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Inflammatory myofibroblastic tumor of the liver: A case report

Karaciğerin inflamatuvar miyofibroblastik tümörü: Bir olgu sunumu

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Inflammatory myofibroblastic tumor of the liver is an uncommon lesion of uncertain pathogenesis that has a unique histological appearance. Symptomatology and clinical findings in most cases suggest malignancy, and despite the advances in imaging techniques, the preoperative diagnosis of this tumor is difficult. We describe herein a case of inflammatory myofibroblastic tumor of the liver with a review of the literature. A mass occupying the right lobe of the liver was excised in a 48-year-old woman, who previously presented with weakness, fever, progressive weight loss, and right upper abdominal pain. The lesion was an unencapsulated light brown tumor (largest diameter 6 cm) without necrosis or hemorrhage. The characteristic histopathological features and the presence of spindle cells expressing smooth muscle actin and anaplastic lymphoma kinase allowed the diagnosis of inflammatory myofibroblastic tumor. The present case and the review revealed that inflammatory myofibroblastic tumor of the liver is not limited to younger age groups and males. Moreover, the rare occurrence of inflammatory myofibroblastic tumor of the liver and the lack of diagnostic clinical signs and symptoms do not exclude consideration of inflammatory myofibroblastic tumor in the differential diagnosis of liver tumors, especially in patients with tumor markers in normal ranges.

Key words: Inflammatory myofibroblastic tumor, liver, anaplastic lymphoma kinase, smooth muscle actin

Karaciğerin inflamatuvar miyofibroblastik tümörü nadir görülen, patogenezi tam olarak bilinmeyen, kendine has histopatolojik görünümü olan bir lezyondur. Çoğu olguda semptomlar ve klinik bulgular maligniteyi düşündürebilmektedir ve görüntüleme yöntemlerindeki gelişmelere rağmen bu tümörün preoperatif tanısı güçtür. Burada, karaciğerinde inflamatuvar myofibroblastik tümör olan olgu literatür gözden geçirilerek sunulmuştur. Daha önce kliniğe güçsüzlük, ateş, süregelen kilo kaybı ve sağ üst karın bölgesinde ağrı şikayetiyle başvuran 48 yaşındaki kadın hastanın karaciğer sağ lobunu tutan kitle eksize edilmiştir. Lezyon kapsülsüz, nekroz ve kanama içermeyen, açık kahve renkte bir tümördü (en büyük çapı 6 cm). Tipik histopatolojik özellikler yanısıra düz kas aktin ve anaplastik lenfoma kinaz eksprese eden iğsi hücrelerin varlığıyla lezyon inflamatuvar miyofibroblastik tümör tanısı aldı. Sunulan olgu ve literatürün gözden geçirilmesi, karaciğerin inflamatuvar miyofibroblastik tümörün sadece erkeklere ve genç yaş gurubuna sınırlı olmadığını göstermektedir. Ayrıca, inflamatuvar miyofibroblastik tümörün karaciğerde ender olarak izlenmesi ve tanısal klinik bulgu ve belirtilerinin olmaması özelikle tümor belirteçleri normal sınırlarda olan hastalarda karaciğer tümörlerinin ayırıcı tanısında dikkate alınmasını gerektirmektedir.

Anahtar kelimeler: İnflamatuvar miyofibroblastik tümör, karaciğer, anaplastik lenfomakinaz, düz kas aktin

INTRODUCTION

Inflammatory myofibroblastic tumor (IMT) is an uncommon, benign lesion. Although IMT is considered a soft tissue lesion, it has also been reported in the mesentery, omentum, major salivary glands, larynx, breast, thyroid gland, and visceral organs such as lung, small intestine, orbit, mediastinum, bronchus, kidney, spleen, stomach, meninges, brain and spinal cord, pancreas, gall bladder, and urinary bladder (1-11). IMT of the liver is rare and was first described by Pack and Baker (12). Because IMTs may mimic malignant tumors, clinical diagnosis of these lesions is not always straightforward. Herein, we present a case of IMT of the liver who presented clinical and radiological findings of malignancy and was diagnosed after histopathological and immunohistochemical evaluation of the resected tumor.

CASE REPORT

A 48-year-old woman admitted with weakness, fever (39.4°C), progressive weight loss (especially in the last 6 months), and right upper abdominal pain. On physical examination, the right upper quadrant was tender at palpation. Laboratory investigations revealed a white blood cell count of 10,900/micL with segmental neutrophilia (75.3%),

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slightly elevated erythrocyte sedimentation rate (ESR) of 120 mm/h, and hemoglobin level of 7.7 g/dl. The liver function tests were within normal limits as were the tests for alpha-fetoprotein (AFP, 1.22 ng/ml), carbohydrate antigen 19-9 (CA19-9, 2.42 U/ml), and carcinoembryonic antigen (CEA, 2.74 ng/ml). Serology for hepatitis markers and infectious agents such as echinococcus was also negative. No microorganisms were detected in blood and urine cultures. Since ultrasound examination showed a single hypoechoic lesion measuring 6 cm in greatest diameter in the right lobe of the liver, a lobectomy was performed. On gross examination, the mass was 6.2 x 5.1 x 5 cm, with no capsule, not easily distinguished from the surrounding parenchyma, and light brown in color. There was no evidence of necrosis or hemorrhage. On microscopic examination, the lesion was composed of spindle cells, granulation-tissue type vessels and chronic inflammatory cells lying on a loose, edematous, myxoid stroma. The spindle cells were arranged in a haphazard fashion. They had bipolar or stellate-shaped cytoplasm and lacked cytologic atypia. There were a few mitotic figures/10 high-power fields, which were not atypical. The chronic inflammatory infiltrate was characterized by proliferation of predominantly plasma cells as well as lymphocytes and histiocytes (Figure 1). Immunohistochemically, plasma cells that expressed CD38 were also stained with both Kappa and Lambda, suggesting that they were polyclonal. Spindle cells were positive for smooth muscle actin (SMA) and anaplastic lymphoma kinase (ALK). Desmin and epithelial membrane antigen (EMA) were negative. According to these clinical and histological findings, the lesion was diagnosed as IMT of the liver.

DISCUSSION

The present case involved a 48-year-old woman with a liver mass located at the right lobe of the liver that, according to the pathological and immunohistochemical findings, was diagnosed as IMT. The present patient is older than the previously reported hepatic IMT cases (mean: 37 years) and

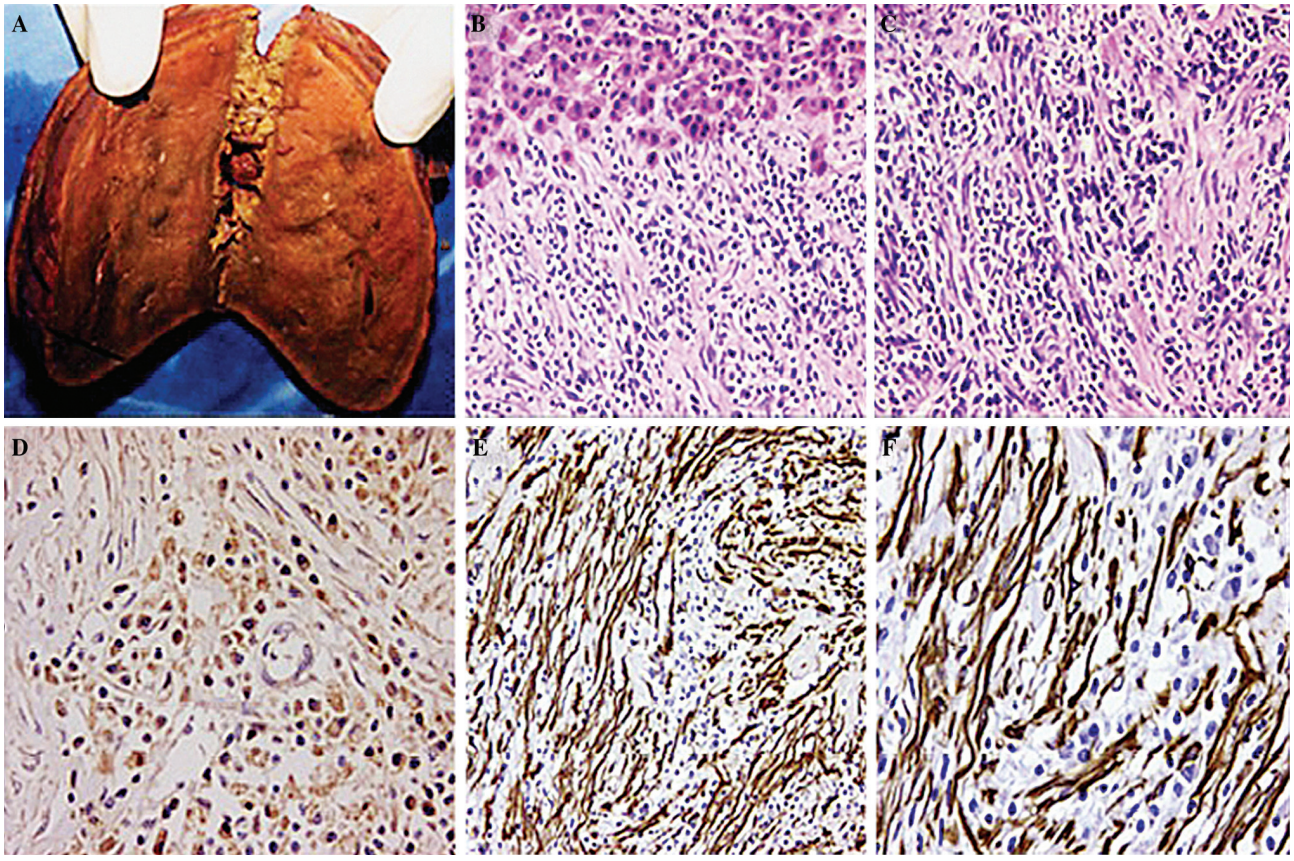

Figure 1. A) An unencapsulated light brown mass in the right lobe of the liver. **B, C)** The lesion was composed of chronic inflammatory cells and spindle cells (hematoxylin & eosin [H&E], X 200). **D)** CD38 immunostaining shows abundant plasma cells in the lesion (X 200). **E, F)** SMA and ALK immunostaining of spindle cells (X 200, X 400).

Table 1. Demographic and pathological findings of previously reported cases of IMT of the liver

Reference	N	Age	Gender	Clinical and laboratory findings	Localization	Size	Other diseases
Schnelldorfer T et al. (32)	1	18	F	AP, vomiting, WL	Perihilar region	1.4-0.8	
Pack et al. (12)	1	40	M	F, WL, PM, ↑ WBC, ↑ Eo	Right lobe	25-13	
Hertzer NR et al. (13)	1	1	F	F, J, HM, ↑ WBC	Porta hepatis	NM	
Anthony PP et al. (14)	1	10	F	AP, vomiting, diarrhea, ↑ neutrophils, ↑ ESR, ↑ serum IgG	Right lobe	9	
	1	61	M	F, ↑ WBC, ↑ ESR	Inferior, both lobes	3	
	1	12	M	AP, night sweats, lethargy, ↑ Eo, ↑ serum IgM and IgG, J	Adjacent to gallbladder	5	
	1	44	M	J	Main hepatic canal	2	
	1	57	M	F, AP, vomiting, J, ↑ neutrophils, ↑ WBC	Disseminated	2	Cholelithiasis
Kafeel G et al. (15)	1	70	F	Intermittent hypothermia, AP, WL, weakness, ↑ ESR	Right lobe inferolateral	4	Klebsiella infection
Saito K et al. (16)	1	48	M	Anorexia, WL, melena, rectal mass, ↑ WBC	Right lobe posterior	2.7-2.1	Rectal adenocarcinoma
Younis N et al. (17)	1	NM	M	F, WL, HM	Disseminated	3-5	DM
Ueda M et al. (29)	1	7	M	F, J, abnormal liver function tests	Hilus	5-4	
Lee SH et al. (18)	1	NM	B	NM	Liver, lung, spleen, left kidney	NM	*Eikenella corrodens* infection
Schneider A et al. (19)	1	NM	B	NM	NM	NM	Hepatitis C
Rai T et al. (20)	1	75	M	Esophageal varices and symptoms related to gastric carcinoma	Disseminated	2	Gastric carcinoma, PBS
Fangusero T et al. (21)	2	-	B	NM	NM	NM	Bone marrow transplantation
Tamsel S et al. (22)	1	40	F	AP, WL	Left lobe, lateral	7-5	Actinomycosis
Lo OS et al. (23)	1	46	F	Hypothermia, AP, ↑ WBC, ↑ ESR	Right lobe	10	GIST, small bowel
Papachristou D et al. (24)	1	68	M	AP, WL, J, ↑ WBC	Hilus	1.2-1.1	Crohn disease
	1	67	M	AP, WL, J, ↑ WBC	Right lobe	3.8-2.8	Crohn disease
Sasahira N et al. (25)	1	59	M	J, ↑ Eo, ↑ IgG, ↑ ESR	NM	NM	Autoimmune pancreatitis
Nishimura R et al. (26)	1	63	F	AP, WL, nausea, hyperglycemia	Left lobe	5.5-5	Gastric carcinoma, PBS
	1	66	M	PM	Right lobe	2.5-1.9	Rectal adenocarcinoma
Al-Lawati T et al. (27)	1	71	F	AP	4th segment	4	Latent SC
Teranishi N et al. (28)	1	81	F	F, AP, ↑ WBC	Spiegel's lobe	4	
Present case	1	48	F	F, WL, weakness, AP, ↑ WBC, ↓ hemoglobin	Right lobe	6-2.5	

* mean. NM: Not mentioned. ESR: Erythrocyte sedimentation rate. PBS: Primary biliary cirrhosis. SC: Sclerosing cholangitis. F: Fever. AP: Abdominal pain. WL: Weight loss. WBC: White blood cell. Eo: Eosinophil. J: Jaundice. PM: Palpable mass. HM: Hepatomegaly. DM: Diabetes mellitus. GIST: Gastrointestinal stromal tumor.

contradicts the frequent male predilection of the lesion (M/F: 1.5/1), demonstrating that IMT of the liver is not limited to only younger age groups and males (11-29) (Table 1).

Clinical findings in most cases are fever, abdominal discomfort, weight loss, weakness, and anorexia. Physical findings include right upper quadrant pain, hepatomegaly, jaundice -if the tumor invades the hepatic hilum and causes obstruction-, and portal hypertension. Laboratory investigations usually suggest an inflammatory process: leukocytosis, neutrophilia, elevated ESR and C-reactive protein (CRP), anemia, thrombocytosis, polyclonal hypergammaglobulinemia, and also slightly elevated liver enzymes. Tumor markers such as serum AFP and CEA are always normal. Although these markers are valuable in the discrimination of IMT from malignant tumors, they can not completely rule out some malignancies such as fibro-lamellar hepatocellular carcinoma, in which AFP levels might be normal. Radiological findings of the lesion are not specific and the discrimination of IMT from malignancy is not always possible (Table 1). Parallel to these observations, our case presented with fever, weight loss, weakness, and abdominal pain, and laboratory investigation revealed only leukocytosis and low hemoglobin levels. AFP and CEA levels were in normal ranges and the nature of the lesion located at right lobe of the liver could not be clarified by radiological investigation.

It was pointed out that percutaneous biopsy can be a reliable method for diagnosis of IMT of the liver and might be useful to avoid unnecessary surgical resection, as some patients can be managed with medical treatment. Colakoglu et al. (30) reported such a case of IMT, which completely resolved with non-steroidal antiinflammatory drugs (NSAID) and antibiotic treatment. On the other hand, since the usefulness of medical treatment depends on the localization as well as the size of IMTs, in a great majority of the cases, surgical treatment is the first choice. To our knowledge, there is no proven role of chemotherapy or radiation therapy in IMT. In our case, the possibility of malignancy could not be ruled out by biopsy and the patient underwent surgical resection.

Although multiple IMTs of the liver are described in some reports (14, 21, 31-33), they are solitary lesions and frequently located at the right lobe, as seen in our case. Rarely, other hepatic locations such as the Spiegel lobe and hilar region have been reported (28, 29, 34) (Table 1).

The size of these lesions ranges from 1 cm to 25 cm In macroscopic examination, they have variegated appearance, and are generally unencapsulated but with well-defined margins with white or tan texture. Fleshy or myxoid cut surface rarely shows hemorrhage, necrosis and calcification. Histologically, these lesions are composed of collagenous stroma consisting of fibroblasts and myofibroblasts infiltrated by inflammatory cells including plasma cells, lymphocytes, foamy macrophages and eosinophils, generally in a whorled architecture. Both benign and malignant soft tissue tumors should be considered in the differential diagnosis, such as leiomyoma, malignant fibrous histiocytoma, neurofibroma, low-grade fibrosarcoma, hepatic abscesses, benign hepatic tumors (focal nodular hyperplasia, adenoma, sclerosing cholangitis), and malignant liver tumors (hepatocellular carcinoma, cholangiocarcinoma, metastatic liver tumors). In the present case, the tumor presented as a 6 cm nodule in its greatest diameter. It had undefined borders and a heterogeneous cut surface without evidence of hemorrhage and necrosis. In our case, the lack of atypical mitoses and cellular atypia together with histopathological and immunohistochemical findings supported the diagnosis of IMT.

At present, the pathogenesis of IMT of the liver remains unclear. Numerous predisposing factors and associations have been suggested, including infections, immunosuppression, radiotherapy, local trauma, autoimmune disorders, cystic lesions and malignancies (11, 21, 34). Infectious agents isolated in such patients were Klebsiella, *Clostridium difficile,* Corynebacterium, *Eikenella corrodens,* actinomycosis, hepatitis C virus (HCV), hepatitis B virus (HBV) and Epstein-Barr virus (EBV) (15, 18, 19, 22, 35-37). The role of immunosuppression in IMT was described in four cases, and all of them were pediatric cases. Two of them were liver and pancreatic transplant recipients, respectively (36, 38). The remaining two cases developed IMT following hematopoietic stem cell transplantation (21). IMT can also be associated with autoimmune disorders like sclerosing pancreatitis, primary sclerosing cholangitis, rheumatoid arthritis and diabetes mellitus (17, 25, 32, 39, 40). Papachristou et al. (24) reported two cases of IMT associated with Crohn's disease. IMT might accompany malignant neoplasms such as rectal adenocarcinoma, gastrointestinal stromal tumor and gastric papillary adenocarcinoma (23, 26, 41) (Table 1). Unusual accompanying malignancies

have also been reported, such as malignant osteoclastoma with in situ carcinoma of intrahepatic bile ducts (34). Recently, two similar cases were reported with the development of an inflammatory pseudotumor following collapse of a liver cyst (35). The case of the present patient, who was otherwise healthy without history of an evident inflammation or autoimmune disease or malignancy, does not support the role of these associations in the development of IMT of the liver.

In the present case, no recurrence was observed during the follow-up (2 years) in accordance with the follow-up information of previous IMT cases of the liver (42). It was supposed that large lesions that were unresectable totally had a greater tendency to recur. Spontaneous regression has also been described in two IMT cases (43, 44).

In conclusion, although the liver is the second most common site of origin following the lungs, IMT of the liver is very rare. The case presented here supports their presence in this localization in older age groups and in females. Moreover, the present case and the review show that the rare occurrence of IMT of the liver and the lack of diagnostic clinical signs and symptoms do not exclude their consideration in the differential diagnosis of liver tumors, especially in patients with tumor markers in normal ranges.

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