Angiomyxoma coexisting with focal nodular hyperplasia: A case report

XIN LI[1], WANGHONG LI[1], CHEN LIU[1], KAI XU[1], CHAO YI[1], JINTIAN TANG[1], ZHIYING JIA[2], XINXIA LI[3], YONG ZHOU[4] and BOQING WANG[1]

[1]Department of Hepatopancreatobiliary Surgery, The Affiliated Tumor Hospital of Xinjiang Medical University, Urumqi, Xinjiang Uygur Autonomous Region 830011, P.R. China; [2]Department of Ultrasound, Affiliated Tumor Hospital of Xinjiang Medical University, Urumqi, Xinjiang Uygur Autonomous Region 830011, P.R. China; [3]Department of Pathology, Affiliated Tumor Hospital of Xinjiang Medical University, Urumqi, Xinjiang Uygur Autonomous Region 830011, P.R. China; [4]Medical Imaging Center, Affiliated Tumor Hospital of Xinjiang Medical University, Urumqi, Xinjiang Uygur Autonomous Region 830011, P.R. China

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Abstract. Angiomyxoma (AM) occurs almost exclusively in the soft tissues of the pelvic and perineal regions. AM is a highly uncommon condition that can be easily misdiagnosed when it is present in other regions of the body. The current study presents a case in which AM of the liver coexisted with focal nodular hyperplasia (FNH). A 56-year-old woman presented with two space-occupying lesions of the liver without any other clinical symptoms, and it was not easy to definitively diagnose the two intrahepatic lesions by imaging examinations. Due to the low incidence of AM in the liver, precise and clear clinical information on the condition is still unavailable, and the lesion was initially misdiagnosed as other hepatic tumors preoperatively. Once a tumor resection had been performed, a histopathological examination revealed that the microscopic features of the lesions were consistent with those of AM and FNH. The patient was followed up for 1 year, and no recurrence or metastasis was found. Surgical excision is an effective treatment for AM, and long-term follow-up is essential due to the risk of recurrence. The joint presentation of AM and FNH is rare in clinical practice, and although FNH of the liver is commonly reported, the difficulty of diagnosis increases when both conditions occur at the same time. Therefore, it is necessary to assist clinicians in making informed decisions regarding diagnosis and treatment.

Correspondence to: Professor Boqing Wang, Department of Hepatopancreatobiliary Surgery, The Affiliated Tumor Hospital of Xinjiang Medical University, 789 Suzhou East Street, Urumqi, Xinjiang Uygur Autonomous Region 830011, P.R. China
E-mail: bqwanghps@163.com

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Introduction

Angiomyxoma (AM) is a rare soft-tissue neoplasm that commonly occurs in the pelvis and perineum in females of reproductive age, while it is uncommon in males, with a female-to-male ratio of approximately 6:1 (1). AM is a mesenchymal tumor that is histologically composed of myxoid stroma and vasculature, and is distinguished by its propensity for numerous local recurrences and lack of metastatic potential. Reports of this disease are limited (1), and it occurs less frequently in the liver. This pathological entity does not have any unique clinical, biological or imaging characteristics that allow differentiation. Therefore, patients are not clearly diagnosed preoperatively and must wait until the postoperative pathological diagnosis has been confirmed. AM characteristically grows slowly and insidiously and carries a risk of local recurrence and distant metastases in patients with AM (2). This aggressive behavior needs to be taken into account, and long-term close follow-up is recommended.

Focal nodular hyperplasia (FNH) is recognized as the second most prevalent benign hepatic mass (3). Although the causes of FNH are considered to be associated with local vascular abnormalities, the exact etiology and pathological mechanism is still poorly understood. The imaging presentation of typical FNH commonly involves a stellate scar located at the center of the lesion, as observed through contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI). The majority of FNH cases can be diagnosed through the use of imaging techniques. To the best of our knowledge, this is the first case of AM arising from the liver combined with FNH. This study aims to provide a new approach for clinical physicians to diagnose patients with AM combined with FNH.

Case report

A 56-year-old woman without any specific symptoms and no history of viral hepatitis or a family history of cancer was

Table I. Currently reported cases of angiomyxoma of the liver.

First author, year	Age, years	Sex	Size, cm	Immunohistochemistry		Treatment method	Complementary treatment; prognosis	(Refs.)
				Positive	Negative			
Qi *et al*, 2015	50	F	2.0x2.0x1.0	Vimentin, CD34, SMA	Desmin, S-100, Ki-67, EMA, ER, PR, CD99, CD10, CAM5.2, CK19	Surgical excision	None; no recurrence	(5)
Sato *et al*, 2017	33	F	8.0x7.5	Vimentin, Desmin, CD34, ER, PR	S-100, EMA, CK19, CD99, HMB45, SMA	S8 sub-segmental resection	None; no recurrence	(6)
Malik *et al*, 2018	46	F	1.3x6.0	SMA	CD31, CD34, CD117, DOG1, Desmin, S100, AE1/AE3, AFP	Right hemihepatecto-my	None; no recurrence	(7)
Sun *et al*, 2019	45	F	2.2x1.8x0.9	CD34, SMA, Ki-67 (2%)	Desmin, S100, CK, ER	Left lateral hepatic lobectomy	None; no recurrence	(8)

EMA, epithelial membrane antigen; ER, estrogen receptor; PR, progesterone receptor; CAM5.2, cytokeratin CAM5.2; AE1/AE3, pan-cytokeratin; CK, cytokeratin; HMB45, human melanoma black-45; SMA, smooth muscle actin; DOG1, anoctamin-1; AFP, α-fetoprotein; M, male; F, female.

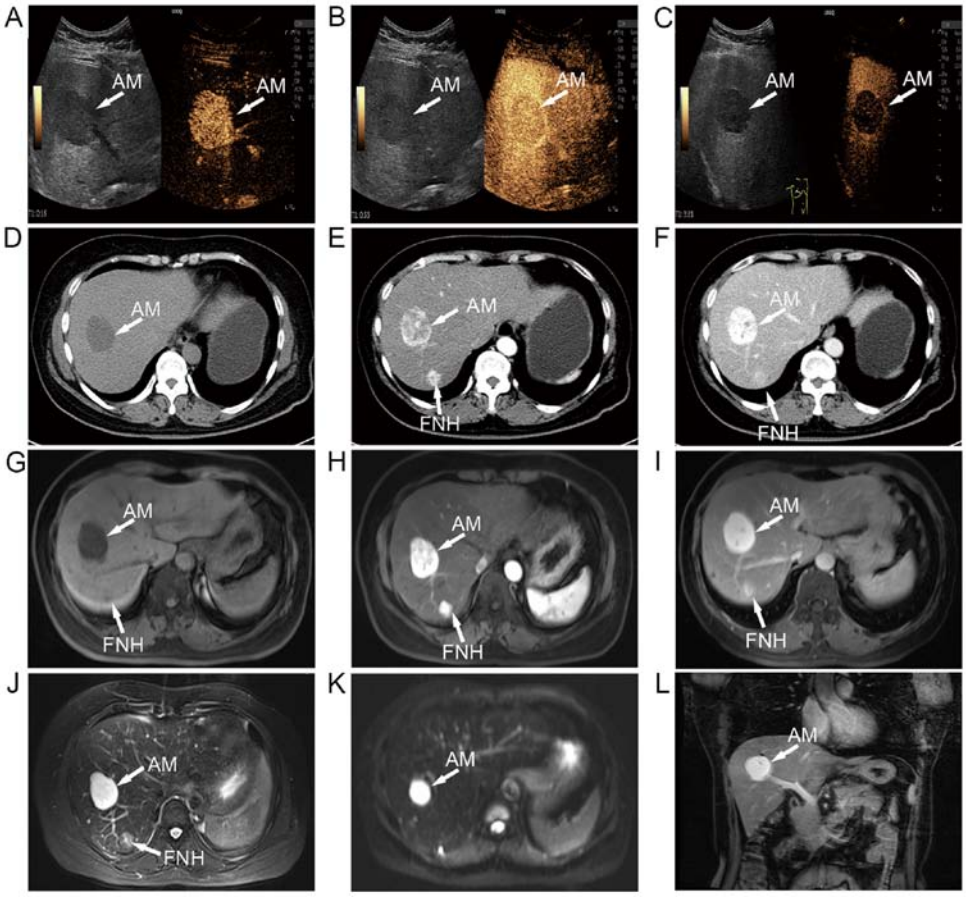

Figure 1. Hepatic imaging examination. Contrast-enhanced ultrasound of the lesions in the (A) arterial, (B) venous and (C) delayed phases. Image of CT plain scan (D) Contrast-enhanced CT of the lesions in the (E) arterial and (F) venous phases. (G) Image of T_1-weighted MRI. T_1-weighted MRI of the lesions in the (H) arterial and (I) delayed scan phases. (J) Image of T_2-weighted MRI. (K) Diffusion-weighted imaging was applied to assess the lesion. (L) Image showing the AM nodule in the coronal view. AM, angiomyxoma; FNH, focal nodular hyperplasia; CT, computed tomography; MRI, magnetic resonance imaging.

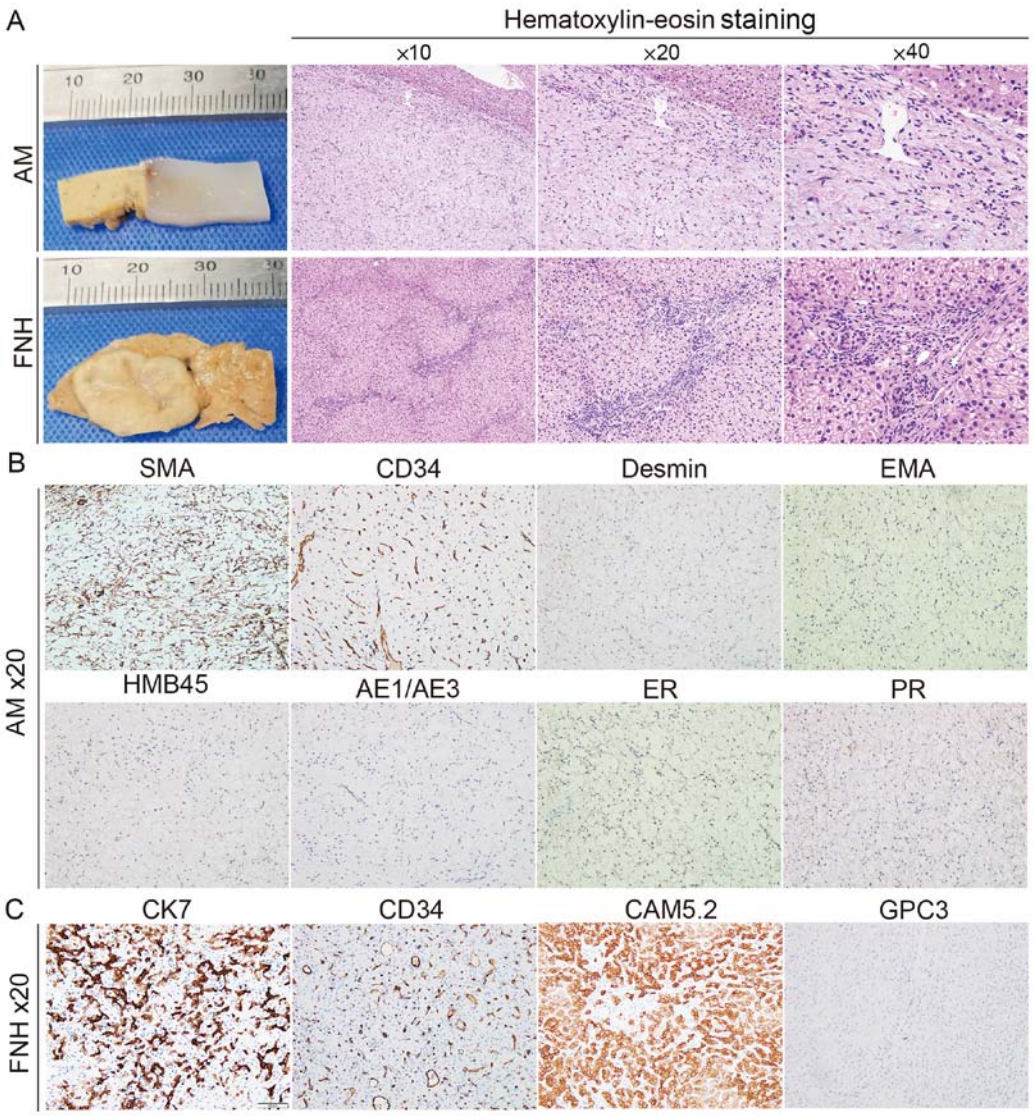

Figure 2. Histopathological analysis of the resected lesions. (A) Formalin was used to fix the AM and FNH lesions. The pathological features of AM and FNH were analyzed by hematoxylin and eosin staining. Immunohistochemistry was implemented to evaluate the markers in AM (B) including SMA, CD34, Desmin, EMA, HMB45, AE1/AE3, ER and PR, and the markers in FNH (C) including CAM5.2, CD34, CK7 and GPC3. AM, angiomyxoma; FNH, focal nodular hyperplasia; EMA, epithelial membrane antigen; ER, estrogen receptor; PR, progesterone receptor; CAM5.2, cytokeratin CAM5.2; AE1/AE3, pan-cytokeratin; CK, cytokeratin; HMB45, human melanoma black-45; SMA, smooth muscle actin; GPC3, glypican 3.

admitted to the Affiliated Tumor Hospital of Xinjiang Medical University (Urumqi, China) in March 2023 due to two intrahepatic lesions found on a routine physical examination. On physical examination, no other abnormalities were detected. The α-fetoprotein and carcinoembryonic antigen levels were 1.68 ng/ml (normal range, 0-13.4 ng/ml) and 2.76 μg/l (normal range, 0-5 μg/l), respectively. Ultrasound suggested two solid nodules in the liver, with clear borders and no blood flow signals. Contrast-enhanced ultrasound revealed a solid, hypoechoic tumor that was relatively well-circumscribed, with rapidly intensified enhancement in segment VIII of the liver in the arterial phase (16 sec post-contrast injection; Fig. 1A), gradually decreased enhancement in the venous phase (33 sec post-contrast injection; Fig. 1B) and further decreased enhancement in the delayed phase (3 min and 21 sec post-contrast injection; Fig. 1C). A CT scan showed a regular, lobular, low-density mass that contained of a pool of highly viscous liquid (Fig. 1D). Next, contrast-enhanced CT of the abdomen revealed uneven enhancement during the arterial phase (Fig. 1E), continuous enhancement in the venous phase and irregular enhancement in the delayed phase (Figs. 1F and S1A). An MRI plain scan displayed T_1-weighted low signal nodules (Fig. 1G). Moreover, it was observed that the mass was obviously hypointense on T_1-weighted images in the arterial phase (Fig. 1H) and slightly less hypointense in the delayed phase (Fig. 1I). MRI showed a T_2 hyperintensity in segment VIII and mild-moderate T_2 hyperintensity in segment VII (Fig. 1J). Diffusion-weighted imaging illustrated the diffuse high signal intensity and restricted diffusion of the lesion (Fig. 1K). Coronal MRI confirmed that the AM nodule was located in segment VIII (Fig. 1L).

Subsequently, a wedge liver resection was performed on the patient. Gross specimens of the masses after surgical removal revealed two separate, differently sized and well-defined masses (Fig. S1B). The resected specimen were fixed overnight in 10% formalin at room temperature,

embedded in paraffin, and sliced into 5-μm thick sections that were mounted on slides. Macroscopic examination revealed a white, rubbery mass with a soft and smooth texture, and myxoid components located in segment VIII of the liver. In the context of hematoxylin and eosin (HE) staining, tissue sections underwent a sequential process that involved incubation in hematoxylin for 2 min, de-staining in 1% hydrochloric acid in 70% ethanol for 5 sec, rinsing in 80% ethanol for 1 min, a brief exposure to eosin for 1 sec, dehydration in ethanol (95 and 100%, three times) and clearing in xylene (three times) at room temperature. HE staining was analyzed using an optical microscope (BX43; Olympus Corporation). The nodule in segment VII was tough, greyish and lustreless, with a marked spoke-wheel scar in the centre (Fig. 2A). HE staining revealed variably sized thick-walled blood vessels in mucinous degeneration in segment VIII of the liver. The nodule in segment VII was composed of disorganizing hepatocyte cords with distinct fibrous septa of varying widths, and hyperplastic small bile ducts, thick-walled vessels and lymphocytic infiltrates were observed within the central stellate fibrous scar tissue (Fig. 2A). The results of immunohistochemical staining (Data S1) in segment VIII showed positive staining for CD34 and smooth muscle actin, and no staining for Desmin, epithelial membrane antigen, human melanoma black-45, pan-cytokeratin (AE1/AE3), estrogen receptor (ER), progesterone receptor (PR), proto-oncogene c-Kit (c-Kit) and anoctamin-1 (DOG1) (Figs. 2B and S1C). Immunohistochemical staining of the lesion in segment VII was positive for cytokeratin CAM5.2, CD34 and CK7 markers, but negative for glypican 3, c-Kit and DOG1 markers (Figs. 2C and S1C). Based on the aforementioned results, the mass in segment VIII was identified as an AM, and the nodule in segment VII was diagnosed as FNH. Based on the risk of recurrence in AM, the patient was required to come to the hospital for follow-up every 3-6 months in the first year. To date, there have been no signs of recurrence. Within the next 3 years, the follow-up will be conducted semi-annually, with subsequent follow-ups for 5 years annually.

Discussion

AM is a distinct mesenchymal tumor with mucinous and vascular components that was first described and reported by Steeper and Rosai in 1983 (4). Currently, AM can be divided into two types. The first type is superficial angiomyxoma, which arises in superficial areas such as the head, neck, trunk and lower limb regions. The other type is deep angiomyxoma, also known as aggressive angiomyxoma (AAM), which develops more frequently in deep tissues such as the pelvis. Apart from the difference in the location of the occurrence, AAMs have aggressive, locally infiltrative and recurrent characteristics. To the best of our knowledge, only four cases of AM have occurred in the liver (5-8), all of which were reported in female patients aged between 30 and 50 years. However, no cases of coexisting FNH were recorded. A summary of reported cases of AM of the liver is presented in Table I.

Several studies have been conducted to examine the imaging characteristics of this rare entity. Detection of intratumor and peritumor blood flow by color Doppler imaging can reveal a number of specific imaging features, including the 'layered' or 'swirled' sign of internal echogenicity and finger-like growth patterns (9). On MRI, AM shows a low signal intensity on T_1-weighted imaging and high-intensity signals on T_2-weighted imaging (10), with a laminar and vortex-like arrangement of low-signal stripes. In the present patient, the imaging features were in agreement with the previous reports.

Myxomatous tumors with thin-walled blood vessels occur infrequently in the liver. Angiomyofibroblastoma (AMFB) is most likely to be confused with AM. AMFBs and AMs are both enriched in blood vessels and mucus, so they are easily confused on microscopic examination; however, AMs show more distinctive myxoid degeneration and more numerous blood vessels than AMFBs. AMFBs generally exhibit much greater cellularity, and their tumor cells are ovoid, numerous and clustered around blood vessels in the form of bundles or nests; by contrast, AM cells are sparsely and diffusely distributed (11). AMFBs are characterized by the expression of vimentin, desmin and CD34. Desmin, in particular, is considered to be the most specific marker for identification. The expression of desmin plays a crucial role in distinguishing AMFB and AM. However, it should be noted that positive desmin expression has been observed in previously documented cases of AM in the liver (5,7-8). Desmin expression in AM may be partially or completely absent, whereas desmin and vimentin expression in AMFB is diffusely positive (12). It is imperative to distinguish myxoid neurofibroma and myxoid liposarcoma from AM in clinical practice. In myxoid neurofibroma, the majority of neoplastic cells are positive for S-100, with a minority of cells expressing CD34 (13). The tumor cells are heterogeneous and show lipoblasts of varying degrees of differentiation, and the interstitial vessels tend to clump or branch. The tumor cells of myxoid liposarcoma are heterogeneous and show lipoblasts of varying degrees of differentiation, and the interstitial vessels tend to be clumped or branched (14). Primary gastrointestinal stromal tumors of the liver have specific histological features and cytological manifestations, including positive expression of c-Kit, CD117 and CD34 (15). Based on the aforementioned findings, AM can be distinguished by pathological and immunohistochemical analysis.

The coexistence of AM and FNH was difficult to identify in the present case. However, ultrasonography of typical FNH is distinctive and reveals a central location of stellate scarring with spoke-like enhancement in the arterial phase. Hepatocellular hyperplastic nodules, abnormal blood vessel growth in the central scar, bile duct hyperplasia and fibrous septa are typical histological features of FNH (16). The present study suggests that both AM and FNH are common conditions among women. AM tumor cells are mostly positive for ER, PR and androgen receptor, which suggests that hormones may manipulate the occurrence and/or development of AM (17). Additionally, exposure to oral contraceptive pills and endogenous hormones is considered to play a role in the development of FNH (18). In summary, further research is needed to determine the potential involvement of hormone exposure in the underlying mechanism of the co-occurrence of AM and FNH.

According to a previous case report, FNH formation has been proposed to occur as a result of a hyperplastic reaction to a vascular anomaly (19). Common microscopic characteristics of AM include a multitude of irregularly shaped, thin-walled blood vessels. Vascular anomalies are common pathological features of both conditions; therefore, we hypothesize that an

underlying pathological change or genetic alteration causes the common histogenesis of abnormal angiogenesis. However, there are no reports in the literature on the possible common aetiology of the two diseases, and perhaps they occur independently of each other, with no pathogenetic link between them. There were some limitations to the present study. Most important of all, there was no macroscopic image containing both lesions, for the reason that the subject would benefit from preserving as much of the normal liver tissue as possible. Therefore, the lesions were resected separately during the surgical procedure.

It has been widely postulated that employing a surgical technique involving a broad incision effectively mitigates the likelihood of postoperative recurrence. However, some studies have shown that there is no significant correlation between surgical margins and postoperative recurrence (20). The recurrence factors of AAM are unknown, and there is a lack of good indicators for predicting the possibility of recurrence. The gold standard for diagnosing AM is postoperative pathology. In the present case, the main microscopic features of the AM included numerous irregularly organized walled vessels and scattered small spindles, ovoids or astrocytes on a loose mucus background. Immunohistochemical analysis indicated that the tumor tissue, which exhibited characteristic differentiation towards fibroblasts and myofibroblasts, likely originated from the mesenchyme.

Gonadotropin-releasing hormone analog therapy is regarded as an effective therapeutic approach for patients whose specimens are positive for ER and/or PR (21). Due to the negative staining result for ER and PR in the present study, the patient was not administered any other adjuvant therapy after the operation. It is possible that distant metastasis and local recurrence could still develop; however, the patient was regularly reviewed, with no signs of recurrence or metastasis as of the 16-month follow-up.

In conclusion, the present study reports a case in which AM of the liver coexisted with FNH. The simultaneous occurrence of AM and FNH in the liver poses diagnostic challenges, and differentiating them from other benign and malignant liver tumors represents a novel and previously unreported challenge. AM is extremely rare clinically and often confused with other diseases. To diagnose AM, a medical history, CT, MRI and cytological examinations, and preoperative and postoperative pathological tests are needed. The preferred treatment is surgery with complete resection, and patients with AM are advised to undergo annual postoperative follow-up examinations.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

XL and BQW made substantial contributions to study conception and design, acquisition of data, and analysis and interpretation of data. XL and KX were involved in drafting the manuscript and revising it critically for important intellectual content. WHL, CL and CY managed the patient. XXL reported the pathological findings. WHL, CL, JTT and BQW performed the surgery. KX, YZ and ZYJ obtained medical images. WHL, JTT and BQW advised on patient treatment and analyzed the patient data. XL, KX and BQW analyzed the patient data. XL and BQW confirm the authenticity of all the raw data. All authors have read and approved the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient provided written consent for the case to be published.

Competing interests

The authors declare that they have no competing interests.

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