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Hepatic Follicular Dendritic Cell Sarcoma with a History of Cervical Cancer: A Rare Case Report of Multiple Primary Malignant Neoplasms

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ABSTRACT

The follicular dendritic cell sarcoma (FDCS) is a rare entity, accounting for only 0.4% of all soft tissue sarcomas. Hepatic FDCS, which represents approximately 30% of extranodal FDCS cases, has been reported in only 30 cases in the English literature. The clinical and imaging features of FDCS are non-specific, and its diagnosis relies heavily on pathological examination. Given that the morphology of FDCS resembles several hepatic tumors, diagnosing it poses significant challenges, requiring the exclusion of multiple differential diagnoses. The final diagnosis is based on immunohistochemical expression results. Multiple primary malignant neoplasms (MPMN) are defined as two or more primary tumors occurring either simultaneously or successively in the same organ (tissue) or different organs (tissues) within the same individual. This is the first reported case of MPMN involving intrahepatic FDCS and cervical cancer.

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Introduction

Follicular dendritic cell sarcoma (FDCS) is a rare, indolently growing mesenchymal tumor characterized by distinct histomorphological and immunophenotypic features of follicular dendritic cell (FDC) differentiation. It was first recognized by Monda and Rosai in 1986 [1]. FDCS constitutes only 0.4% of all soft tissue sarcomas [2]. While the majority of cases originate within lymph nodes, at least one-third arise in extranodal locations. Hepatic FDCS, accounting for approximately 30% of extranodal FDCS cases, has been documented in merely 30 cases in the English literature to the best of our knowledge [3]. The clinical and imaging characteristics of FDCS are non-specific, and its diagnosis is heavily reliant on pathological evaluation. Given its morphological resemblance to several hepatic tumors, diagnosing FDCS presents significant challenges and necessitates the exclusion of multiple differential diagnoses. The definitive diagnosis is established based on immunohistochemical findings, with positive expression of CD21, CD23, CD35, and/or D2-40 serving as specific and sensitive markers for FDCS. Complete surgical resection is regarded as the optimal treatment approach. Chemotherapy and/or radiotherapy may be considered for patients with recurrent, metastatic, or unresectable disease [4].

Multiple primary malignant neoplasms (MPMN) are defined as the occurrence of two or more primary tumors, either simultaneously or successively, in the same or different organs/tissues within an individual [5]. Cervical cancer is one of the most common malignancies of the cervix and is frequently associated with human papillomavirus (HPV) infection. Intrahepatic FDCS has been rarely reported both domestically and internationally. This represents the first documented case of MPMN involving intrahepatic FDCS and cervical cancer.

Case Report

A 57-year-old woman underwent a total hysterectomy and bilateral adnexectomy for cervical cancer 20 years ago. No recurrence or metastasis was observed during postoperative follow-up. She has a 6-year history of untreated hyperthyroidism. Six years ago, a slight increase in aminotransferase levels was noted during a physical examination. After oral administration of bicyclic alcohol tablets, the aminotransferase levels normalized; however, discontinuation of the medication resulted in a recurrent elevation of aminotransferase. Two days ago, the patient developed unprovoked mid-upper abdominal pain accompanied by nausea.

To pursue further diagnosis and treatment, the patient was admitted to the hepatobiliary department of our hospital, where relevant laboratory tests and imaging examinations were conducted. Computed tomography (CT, Figure 1A-B) and magnetic resonance imaging (MRI, Figure 1C-E) revealed a space-occupying lesion

in the liver with an clear margin. Additionally, lymph nodes in the porta hepatis region exhibited suspicious metastatic features. Based on the combined imaging findings, hepatocellular carcinoma or intrahepatic cholangiocarcinoma should be considered as potential diagnoses.

The laboratory test results revealed abnormally elevated levels of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST), with slight elevation in alpha-fetoprotein (AFP). However, serum total protein and albumin levels were decreased. Carcinoembryonic antigen (CEA) and carbohydrate antigens (CA-125, CA 15-3, CA 19-9) were within normal limits. Since the onset of the disease, the patient has experienced poor appetite, diaphoresis, back pain, and a weight loss of 2 kg. After multidisciplinary consultation, the patient underwent laparoscopic radical hepatectomy and cholecystectomy by famous specialist in hepatobiliary surgery. Pathological examination was performed after operation.

Macroscopically, the liver tissue section revealed a mass measuring 5.7×3.2×3.0 cm, appearing grayish-white, nodular, with distinct margins and a hard consistency (Figure 2). Enlarged lymph nodes were identified in the hepatic hilum and gallbladder neck, ranging in maximum diameter from 0.2 to 2.5 cm. Microscopically, the tumor exhibited clear boundaries with adjacent liver tissue (Figure 3A) and was composed of proliferating round, oval, and spindle-shaped cells arranged in sheets, clusters, storiform patterns, or spirals (Figure 3B). The tumor cells displayed mildly eosinophilic cytoplasm with indistinct cellular borders. The nuclei were round or ovoid, featuring vesicular chromatin and prominent nucleoli (Figure 3C). Atypical mitoses were frequently observed (>10/10 HPF), and areas of partial hemorrhage and necrosis were also noted. Metastatic involvement was confirmed in the lymph nodes.

Immunohistochemica (IHC)l results: The tumor cells demonstrated diffuse and strong positivity for CD21 (Figure 4A), focal positivity for CD23 (Figure 4B), and scattered positivity for CD68. The tumor proliferation index (Ki-67) was approximately 80-90%. In contrast, the tumor cells were negative for pancytokeratin, CAM5.2, CK7, CK19, AFP, HepPar-1, Glypican-3, LCA, SMA, Desmin, S-100, SOX-11, CD34, CD117, DOG-1, STAT6, CD99, WT-1, EMA, HMB45, and Melan-A. In situ hybridization for Epstein-Barr virus-encoded RNA (EBV-EBER) (Figure 4C) was also negative. The final histopathological diagnosis was hepatic FDCS with lymph node metastases (in the hepatic hilum and gallbladder neck). The pathological stage was determined as pT4N1M0.

Three months postoperatively, a follow-up CT scan revealed multiple intrahepatic metastases, multiple lymph node metastases (located in the abdominal aorta, common hepatic artery, left gastric artery, and hepatoduodenal ligament), and multiple implantation metastases of the omentum in the right upper abdomen. The clinical stage was determined as T4N2M1. The patient subsequently received five cycles of chemotherapy. One year after treatment initiation, the patient succumbed to the disease due to extensive systemic metastases and cachexia.

Discussion

FDCS is an uncommon tumor with low-to-moderate malignant potential, exhibiting histomorphological and immunophenotypic features indicative of follicular dendritic cell (FDC) differentiation. While approximately 60% of FDCS cases originate in lymph nodes, extranodal involvement can occur, including sites such as the liver, lung, tonsil, spleen, soft tissue, digestive tract, retroperitoneum, nasopharynx, oral cavity, or breast. Primary FDCS of the liver constitutes less than 0.1% of all primary liver neoplasms [6]. To the best of our knowledge, this case represents the 32nd reported instance of hepatic FDCS in the English literature, following the 31st case reported by Panigrahi C, et al. [3]. This marks the first documented case in our hospital, which is the largest and most prestigious medical center in our region.

The preoperative diagnosis of FDCS relies on clinical features and imaging examinations. While CT/MRI can detect occult lesions, determine the extent of the lesions, and provide staging information, these findings are nonspecific and often overlap with those of other common intrahepatic neoplasms, making preoperative diagnosis of hepatic FDCS challenging. Histopathological examination remains the gold standard for diagnosing FDCS. Histomorphologically, FDCS is predominantly composed of spindle-shaped, round, and ovoid cells arranged in sheet-like, cluster, storiform, or spiral patterns, along with scattered or diffusely distributed lymphoplasmacytic cells. These features resemble those of many other intrahepatic tumors, leading to its under-recognition by pathologists due to its rarity and nonspecificity. Consequently, it is easy to fall into diagnostic pitfalls, complicating the pathological diagnosis.

Due to its rarity, the etiology of FDCS, prognostic factors, and the most appropriate treatment remain poorly understood. Recent investigations have revealed an association between FDCS and hyaline-vascular Castleman disease, wherein FDC hyperplasia may progress to FDCS [7]. Wang RF, et al. [8] demonstrated that 10 out of 11 cases of hepatic FDCS exhibited positive EBER expression by in situ hybridization, suggesting that EBV infection might be one of the potential causes of intrahepatic FDCS. However, EBER expression was negative in our case. Hsu C, et al. [9]. Hypothesized that FDCS might be linked to aberrant immune activation. Similarly, our patient had a history of hyperthyroidism, an autoimmune condition. The biological behavior of FDCS is difficult to predict, as it is generally considered a low-to-intermediate-grade malignant tumor with the potential for recurrence and metastasis. Sosa-Luis AS, et al. [10]. Believed that the prognosis of FDCS depends on the clinical stage at which the disease is detected. Poor outcomes with short survival are typically observed when the clinical stage is advanced. Our reported case, diagnosed at clinical stage IV, exhibited high morbidity and short survival (only 1year post-operation), consistent with findings in the literature [10]. Saygin C, et al. [11]. Demonstrated that local recurrences occur in 28% of FDCS cases, while distant metastasis occurs in approximately 27% of cases. The liver is one of the common sites for recurrence. Large tumor size (>6 cm), intra-abdominal tumors, presence of coagulative necrosis, mitotic count >5/10 HPF, and significant cellular atypia have been described as unfavorable prognostic factors, all of which were present in our reported case [11].

Compared with inflammatory pseudotumor-like (IPT-like) FDCS, which is characterized by scattered spindle and oval cells on a background of abundant lymphoplasmacytes, frequently involving intra-abdominal organs (particularly the liver and spleen), and almost invariably associated with EBV infection, classic FDCS consists of spindle-shaped to ovoid tumor cells arranged in storiform, whorled bundles, fascicles, or diffuse sheets, interspersed with small mature lymphocytes. Classic FDCS predominantly affects extra-abdominal organs/tissues, lacks EBV infection, and is associated with poorer clinical outcomes [12]. Our present case, located in the liver, represents classic FDCS, which is rarely encountered in hepatic involvement. Chen S, et

al. [13]. identified age >60 years at diagnosis, metastatic disease, and thoracic organ involvement as negative prognostic factors. Both patients with localized disease and those with metastatic disease may benefit from surgical intervention [14]. However, adjuvant radiotherapy or chemotherapy does not significantly improve overall survival, as observed in our present case. Our patient experienced hepatic local recurrence, multiple lymph node metastases, and peritoneal implantation metastases. Despite receiving five cycles of chemotherapy following radical surgery, the prognosis remained unfavorable, indicating that chemotherapy did not improve the clinical outcome.

MPMN is uncommon, accounting for 0.52%-11.7% of all malignant tumors [5]. Based on the time interval between the occurrence of different primary tumors, MPMN can be further classified into synchronous (<6 months) and metachronous (≥6 months), with the latter comprising approximately 90% of MPMN cases. The pathogenesis of MPMN remains unclear but may involve genetic factors, host susceptibility, immune deficiencies, hormonal influences, unhealthy lifestyles, oncogenic side effects from prior cancer treatments, and environmental exposures. Clinically, MPMN involving FDCS is rare, with only a few cases reported in the English literature. Sun J, et al. [15]. Reported the coexistence of FDCS and urothelial carcinoma (UC) in the urinary bladder of an elderly patient. Despite undergoing transurethral resection twice and receiving chemotherapy, the patient experienced multiple recurrences, indicating a poor prognosis. Barsoum, et al. [16]. Described a case of meta-synchronous double primary tumors, including cervical FDCS and invasive breast cancer. The patient was treated with multimodal therapies, including surgery, chemotherapy, and radiotherapy, achieving a favorable response with no recurrence during a ten-year follow-up, suggesting that surgical resection combined with chemotherapy and radiotherapy could be an effective therapeutic option for such cases. McClelland E, et al. [17]. Reported an unusual case of parotid gland FDCS with a history of Hodgkin's lymphoma treated with combination chemotherapy and radiotherapy. She underwent superficial parotidectomy and level 2/3 neck dissection, with no recurrence or metastasis observed during postoperative follow-up, raising the possibility of radiotherapy-induced FDCS. Our present case represents the first report of metachronous MPMN involving hepatic primary FDCS and cervical cancer. Our patient had low immunity and a history of hyperthyroidism, suggesting that immune abnormalities may play a role in the development of this extremely rare form of MPMN. However, the precise etiology of MPMN associated with intrahepatic FDCS remains elusive, and a larger cohort of cases is required to further substantiate this association.

In conclusion, Hepatic FDCS, as a rare and frequently misdiagnosed malignant tumor, can be better recognized through increased awareness of its morphological spectrum and appropriate immunohistochemical staining. FDCS should be included in the differential diagnosis, especially when encountering spindle/oval cell tumors arranged in various patterns, regardless of the lesion's location. Our aim is to enhance the awareness of clinical physicians and pathologists regarding this rare disease.

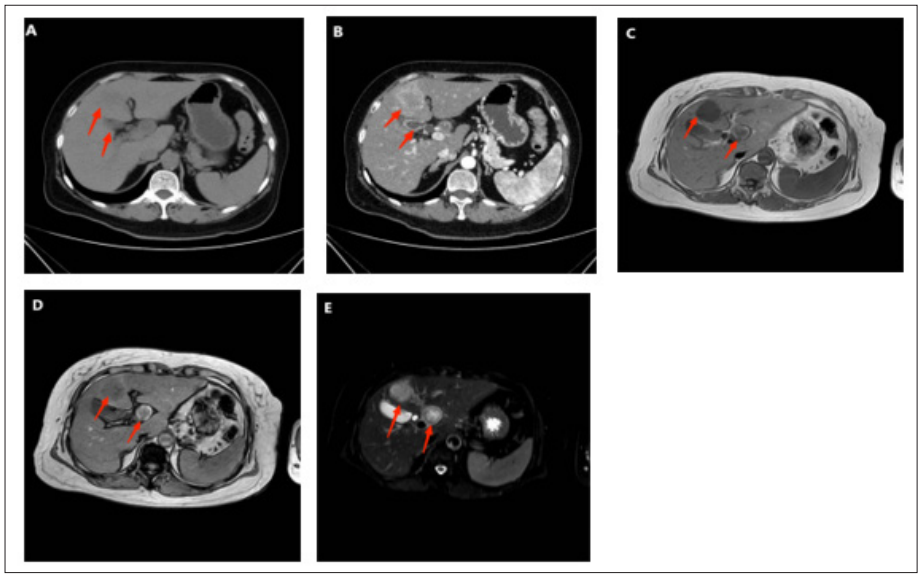

Figure 1: Imaging Findings

Figure 1A shows the plain CT scan, with red arrowheads indicating an ill-defined hypodense mass in the medial segment of the left hepatic lobe and a well-defined hypodense nodule at the porta hepatis. Figure 1B shows the enhanced CT scan, with red arrowheads indicating that the mass exhibits heterogeneous sustained hypoenhancement with internal necrosis, while the nodule at the porta hepatis demonstrates ring enhancement, which was confirmed as a metastatic lymph node postoperatively. Figure 1C shows T1-weighted imaging (T1WI), with red arrowheads indicating an oval-shaped mass with heterogeneous hypointense signals in the left hepatic lobe and a hypointense nodule at the porta hepatis. Figure 1D shows T2-weighted imaging (T2WI), with red arrowheads indicating that both lesions exhibit heterogeneous hyperintense signals. Figure 1E shows diffusion-weighted imaging (DWI), with red arrowheads indicating that both lesions appear unevenly hyperintense.

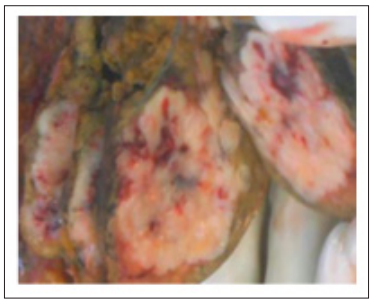

Figure 2: The Tumor Section Appeared Grayish-White, Nodular, with Distinct Margins and a Hard Consistency, Measuring 5.7 × 3.2 × 3.0 cm

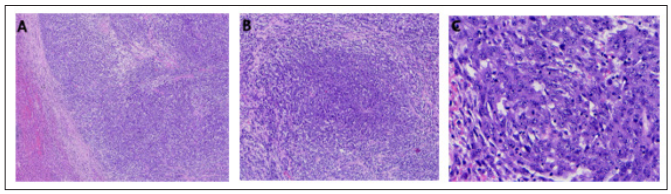

Figure 3: The Microscopic Morphological Characteristics of Tumors

The tumor exhibited clear boundaries with the adjacent liver tissue (Figure 3A, H&E×40). The tumor was arranged in sheet-like and swirling patterns (Figure 3B, H&E×100). and the tumor was composed of round, oval, and spindle-shaped cells with vesicular chromatin, prominent nucleoli, and atypical mitoses (Figure 3C, H&E×400).

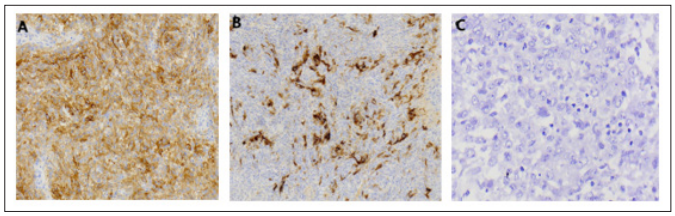

Figure 4: Immunohistochemical Stainings (IHC) Results

IHC staining results demonstrated diffuse and strong positivity for CD21 (Figure 4A), focal positivity for CD23 (Figure 4B), and negativity for EBV-EBER (Figure 4C). (EnVision ×200)

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