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Case Report

Solitary Hepatic Eosinophilic Granuloma Accompanied by Eosinophilia Without Parasitosis: Report of a Case

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A 43-year-old Japanese woman visited for a hepatic tumor incidentally found. We suspected eosinophilic granuloma of the liver (EGL) due to visceral larva migrans (VLM). However, neither past history nor medical interview indicated a risk of parasitosis. Blood testing revealed eosinophilia, serum examination showed normal results for immunoglobulin E, and enzyme-linked immunosorbent assay yielded negative for *Toxocara* and *Anisakis*. Gastric and colonic endoscopy revealed normal features. Several imagings showed central necrosis of the tumor. After informed consent, laparoscopic resection was performed. Histopathological examination showed EGL without parasites. No recurrence had occurred postoperatively. Most reports documented that EGL are caused by VLM. However, parasites are not always demonstrable on serum, histopathological, or immunochemical examinations. When acting as allergens to induce type I responses, microscopic agents other than parasites in the intestinal tract could induce eosinophilic inflammation in the liver. Accumulation of more cases should help clarify other pathogeneses for EGL.

Key words: Eosinophilic granuloma of the liver – Parasitosis – Type I allergy – *Toxocara* – Hepatic granuloma

Although systemic eosinophilic granulomas can be caused by various diseases, eosinophilic granuloma of the liver (EGL) is predominantly caused by visceral larva migrans (VLM) caused by *Toxocara* and *Capillaria* species. Type I allergic reaction to antigens from the worms has been suggested to induce vasculitis, eosinophilic aggregation, and secondary EGL. We encountered a rare

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case of EGL in which we could not demonstrate any correlation between EGL and VLM, despite various pre- and postoperative examinations. We report this case herein and discuss our speculations.

Case Report

A 43-year-old Japanese woman visited our hospital with a hepatic tumor that had been incidentally identified on ultrasonography during an annual medical examination. She was married with no children, was born and lived in Osaka, was employed as an office worker, and had no pets. She had no habits of drinking alcohol, smoking, or eating raw meat from mammals or birds. She had not eaten any raw fish during the previous 3 months, and had no relevant medical history or history of drug use. Her temperature was normal, and physical examination revealed no obvious symptom such as icterus, dyspnea, ophthalmopathy, gynecologic abnormality, or abdominal complaints.

Other than an increased level of eosinophils in peripheral white blood cells (10%), results of blood cell tests, serologic examinations including immunoglobulin (Ig)G, IgM, IgE, and enzyme-linked immunosorbent assay (ELISA) for *Toxocara* and *Anisakis* species were within the normal range (Table 1). Endoscopy of the upper digestive tract and colon revealed normal features.

Ultrasonographic examination showed a single, low-echoic mass with irregular margins 2 cm in diameter in segment 6 of the liver, and Doppler ultrasonography revealed high arterial flow around the tumor, but no blood flow within the tumor (Fig. 1A). Positron emission tomography showed a standardized uptake value of 2.4 in the tumor (Fig. 1B), while plain CT showed a low-density lesion, and dynamic CT of the liver depicted rim enhancement of the tumor in both early and late phases (Fig. 1C–E). Magnetic resonance imaging (MRI) depicted a slight low-intensity lesion on T1-weighted imaging (Fig. 2A), and gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) MRI depicted rim enhancement of the tumor in the early phase of T1 (Fig. 2B), and defect of Gd-EOB-DTPA uptake to the tumor in the late phase of T1 (Fig. 2C, 2D). Imaging series showed no tumors in other organs and no changes in tumor size over the course of 2 months.

We could not reach a clear decision between the differential diagnoses of inflammatory pseudotu-

Table 1 Laboratory data on admission

Complete blood count	
White blood cells	5030/μL
Red blood cells	383×10^4/μL
Hemoglobin	12.8 g/dL
Hematocrit	37.40%
Platelets	17.8 × 104/μL
Neutrophils	49.10%
Lymphocytes	33.60%
Monocytes	5.40%
Eosinophils	10.70%
Basophils	1.20%
Blood chemistry	
Total protein	7.2 g/dL
Albumin	3.8 g/dL
Globulin	3.4 g/dL
α1 globulin	2.80%
α2 globulin	6.30%
β globulin	6.90%
γ globulin	18.20%
Total bilirubin	0.7 mg/dL
Aspartate aminotransferase	22 IU/L
Alanine aminotransferase	16 IU/L
Alkaline phosphatase	145 IU/L
Lactate dehydrogenase	165 IU/L
γ-glutamyl transpeptidase	13 IU/L
Cholinesterase	212 IU/L
Amylase	82 IU/L
Blood urea nitrogen	10.5 mg/dL
Creatinine	0.51 mg/dL
Uric acid	4.9 mg/dL
Total cholesterol	213 mg/dL
C-reactive protein	0.05 mg/dL
Na	139 mEq/L
K	4.4 mEq/L
Cl	105 mEq/L
Blood sugar	81 mg/dL
Hemoglobin A1c	5.10%
Indocyanine green retention rate at 15 min	6%
Type III procollagen-N-peptide	0.5 U/mL
Type IV collagen 7S	3.0 ng/mL
Serology	
Hepatitis B surface antigen	Negative
Hepatitis B core antibody	Negative
Hepatitis B surface antibody	Negative
Hepatitis C virus antibody	Negative
Antinuclear antibody	Negative
Antimitochondrial antibody	Negative
Enzyme-linked immunosorbent assay for *Toxocara* and *Anisakis* species	<0.1 U_A/mL
Immunoglobulin E	50.8 IU/mL
Tumor marker	
Protein induced by vitamin K absence/antagonist-II	16 IU
Cytokeratin 19 fragment	1.6 ng/mL
α-fetoprotein	4.9 ng/mL
Carcinoembryonic antigen	1.3 ng/mL
Carbohydrate antigen 19-9	4.1 U/mL
Coagulation test	
Prothrombin time %	72.80%
Prothrombin time international normalized ratio	1.27

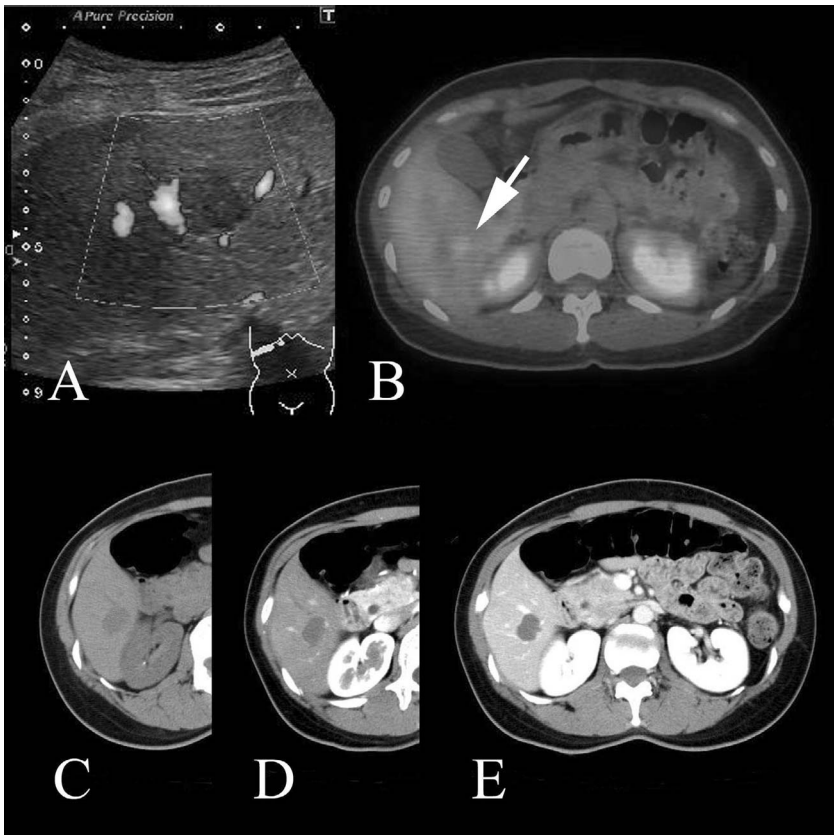

Fig. 1 Imaging series for the present case. (A) Doppler ultrasonography shows a low-echoic lesion and hyperarterial flow surrounding the lesion. (B) Positron emission tomography shows slightly high standardized uptake value in the lesion (arrow). (C–E) Dynamic computed tomography shows a low-density lesion with rim enhancement near the portal tract (arrow).

mor and EGL of unknown cause. As a result, we informed the patient and her husband of the clinical options, including follow-up, biopsy or laparoscopic resection for differential diagnosis, and they decided on laparoscopic resection. Two months after presentation, laparoscopic hepatic resection of segment 6 was performed. Laparoscopically, the liver appeared normal. The cut surface of the tumor was 2.2 × 1.7 cm in size, near Glisson's sheath, and showed irregular margins and homogeneous lustrous yellow material (Fig. 3A). Microscopically, the tumor consisted of central necrotic material and peripheral granulation (Fig. 3B). The central necrotic material stained homogeneously with eosin, but contained no apparent parasitic organ or egg. Peripheral granulation contained eosinophils, monocytes, lymphocytes, macrophages, multinucleated giant cells, capillaries, and fibroblasts. No caseous necrosis, vasculitis, or Charcot-Leyden crystals were found. EGL due to unknown cause was thus diagnosed. The postoperative course was uneventful, and although peripheral eosinophils remained persistently high (11%), the tumor has not recurred as of the time of writing, 1 year postoperatively.

Discussion

Eosinophilic granuloma is a name for the histopathologic features of a form of allergic reaction. The same histopathologic features are seen in diseases such as necrotizing vasculitis,[1] sarcoidosis,[2] Langerhans cell histiocytosis, Churg-Strauss syndrome,[3] Kimura's disease,[4] rheumatoid fever,[5] hypereosinophilic syndrome,[6] and allergic reactions to norfloxacin,[7] glyburide,[8] and parasites (fascioliasis, ascariasis, clonorchiasis, schistosomiasis, and anisakiasis).[9–18] Because eosinophilic granuloma appears to represent a kind of type I allergic reaction, eosinophilic granuloma concurrently occurs systemically or in organs where type I allergic reactions arise. In a broad sense, EGL simply indicates that the liver is one of the organs where a type I allergic reaction can occur. As most EGLs are actually caused by an allergic reaction to parasites migrating through the liver, the term EGL in a narrower sense commonly indicates a specific local allergic reaction to parasites in the liver with or without digestive tract parasitosis. The parasites in question migrate to the liver from the digestive system through the portal vein, as VLM, where

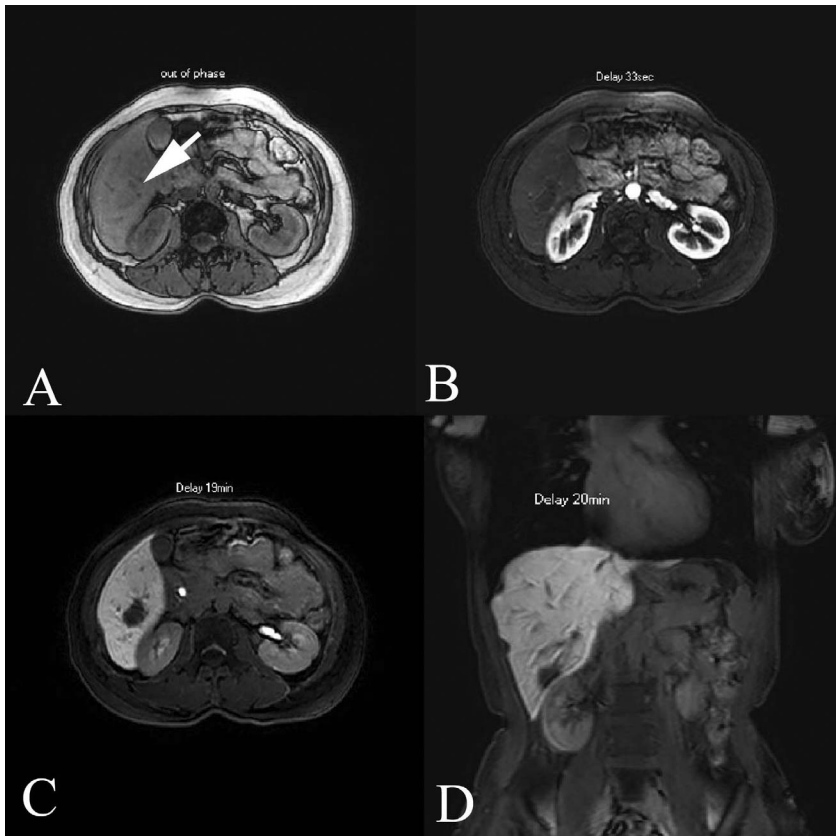

Fig. 2 Imaging series of gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) magnetic resonance imaging (MRI). (A) Plain MRI showed a slightly hypointense lesion (arrow). (B) Early-phase Gd-EOB-DTPA MRI shows a hypointense lesion with rim enhancement. (C, D) Late-phase Gd-EOB-DTPA MRI shows a low-intensity lesion and enhancement of parenchyma in the liver.

antigens from the parasites induce local allergic reactions in the liver.

Fascioliasis, ascariasis, clonorchiasis, schistosomiasis, and anisakiasis have all been reported to cause EGL by VLM. Although the patients displaying these pathologies have been reported from all generations, both sexes, and worldwide, patients tend to be children, of Asian or Middle Eastern ethnicity, and with a background of habitually eating raw meat or fish.[17,19] Most cases of EGL by VLM were reportedly caused by migration of *Toxocara canis*.[15] In Japan, cases of EGL due to *Ascaris suum* are often reported in the Kyushu region,[12,13] while cases in western Japan typically involve schistosomiasis.[17]

Clinical symptoms of EGL by VLM include fever, abdominal discomfort, general fatigue, and/or cough. However, the majority of asymptomatic patients are incidentally diagnosed with EGL by VLM when laboratory examinations reveal eosinophilia and a high ELISA titer for parasite antigens. Most adult cases of EGL by VLM show eosinophilia, while cases involving younger children and babies often show levels of eosinophils within the normal

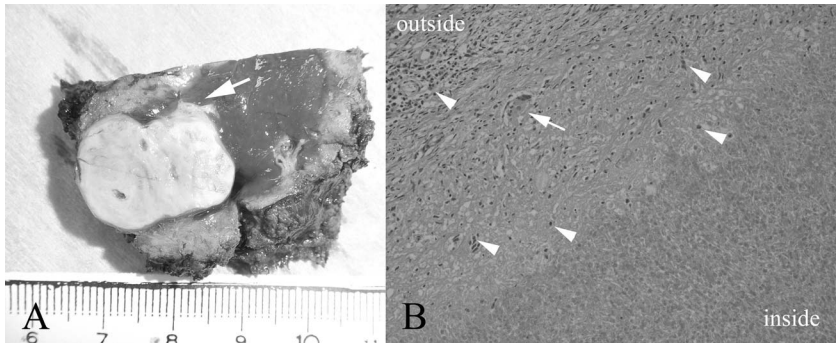

Fig. 3 Pathologic feature of eosinophilic granuloma. (A) The tumor macroscopically shows white-yellow coloration, and is present near Glisson's sheath (arrow). (B) The tumor histopathologically consists of inner necrotic/degenerative material and outer eosinophilic granulative inflammation. Inflammatory cells variously consist of eosinophils (arrowheads), monocytes, lymphocytes, macrophages, and multinucleated giant cells (arrow).

range. Sensitivities of ELISA and eosinophilia reportedly vary, although serum examination using ELISA offers the most important diagnostic clue. Some reports have documented high sensitivity and specificity of ELISA in adults and older children with EGL by VLM,[20,21] while others have described low sensitivity of ELISA.[22]

On imaging,[23] EGL by VLM appears as a macroscopic nodule, rather than microscopic diffuse inflammation. Imaging series show solitary or plural nodules with irregular shape, ranging in diameter from 5 mm to 2 cm. Ultrasonographically, EGL by VLM is depicted as a low-echoic lesion, frequently accompanied by linear shadows within the nodule (bead sign). CT depicts a lesion of low density on plain imaging, and a hypodense lesion with rim enhancement in both early and late phases of dynamic enhanced CT. MRI depicts a hypointense lesion on T1-weighted imaging, and a hyperintense lesion on T2-weighted imaging. Findings on positron emission tomography (PET)-CT and Gd-EOB-DTPA MRI have not previously been reported. The present case showed a lesion with slightly high standardized uptake value (SUV) on PET-CT, and low intensity with rim enhancement in the early phase of Gd-EOB-DTPA MRI and defective uptake in the late phase.

In the surgical/biopsy specimen, macroscopic examination of EGL by VLM showed a white-yellow nodule, and microscopic features included central necrosis and peripheral infiltration of eosinophils, neutrophils, lymphocytes, epithelioid cells, and multinucleated giant cells with hyperplasia of capillaries and fibroblasts. When hyperinfiltration of eosinophils is seen, Charcot-Leyden crystals are also evident. Within the region of central necrosis, the bodies of parasites are often seen. An obstructed portal vein, ultrasonographically depicted as the "bead sign," is also frequently evident within the area of central necrosis. Some investigators have emphasized the high frequency of this "bead sign."

In general, the presence of parasites on histopathologic examination or positive ELISA results for parasites allow definitive diagnosis. When EGL by VLM is suspected, a medical interview to elicit histories of ingesting raw meat or fish, involvement in animal husbandry, or keeping pets is most important to reach a diagnosis and confirm a therapeutic plan. Referring to the medical interview, blood and serologic examinations, imaging examinations, and liver biopsy can be planned. When a patient is diagnosed with EGL by VLM and has some clinical symptoms or complaints, antiparasitic agents such as albendazole, mebendazole, thiabendazole, or diethylcarbamazine can be administered.[24] When the patient is asymptomatic, follow-up without antiparasitic agents is usual, with periodic imaging examinations. When EGL by VLM is diagnosed, surgical resection of the granuloma is not usually performed, as most cases without clinical symptoms show spontaneous remission and disappearance of the EGL by VLM.[23] Resection of EGL by VLM should be limited to cases in which confirmation of EGL is difficult.

Examinations for definitive diagnosis include ELISA and pathologic demonstration of parasites within the EGL. The sensitivity of ELISA, however, appears variable, and the rate for pathologic demonstration of parasites is low. Nakashima *et al* reviewed 14 cases of EGL, finding parasites in none of the cases.[25] Kaplan *et al* also reviewed 43 cases of EGL according to histopathologic and immunohistopathologic findings,[26] but failed to identify parasites in 28 cases (65%).

In the present case, as the patient showed mild eosinophilia and no chronic hepatitis, we suspected EGL by VLM from the beginning. Physical examination, laboratory examination, and medical interviews revealed no findings specific for EGL by VLM other than eosinophilia. IgE and ELISA titers for *Ascaris* and *Anisakis* antigens showed results within normal ranges. Imaging did not demonstrate eosinophilic granulation in any other organs. In addition, the lesion in the liver did not show any improvement over the course of the 2 months before surgical treatment, and parasites were not seen in the center of the EGL on histologic examination. The possibility that the present case might not have been caused by a parasite thus cannot be excluded.

Some investigators have suggested that Glisson's sheath in the area of central necrosis represents the pathway for the flow of parasite ova from the digestive tract through the supramensenteric vein, and that the obstructed Glisson's sheath is depicted as the "bead sign" without blood flow.[25] Obstruction of Glisson's sheath would induce peripheral parenchymal necrosis of the liver, and parasite ova or the parasites themselves would induce type I allergic inflammation. Presinusoidal necrosis and granulation can also be caused by copper,[27,28] arsenic,[29] vinyl chloride,[27] systemic mastocytosis,[6] some cytotoxic drugs,[30,31] and pathogenic bacteria[32] such as *Coxiella burnetii*,[33] although inflammatory granulation does not always represent a type I allergic reaction. Some

allergens carried by the intestinal veins (or hepatic arteries) could cause EGL in the same manner as VLM. Although most allergens ingested would be removed in feces, some residual allergens might migrate through the intestinal veins and drift from portal veins to the liver. In the present case, medical interviews, serologic examinations, and histopathologic examinations did not demonstrate VLM, although we suspected EGL caused by VLM from the beginning. The present case suggests that some solitary eosinophilic granulomas localized in the liver, as in some cases reported by Kaplan and Nakashima,[25,26] might not be caused by VLM.

In conclusion, we encountered a rare case of EGL that did not demonstrate any correlation with parasitosis. The present case and some other cases, such as those reported by Kaplan and Nakashima,[25,26] suggest the possibility of EGL caused by allergens other than parasites. Accumulation of more data from future cases with EGL, especially resectable cases by minimal invasive surgery and examined histopatologically, should help clarify other potential pathogeneses of EGL.

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