Metastatic melanomas have extremely grave outcomes with median survival of around 6 months and a 5-year survival rate of 5% (2,3). The most common cancers metastasizing to the adrenal glands are cancers of the lung and the gastrointestinal tract (8). In a study of nearly 6,000 malignant melanoma patients, metastases to the adrenal glands were seen in 13% of patients and were associated with mortality rates of over 75% (2).

EUS-FNA is a novel method for diagnosing adrenal lesions. When it is compared with the traditional diagnostic modalities, it is not only more accurate than imaging studies such as computated tomography, positron emission tomography, and magnetic resonance imaging, but it is also a very safe procedure with fewer complications than transcutaneous biopsies (5,6). EUS-FNA of the left adrenal gland is a relatively simple procedure and can be performed by passing either a 22- or 25-gauge needle through the gastric wall using a curvilinear echoendoscope (4). On the other hand, EUS-FNA of the right adrenal gland is more challenging because the echoendoscope must be maneuvered carefully from within the second portion of the duodenum in order to visualize the gland between the liver and the inferior vena cava (5). When compared with the 22-gauge needle, 25-gauge needles are relatively more flexible and are preferred for performing trans-duodenal FNAs. Although one report of successful utilization of EUS-FNA to diagnose bilateral adrenal histoplasmosis exists in the literature (9), this case highlights the use of EUS-FNA for the diagnosis of bilateral metastatic melanoma of the adrenal glands.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Splenic Littoral Cell Hemangioendothelioma in a Patient With Crohn's Disease Previously Treated With Immunomodulators and Anti-TNF Agents: A Rare Tumor Linked to Deep Immunosuppression

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To the Editor: The risk of malignancy in Crohn's disease (CD) has been well described. Moreover, immunomodulators, such as azathioprine (AZA) and 6-mercaptopurine (6-MP), and biological agents, such as infliximab and adalimumab, may promote carcinogenesis (1–3). Splenic littoral cell tumors are recently described tumors of vascular origin composed of endothelial cells, with typical microscopic and immunohistochemical features of splenic sinus lining cells (4). Clinical findings are not specific, and outcome is unpredictable but usually benign, although a few cases with a malignant behavior have been reported (5,6).

We report a 58-year-old Caucasian man with a long history of ileocolonic CD. He had required multiple resections. He had been steroid dependent since 2002 and had received repeated antibiotics because of perianal abscesses. In June 2003, he received infliximab (5 mg/kg) induction therapy, discontinued later on because of an infusion reaction. He was put on AZA (2 mg/kg/day), which was stopped owing to severe bone marrow toxicity, and was then put on 6-MP, which was withdrawn owing to liver and pancreatic enzyme alterations. In 2004, he had a severe relapse of perianal disease, which required multiple surgical drainages and local injections of infliximab. In September 2009, he started adalimumab, which was again interrupted because of development of pancytopenia. Ten months later, the patient was admitted to our hospital because of diarrhea, abdominal pain, fever (40°C), fatigue, and active drainage of perianal fistulas. Physical examination revealed a splenomegaly, but no peripheral palpable lymph nodes. Blood tests showed pancytopenia with severe anemia (hemoglobin level 7.8 g/dl), lymphocytopenia (white blood cell count 3,900/μl, lymphocytes 10%), and thrombocytopenia (platelets 67,000/μl). Evaluation for infectious agents was negative. Abdominal ultrasound and computerized tomography (CT) scan showed splenomegaly (22 cm long on its major axis) with multiple hypodense lesions; liver was normal. Previous abdominal imaging, available since 2002, did not show any organomegaly. During hospitalization, leukocytes went down to 770/μl. Bone marrow biopsy revealed a T-lymphocyte infiltration (CD3+; CD2+; CD4>CD8) not diagnostic for lymphoproliferative disease; splenectomy was performed. The spleen

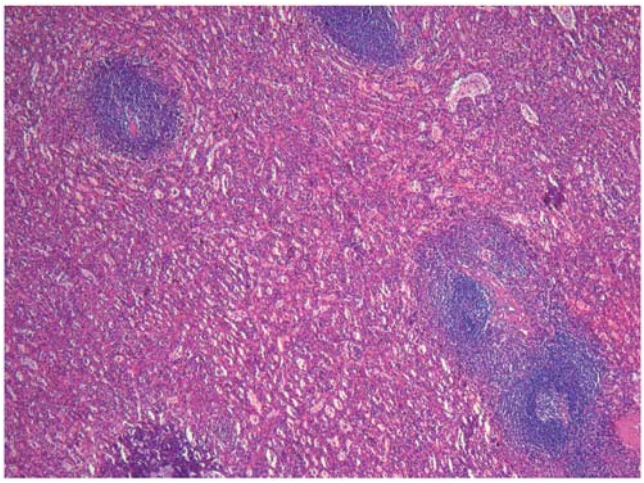

Figure 1. The splenic parenchyma is almost entirely replaced by a vascular proliferation of branching slit-like small blood vessels with solid areas and focal spotty necrosis. The proliferation surrounds the residual lymphoid structure (EE, overall magnification ×40).

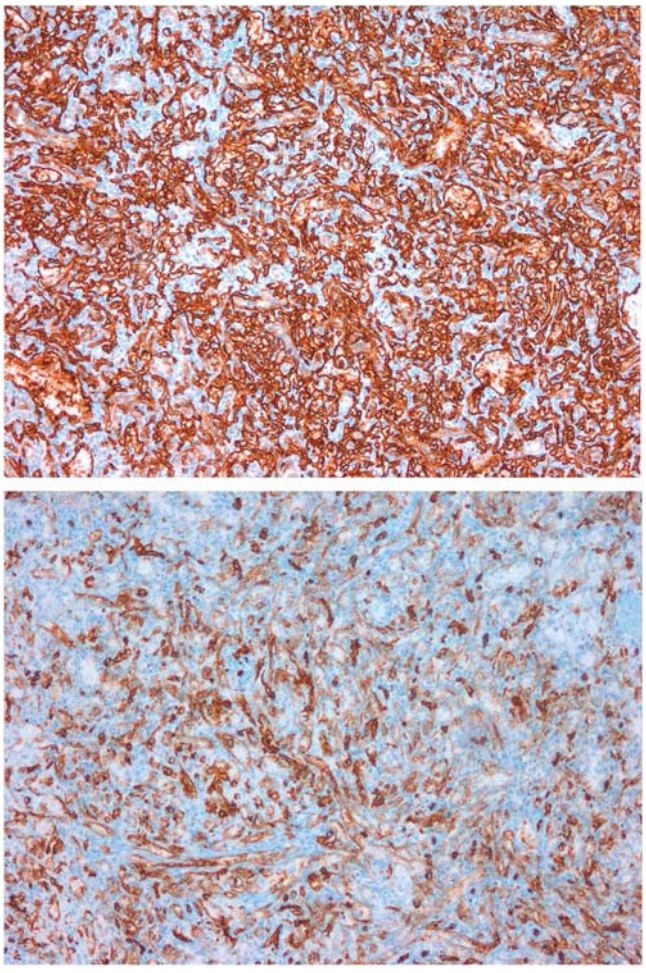

Figure 2. The vascular proliferation shows marked and diffuse expression of endothelial markers (immunohistochemical staining for CD34; overall magnification ×100) and histiocytic cell line markers (immunohistochemical staining for Kp1; overall magnification ×100).

weighed 1,150 g. Macroscopically, the organ looked well capsulated, lacking significant alteration. On histology, spleen parenchyma showed a slit-like anastomosing vascular proliferation with solid areas, with high proliferation index (Ki-67+ cells 25%) and spotty necrosis. On immunohistochemistry, the cell lining the vascular spaces showed coexpression of factor VIII and other endothelial line markers, as well as histiocytic line markers such as KP1. This phenotype was consistent with littoral cell differentiation (**Figures 1–2**). The final diagnosis was littoral cell hemangioendothelioma (HE). Laparotomic liver biopsy evidenced a normal liver architecture. Postoperative course was uneventful. Blood cell count went back to normal. Littoral cell HE is frequently associated with cancers in other visceral organs or malignant lymphoma, but total body CT scan, technetium bone scintigraphy, and positron emission tomography excluded neoplastic infiltration of other organs.

In conclusion, our patient with a long-standing CD had a littoral splenic HE presenting with splenomegaly and hypersplenism. This presentation is not unusual: most cases of this tumor are asymptomatic (>55%) and are only discovered incidentally, but clinically splenomegaly is almost always present; abdominal pain, pyrexia of unknown origin, symptoms of hypersplenism (thrombocytopenia and anemia), and portal hypertension may occasionally be seen. He had received both immunomodulators and anti-tumor necrosis factor (TNF) agents and had experienced recurrent perianal abscesses, suggesting a possible promoting role of chronic infection and immunosuppression in the pathogenesis of this rare tumor, as suggested by other authors. Bi *et al.* (7) have noted that 17% of the cases of littoral splenic HE were associated with immunological or congenital disorders, such as CD, Wiskott–Aldrich syndrome, Epstein syndrome, lymphocytic colitis, ankylosing spondylitis, Gaucher's disease, myelodysplastic syndrome, chronic glomerulonephritis, or aplastic anemia. To our knowledge, only one case of littoral HE in CD has been previously reported (8). Our patient is the first one to be exposed to the new anti-TNF agents. Cancer risk

in patients treated with TNF-α antagonists is considered low, and a meta-analysis of randomized trials has found no difference between CD patients treated with biologics and controls (9). Recently, the rare hepatosplenic T-cell lymphoma (3) has been described in young subjects, and another meta-analysis has confirmed an increased risk of lymphoma related to anti-TNF therapy (10). Lymphoma was our first diagnostic hypothesis before splenectomy. Physicians caring for patients treated with biologics should be aware of the possibility of rarer tumors in the differential diagnosis of splenic focal lesions. On the basis of this case and previous reports on the occurrence of lymphoproliferative disorders and severe infections (tuberculosis) (11), we recommend regular follow-up abdominal ultrasound in the long-term monitoring of safety of anti-TNF agents.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Could Trastuzumab Suppress Hepatitis C Virus in a Patient With Chronic Hepatitis and Breast Cancer?

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To the Editor: Now, molecular designed drugs can completely eliminate hepatitis C virus (HCV) without the use of interferon (1,2). Coincidently, some drugs that are used to treat other diseases have been found to suppress HCV replication (3,4). A recent study reported that sorafenib, a standard drug for the management of advanced hepatocellular carcinoma, inhibits HCV replication by suppressing c-Raf (5).

We describe a patient in whom HCV disappeared during chemotherapy with trastuzumab, a monoclonal antibody that binds to human epidermal growth factor receptor 2 (HER-2, also known as ErbB-2, or c-neu) and is used to treat breast cancer (6). Inhibition of HER-2 might be associated with HCV replication.

A 67-year-old woman with chronic hepatitis C genotype 2a infection started to receive chemotherapy for advanced breast cancer on 30 July 2009. Screening tests showed that she was anti-HCV positive. A tumor in left mammary gland and the left axillary lymph nodes were palpable. Computed tomography showed upper mediastinal lymphadenopathy. Stage IV breast cancer (T1N2M1) was diagnosed. Histological examination showed that breast cancer cells were positive for estrogen receptor and HER-2, but negative for progesterone receptor. At the start of chemotherapy with 1 mg of anastrozole per day, she was well, with a height of 155 cm and a body weight of 58 kg. The laboratory values were as follows: hemoglobin concentration 15.5 g/dl, white blood cell count 5,400/mm^3, platelet count 204,000/mm^3, aspartate aminotransferase 56 IU/l, alanine aminotransferase 93 IU/l, γ-glutamyltransferase 52 IU/l, bilirubin 0.8 mg/dl, albumin 4.1 g/dl, and HCV RNA 3.8 Log copies/ml by the COBAS TaqMan HCV assay (Roche Diagnostics, Tokyo, Japan), with a lower limit of detection of 10 IU/ml. Serological test showed that both hepatitis B surface antigen and anti-HB core were negative. Ultrasonography showed liver deformity with mild splenomegaly and no space-occupying lesions in the liver. Elastography showed mild hepatic fibrosis. On 11 January 2010, tamoxifen citrate was substituted for anastrozole because of tumor progression. From the start of chemotherapy, the serum HCV RNA level gradually increased. On 21 March 2010, the regimen for chemotherapy was switched to a combination of trastuzumab and S-1 (a combined preparation of tegafur, gimeracil, and oteracil potassium). After 3 months, HCV RNA was not detected on real-time PCR. On 22 September 2010, the treatment regimen was changed to a combination of trastuzumab and exemestane. HCV RNA remained undetectable for 9 months. The serum alanine aminotransferase level fell to < 40 IU/l since the time that HCV RNA had become undetectable (**Figure 1**).

In vitro analysis indicated that NS5A protein of HCV altered epidermal growth factor (EGF) receptor trafficking (7) and inhibited mitogen-activated protein kinase signal transduction by binding to EGF receptor (8). These findings suggested that EGF signaling might be biologically relevant to HCV infection. HER-2 is a transmembrane tyrosine kinase with 40%