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【 CASE REPORT 】

Hypereosinophilia with Hepatic Nodule Formation Caused by *Ganoderma lucidum*

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Abstract:

A 61-year-old man who underwent surgery for rectal adenocarcinoma developed multiple hepatic nodules. The nodules were 1-3 cm without a capsular structure or contrast enhancement on computed tomography/magnetic resonance imaging, findings that were atypical for adenocarcinoma metastases. A biopsy showed the aggregation of eosinophils without larval bodies, ova, or granulomas. Laboratory tests showed a marked increase in eosinophils and a slight liver enzyme elevation. He had been taking the commercial herbal medicine *Ganoderma lucidum* for his liver function. After discontinuing *G. lucidum*, the eosinophil counts and liver enzyme levels rapidly resolved, and the nodules disappeared completely. This is a rare case of hypereosinophilia with hepatic nodules reactive to herbal medicine rather than a parasitic infection.

Key words: hypereosinophilia, hepatic nodules, *Ganoderma lucidum*

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Introduction

Hypereosinophilia includes primary diseases caused by myeloid neoplasms and hypereosinophilic syndromes or secondary diseases caused by parasitic infections, drug reactions, allergy/atopy, collagen diseases, pulmonary disorders, and non-myeloid malignancies, including solid tumors (1). Hypereosinophilia affects various organs, although the involvement of the liver is less frequent (2). In addition to liver damage, it can form hepatic nodules detected on radiological imaging (3).

The most common causes of hepatic nodules associated with hypereosinophilia are parasitic infections. Non-parasitic hepatic nodules associated with hypereosinophilia are rare, and the pathogenic cause is rarely identified (4, 5).

We herein report a case of hypereosinophilia and hepatic nodule formation without parasitic disease caused by the herbal medicine *Ganoderma lucidum*.

Case Report

A 61-year-old man who underwent surgery for rectal cancer was referred to our division due to multiple hepatic nodules detected on diagnostic imaging in April 2018. The patient underwent low anterior resection for rectal adenocarcinoma in September 2017. The rectal adenocarcinoma was a 7×5-cm type II tumor located 10 cm from the anal verge, and curative resection was performed. The pathology of the tumor was moderately differentiated adenocarcinoma with invasion into the subserosa. Lymphovascular and venous invasion as well as lymph node metastasis were noted.

The patient started oral S-1 medication (tegafur, gimeracil, and oteracil potassium) following the surgery but discontinued it due to liver injury in January 2018. In April 2018, computed tomography (CT) and magnetic resonance imaging (MRI) showed multiple hepatic nodules. As the nodules' imaging characteristics were not typical of liver metastasis of rectal adenocarcinoma, he was referred to our division for a pathological diagnosis by a needle biopsy.

The patient had undergone curative surgery for a right in-

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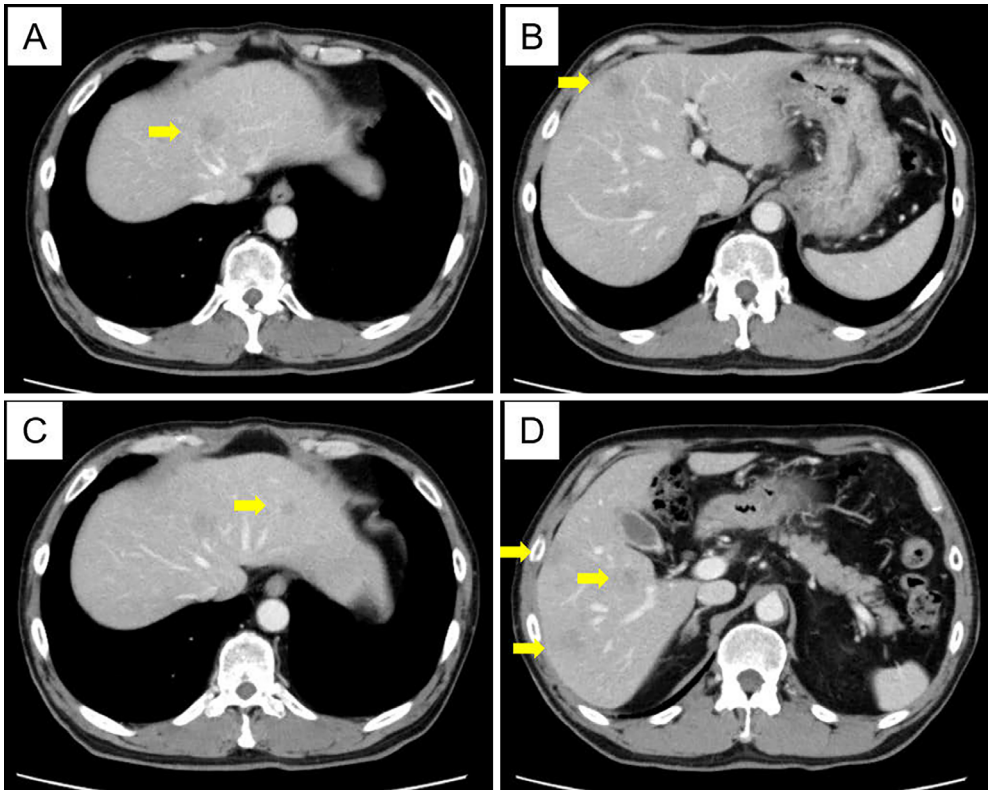

Figure 1. **Abdominal CT images at referral to our division. Multiple spherical hepatic nodules, ranging in size from 1-3 cm, are distributed in both liver lobes (A-D, arrows). The nodules showed two types: those with well-defined borders (A, C) and those with ill-defined borders (B, D). The nodules had no capsular structure and very weak contrast enhancement.**

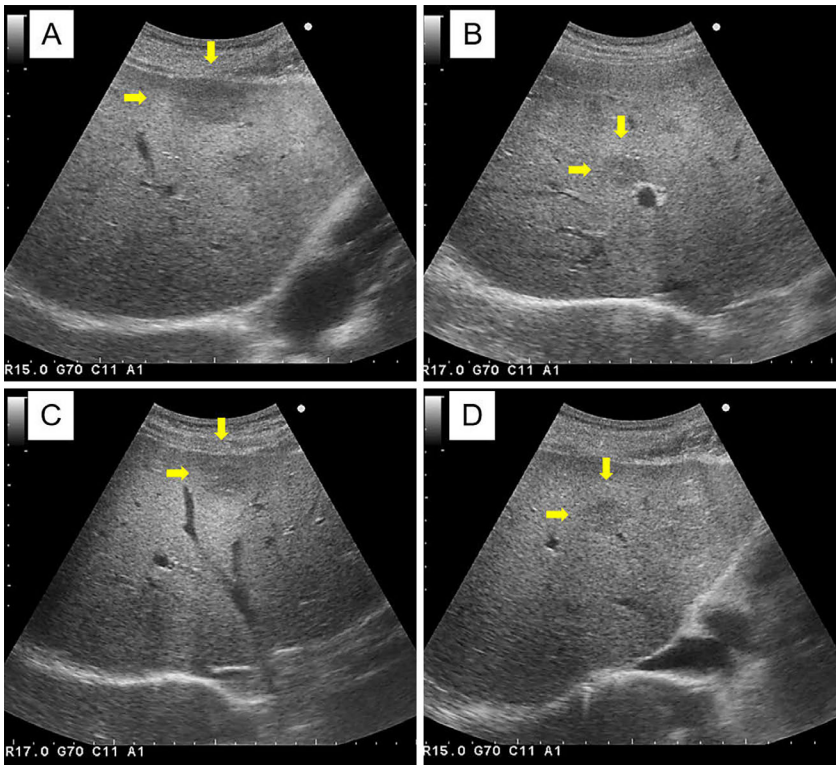

Figure 2. **Abdominal ultrasound images. Multiple spherical nodules corresponding to the nodules on CT are detected. The nodules showed two types: those with well-defined borders (A, B; arrows) and those with ill-defined borders (C, D; arrows).**

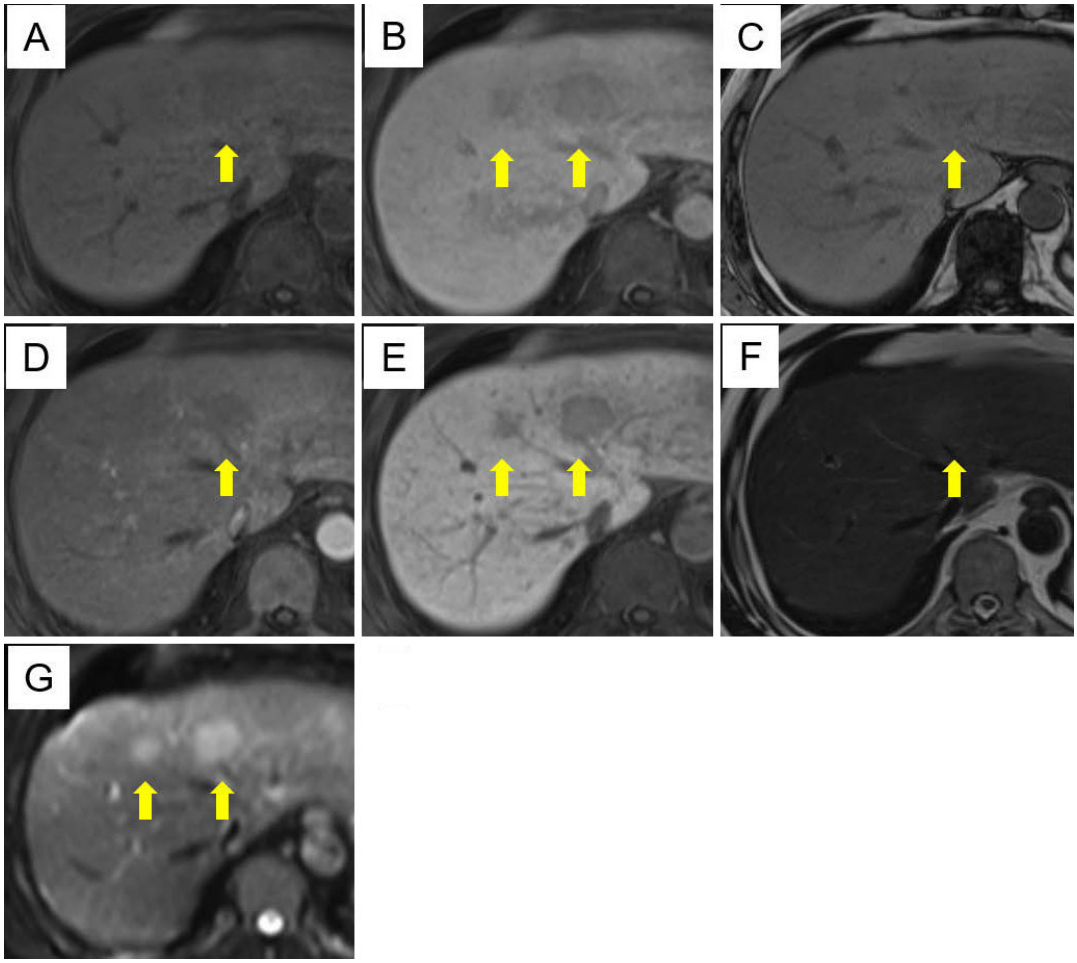

Figure 3. Abdominal MRI findings at referral to our division. (A) T1-weighted image, (B) T1 early phase, (C) T1 portal phase, (D) T1 late phase, (E) T1 hepatocyte phase, (F) T2-weighted image, (G) diffusion-weighted image. The hepatic nodules have a low signal intensity on T1 imaging with very weak contrast enhancement and slightly high signal intensity on T2 imaging. The nodules are distinguished clearly on diffusion-weighted imaging.

guinal hernia at 12 years of age. At the diagnosis of rectal cancer, bladder cancer (low-grade non-invasive superficial papillary tumor) was detected, and transurethral tumor resection was performed simultaneously with the rectal cancer surgery. He had been diagnosed with type 2 diabetes mellitus, dyslipidemia, and hypertension at 57 years of age. He had been taking glimepiride and sitagliptin for type 2 diabetes mellitus, fluvastatin and ezetimibe for dyslipidemia, and losartan and amlodipine for hypertension continuously for over three years. He had no history of any allergic diseases, including bronchial asthma. He had no alcohol consumption or smoking habits and no history of travel overseas.

After ceasing S-1 medication due to liver injury, he started taking the commercial herbal medicine *G. lucidum*, or Reishi (in Japanese), hoping it would help his liver function. He developed general malaise and nausea in March 2018, but no abnormal findings were detected with upper gastrointestinal endoscopy or whole-body CT.

The patient was 178 cm tall, weighed 68 kg, and had no abnormalities in blood pressure or his pulse rate at the first visit to our division. He had no rash, erythema, and edema on his body surface. The physical examination of the chest and abdomen revealed no abnormal findings. The initial laboratory tests showed no specific findings other than slightly abnormal liver enzyme levels and anemia [aspartate aminotransferase 22 IU/mL, alanine aminotransferase (ALT) 43 IU/mL, lactate dehydrogenase 165 IU/mL, alkaline phosphatase 196 IU/mL, γ-glutamyl transpeptidase 32 IU/mL, total bilirubin 0.7 mg/dL, white blood cells 4,300/μL, eosinophils 120/μL (2.8%), red blood cells 3,740,000/μL, hemoglobin 13.3 g/dL, platelet count 239,000/μL]. The levels of the tumor markers carcinoembryonic antigen, carbohydrate antigen19-9, α-fetoprotein, and des-γ-carboxy prothrombin were normal, and there were no abnormalities suggesting persistent hepatitis B virus or hepatitis C virus infection, autoimmune, or metabolic liver diseases.

Abdominal contrast-enhanced CT showed multiple spherical hepatic nodules, ranging in size from 1-3 cm (Fig. 1). The nodules included two types: ones with well-defined borders (Fig. 1A, C) and ones with ill-defined borders (Fig. 1B, D). The nodules had no capsular structure and showed very weak contrast enhancement in all phases. On

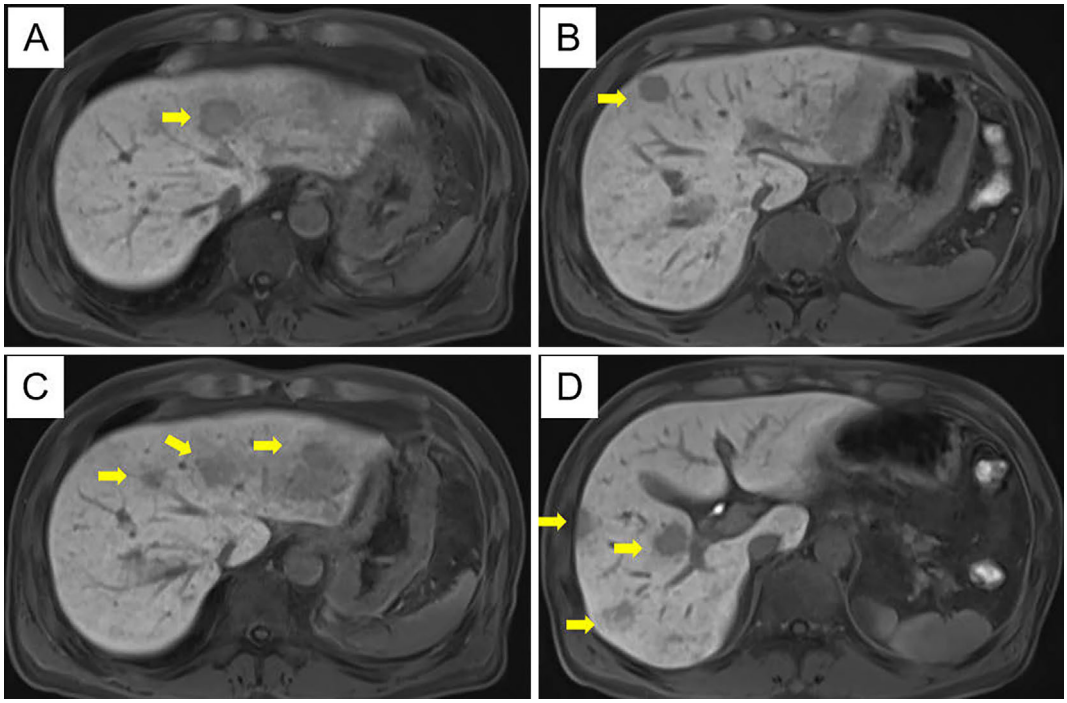

Figure 4. Abdominal MRI findings in the hepatocyte phase. The nodules lack a hepatic uptake of the contrast agent in the hepatocyte phase of a gadolinium-EOB-DTPA contrast study, consisting of well-defined and ill-defined nodules.

ultrasound imaging, multiple spherical nodules were detected, corresponding to the nodules on the CT (Fig. 2). On abdominal MRI, the nodules had a low signal intensity on T 1 and slightly high signal intensity on T2 and were distinguished clearly on diffusion-weighted imaging (Fig. 3). The nodules showed no hepatic uptake of the contrast agent in the hepatocyte phase of a gadolinium-EOB-DTPA contrast study, consisting of well- and ill-defined nodules (Fig. 4). As the nodules did not show features typical of liver metastasis from rectal cancer, we decided to perform a percutaneous needle biopsy for a pathological diagnosis.

On admission for the biopsy, the patient showed a low-grade fever of 37.4°C without other significant physical findings. Laboratory tests on admission showed a marked increase in white blood cell count with an absolute eosinophil count of 14,210/μL and a slight elevation of liver enzymes. Immunoglobulins, including IgG, IgM, and IgE, were normal (Table). An ultrasound-guided percutaneous tissue sampling was performed from a nodule in segment 4 using an 18-gauge tru-cut needle. The biopsy sample was obtained with a single puncture across the nodule and adjacent liver tissue. The biopsy showed marked aggregation of immune cells in the nodule (Fig. 5A, B). The immune cells were identified as eosinophils, containing eosinophilic granules in the cytoplasm by direct fast scarlet staining (Fig. 5C). Eosinophils infiltrated the portal areas and the surrounding central veins in the parenchyma adjacent to the nodule. We found no evidence of larval bodies, ova, granulomas, or any malignancy. The structure of the adjacent liver was maintained with no findings suggestive of chronic liver diseases.

Based on the markedly increased number of eosinophils in peripheral blood and hepatic nodule formation by aggregation of eosinophils, we diagnosed focal eosinophilic infiltration of the liver associated with hypereosinophilia. The differential diagnosis of diseases causing hypereosinophilia includes myeloid neoplasms, hypereosinophilic syndrome, parasitic infections, drug reactions, allergy/atopy, collagen diseases, pulmonary diseases, and non-myeloid malignancies, including solid tumors. A full workup for any other organ damages detected no significant findings and no rectal or bladder cancer recurrence. Endoscopy of the upper and lower gastrointestinal tract revealed no specific results, and a random biopsy of the mucosa showed no eosinophilic infiltration. The fecal examination detected no parasite ova.

Considering these observations, we concluded that the patient had developed hypereosinophilia due to a reaction to *G. lucidum* medication or developed hypereosinophilic syndrome. We decided to discontinue the herbal medicine *G. lucidum* first in order to evaluate whether or not the eosinophilia would improve without further action.

After discontinuing *G. lucidum*, the peripheral eosinophil count and ALT level rapidly decreased (Fig. 6). He also experienced improvement in his symptoms, such as the fever, nausea, and malaise. Two months after the discontinuation of *G. lucidum*, MRI revealed that most of the hepatic nodules had disappeared with some residual scar-like structures (Supplementary material 1C, D). The hepatic nodules had disappeared entirely on CT performed three months after discontinuing *G. lucidum* (Supplementary material 1G, H).

Table. **Clinical Characteristics.**

White blood cells (/μL)	19,200
Neutrophils (/μL)	2,690
Eosinophils (/μL)	14,210
Basophils (/μL)	0
Lymphocytes (/μL)	1,920
Monocytes (/μL)	380
Red blood cells (/μL)	3,570,000
Hemoglobin (g/dL)	12.2
Platelet (/μL)	291,000
Prothrombin time (%)	96.8
Total bilirubin (mg/dL)	0.4
Direct bilirubin (mg/dL)	0.1
AST (IU/L)	45
ALT (IU/L)	66
LDH (IU/L)	240
ALP (IU/L)	445
γ-GTP (IU/L)	101
Total protein (g/dL)	6.5
Albumin (g/dL)	3.2
Total cholesterol (mg/dL)	129
Triglyceride (mg/dL)	147
Glucose (mg/dL)	189
Hemoglobin A1c (%)	8.5
Urea nitrogen (mg/dL)	20.0
Creatinine (mg/dL)	0.8
Sodium (mEq/L)	142
Potassium (mEq/L)	4.0
Chloride (mEq/L)	108
Immunoglobulin G (mg/dL)	1,096
Immunoglobulin A (mg/dL)	321
Immunoglobulin M (mg/dL)	77
Immunoglobulin E (mg/dL)	123

AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γ-GTP: γ-glutamyl transpeptidase

Based on this clinical course of events, although we did not conduct a drug lymphocyte stimulation test, we concluded that he had developed secondary hypereosinophilia with hepatic nodule formation as a response to the herbal medicine *G. lucidum*.

Discussion

Eosinophilia is defined as an increase in the number of eosinophils in the peripheral blood above the upper limit of normal. The normal upper limit of eosinophils is 3%-5% as a percentage of peripheral white blood cells, and it is 350-500 cells/μL as an absolute number of eosinophils. The severity of eosinophilia is classified as mild with an absolute eosinophil count from the upper limit of normal to 1,500/μL, moderate with 1,500-5,000/μL, and severe with >5,000/μL (6). Hypereosinophilia is defined as persistent eosinophilia with an absolute eosinophil count of more than 1,500/μL associated with end-organ damage (7). Hypereosinophilia is broadly classified as reactive (secondary) and clonal (primary). The primary causes of hypereosinophilia include neoplastic eosinophilia, which are myeloid/lymphoid neoplasms and chronic eosinophilic leukemia, and idiopathic eosinophilia (hypereosinophilic syndrome) (7).

The causes of secondary hypereosinophilia are quite diverse. In developing countries, tissue-invasive parasitic infections are the most common causes (2). Other causes include allergy/atopy, drug reactions, collagen diseases (e.g. Churg-Strauss syndrome, Wegener's granuloma, systemic lupus erythematosus), pulmonary eosinophilic diseases (e.g. eosinophilic pneumonia, allergic bronchopulmonary aspergillosis), and non-myeloid malignancies, including solid tumors (1, 8, 9).

Drug reactions are a common cause of secondary hypereosinophilia in clinical practice. Secondary hypereosinophilia is thought to be mediated by the overproduction of cytokines, such as interleukin (IL)-5, IL-3, and granulocyte-macrophage colony-stimulating factor, which promote the differentiation and survival of eosinophils; however, the mechanism underlying organ-targeted involvement in hypereosinophilia has not been clarified (10).

Hypereosinophilia can induce the infiltration of eosinophils into all organ systems. Eosinophilic infiltration into the liver is believed to be one of the manifestations of organ damage associated with hypereosinophilia. The most common clinical manifestations of hypereosinophilia are in the skin (69%), lung (44%), and gastrointestinal tract (38%), with liver infiltration being very rare (2).

In patients with hypereosinophilia who show elevated liver enzyme levels, a liver biopsy may reveal eosinophilic infiltration without morphologic abnormalities on diagnostic imaging. However, eosinophilic infiltration into the liver can form nodular lesions on CT, MRI, and ultrasonography. The underlying pathogenesis of eosinophilic infiltration and formation of nodules is not fully understood, so the disease concept has not yet been established. The terms focal eosinophilic infiltration of the liver, hepatic eosinophilic granuloma, and eosinophilic liver abscess have been used to describe this clinical presentation (4).

The diagnostic imaging features of hepatic nodules in hypereosinophilia have been reported (5). Ultrasonography depicts the nodules as a spherical, hypoechoic lesion. Most nodules show iso- or low-density lesions with ill-defined borders in the arterial phase on CT. According to CT imaging, about 50% of patients have a single lesion, and the remaining have multiple lesions. Most of the lesions are less than 2 cm in size. On gadolinium contrast-enhanced MRI, 77% of lesions have ill-defined borders, and 36% are spherical, as reported by Lee et al. (11). On T1-weighted images, 82% show iso- or high-signal intensity, and on T2-weighted images, 92% show high-signal intensity (11). Most metastatic liver tumors are well-defined, T1 low-signal lesions,

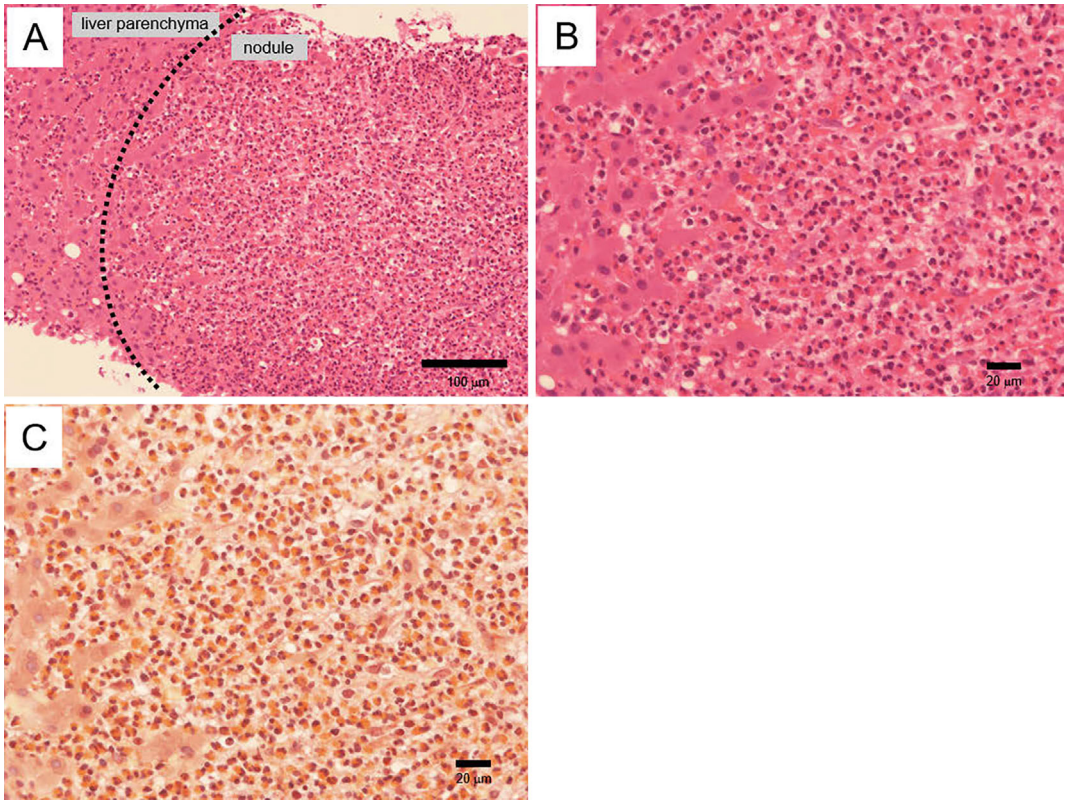

Figure 5. **Pathological images of a nodule in the medial segment. (A) A low-magnification image with Hematoxylin and Eosin (H&E) staining. (B) A high-magnification image with H&E staining. (C) A high-magnification image with direct fast scarlet staining.**

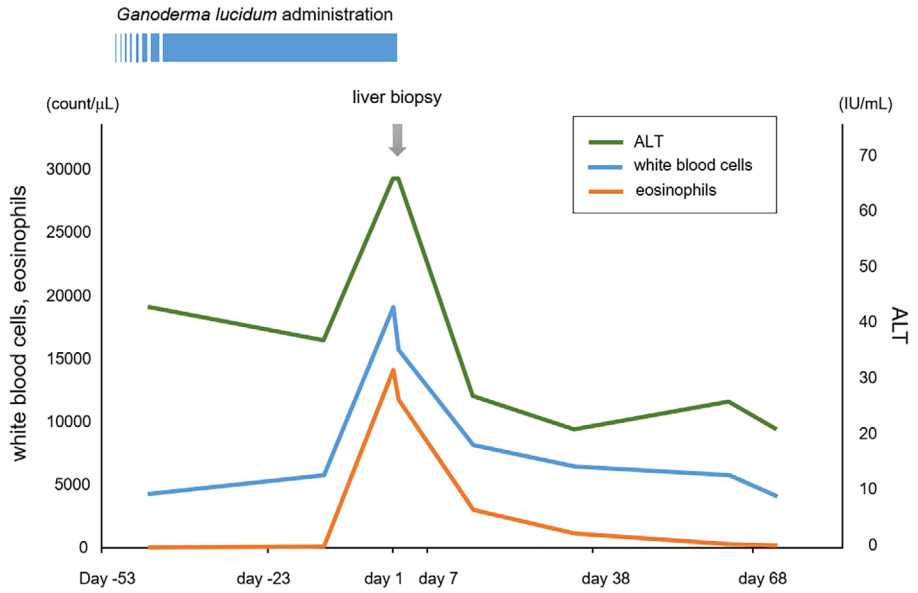

Figure 6. **Clinical course. Serum alanine aminotransferase (ALT) levels, white blood cell count, and eosinophil count in peripheral blood.**

while hepatic nodules associated with hypereosinophilia show T1 iso- or high-signal lesions with ill-defined borders, which may aid in distinguishing between them (11). In the present case, since the patient had received surgery for rectal cancer, it was essential to distinguish his hepatic nodules from liver metastases of rectal cancer. The patients' hepatic nodules lacked certain characteristics of liver metastasis, such as ring-like enhancement, so we considered the possibility of metastases to be low and thus performed a percutaneous needle biopsy for a pathological diagnosis.

Most causes of hepatic nodules associated with hypereosinophilia have been reported to be parasitic diseases (4, 5). Allergic reactions induced by parasite larvae migrating from the intestine to the liver may result in nodule

formation. Pathologically, Charcot-Leyden crystals, larval bodies, or ova are detected in granulomas with the aggregation of eosinophils in some cases (12). Non-parasitic causes are rare, and in most such cases, the pathogenic causes remain unknown (12). Silica, copper sulfate, beryllium compounds, talc, polyvinyl pyrrolidone, barium sulfate, and thorium dioxide have been reported as rare causes (13). Certain medications can also be causes; however, the details of such cases have not been reported (14). In the present case, the patient showed extreme eosinophilia (maximum 14,200/μL) in the peripheral blood, accompanied by liver enzyme elevation and multiple hepatic nodules. He had anorexia and a low-grade fever, but a full systemic examination, including gastrointestinal endoscopy, showed no evidence of parasitic infections or organ damage other than to the liver. After discontinuing the herbal medicine, the patient's increased eosinophils in the peripheral blood quickly resolved, and the abnormal liver enzymes and symptoms improved. The nodules also disappeared in the following months; thus, we confirmed that the herbal medicine had caused the hypereosinophilia and hepatic nodules.

Although eosinophilia induced by drug reaction occurs commonly in clinical practice as drug-induced liver injury, the development of hepatic nodules associated with hypereosinophilia is extremely rare (12). *G. lucidum*, the drug that caused the hypereosinophilia in this case, is a medicinal mushroom widely used as an herbal medicine in China and Japan and is believed to have various pharmaceutical and therapeutic properties (15). The primary pharmacologically active substances of *G. lucidum*, lanostane triterpenoids (e.g., ganoderiole F and ganoderic acid B), have been found to have many effects, including anticancer, immunomodulatory, antihypertensive, prostate enlargement-ameliorating, antidiabetic, and antiviral activities (16, 17). No previous cases of hypereosinophilia and hepatic nodule formation caused by *G. lucidum* or triterpenoids have been reported. The infiltration of eosinophils into the liver in the present case may not be a specific feature of *G. lucidum* but instead possibly due to the patient's idiosyncrasy.

In conclusion, this is a unique case of hepatic nodules associated with hypereosinophilia in which the causative drug was identified, and the clinical condition improved by discontinuing the medication.

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

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