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Case Report

Alpha-fetoprotein-producing hepatoid adenocarcinoma of the gallbladder: a case report and review of literature

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Abstract: Hepatoid adenocarcinoma (HAC) is an uncommon type of malignancy in extrahepatic tissues. It was named for its histopathological resemblance of hepatocellular carcinoma, the most common form of liver cancer. The occurrence of HAC in the gallbladder is very low, and tumours that produce alpha-fetoprotein are even rarer. Clinically, it is usually diagnosed histopathologically; and the prognosis is generally poor, largely due to its metastasis to the liver and peripheral lymph nodes. Currently, laparoscopic cholecystectomy combined with lymphadenectomy is the major therapeutic strategy for this type of cancer. Postoperative chemotherapy and periodic review are required to reduce the chance of recurrence. Because of the low occurrence of HAC in the gallbladder, our knowledge and therapeutic options against this malignancy are limited. Understanding the characteristics of the progression of this malignancy would be beneficial to its diagnosis and treatment in future clinical practice. In this study, we report a case of HAC of the gallbladder in a 55-year-old male, who presented a significant increase of alpha-fetoprotein and a marginal elevation of carcinoembryonic antigen in serum. The patient underwent laparoscopic cholecystectomy and lymphadenectomy, followed by sorafenib administration. As a result, no recurrence was found during the follow-up period, and the patient maintained a general quality of life.

Keywords: Alpha-fetoprotein, hepatoid adenocarcinoma, gallbladder cancer, hepatocellular carcinoma, metastasis

Introduction

Hepatoid adenocarcinoma (HAC) is an extraordinary type of adenocarcinoma with hepatocellular features [1]. Histologically, it contains both adenocarcinoma and hepatocellular carcinoma components, manifesting morphological and functional characteristics of liver-like differentiation [2-4]. Hepatoid adenocarcinoma producing alpha-fetoprotein (AFP) was first reported in 1985 as a subtype of stomach cancer [1, 5, 6], which was later found in other organs such as lung [7, 8], kidney [9, 10], spleen [11], and female genital tract [12, 13]. In this study, we report a case of AFP-producing HAC in the gallbladder, which was treated at our clinic by surgery and chemotherapy.

Case report

In 2014, a 55-year-old male patient, who had otherwise been healthy, presented at the First Affiliated Hospital of Jilin University with intermittent discomfort in the upper right abdomen that lasted for two weeks. Physical examination at admittance showed no yellowing of the skin and sclera. The abdomen was flat, but with tenderness in the upper right area; and no Blumberg's sign or muscular tension was found. Abdominal ultrasound indicated a 43×20 mm irregularly-shaped solid lesion on the posterior gallbladder wall, extending to the end of the gland. The lesion protruded into the gallbladder cavity and showed no mobility with the change of body postures. The liver capsule was smooth and intact, and its shape was normal. Fine and dense dotty resonance was seen in the liver parenchyma. Horizontal and three-phase spiral computed tomography (CT) demonstrated irregular thickening of the gallbladder wall, with localized soft tissue masses of up to 3.4×2.1 cm in size. Arterial phase enhancement was obvious, and pathology has likely spread to the serous layer (**Figure 1**). Laboratory analysis suggested that the patient had a significantly high-

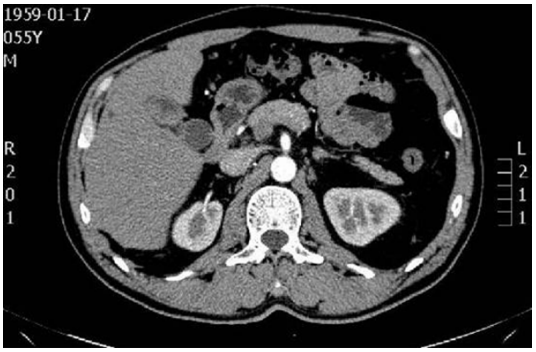

Figure 1. Pre-operative three-phase spiral CT of liver and gallbladder demonstrated arterial phase enhancement in the gallbladder.

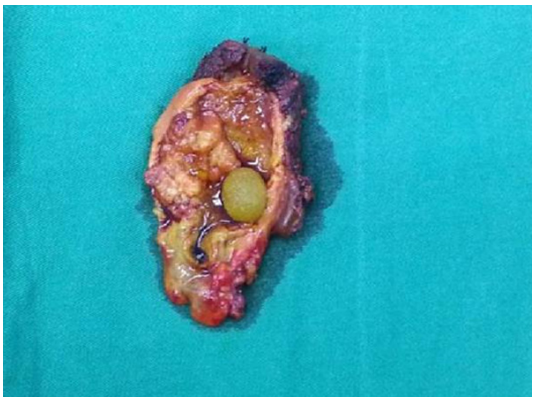

Figure 2. A cauliflower-like mass was observed at the gallbladder end with a greyish cutting surface.

er serum AFP level (440.9 ng/ml; normal value is ≤ 7.0 ng/ml). Carcinoembryonic antigen (CEA) in serum increased to 4.8 ng/ml (normal value is < 3.4 ng/ml) and carbohydrate antigen 19-9 (CA19.9) was 23.4 U/ml (normal value is < 27.0 U/ml). Liver function was normal, and no infection by hepatitis B and C were detected. Based on these clinicopathological features, the patient was diagnosed with gallbladder cancer; and radical resection surgery was scheduled.

During the operation, the surface of the liver was observed to be smooth; but the gallbladder shrunk to 6.0×4.0×2.0 cm. Folded dysplasia with a tough and stringy texture was found on the gallbladder wall, and a cauliflower-like mass could be reached. The gallbladder adhered with the surrounding liver tissues. Therefore, the gallbladder and the attached liver tissues were removed. Then, lymphadenectomy was performed along the liver-duodenum ligament. The size of the gallbladder was 7×3×1.5 cm and the

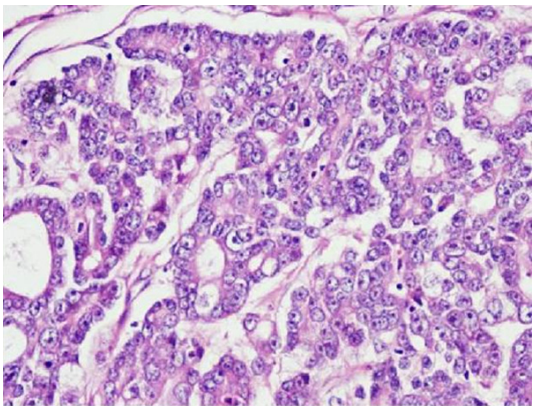

Figure 3. Cancer cells organized in nest and trabecular patterns were visualized after hematoxylin and eosin staining (magnification, 400×).

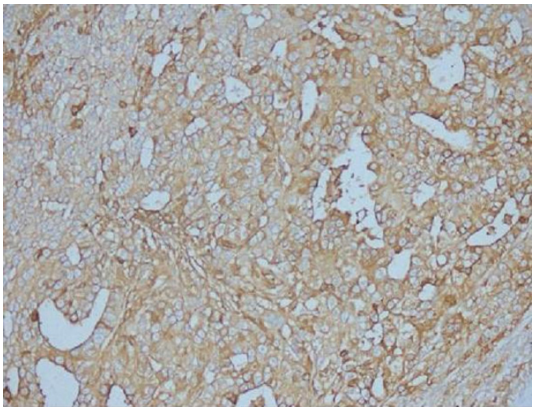

Figure 4. Immunohistochemical staining showed AFP in cancer cells (magnification, 200×).

thickness of the gallbladder was 0.1-0.2 cm, as confirmed by post-operative pathological analysis. Close to the gallbladder end, a 3.3×2.5×1.0 cm cauliflower-like mass was found with a greyish cutting surface and a solid and hard texture (**Figure 2**). In the vicinity of the tumour mass, the serous layer of the gallbladder attached to a portion of the liver tissue, which was 6.0×4.0×1.5 cm in size with a red-brownish cutting surface and soft texture. No lymph node metastasis was found along the liver-duodenum ligament. In addition, there was a mobile gallbladder stone, which was green in colour and 2 cm in diameter.

Pathological analysis demonstrated that cancer cells were organized in a nest or trabecular pattern (**Figure 3**), showing the histological features of a medium-to-poorly differentiated adenocarcinoma with a HAC component. Immuno-

Table 1. Clinical and pathological features of patients with hepatoid adenocarcinoma of the gallbladder reported in the literature

Tumor size (cm)	Stone	Cellular order	Liver metastasis	Lymph node metastasis	Reference
4.5	No	Nest, trabecular	Multiple	No	{Nakashima, 2000} [21]
6	No	Trabecular	Multiple	Multiple	{Sakamoto, 2004} [24]
5	Yes	Nest, trabecular	No	No	{Sakamoto, 2005} [23]
6.5	No	Nest, trabecular	No	No	{Sakamoto, 2005} [23]
2.5	No	Nest, trabecular	No	Not recorded	{Gakiopoulou, 2007} [20]
2	Yes	Trabecular	Yes	Yes	{Lee, 2011} [15]
2	Yes	Trabecular	No	No	{Koswara, 2007} [25]
11	No	Nest, trabecular	Yes	No	{Ellouze, 2011} [17]
5	Yes	Not recorded	No	Yes	{Hu, 2010} [36]
3.5	Yes	Sheets, trabecular	No	Yes	{Lin, 2008 16} [29]
6	No	Clusters and cords	No	No	{Li, 1999 14} [37]
3	No	Nest, trabecular	No	No	{Yi, 1997 13} [38]
5	No	Nest, trabecular	Yes	Yes	{Li, 1998 12} [27]
3	Yes	Nest, trabecular	No	No	Current case

Table 2. Immunohistochemical characteristics of hepatoid adenocarcinoma reported in the literature

Reference	AFP	Hep Par-1	Cytokeratin 8	Cytokeratin 7	Cytokeratin 19
{Nakashima, 2000 9} [21]	N	NC	LP	P	LP
{Sakamoto, 2004 8} [24]	N	P	P	N	P
{Sakamoto, 2005 7} [23]	N	P	P	N	P
{Sakamoto, 2005 7} [23]	P	P	P	N	P
{Gakiopoulou, 2007 6} [20]	WP	SP	NC	N	NC
{Lee, 2011 2} [15]	LP	N	NC	N	NC
{Koswara, 2007 19} [25]	SP	NC	NC	NC	NC
{Ellouze, 2011 4} [17]	P	P	NC	NC	NC
{Hu, 2010 15} [36]	NC	NC	NC	NC	NC
{Lin, 2008 16} [29]	N	P	SP	SP	SP
{Li, 1999 14} [29]	P	NC	NC	NC	NC
{Yi, 1997 13} [38]	P	NC	NC	NC	NC
{Li, 1998 12} [27]	P	NC	NC	NC	NC
Current case	P	NC	NC	NC	NC

N, Negative; P, Positive; LP, Localized positive; WP, Weakly positive; SP, Strongly positive; NC, Not checked.

histochemical analysis indicated that cancer cells were positive for AFP (**Figure 4**). The patient was discharged from the hospital one week after radical resection surgery. Re-examination at week three after the surgery revealed that AFP serum level decreased to 40.4 ng/ml, and CEA dropped to 2.2 ng/ml. One month after the surgery, the patient was further treated with two courses of sorafenib, each for four weeks at a dose of 200 mg (twice a day, orally).

Follow-ups at three and six months after surgery revealed that AFP levels were 38.5 and 35.6 ng/ml, respectively; which remained higher than normal. However, color Doppler ultrasound and CT demonstrated no obvious abnormality in the cavity. The patient was on a normal diet, had been urinating and defecating normally, and body weight of the patient remained unchanged. The general life quality of the patient was maintained.

Literature review and discussion

In this study, we report a case of HAC of the gallbladder producing high level of AFP. For this rare case, we have detailed the clinicopathological characteristics and diagnosis, therapeutic decision, and clinical outcome. This case study increased the awareness of HAC of the gallbladder. The diagnosis and treatment procedure will be helpful in future clinical practice to avoid its misinterpretation as metastatic hepatocellular carcinoma.

A previous statistical analysis on 262 cases of HAC suggested that this malignancy commonly occurred in the stomach and ovary, which accounts for 63% and 10% of cases, respec-

tively [14]. It can also be found in lung, pancreas, uterus, and gallbladder; but with much lower incidences [14]. AFP-producing HAC in the gallbladder is very rare. The first such a case with a full description was documented in 1995 by Vardaman and Albores-Saavedra, who found cancer tissues with hepatic differentiation in a bulk of gallbladder clear-cell carcinoma, and these tissues were positive for AFP and CEA [15, 16]. Its liver-like feature with a *cholangiole* component was confirmed under an electron microscope [16]. Since then, approximately 10 articles on cases of HAC of the gallbladder have been published [15, 17-25]. The visual characteristics of this malignancy, as well as their pathological and immunohistochemical features, are summarized in **Tables 1** and **2**.

Metzgeroth *et al.* demonstrated that HAC of the gallbladder commonly occurred in elderly patients (74 years old in average) at a male to female ratio of 1:4.5 [14]. However, our patient was young and had a gallbladder stone, a pathological feature frequently observed in patients with HAC of the gallbladder. In **Table 2**, 5 of 13 patients had a history of gallbladder stones, suggesting the potential association of HAC with the gallbladder stones. In fact, asymptomatic stones larger than 2 cm had been recommended as a risk factor for gallbladder cancer [26-28].

HAC of the gallbladder is currently diagnosed based on the clinicopathological features of the patients, particularly the elevation of a group of liver-specific proteins in blood, including AFP, albumin, transferrin, and α1-antitrypsin. However, the reliability of these proteins as markers in the diagnosis of HAC is questionable. For example, AFP is most relevant to HAC, however, its increase is not essential for HAC of the gallbladder [15], as indicated by the previously reported cases with no increase of AFP in serum [21, 23, 24, 29]. Hepatocyte specific antigen (Hep Par-1) has been regarded as a marker for the hepatic differentiation of cancer cells [30, 31], but its specificity and sensitivity are in dispute [20]. Thus, further studies are needed to screen for appropriate markers for HAC in the gallbladder.

Furthermore, differentiating HAC of the gallbladder from the metastases of hepatocellular carcinoma to the gallbladder is critical for its clinical outcome [17, 32]. Hepatocellular carcinoma is usually associated with liver cirrhosis, hepatitis, and other risk factors which cause damage to the liver function [33]. Patients with normal liver function rarely have hepatocellular carcinoma spreading to the gallbladder [34]. At molecular level, the expression of cytokeratin 19 can be helpful in the diagnosis of HAC, because this protein is rarely expressed in hepatocellular carcinoma but commonly expressed in HAC [35]. In addition, HAC of the gallbladder exhibited an intensified signal on the edge on T2 weighted magnetic resonance imaging, but without a visible capsule.

The mechanism of HAC tumourigenesis remains unknown. These tumours were originally believed to be adenocarcinomas acquiring hepatic differentiation features during progression, or tumours arising from the endoderm that are capable of differentiating into glandular and hepatoid cells [24, 25]. A recent study suggested that this malignancy may originate from hepatobiliary stem cells and progenitors {Dettoni, 2014 1}. Future phylogenetic studies, particularly genetic fingerprinting by cancer genome and transcriptome sequencing, are needed to identify the origin of this type of cancer.

In summary, HAC of the gallbladder is a rare but aggressive malignancy, which mostly occurs in the elderly population. The tumour often metastasizes to liver and peripheral lymph nodes, which predicts a poor prognosis. Although the occurrence of gallbladder stone, increase of AFP in serum, and imaging are important, pathological and immunohistochemical confirmation is essential for the diagnosis of HAC. Currently, laparoscopic cholecystectomy with lymphadenectomy represents an ideal therapeutic strategy [15], and postoperative chemotherapy and periodic re-examination are usually recommended. When surgery is unfeasible or tumour metastasis occurs, sorafenib or other tyrosine kinase inhibitors can be used [18]. In general, an early and precise diagnosis, radical resection surgery, and appropriate chemotherapy are key strategies in the treatment of HAC in the gallbladder.

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Disclosure of conflict of interest

None.

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References

[1] Ishikura H, Fukasawa Y, Ogasawara K, Natori T, Tsukada Y and Aizawa M. An AFP-producing gastric carcinoma with features of hepatic differentiation. A case report. Cancer 1985; 56: 840-848.

[2] Kashani A, Ellis JC, Kahn M and Jamil LH. Liver metastasis from hepatoid adenocarcinoma of the esophagus mimicking hepatocellular carcinoma. Gastroenterol Rep (Oxf) 2015; [Epub ahead of print].

[3] Pan JH, Dong MJ and Ouyang XB. A hepatoid adenocarcinoma of the stomach with liver metastasis mimicking hepatocellular carcinoma detected by F-18 FDG PET/CT imaging. Clin Nucl Med 2011; 36: 1137-1139.

[4] Terracciano LM, Glatz K, Mhawech P, Vasei M, Lehmann FS, Vecchione R and Tornillo L. Hepatoid adenocarcinoma with liver metastasis mimicking hepatocellular carcinoma: an immunohistochemical and molecular study of eight cases. Am J Surg Pathol 2003; 27: 1302-1312.

[5] Caruso RA. Hepatoid gastric adenocarcinoma. A histological and immunohistochemical study of a case. Eur J Basic Appl Histochem 1991; 35: 203-209.

[6] Ebihara T, Koyama S, Hirai S, Nakahara A, Tanaka N, Yamagata S, Muto H, Fukutomi H, Osuga T, Doi M, et al. [An autopsy case of AFP-producing gastric carcinoma resembling hepatocellular carcinoma on light microscopy]. Gan No Rinsho 1987; 33: 399-405.

[7] Arnould L, Drouot F, Fargeot P, Bernard A, Foucher P, Collin F and Petrella T. Hepatoid adenocarcinoma of the lung: report of a case of an unusual alpha-fetoprotein-producing lung tumor. Am J Surg Pathol 1997; 21: 1113-1118.

[8] Ishikura H, Kanda M, Ito M, Nosaka K and Mizuno K. Hepatoid adenocarcinoma: a distinctive histological subtype of alpha-fetoprotein-producing lung carcinoma. Virchows Arch A Pathol Anat Histopathol 1990; 417: 73-80.

[9] Ishikura H, Ishiguro T, Enatsu C, Fujii H, Kakuta Y, Kanda M and Yoshiki T. Hepatoid adenocarcinoma of the renal pelvis producing alpha-fetoprotein of hepatic type and bile pigment. Cancer 1991; 67: 3051-3056.

[10] Shim J, Go H, Lim YS, Moon KC, Ro JY and Cho YM. Hepatoid differentiation in renal cell carcinoma: a rare histologic pattern with clinical significance. Ann Diagn Pathol 2014; 18: 363-368.

[11] Deng Z, Yin Z, Chen S, Peng Y, Wang F and Wang X. Metastatic splenic alpha-fetoprotein-producing adenocarcinoma: report of a case. Surg Today 2011; 41: 854-858.

[12] Matias-Guiu X, Lerma E and Prat J. Clear cell tumors of the female genital tract. Semin Diagn Pathol 1997; 14: 233-239.

[13] Shintaku M, Kariya M, Shime H and Ishikura H. Adenocarcinoma of the uterine cervix with choriocarcinomatous and hepatoid differentiation: report of a case. Int J Gynecol Pathol 2000; 19: 174-178.

[14] Metzgeroth G, Strobel P, Baumbusch T, Reiter A and Hastka J. Hepatoid adenocarcinoma- review of the literature illustrated by a rare case originating in the peritoneal cavity. Onkologie 2010; 33: 263-269.

[15] Lee JH, Lee KG, Paik SS, Park HK and Lee KS. Hepatoid adenocarcinoma of the gallbladder with production of alpha-fetoprotein. J Korean Surg Soc 2011; 80: 440-444.

[16] Vardaman C and Albores-Saavedra J. Clear cell carcinomas of the gallbladder and extrahepatic bile ducts. Am J Surg Pathol 1995; 19: 91-99.

[17] Ellouze S, Slim C, Ahmad G, Naourez G, Ali A, Hela M, Mariem K, Mohamed BA and Tahia B. Hepatoid adenocarcinoma of the gallbladder. World J Surg Oncol 2011; 9: 103.

[18] Karayiannakis AJ, Kakolyris S, Giatromanolaki A, Courcoutsakis N, Bolanaki H, Chelis L, Sivridis E and Simopoulos C. Hepatoid Adenocarcinoma of the Gallbladder: Case Report and Literature Review. J Gastrointest Cancer 2012; 43 Suppl 1: 139-144.

[19] van den Bos IC, Hussain SM, Dwarkasing RS, Stoop H, Zondervan PE, Krestin GP and de Man RA. Hepatoid adenocarcinoma of the gallbladder: a mimicker of hepatocellular carcinoma. Br J Radiol 2007; 80: e317-320.

[20] Gakiopoulou H, Givalos N, Liapis G, Agrogiannis G, Patsouris E and Delladetsima I. Hepatoid adenocarcinoma of the gallbladder. Dig Dis Sci 2007; 52: 3358-3362.

[21] Nakashima H, Nagafuchi K, Satoh H, Takeda K, Yamasaki T, Yonemasu H and Kishikawa H. Hepatoid adenocarcinoma of the gallbladder. J Hepatobiliary Pancreat Surg 2000; 7: 226-230.

[22] Nishiwaki M, Kimura M, Gega M, Ohi Y, Nishioka A, Ashida H, Yamamura T, Utsunomiya J and Nishigami T. [A case of adenocarcinoma

of the gallbladder with lymph node metastasis showing hepatoid adenocarcinoma and producing alfa-fetoprotein]. Nihon Shokakibyo Gakkai Zasshi 1997; 94: 874-878.
[23] Sakamoto K, Kimura N, Tokumura H, Ogasawara T, Moriya T and Sasano H. Hepatoid adenocarcinoma of the gallbladder. Histopathology 2005; 47: 649-651.
[24] Sakamoto K, Monobe Y, Kouno M, Moriya T and Sasano H. Hepatoid adenocarcinoma of the gallbladder: Case report and review of the literature. Pathol Int 2004; 54: 52-56.
[25] Koswara T, Marwoto W, Siregar NC, Gumay S, Azis H, Abdullah M and Himawan S. Hepatoid carcinoma of the gallbladder. Acta Med Indones 2007; 39: 179-182.
[26] Csendes A, Becerra M, Rojas J and Medina E. Number and size of stones in patients with asymptomatic and symptomatic gallstones and gallbladder carcinoma: a prospective study of 592 cases. J Gastrointest Surg 2000; 4: 481-485.
[27] Li XZ, Zhang DQ, Wang CS, Mi FY and Yang HC. Case reports of hepatoid adenocarcinoma of the ballbladder and common bile duct. Chinese Clinical Oncology 1998; 3: 46.
[28] Serra I and Diehl AK. Number and size of stones in patients with asymptomatic and symptomatic gallstones and gallbladder carcinoma. J Gastrointest Surg 2002; 6: 272-273; author reply 273.
[29] Lin M, Ye Q and Chen J. A case report of hepatoid adenocarcinoma of gallbladder. National Medical Journal of China 2008; 88: 69-70.
[30] Minervini MI, Demetris AJ, Lee RG, Carr BI, Madariaga J and Nalesnik MA. Utilization of hepatocyte-specific antibody in the immunocytochemical evaluation of liver tumors. Mod Pathol 1997; 10: 686-692.
[31] Wennerberg AE, Nalesnik MA and Coleman WB. Hepatocyte paraffin 1: a monoclonal antibody that reacts with hepatocytes and can be used for differential diagnosis of hepatic tumors. Am J Pathol 1993; 143: 1050-1054.
[32] Tian YF and Wei BY. A case report of hepatocellular carcinoma in gallbladder. Chinese Journal of Hepatobiliary Sergery 2001; 7: 118-118.
[33] El-Serag HB. Hepatocellular carcinoma. N Engl J Med 2011; 365: 1118-1127.
[34] Murakami M, Kobayashi S, Marubashi S, Eguchi H, Takeda Y, Tanemura M, Wada H, Umeshita K, Kennichi W, Doki Y, Mori M and Nagano H. Isolated metastasis to the gallbladder from hepatocellular carcinoma. Hepatol Res 2010; 40: 793-798.
[35] Su JS, Chen YT, Wang RC, Wu CY, Lee SW and Lee TY. Clinicopathological characteristics in the differential diagnosis of hepatoid adenocarcinoma: a literature review. World J Gastroenterol 2013; 19: 321-327.
[36] Hu JY, Li JJ and Qiu SB. A case of gallbladder cancer with elevated afp. Journal of Hepatopancreatobiliary Surgery 2010; 22: 259.
[37] Li SQ, Zhong YF, Liao SL, ZHang CX, Zhu YM and Zhang CB. A case report of hepatoid adenocarcinoma of the gallbladder. Chinese Journal of Pathology 1999; 79.
[38] Yi GZ, Ming JQ and Hu W. Hepatoid adenocarcinoma of the gallbladder. Chinese Journal of Clinical and Experimental Pathology 1997; 75.