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Focal eosinophilic infiltration in the liver: radiologic findings and clinical course

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Abstract

Background: We investigated the radiologic findings and clinical course of focal eosinophilic infiltration in the liver.

Methods: We retrospectively reviewed computed tomographic (CT) and sonographic scans in 20 patients (18 male, two female; mean age, 50 years) with pathologically or clinically proven focal eosinophilic infiltration in the liver by two experienced radiologists in our institute from August 1995 to June 1999. We also correlated radiologic findings with peripheral eosinophil count. Radiologic and clinical findings during the follow-up (range, 2–49 months; mean, 19.5 months) also were analyzed.

Results: Clinical symptoms and signs included abdominal pain ($n = 4$), easy fatigability ($n = 3$), weight loss ($n = 1$), and peripheral eosinophilia ($n = 19$). Twelve patients were asymptomatic. On sonographic examinations, all lesions were seen as focal, low echoic nodules. On CT, the lesions appeared isoattenuated or low attenuated in the arterial phase and low attenuated in the portal phase, except one case that showed high attenuation in the arterial phase. The margins of most lesions appeared poorly defined. Lesions were single ($n = 9$) and multiple: two to five ($n = 6$), six to 10 ($n = 3$), and more than 10 ($n = 2$). Each lesion was smaller than 2 cm; only one was 4 cm in diameter. The distribution of the lesion was subcapsular in 14 patients and central in five. Diffuse dissemination was observed in one. Eosinophil-associated abnormality was not present in other abdominal organ in all cases. The peripheral eosinophil count correlated closely with the number but not with the size of lesions. Sixteen patients who had follow-up images showed complete ($n = 14$) or partial regression of the lesions with a decrease in size ($n = 1$) or number ($n = 1$) after 2–22 months (mean, 6.4 months).

Conclusion: Focal eosinophilic infiltration in the liver had somewhat characteristic radiologic findings on sonography and CT. In the correct clinical context of peripheral eosinophilia and self-limited course, these radiologic findings may be helpful in differentiating this condition from other focal hepatic lesions.

Key words: Eosinophil—Liver—Computed tomography—Ultrasound.

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Peripheral eosinophilia is associated with various conditions such as parasitic infestations, allergic reactions, connective tissue diseases, and neoplasms. The radiologic findings of parasitic infestations of the liver such as fascioliasis, clonorchiasis, and echinococcal cyst have been described frequently in the radiologic literature [1–3]. The eosinophilic abscess associated with these parasitic infestation is caused by direct parasitic invasion to the liver. Several reports, however, have suggested that the eosinophils themselves can cause tissue damage by infiltrating into the liver, mainly into the periportal space [4–6]. For example, in hypereosinophilic syndrome (HES), hepatic involvement is characterized by periportal infiltration of mature eosinophils. [7–10]. In daily practice, we have observed, not so infrequently, focal hepatic nodule(s) in patients with mild degrees of peripheral eosinophilia without definite demonstrable cause. Radiologically and clinically, these lesions are important because they can mimic other tumorous conditions of the liver. However, few reports about the imaging features of this condition have been published. In this study, we analyzed radiologic findings of 20 patients who were diagnosed with focal eosinophilic infiltration in the liver and assessed their clinical courses.

Materials and methods

Patients

We retrospectively reviewed the clinical and imaging features in 20 patients who were diagnosed with focal eosinophilic infiltration in the liver while being treated in our institute from August 1995 to June 1999. There were 18 male and two female patients. Age at diagnosis ranged from 32 to 70 years (mean, 50 years). The patients underwent computed tomography (CT; $n = 20$, with 15 dual phase scans and five single delayed scans) and sonography ($n = 18$).

Histopathologic confirmation ($n = 16$) was obtained by sonographically guided biopsy ($n = 15$) and peritoneoscopic biopsy ($n = 1$). Four patients were diagnosed clinically by the combination of radiologic features and laboratory findings including eosinophil count, negative serology, and stool examination for the parasite. Of four patients who had no histologic proof, three underwent follow-up sonography. The interval between initial CT scan and biopsy ranged from 5 to 28 days (mean, 14 days). Patients who had definite parasitic infestations such as fascioliasis, clonorchiasis, and echinococcal cyst were excluded from our series.

Analysis

The margin, echogenicity, shape, hyper- versus hypoechoic rim, and posterior sonic shadowing or enhancement were evaluated on sonography. On CT, attenuation, margin, number, size, and distribution (subcapsular, central, or diffuse) were analyzed. Subcapsular distribution was defined as no farther than 2 cm from capsule. All CT and sonographic findings were reviewed retrospectively by two radiologists on a consensus basis.

Clinical manifestation and underlying disease with the presence and degree of peripheral eosinophilia were analyzed. In all cases, radiologic findings (number and size of the lesions on CT) were correlated with peripheral eosinophil counts by statistical analysis by using SPSS 7.5 software (Kendall tau-b test). Clinical courses of the lesions also were analyzed by follow-up sonography ($n = 18$) and eosinophil count ($n = 8$).

Techniques of imaging and biopsy

CT scans were performed with a HiSpeed helical scanner (GE Medical Systems, Milwaukee, WI, USA) or a Somatom Plus-S scanner (Siemens Medical Systems, Erlangen, Germany). Fifteen dual-phase CT scans were obtained during hepatic arterial and portal venous phases, and five single phase CT scans were obtained during the venous phase. The hepatic arterial phase was obtained at 30 s and the portal venous phase was obtained at 65 s after initiation of intravenous injection of contrast material. A total of 120 mL of nonionic contrast material (Ultravist 300; Schering, Berlin, Germany) was injected into a forearm vein at a rate of 3 mL/s with a power injector (MK-IV, Medrad, Pittsburgh, PA, USA). We used a beam collimation of 7–10 mm and a table speed of 7–10 mm/s (pitch = 1).

Sonography was performed with an ATL HDI 3000 (Advanced Technology Laboratories, Bothell, WA, USA) scanner with 3.5–5.0-MHz convex transducers. Sonographically guided percutaneous biopsy was performed with a 19.5-gauge automated biopsy gun in 15 patients. After confirming the proper placement of the needle tip within a lesion, two or three cores of tissue were retrieved from the most representative lesion.

Results

Clinical features

Clinical symptoms and signs included abdominal pain ($n = 4$), easy fatigability ($n = 3$), weight loss ($n = 1$), and peripheral eosinophilia ($n = 19$). Twelve patients were asymptomatic. All but one patient had eosinophilia of varying degrees, ranging from 10% to 77% (mean, 31.7%), in the peripheral blood (normal range, $<6\%$ of white blood cells).

Liver function tests at presentation were within normal limits, except for four patients who had mild elevations of aspartate transferase and alanine transferase. The viral marker for hepatitis B was positive in four patients. Underlying diseases were as follows: hypereosinophilic syndrome ($n = 3$), chronic liver disease ($n = 2$), malignancy ($n = 3$), and chronic pancreatitis ($n = 1$). The other patients ($n = 11$) had no underlying disease and no history of allergy or medication.

The initial, most probable radiologic diagnoses on CT included inflammatory lesions such as focal eosinophilic infiltration ($n = 13$), metastasis ($n = 3$), hemangioma ($n = 2$), dysplastic nodule ($n = 1$), and simple cyst ($n = 1$).

Sonographic findings

Eighteen cases were evaluated with sonography, and all lesions appeared as poorly defined, oval, homogeneous, low echoic nodules without hyper- or hypoechoic rims (Fig. 1). Posterior sonic shadowing was not observed in any case, and posterior enhancement was noted in one. Fatty liver association was found in three patients.

CT findings

On dual phase spiral CT ($n = 15$), the lesions had iso-/low ($n = 8$; Figs. 1, 2), low/low ($n = 6$; Fig. 1), and

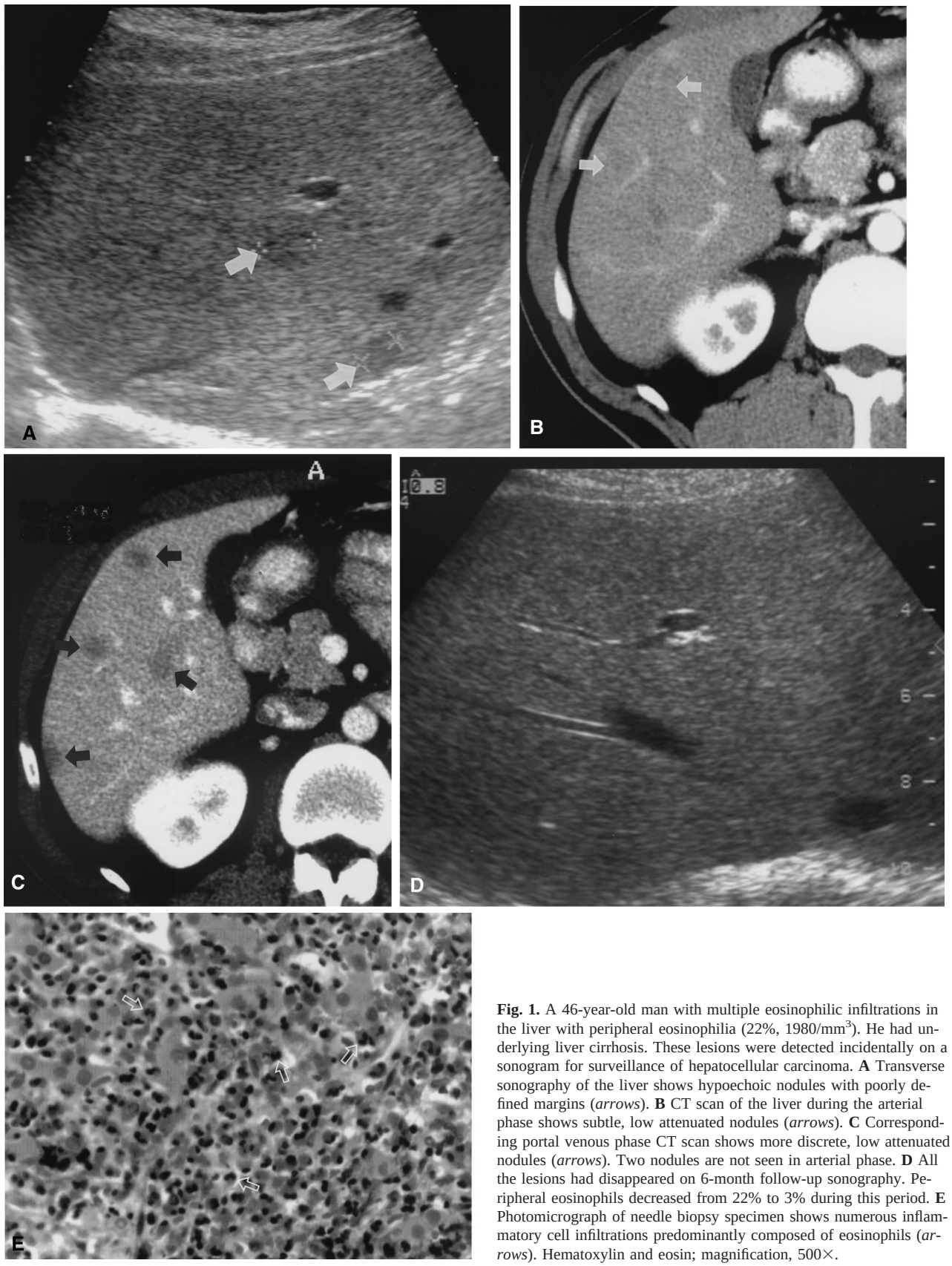

Fig. 1. A 46-year-old man with multiple eosinophilic infiltrations in the liver with peripheral eosinophilia (22%, 1980/mm^3). He had underlying liver cirrhosis. These lesions were detected incidentally on a sonogram for surveillance of hepatocellular carcinoma. **A** Transverse sonography of the liver shows hypoechoic nodules with poorly defined margins (*arrows*). **B** CT scan of the liver during the arterial phase shows subtle, low attenuated nodules (*arrows*). **C** Corresponding portal venous phase CT scan shows more discrete, low attenuated nodules (*arrows*). Two nodules are not seen in arterial phase. **D** All the lesions had disappeared on 6-month follow-up sonography. Peripheral eosinophils decreased from 22% to 3% during this period. **E** Photomicrograph of needle biopsy specimen shows numerous inflammatory cell infiltrations predominantly composed of eosinophils (*arrows*). Hematoxylin and eosin; magnification, 500×.

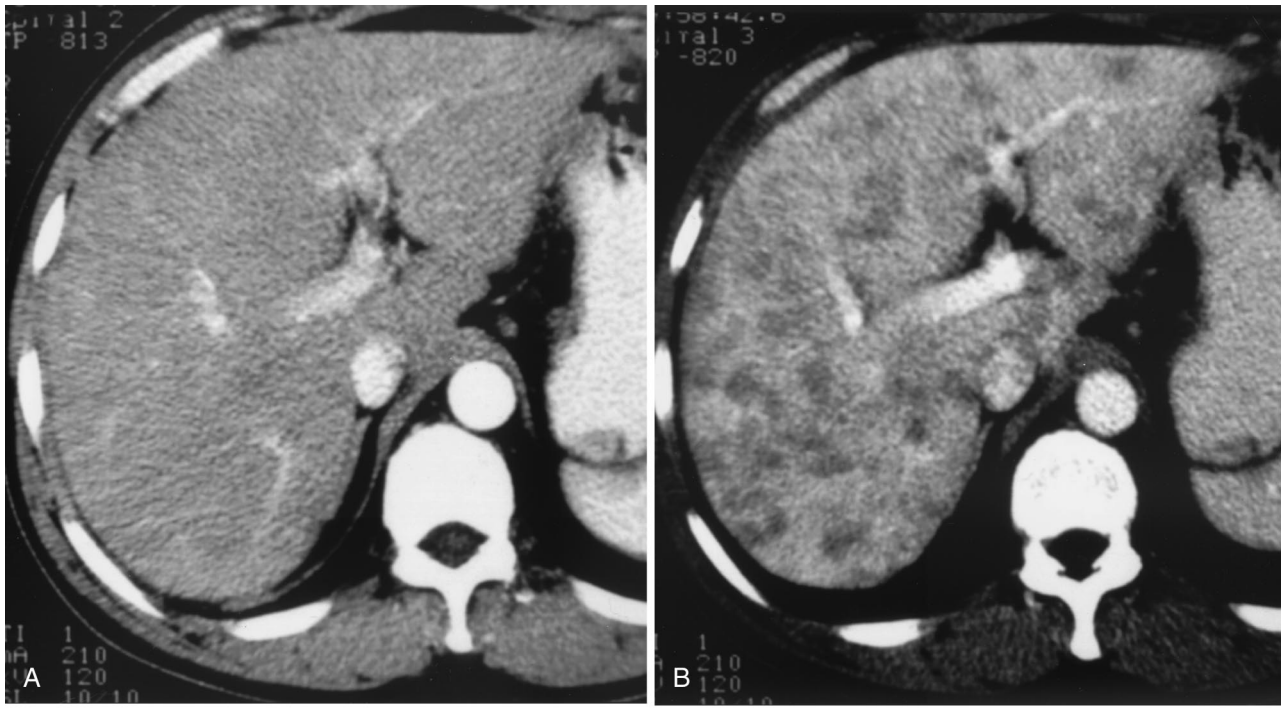

Fig. 2. A 48-year-old man with hypereosinophilic syndrome and numerous eosinophilic infiltrations at 81% serum eosinophils (35,900/mm^3). **A** CT during the arterial phase shows no definite nodule. **B** Corresponding portal phase scan shows numerous, low attenuated nodules disseminated throughout the entire liver.

mixed (high/low and iso-/low, $n = 1$) attenuation in the arterial/portal phases. On the single venous phase scan ($n = 5$), all lesions showed low attenuation (Fig. 3). Rim enhancement with central low attenuation, which is the classic finding of an abscess, was not noted in any case. Margins of all lesions appeared poorly defined. The number of lesions was single ($n = 9$), two to five ($n = 6$), six to 10 ($n = 3$), and more than 10 ($n = 2$). In 16 (80%) cases, the lesion diameter was 1–2 cm. The lesion was smaller than 1 cm in two patients. Large lesions with a diameter larger than 2 cm (maximum, 4 cm; Fig. 4) were observed in two patients. Distribution of lesions was subcapsular in 14 (70%) and central in five patients. Diffuse distribution with innumerable hepatic lesions was observed in one patient who was diagnosed with hypereosinophilic syndrome (Fig. 2). There was no preferential lobar or segmental distribution of the lesions.

Associated findings were lymph node enlargement ($n = 2$), hemangioma of the liver ($n = 1$), liver cirrhosis ($n = 1$), focal intrahepatic duct dilatation ($n = 1$), pancreatic pseudocyst ($n = 2$), eosinophilic pneumonia ($n = 1$), and stomach cancer ($n = 1$).

The number of lesions had a significant positive correlation with the corresponding eosinophil count ($R = 0.52$, $p < 0.05$; Fig. 5), but there was no correlation between lesion size and eosinophil count.

Clinical course

Follow-up sonographic examinations (duration, 2–22 months; mean, 6.4 months; $n = 18$) showed complete ($n = 14$) or partial regression of the lesions by a decrease in size ($n = 1$) or number ($n = 1$). Two cases showed no change after 2 and 3 months of follow-up, respectively. Of the patients who had complete or partial regression, 10 (63%) had no treatment, four had been treated with praziquantel, and two had been treated with steroids. Follow-up eosinophil count was available in eight patients. In five patients, eosinophil count decreased with the radiologic regression. In two patients, eosinophil count decreased without follow-up sonography. In one patient, eosinophil increased despite radiologic regression. Of four patients who had no histologic proof, three underwent follow-up sonography, which showed that the lesions had regressed partially ($n = 1$) or completely ($n = 2$). One patient who had neither histologic proof nor follow-up imaging was diagnosed clinically with hypereosinophilic syndrome, and numerous, low attenuated foci of the liver were seen on portal phase CT (Fig. 2).

Discussion

Eosinophilic infiltration of the liver can occur in various conditions such as parasitic infestations, neoplastic dis-

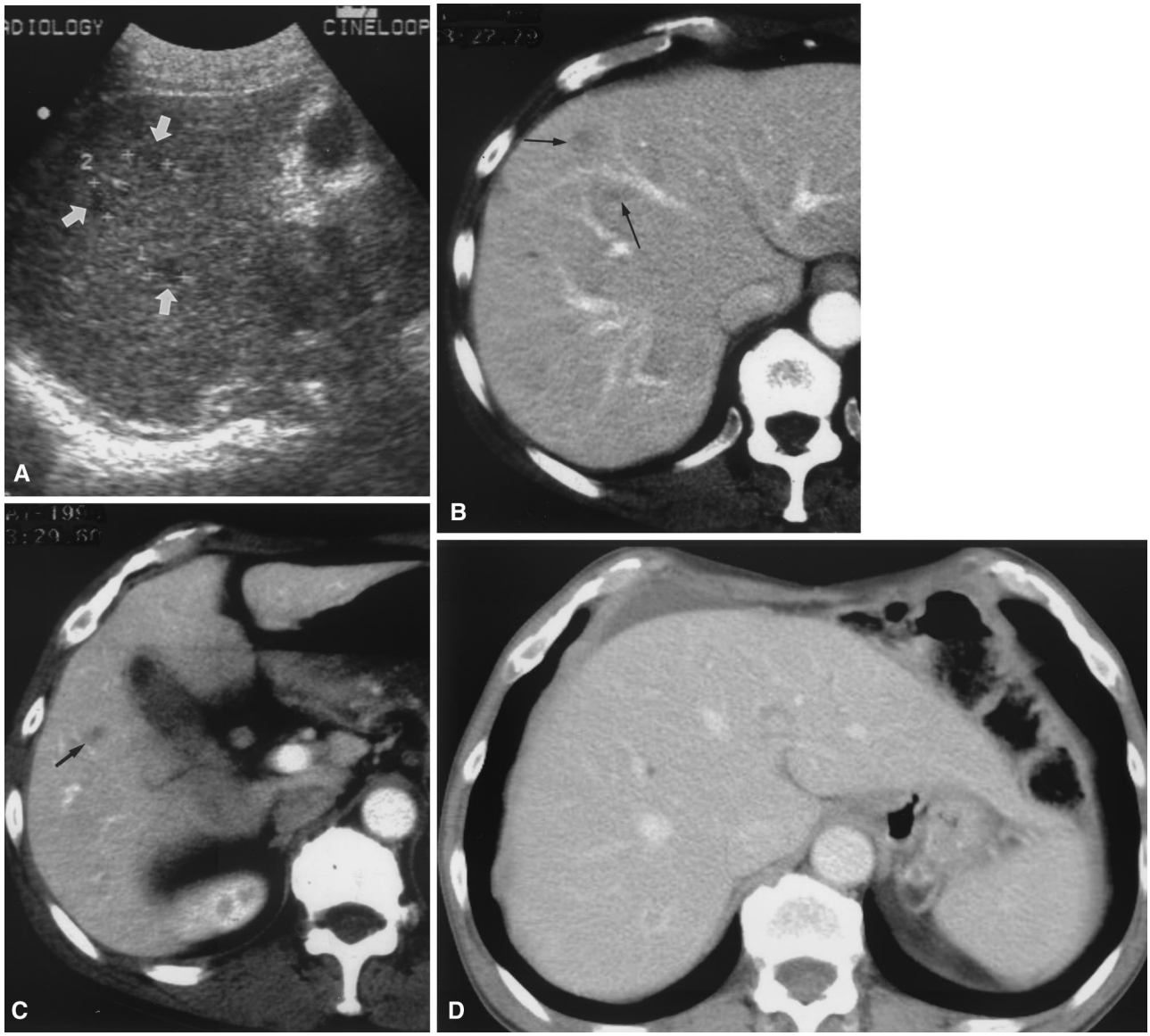

Fig. 3. A 59-year-old man with advanced gastric cancer and multiple eosinophilic infiltrations in the liver at 32% serum eosinophils (2200/mm^3). **A** Sonography shows multiple, poorly defined hypoechoic nodules in the right lobe of the liver (*arrows*). **B, C** CT scans in the venous phase at different levels show multiple, poorly defined, low attenuated nodules (*arrow*). They appear to be smaller than 1 cm. **D** Ten-month follow-up CT after gastrectomy showed complete regression of these lesions with a normalized eosinophil count.

eases, allergy, drug hypersensitivity, and hypereosinophilic syndrome. In our study, we excluded those cases with definite parasitic infestation such as fascioliasis, clonorchiasis, and echinococcal cysts, which produce focal hepatic lesions by direct invasion or hematogenous migration into the liver parenchyma. The lesion is an abscess or granuloma with eosinophilic infiltrates on pathology. The imaging findings of these parasitic infestations in the liver have been described elsewhere [1–3]. Several reports, however, have suggested that the eosinophils themselves can cause tissue damage by infiltrating into the liver, mainly into the periportal space [4–6]. In our series, many foci showed periportal distribution on radiologic and pathologic examinations. Although the precise mechanisms of eosinophil-related tissue damage are not fully understood, the process might occur as follows: infiltration of eosinophils into tissue, damage related to eosinophil function and products (e.g., the eosinophil major basic protein and eosinophil cationic protein), and occurrence of thromboembolic phenomena [11]. According to a previous study [4], the pathogenesis of eosinophil-related lesion is regarded as focal necrosis induced by infiltrated eosinophils with an ensuing inflammatory process, which differs from eosinophilic abscess

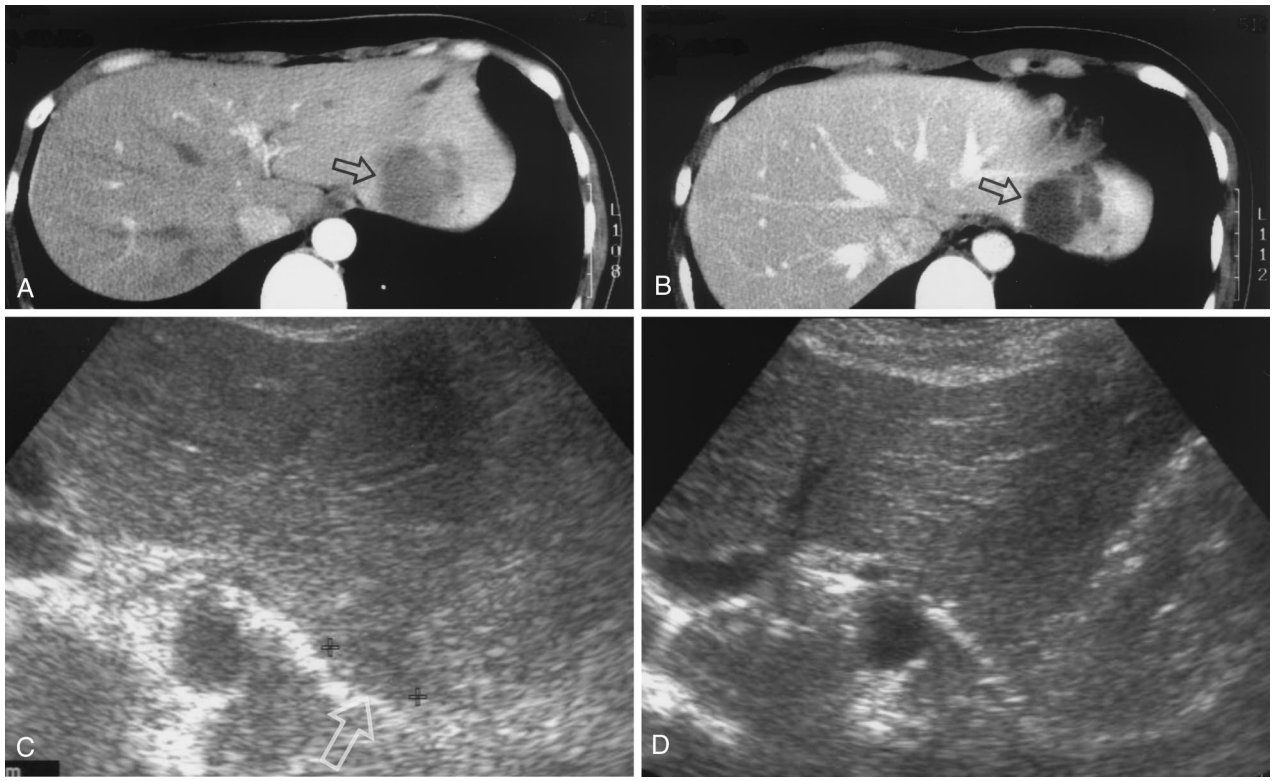

Fig. 4. A 32-year-old woman with incidentally detected focal eosinophilic infiltrations in the liver with 28% serum eosinophils (1540/mm^3). Spiral CT scans during the (**A**) arterial and (**B**) portal phases show a large, 4-cm, low attenuated mass with well-defined margins (*arrow*). Pathologic examination confirmed eosinophilic infiltration. This lesion (**C**, *arrow*) shrank spontaneously (to 2 cm) on 6-month follow-up sonography and (**D**) disappeared completely on 11-month follow-up sonography. During this period, the percentage of eosinophils decreased from 28% to 3% (from 1540 to 150/mm^3).

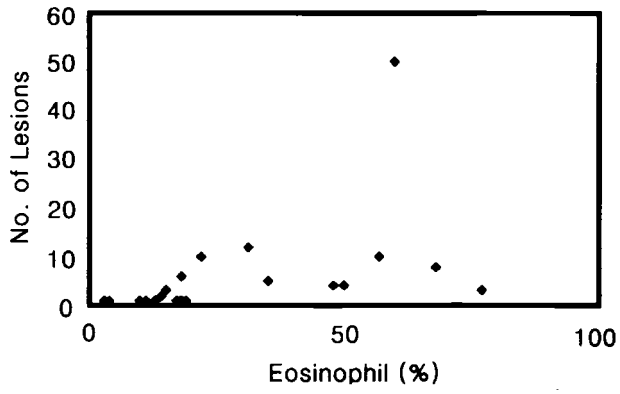

Fig. 5. Plot showing the correlation between number of lesions and serum eosinophil count ($R = 0.52$, $p < 0.05$).

or granuloma caused by direct parasitic invasion. In the parasitic infestation such as *Anisakis* and *Clonorchias*, these focal hepatic lesions reportedly are caused not by direct invasion of worms but by eosinophilia [4]. We also believe that the occult parasitic infestations that were not proven might result in such hepatic lesions in some patients in our series. In our series with 20 patients, all lesions on CT showed low attenuation in the portal or delayed phase, but variable enhancement patterns (isoattenuation in eight, low attenuation in six) was observed in the arterial phase. In one patient, four foci showed iso- and low attenuation and two showed high and low attenuation in the arterial and portal phases. Although biopsy was done only in one of these lesions, all foci appeared as low echoic nodules on sonographic examination and disappeared on follow-up examination over 6 months. The variable enhancement patterns on the arterial phase have not been reported. According to Lee et al. [4], these hepatic lesions are observed as focal hypoattenuating lesions on all phases of helical CT.

In our series, three patients with HES were included. HES is defined as persistent eosinophilia of 1500 eosinophils/mm^3 for longer than 6 months or death before 6 months; absence of parasitic, allergic, or other known causes of eosinophilia; and evidence of organ involvement, mostly the hematopoietic, cardiovascular, nervous, hepatosplenic, and pulmonary systems [12]. The common histopathologic finding is infiltration of tissues by relatively mature eosinophils, with overall normal histologic

architecture. In the liver, periportal infiltration is the primary feature [5, 11]. Few reports of imaging findings of hepatic involvement in patients with HES have been published. In previous reports [4, 5], the multifocal hepatic lesions were seen as hypodense nodules with poorly defined margins on CT. On sonograms, the lesions were usually small (<2 cm in diameter), sharply or poorly defined nodules with varied echogenicity. In our series, CT and sonographic findings of focal hepatic lesions in HES patients were essentially the same as those in the former two studies. Among the three patients with HES in our series, one patient who had innumerable lesions throughout the liver (Fig. 2) died from heart failure without image follow-up and another patient had decreases in lesion number and eosinophil count after steroid therapy. The third had no further examinations and lost to follow-up.

In malignant tumors such as gastrointestinal carcinoma, lymphoma, and leukemia, peripheral eosinophilia is often associated with the disease [13–16]. In our review of the radiologic literature, there were six cases of histologically proven eosinophilic infiltration of the liver in malignant tumors, including gastric cancer ($n = 3$), hepatocellular carcinoma ($n = 1$), rectal carcinoid ($n = 1$), and lymphoma ($n = 1$) [4, 6]. In our series, a patient with advanced gastric cancer had eight foci of eosinophilic infiltration in the liver, all of which disappeared after 1 year of gastrectomy, with the eosinophil count normalized (Fig. 3). Although the mechanism of eosinophilic infiltration in the liver has not been well documented, several reports have suggested that eosinophils are aggregated into the liver by the eosinophilic chemotactic factor, which is released from the primary cancer cell and then transported into the liver [4, 6, 13, 14]. In patients with malignant neoplasm, it is difficult to differentiate eosinophilic infiltration from the metastatic lesion by radiologic finding alone. Even though the patients with malignancy have concurrent eosinophilia, it is recommended that focal hepatic lesion in these patients be confirmed histologically.

Our series had some limitations. First, not all patients had pathologically proven disease. However, three patients who had no histologic proof showed imaging features characteristic of peripheral eosinophilia, and follow-up sonography showed that the lesions regressed partially or completely. One patient who had neither histologic proof nor follow-up imaging was diagnosed clinically with hypereosinophilic syndrome. As Figure 2 shows, the lesions were innumerable, which was unique in our series. Each lesion, however, showed the characteristic appearance of focal eosinophilic infiltration. Second, not all lesions were biopsied in patients with multiple lesions. We believe this limitation is inevitable and that follow-up study is necessary. Actually, the multiple lesions in each patient of our series followed the similar clinical course on follow-up examinations.

In summary, the characteristic radiologic features of a poorly defined margin, low attenuation, and subcapsular distribution may suggest the diagnosis of focal eosinophilic infiltration in the correct clinical setting. Careful imaging and clinical follow-up may be needed, if no biopsy is obtained, to exclude other etiologies, especially in patients with concurrent disease, e.g., malignancy or cirrhosis.

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