Letter to the Editor

A 47-year-old female with primary hepatoid adenocarcinoma in the pelvic retroperitoneum

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Background

Hepatoid adenocarcinoma (HAC) refers to a primary extrahepatic origin that histologically resembles a typical hepatocellular carcinoma (1). HAC, which is highly malignant, aggressive, and very rare (2) , can occur in the lung and gastrointestinal tract (3,4), but occurrence in the pelvic retroperitoneum is rare. The disease is mainly diagnosed by pathology; that is, detection of both hepatocellular and adenocarcinoma differentiated areas in the tumor. Immunohistochemistry is usually positive for one or more markers, such as alpha fetoprotein (AFP), spalt-like transcription factor 4 (SALL4), and glypican-3 (GPC3) (5), and imaging presentations may also provide valuable information for the diagnosis of this disease, as it usually manifests with clear localization, thus providing a basis for clinical surgery. Most hepatoid adenocarcinomas present with elevated serum AFP level. The survival rate of this disease is low, and the prognosis is usually poor (6).

Case presentation

All procedures performed in this study were in accordance with the ethical standards of the Ethics Committee of Beijing Friendship Hospital Affiliated to Capital Medical University and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

A 47-year-old female arrived at Beijing Friendship Hospital of Capital Medical University due to abnormal blood discharge from the vagina for 1 year. The patient reported persistent elevated serum AFP for 5 years and right upper abdominal pain for 4 years; biochemical examination showed an elevated serum AFP level of 96.69 ng/mL (the normal reference value is 0–15 ng/mL) and an CA125 level of 86.70 U/mL (the normal reference value is 0–35 U/mL). Chronic nonatrophic gastritis with erosion was diagnosed with gastroscopy, but colonoscopy showed no abnormality.

The patient underwent a gynecologic physical examination. There was a small amount of light pink discharge from the vagina and a 16-week-size uterus. No abnormalities or tenderness were found in the bilateral appendages. Human papillomavirus (HPV) testing was negative. ThinPrep cytology test (TCT) showed no intraepithelial lesions or carcinogenesis. No history of vaccination was recorded. Gynecologic ultrasound in our hospital showed adenomyosis and fibroids. The bilateral ovaries were normal. Hysteroscopy and related examinations were further performed in the gynecology department, and the pathology was considered to be endometrial hyperplasia

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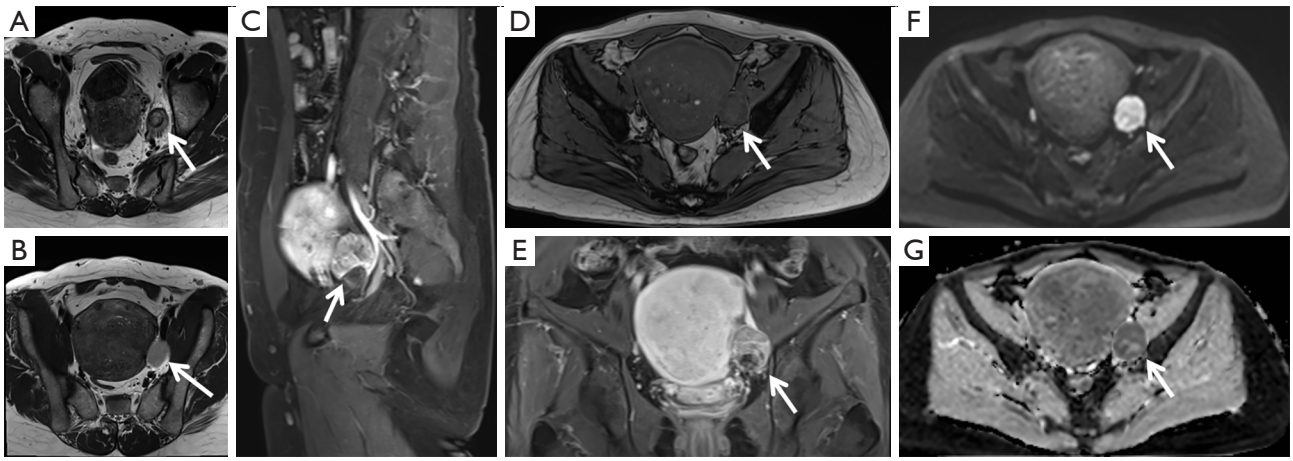

Figure 1 Radiologic imagining of the patient: magnetic resonance imaging clearly localizes the mass and signal characteristics. (A) Axial T2-weighted image showing the inferior pole of the mass (white arrow) located lateral to the left ureter and left peritoneal line. (B) Axial T2-weighted image showing the superior pole of the mass (white arrow) located below the bifurcation of the left external iliac artery and internal iliac artery vessels. (C) Sagittal enhanced T1-weighted image showing the mass (white arrow) located lateral to the internal iliac artery, with an uneven signal on the enhanced scan. (D) Axial T1-weighted image showing an equal or slightly low signal mass (white arrow). (E) Coronal enhanced T1-weighted image showing heterogeneous enhancement in the delayed phase of the mass (white arrow), with mild-to-moderate enhancement in some areas. (F) Axial DWI (b=1,000) image and (G) axial ADC image showing the mass (white arrow) with diffusion-limited intensification. DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient.

with atypical cellular changes. In order to further clarify the cause of the disease, an enhanced magnetic resonance imaging (MRI) examination of the abdominopelvic region was performed in the radiology department; MRI results and ultrasound findings included a round abnormal signal shadow at the bifurcation of the left external iliac artery and internal iliac artery in the retroperitoneum, with a clear demarcation between the lesion and the uterus and a slight posterior displacement of the left internal iliac artery (*Figure 1A-1C*) about 4.1 cm × 3.0 cm × 3.4 cm size with a heterogeneous signal. On imaging, it usually appeared as a solid mass without central cystic changes due to hemorrhage and necrosis. The signal was equal or slightly low on T1-weighted imaging (T1WI), slightly high on T2-weighted imaging (T2WI), significantly high on diffusion-weighted imaging (DWI), and hypointense on apparent diffusion coefficient (ADC). In the arterial phase, the enhancement was uneven and mild to moderate, and in the delayed phase, partial delayed enhancement with small patchy unreinforced foci could be observed (*Figure 1D-1G*). Thus, a diagnosis of retroperitoneal cystic masses was excluded. Retroperitoneal liposarcoma is a solid soft tissue mass with mixed density, and the lesion is mainly composed of adipose tissue. This diagnosis of was ruled out after the patient's MRI imaging was compared with the typical imaging features of liposarcoma. Therefore, the diagnoses of cystic masses (yolk-sac tumors), liposarcoma, and teratomas were excluded. Although human chorionic gonadotropin (hCG) levels were within the normal range, extragonadal germ cell tumors cannot be completely excluded. On imaging, a poly-cyclic mass is frequently seen close to the large vessels, but a more well-defined lesion can also be observed. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography computed tomography (PET-CT) was suggested to determine the presence of malignancy and tumor staging. However, the patient and her family refused PET-CT and requested that the mass be surgically removed. Based on the patient's medical history, and with no fertility requirements, the gynecologist thought there was an indication for surgery. The preoperative lung CT showed no abnormalities. An abdominal enhanced MRI showed no liver lesion or other lesions. After the preoperative preparations were completed, the surgery was scheduled.

Two months later, the patient underwent hysterectomy, bilateral salpingo-oophorectomy, pelvic retroperitoneal mass resection, and vascular exploration in our hospital. During the operation, a 16-week-size uterus were found. No abnormalities were found in the bilateral appendages. No cancer cells were found in the preoperative peritoneal

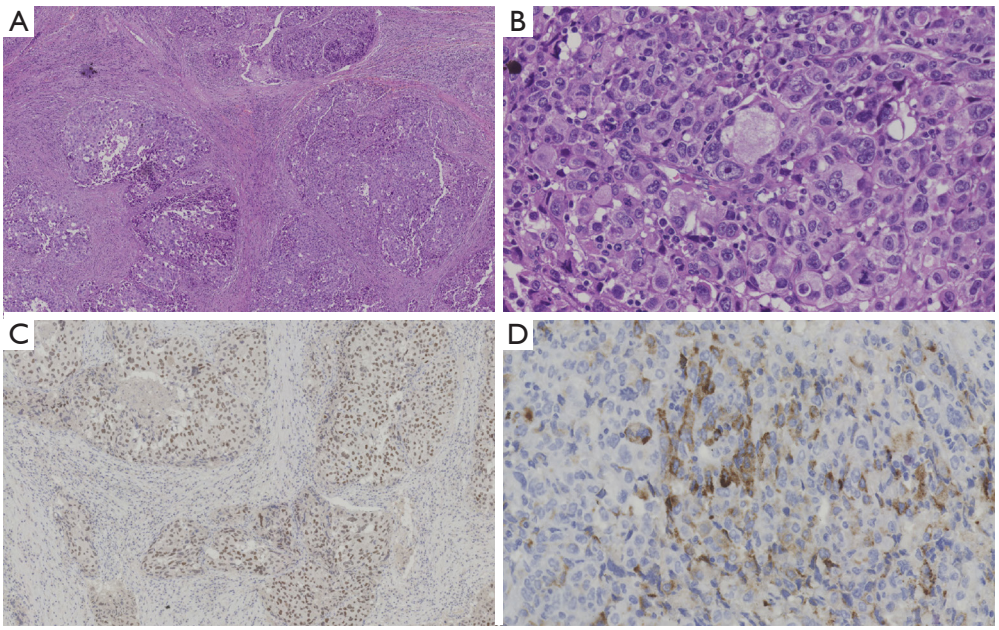

Figure 2 Pathological morphology. (A) Solid nest-like infiltration of tumor cells was visible in the fibrous tissue (HE, 50×). (B) The tumor cell was large with rich cytoplasm and round- or oval-shaped nuclei. The chromatin was vacuumed, and some tumor cells showed significant large nucleoli. Scattered multinucleated giant were apparent (HE, 400×). (C) Approximately 100% of tumor cells expressed SALL4 (immunohistochemical staining, 100×). (D) The scattered tumor cells with few cells expressing AFP (immunohistochemical staining, 400×). SALL4, spalt-like transcription factor 4; AFP, alpha fetoprotein; HE, hematoxylin and eosin.

fluid. A solid mass with a purplish-black surface at the bifurcation of the left external iliac artery and internal iliac artery, about 5.0 cm × 4.0 cm × 4.0 cm, was completely resected, and no metastatic nodules were seen in the pelvis and retroperitoneum. Postoperative pathological findings showed the following: (pelvic mass) 6 grayish nodules, a diameter of 7–35 mm, solid cancer nest infiltration in the fibrous tissue [hematoxylin and eosin (HE); 50×] (*Figure 2A*), no vascular or lymphatic invasion, no cancer cells apparent at the margins, large tumor cells, a rich cytoplasm, round- or oval-shaped nuclei, a vacuumed chromatin, some tumor cells with significant large nucleoli, and scattered multinucleated giant cells seen (HE; 400×) (*Figure 2B*). Immunohistochemistry indicated the following: SALL4 (+) (*Figure 2C*), GPC3 (partial +), AFP (scattered few cells +) (*Figure 2D*), CDX-2(+), HepPar-1(–), CK8(+), CK19(+), and CK7(–); HAC was considered. The endometrium was extensive with atypical endometrial hyperplasia and small foci up to highly differentiated endometrioid carcinoma, confined to the endometrium, without myometrial infiltration (stage IA endometrial cancer); The morphology and immunohistochemistry of retroperitoneal lesions were not associated with endometrial cancer. Diffuse adenomyosis between the myometrium and multiple smooth muscle tumors between the myometrium and submucosa.

One month after the operation, a follow-up ^{18}F-FDG PET-CT scan revealed no abnormal uptake of FDG, except for in the operative area. Meanwhile, ^{18}F-FDG PET-CT showed no lesion in the liver and gastrointestinal tract. The serum AFP was 9.8 ng/mL, and the serum CA125 was 5.1 U/mL. Because HAC is characterized by high malignancy, aggressiveness, rapid progression, and poor prognosis, the patient received 6 cycles of adjuvant chemotherapy, molecular targeted therapy, and immunotherapy (paclitaxel + anlotinib + penpulimab) after surgery. The serum AFP was 12.4 ng/mL, the serum CA125 was 4.6 U/mL, and no clear metastatic lesions were seen on abdominopelvic MRI at 7 months postoperation.

Discussion

Hepatoid adenocarcinoma (HAC), first described by Ishikura *et al.* (7) in 1985, is a particular subtype of adenocarcinoma referred to as such due its immunophenotypic and histomorphologic similarities to hepatocellular carcinoma

(HCC). Extrahepatic hepatoid adenocarcinoma can occur in gastric (63%), ovarian (10%), lung (5%), and uterine (4%) cancers (8). HAC is highly aggressive, prone to liver metastases, and has a very poor prognosis, with a five-year survival rate of less than 41.1% (4). HAC can occur in almost all digestive organs, especially the stomach, likely because the stomach and the liver originate from the same part during the embryonic stage (9). In addition, HAC can also occur in the ovaries, gallbladder, and uterus (10-12), but its occurrence in the pelvic retroperitoneum is rare.

The clinical presentation of patients with HAC is dominated by abdominal symptoms such as abdominal distension and abdominal pain, which lack specificity. For instance, it was challenging to pinpoint the location of the lesion in this case despite the patient`s history of abdominal pain, and it is generally difficult to identify the mass until it is sufficiently large to cause symptoms such as compression of the surrounding tissues. Although normal serum AFP expression can occasionally be found, excessively increased serum AFP levels are more common in patients. The makeup of the histology sample may be connected to the level of serum AFP. In a large-sample study by Lin *et al.* (13), it was found that in HAC of the stomach (HAS), the level of serum AFP was related to tumor composition. In 137 patients, the tumor tissue contained hepatoid differentiation areas only, and in 178 patients, the tumor tissue included hepatoid differentiation areas plus common adenocarcinoma areas, with the former having significantly higher serum AFP levels than the latter (195.9 *vs.* 48.9 ng/mL; P<0.001). The study found that patients with HAS had higher preoperative serum AFP levels and a higher rate of liver metastases (13). Serum AFP levels have been reported to be associated with prognosis in patients with HAC (14). Elevated AFP may induce liver metastasis and a poorer prognosis via the increased frequency of microvessel density and increased expression of c-Met/hepatocyte growth factor (HGF) and vascular endothelial growth factor-C (VEGF-C) (15).

While ultrasonography is the preferred method of pelvic examination in females, it is susceptible to influences such as intestinal gas and frequently struggles to discern lesions due to the pelvic retroperitoneum. Enhanced CT is a valuable imaging method for evaluating the retroperitoneal tumor location, size, origin, and relationship to adjacent tissues and organs (16). However, CT is not fully applicable to the uterus and its appendages. In contrast, MRI has been extensively employed in the screening of abdominal and pelvic malignancies by virtue of its good soft tissue resolution and can clarify the boundary of the peritoneum, ureter and vascular course. According to the anatomical demarcation (17), the application of pelvic MRI enhancement examination in this case was able to clearly identify the mass located in the lateral aspect of the peritoneum and left ureter, below the bifurcation of the left external iliac artery and internal iliac artery vessels, with the lower pole of the mass being located in the anterolateral aspect of the left internal iliac artery. Based on this, we could clearly identify the lesion as being located in pelvic retroperitoneum rather than in the endoperitoneal organs such as uterus and ovary, and no other homologous lesions were found in the pelvis. Therefore, this case suggests that the fine localization of lesions with MRI is superior to any other imaging means. If the patient has unexplained elevated serum AFP with abdominal pain and no obvious abnormalities in the abdomen according to ultrasound examination, then the patient should be advised to undergo pelvic MRI multiphase enhancement examination to observe the signal changes of the lesion. In this way, even if the pathology is diagnosed as a rare disease, the patient's chance of survival can be improved by precise localization, early detection, and early treatment in the process of imaging screening. It can also assist the pathology department in clarifying whether the lesion is a primary or metastatic lesion. In this case, MRI of the mass showed a solid mass without fatty components with inhomogeneous signal and clear borders and mild-to-moderate enhancement, which was basically the same as the HAC MRI signal of the peritoneal cavity reported by Chen *et al.* (18), with a mild low signal in T1WI and a high signal in DWI; only the T2WI signal was different, probably due to the high fibrous component of the mass in this case. In the case reported by Chen *et al.*, the lesion was likely widely distributed in the peritoneal cavity in the form of multiple nodules or confined between the left diaphragm and the upper pole of the spleen with poorly defined borders; meanwhile, in our case, it only occurred outside the pelvic peritoneum with clear borders, which may be related to the space in which the lesion was located and its aggressiveness. Therefore, the presentation of HAC may vary depending on the location of its onset.

The entire tumor was solid with a purplish-black surface at the bifurcation of the left external iliac artery and internal iliac artery. The postoperative morphological features were relatively similar to those of HCC. Immunohistochemistry showed the HAC in the pelvic retroperitoneum was positive for SALL4, GPC3, AFP, CDX-2, CK8, and CK19 (5). An abdominal enhanced MRI showed no liver

lesion, which excluded primary hepatic carcinoma, and a subsequent ^{18}F-FDG PET-CT scan showed no other lesion, which excluded HAC of gastrointestinal origin (12). Taking into consideration the clinical, morphological and immunohistochemical features, we diagnosed the mass as primary HAC in the pelvic retroperitoneum.

The clinical treatment is also related to the location of HAC. Gastric HAC is more common than is HAC in other locations, so studies on this special type of tumor mainly focus on gastric HAC. The clinical treatment of gastric HAC is usually preceded by radical gastrectomy. At present, there is no definitive report regarding the specific efficacy of postoperative adjuvant therapy (19). Surgical treatment is the first choice, followed by chemotherapy and radiotherapy. The 3-year survival rates for patients with gastric cancer with 20 ng/mL < AFP <300 ng/mL and AFP >300 ng/mL have been reported to be 28.9% and 7.7%, respectively (14). Another study (13) found that elevated AFP (≥20 ng/mL) was not associated with prognosis among those with HAS, with preoperative carcinoembryonic antigen (CEA) ≥5 ng/mL being one of the independent risk factors for worse overall survival (OS). Moreover, the 3-year OS rate in the total sample of 315 patients with HAS was 58.1%. In addition, there was no significant difference in survival between patients who received traditional chemotherapy and those who did not. In recent years, with the remarkable development of gene molecular technology, targeted therapy and immunotherapy have become popular treatment methods in tumor treatment. Chen *et al.* (20) used a therapeutic regimen combining adjuvant chemotherapy with pemetrexed and cisplatin and targeted therapy with icotinib in a patient with HAC of the lung. The patient then received osimertinib and anlotinib for EGFR mutation and achieved progression-free survival of several months, the disease remained stable, and the patient is still alive. Given the low incidence of HAC, its poor prognosis, and the lack of a clear standard of care, we recommended adjuvant chemotherapy, molecular targeted therapy, and immunotherapy despite this patient's preoperative CEA being 0.57 ng/mL (0–5 ng/mL).

Conclusion

In this case, the primary lesion was in the pelvic retroperitoneum, which is very rare and not easily detectable. The significance of reporting this case is first that for rare tumors, imaging is required for accurate positioning on the premise of pathological diagnosis. As the one-stop diagnosis of rare diseases by imaging is difficult to achieve and not objective, it is obviously necessary to select the correct imaging tool for screening. In this case, the patient underwent timely pelvic MRI multiphase enhancement examination, and with its precise localization, the signal characteristics of multiphase enhancement also helped provide a clear direction for late clinical surgical intervention. Moreover, HAC can continuously increase serum AFP without the presence of an abnormal liver and can accumulate in the lung, gastrointestinal tract, retroperitoneum, and other parts, especially the pelvic retroperitoneum. This suggests that physicians should pay more attention to the dual clinical and imaging diagnosis to reduce the postoperative recurrence rate and improve the 5-year survival rate of patients.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-22-1290/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the Ethics Committee of Beijing Friendship Hospital Affiliated to Capital Medical University and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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