Eosinophilic Granuloma of the Liver Mimicking Metastatic Liver Tumor

Yotaro Uchida, Keiji Yokoyama, Tomotaka Higashi, Takanori Kitaguchi, Hiromi Fukuda, Ryo Yamauchi, Naoki Tsuchiya, Atsushi Fukunaga, Kaoru Umeda, Kazuhide Takata, Takashi Tanaka, Yasuaki Takeyama, Satoshi Shakado, Shotaro Sakisaka, Hiroyuki Hayashi, Yoshihiro Hamada, Kazuki Nabeshima, and Fumihito Hirai

Abstract:
We herein report a case of coagulation necrosis with granulation and eosinophilic infiltration of the liver. A 37-year-old woman was diagnosed with a new mass lesion in the liver 1 month after breast cancer surgery and admitted for a further examination. Because the tumor occurred immediately after surgery, it was considered essential to determine whether or not it was a metastatic liver tumor from breast cancer. A percutaneous liver tumor biopsy revealed eosinophilic granuloma of the liver, which is considered to have a high possibility of visceral larva migrans with suspected gnathostomiasis infection. A detailed medical history and histological diagnosis are important for making a differential diagnosis.

Key words: liver tumor, eosinophilic granuloma of the liver, visceral larva migrans, gnathostomiasis infection, percutaneous biopsy

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Introduction
Eosinophilic granuloma of the liver (EGL) is caused by chronic inflammation, such as that due to larva migrans, chronic bacterial liver abscess, tuberculosis, fungi, necrotizing vasculitis, sarcoidosis, or drug use (1-8). The most common subjective symptom is abdominal pain, but it is not uncommon for patients to have no symptoms. Blood test results are characterized by elevated eosinophil and immunoglobulin E (IgE) levels (1). However, it is often difficult to make a clear diagnosis of EGL based solely on imaging findings, and a liver tumor biopsy is often useful for making a definitive diagnosis.

We herein report a case of coagulation necrosis with granulation and eosinophilic infiltration of the liver with characteristic histological findings that was diagnosed by a liver tumor biopsy.

Case Report

Patient information and clinical findings
A 37-year-old woman visited our hospital for the evaluation of a liver tumor. The patient had undergone left mastectomy and a sentinel lymph node biopsy for left breast cancer (stage II) at a local doctor in December X-1. The lymph node metastasis had been ≤2 mm in size and seen at a single location, so axillary lymph node dissection had been omitted, with follow-up continued. In January X, 1 month after breast cancer surgery, she had been diagnosed with a new mass lesion (diameter, approximately 30 mm) in segment 5 of the liver after undergoing magnetic resonance imaging (MRI) for postoperative follow-up, and she was admitted to our hospital for a further examination.

The patient showed no significant symptoms upon admission. Her vital signs were stable. She had no history of alco-
Diffusion-weighted imaging showed an indistinct high signal and non-uniform high signal on T2-weighted imaging. Revealed a tumor showing a low signal on T1-weighted imaging. At the same nodule site, abdominal contrast-enhanced MRI showed a hypovascular tumor with a faint contrast effect on the margin and a diameter of 28 mm at segment 5 of the liver (Fig. 2). In addition, positron emission tomography (PET) revealed a mild abnormal accumulation of fluorodeoxyglucose (FDG) (early maximum standardized uptake value=2.92, delayed maximum standardized uptake value=2.98) (Fig. 4).

### Progress after hospitalization

Breast cancer histopathology revealed a luminal A-like pattern (negative for the human epidermal growth factor receptor type 2, high expression of the hormone receptor, low proliferative capacity, and low grade). The histological findings were low for malignancy and considered unlikely to lead to distant metastasis; however, since the liver tumor was a new lesion that occurred after breast cancer surgery, it was considered essential to determine whether or not it was a metastatic liver tumor from breast cancer, so a percutaneous tumor biopsy was performed. The target nodule was extremely elastic and hard, making it difficult for the biopsy needle to advance into the nodule, but tumor tissue was ultimately able to be collected.

Histopathological results showed coagulative necrotizing nodules with marked eosinophil infiltration (Fig. 5), granuloma tissue (Fig. 6a), and some Langhans giant cells in the nodules (Fig. 6b). Immunostaining was negative for gross cystic disease fluid protein-15, mammaglobin, and estrogen receptor (Fig. 7a-c) and positive for only cytokeratin-7 in the glandular duct where a non-neoplastic glandular duct existed (Fig. 7d). Therefore, liver metastasis of breast cancer was considered negative. In addition, Ziehl-Neelsen staining (Fig. 7e) and periodic acid Schiff-Alcian Blue staining did not confirm any pathogens, such as bacteria, tubercle bacilli, fungi, or amoeba. Furthermore, no evidence of vasculitis was observed by Elastica van Gieson staining.

The pathological diagnosis was coagulation necrosis with granuloma and eosinophil infiltration. In this patient, there were some typical images suggesting granulomatous inflammation; for example, Langhans giant cells were observed, and eosinophil infiltration in the tissue was also clear, suggesting the possibility of parasite-related lesions. In the serum parasite antibody qualitative screening test performed to determine the cause, the gnathostomiasis antibody was Class 1, suggesting an early or chronic stage of infection. Subsequent re-collection of her life history revealed that she had a history of having eaten raw carp at a travel destination just before her breast cancer surgery, suggesting a potential infection route.

### Outcome and follow-up

The liver nodule on abdominal ultrasonography showed a shrinking tendency and became obscure over the natural course of the infection (Fig. 8), and the gnathostomiasis an-
Figure 1. Abdominal ultrasonographic imaging findings. (a) Hypoechoic lesion in segment 5 of the liver (arrow). (b) Two linear echoes inside the nodule (arrowhead; bead sign).

Figure 2. Abdominal contrast-enhanced computed tomography imaging findings of the nodule in segment 5 of the liver. (a) Early phase (arrow). (b) Portal phase (arrow). (c) Late phase (arrow).

Figure 3. Abdominal contrast-enhanced magnetic resonance image findings of the nodule in segment 5 of the liver. (a) T1-weighted imaging (arrow). (b) T2-weighted imaging (arrow). (c) Diffusion-weighted imaging (arrow). (d) Apparent diffusion coefficient mapping image (arrow). (e) Dynamic phase (arrow). (f) Hepatobiliary phase (arrow).
Figure 4. Positron emission tomography imaging findings of the nodule in segment 5 of the liver. The accumulation of FDG in the axial view (arrow). (b) FDG accumulation in the coronal view (arrow). FDG: fluorodeoxyglucose

Figure 5. Histopathological results of the nodule in segment 5 of the liver. The coagulative necrotic nodule with marked eosinophil infiltration. (a) Findings at 100× magnification. (b) Findings at 600× magnification; the part surrounded by the red frame in (a) is magnified.

Figure 6. Histopathological results of the nodule in segment 5 of the liver (findings at 200× magnification). (a) The coagulative necrotic nodule with granulation tissue. (b) Langhans giant cells in the nodule (arrowhead).

tibody qualitative test became negative six months later. In addition, the eosinophil ratio decreased from 5.2% to 2.4%, and the IgE level decreased from 252 to 167 mg/dL. She is currently being followed up on an outpatient basis.

Discussion

The possibility of EGL caused by type I allergy-induced antigens, such as chronic bacterial liver abscess, tuberculo-
VLM is the most common cause of EGL; however, it is often not possible to confirm the parasite body. Indeed, Woodruff et al. reported that 65% of 43 cases of EGL had no parasite bodies (9). Since there are many cases in which a diagnosis is made based on the medical history and serum antibodies, as in this case, it is necessary to continue to accumulate cases in which careful listening of the medical history and various tests, such as serum antibodies have been performed.

Larvae that cause VLM-related liver granulomatous nodules include Schistosoma japonicum, Clonorchis sinensis, Fasciola hepatica, dog/cat/pig roundworm, fecal nematode, tapeworm, Anisakis, and gnathostomiasis (10-17), and sources of infection include pet breeding and eating raw meat from cattle, chicken, and river fish. However, people may incidentally become infected with such eggs either excreted or spread by dogs and cats in sandboxes and park pathways. In addition, a person’s exact history of previously consuming raw meat of fish is often not clear. As a result, it is often difficult to identify the cause of such infections.

In the present case, gnathostomiasis was Class 1 according to the parasite antibody qualitative screening test. Human gnathostomiasis is most frequently caused by the nematode Gnathostoma spinigerum. This disease is endemic to Southeast Asia, particularly Thailand and Japan. Infection has been reported to occur from consuming raw freshwater fish, such as black bass, raigyo, carp, and catfish as well as
snakes (18). In the human body, the parasite moves under the skin as a larva, causing a linear repelling rash of the skin and migratory edema. Occasionally, invasion of the liver, eyes, nerves, spinal cord, and brain has been reported (17). Most patients heal spontaneously within two to three months, and indeed, in the present case, the liver nodules tended to become obscure and shrink over the natural course of the infection.

The characteristics of image inspection were compared with those of previous reports (19-24); abdominal ultrasonography often shows a single lesion on the liver surface visualized as having clear boundaries and a hypochoic nodule. The bead sign, which is two linear echoes that emphasize the portal vein branch in the granuloma, was suspected in this case (Fig. 1b). This sign is characteristic of granulomas with eosinophilic infiltrate and is found in about 70% of cases (25, 26).

In the current case, a faint but dark stain around the area was observed in the early phase of CE-CT, which was consistent with previously reported findings (19-21). On MRI, the tumor lumen often shows a low signal on T1-weighted imaging and a medium to high signal on T2-weighted imaging. In our case, T1-weighted imaging revealed a low signal, while T2-weighted imaging showed a faint high signal, which was consistent with previously reported findings (19, 22). In addition, PET-CT revealed the mildly abnormal accumulation of FDG. There have been several reports of hepatic granulomas showing the accumulation of FDG on PET-CT, similar to this patient (23, 24). However, these findings may not be typical, as the imaging features vary depending on the stage.

Several cases in which the imaging findings of VLM syndrome mimic malignant lesions have been reported (27, 28). In addition, owing to its non-specific appearance on CT, hepatic toxocariasis can often be mistaken for other conditions. Differential diagnoses for multiple low-density liver nodules include microabscesses, other granulomatous diseases (i.e. sarcoidosis), and hepatocellular carcinoma or liver metastasis (29). Hepatic lesions associated with VLM usually appear as multiple ill-defined, oval-shaped, low-attenuating nodules that are best seen in the portal phase on CT. These findings seem to be somewhat characteristic of eosinophilic infiltration or granuloma and can thus distinguish such processes from malignant lesions. Histologic confirmation is one of the most important ways of making a differential diagnosis.

The pathological findings showed granulation tissue and coagulative necrosis, and eosinophil-based inflammatory cell infiltration was characteristic, which was consistent with this case. Although Charcot-Leyden crystals were not observed in this case, about half of the cases of VLM have diamond-shaped crystals that stain red with the growth of collagen fibers that crystallize after degranulation of eosinophil granules. This is a useful characteristic finding (30, 31).

In conclusion, in the present patient, although it was difficult to determine whether or not this case involved a metastatic liver tumor from breast cancer, a percutaneous tumor biopsy revealed a coagulative necrotic nodule with granulation and eosinophilic infiltration that was suspected to be VLM. Collecting a detailed medical history and obtaining a histological diagnosis are important for making a differential diagnosis.

Written informed consent was obtained from the patient for publication of this manuscript. Patient identifiers, aside from age and sex, were removed, and the images provided were anonymized to protect patient confidentiality.

The authors state that they have no Conflict of Interest (COI).

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