be expressed to Dr.Kondou for his kind advice.

Commented [A25]: Focus area: This discussion is not relevant for this study
Recommended action: Please do not describe the findings of another case report. Please provide the main conclusions in a brief sentence. This description is unnecessary.

Commented [A26]: Focus area: A brief paragraph summarizing the importance of these cases and the need for future research would be helpful.
Recommended action: Please discuss, if there are other cancers, besides cholangioma, that can cause similar signs and symptoms in a patients with diabetes.

Commented [A27]: Focus area: The discussion does not describe the authors' interpretation of the study.
Recommended action: Please discuss the interpretations of your findings and future implications. Please keep the discussion brief.

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Commented [A28]: Focus aera: References are too many and not recent.
Recommended action: Please consider including only the most important recent references as most journals limit the number of references to around 15 for case reports.

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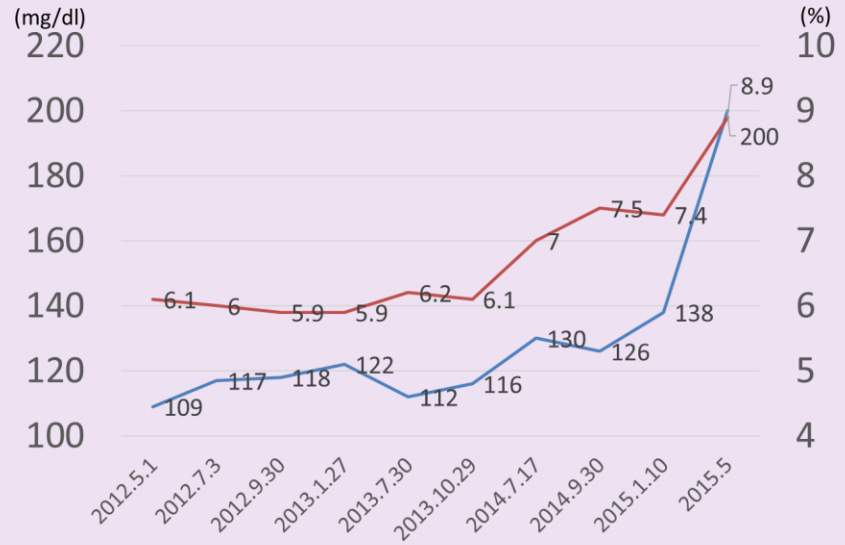
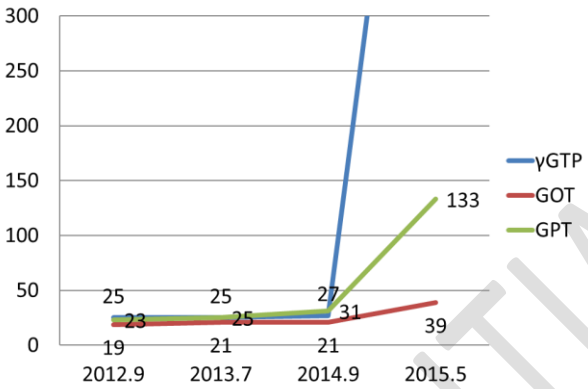
Diabetes: risk factor for the development of pancreatic cancer or manifestation of the disease?

(Fig 1)



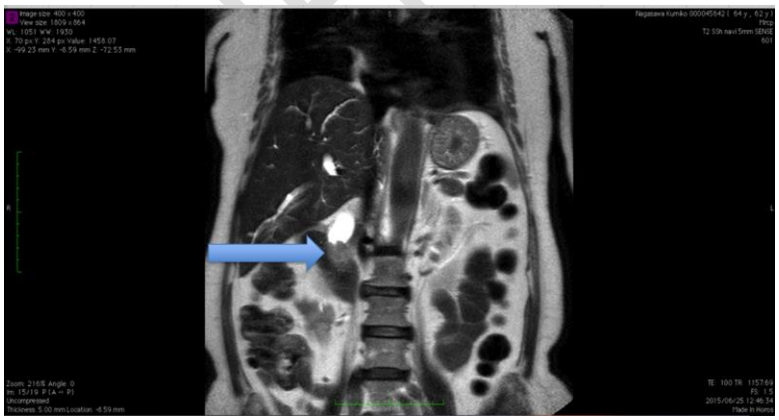
Commented [A29]: Focus are: Most journals usually limit the number of figures in a case report to 2-3. This study presently has too many figures. Recommended action: Please reduce the number of figures. It will be adequate to include only the CT, ERCP, and 1-2 histology images for each case. If you select similar images for the two cases, multiple images could be combined into one figure. The information in the graphs could be adequately stated in a text form in the manuscript.

(Fig2)



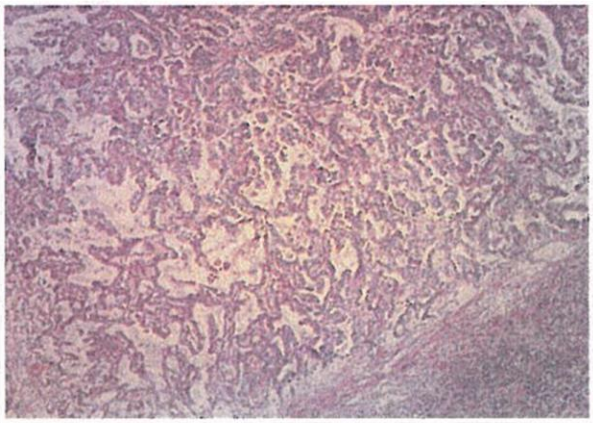
	γGTP	GOT	GPT
2012.9	25	19	23
2013.7	25	21	25
2014.9	27	21	31
2015.5	780	39	133

(Fig3)



MRI of abdomen(coronal plane) showing 2.4x2.1cm mass(arrow) at the end of dilated common bile duct

(Fig4)

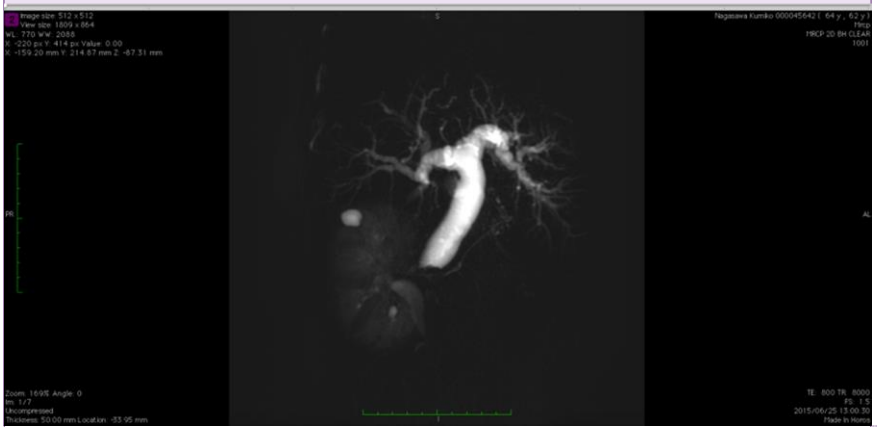


MRI of abdomen(coronal plane) showing
2.4x2.1cm mass(arrow)
at the end of dilated common bile duct

(x10)

A tumor at the distal bile duct was well differentiated adenocarcinoma (hematoxylin-eosin stain, original magnification, x10)

(Fig4)



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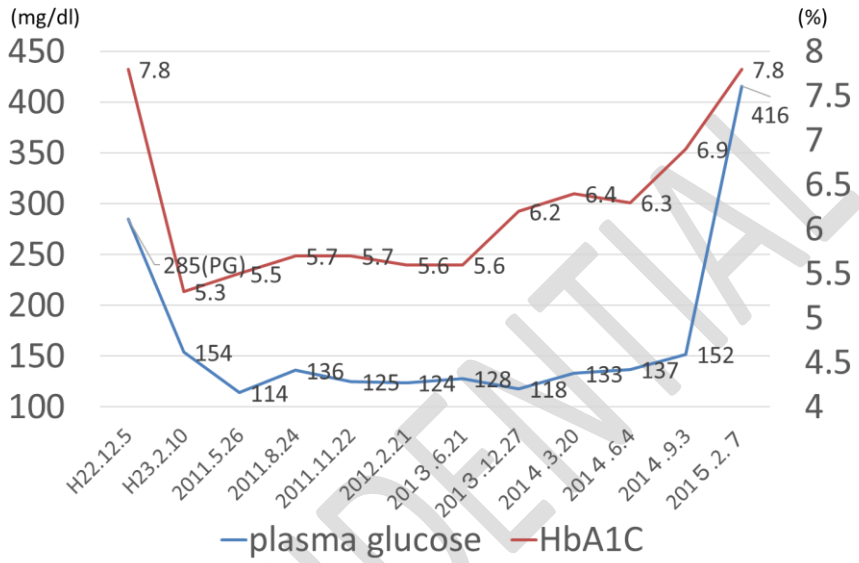
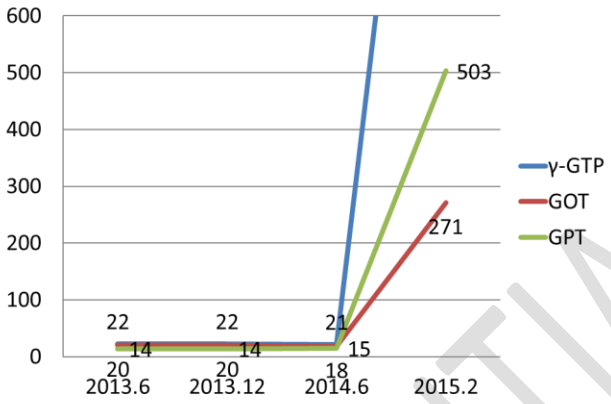
(Fig5)

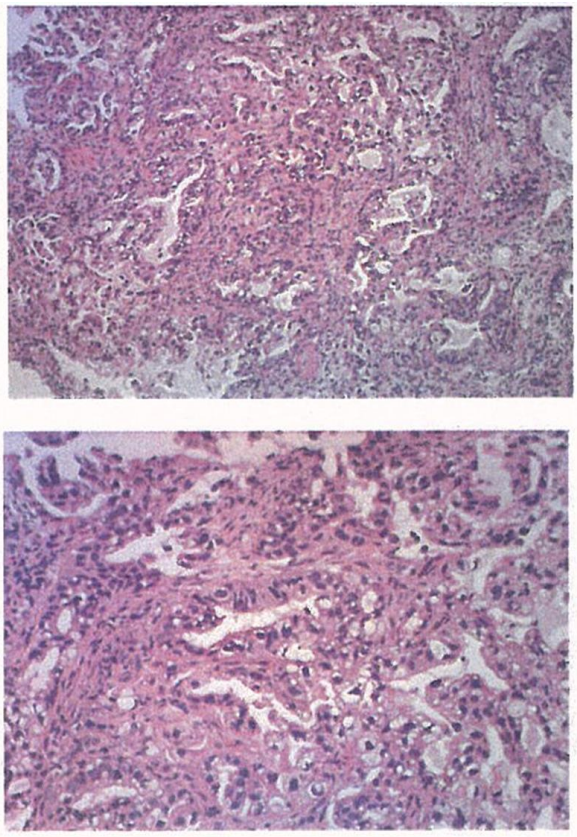


(Fig6)



	γ-GTP	GOT	GPT
2013.6	22	20	14
2013.12	22	20	14
2014.6	21	18	15
2015.2	1635	271	503

(Fig6)



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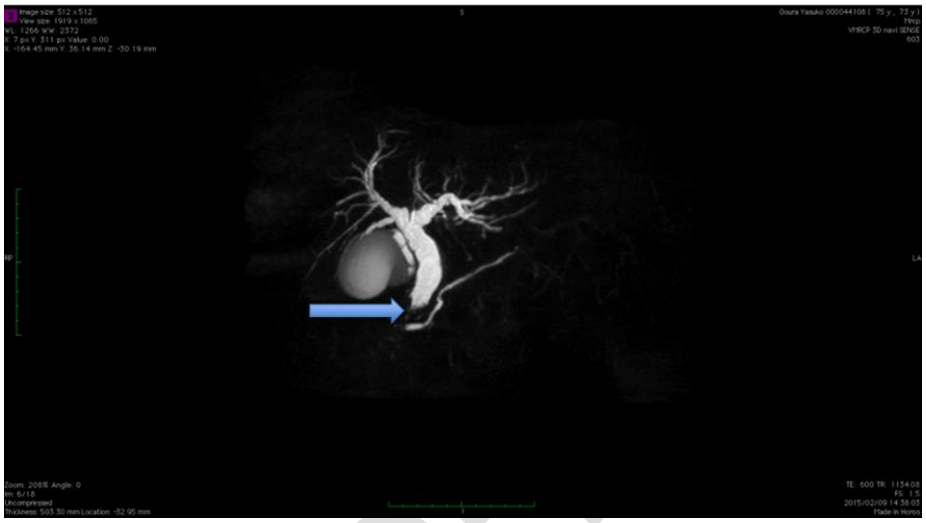
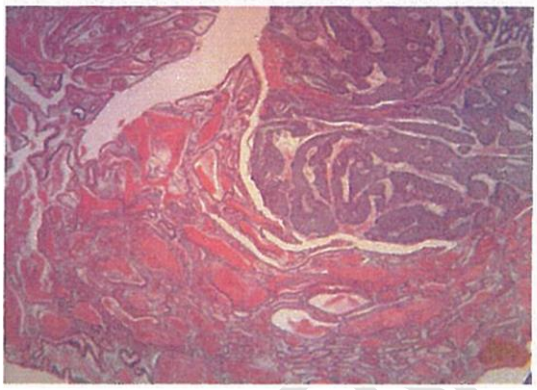
(Fig7)



MRCP(magnetic resonance cholangiopancreatography) showing obstruction of a dilated common duct (arrow) and normal appearance of pancreatic duct

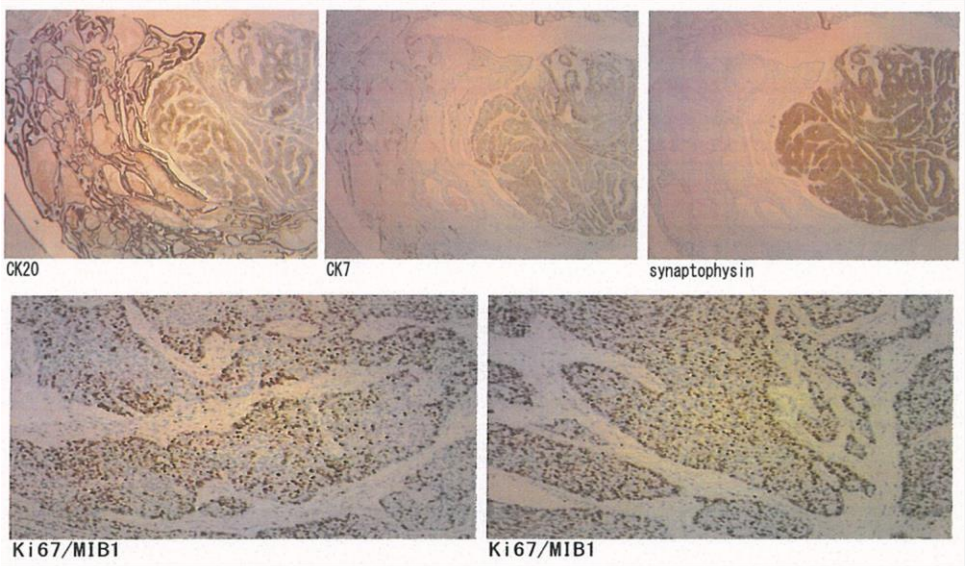
(Fig8)



The collision point of the adenocarcinoma(lower)
with the NEC(neuroendocrine carcinoma)(upper) (x10)
original magnification, x10

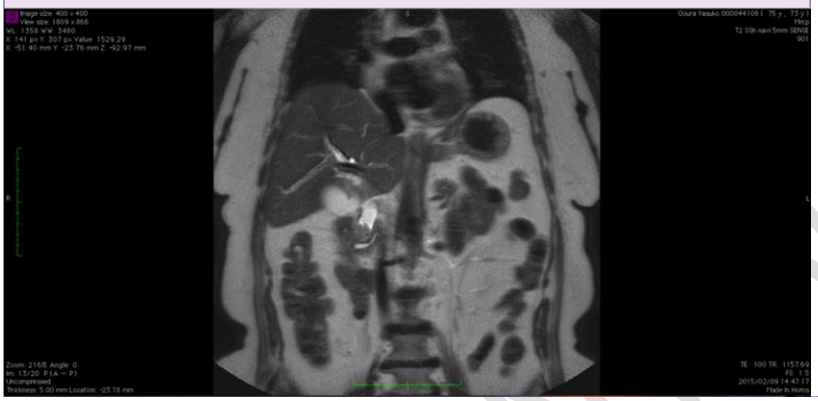
The collision point of the adenocarcinoma(lower)
with the NEC(neuroendocrine carcinoma)(upper)
original magnification, x10

(Fig9)



immunostaining (original magnification, x10)
epithetial marker(CK20) was strong positive,CK7 was slight positive
synaptophysin was strong positive. KI-67/MIBI was positive(30-40%)

(Fig9)



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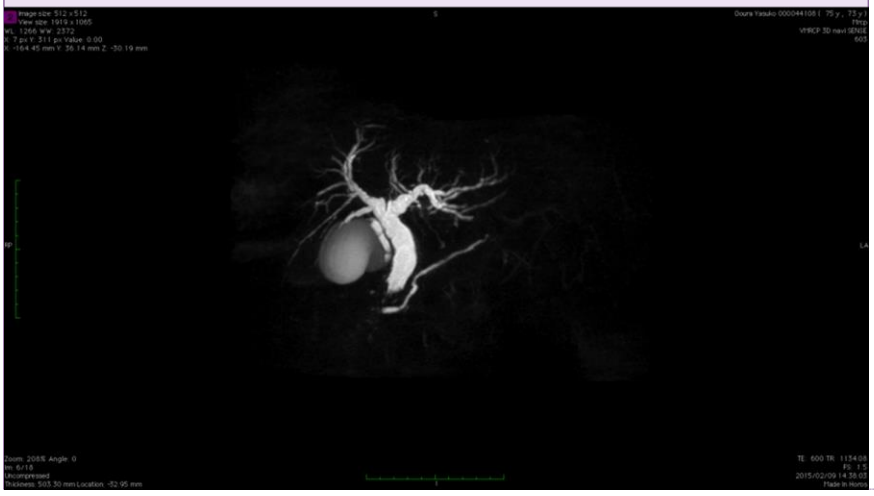
(Fig10)



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