

Case Report

A case of cerebral paragonimiasis misdiagnosed as eosinophilic granulomatosis with polyangiitis

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Paragonimiasis is a parasitic disease caused by *Paragonimus westermani* infection, and migration to the brain results in cerebral paragonimiasis. Cerebral paragonimiasis is now extremely rare, but a few cases are still reported. A 48-year-old Japanese woman presented with right-hand convulsion, right-hand numbness, sputum, and fatigue. Chest computed tomography demonstrated multiple nodular lesions, and head computed tomography revealed a hemorrhagic lesion in the left motor cortex. Magnetic resonance imaging revealed multiple small ring-shaped lesions with surrounding edema. Laboratory evaluation demonstrated peripheral eosinophilia. We considered eosinophilic granulomatosis with polyangiitis and started steroid treatment as a diagnostic therapy since we wanted to avoid cerebral lesion biopsy if possible. However, the patient underwent craniotomy surgery after steroid treatment for four months because a new intracerebral mass lesion had appeared. Trematode eggs were detected in the sample, and the final diagnosis was cerebral paragonimiasis. The patient was successfully treated with praziquantel. Cerebral paragonimiasis is extremely rare but should be considered in the differential diagnosis if atypical intracranial hemorrhage and peripheral eosinophilia are observed.

Key words: granulomatosis with polyangiitis, intracranial hemorrhage, paragonimiasis, *Paragonimus westermani*, trematode eggs.

ABBREVIATION LIST

CT	computed tomography
EGPA	eosinophilic granulomatosis with polyangiitis
MMT	manual muscle testing
MR	Magnetic resonance
SEP	somatosensory evoked potential

INTRODUCTION

Paragonimiasis is a parasitic disease caused by *Paragonimus westermani* infection, which typically infects humans via ingestion of freshwater crab, crayfish, or game meat, including wild boar or deer.¹ Cerebral paragonimiasis is caused by migration of *Paragonimus westermani* to the brain, which is the most common site of migration.² Paragonimiasis was once common in South America, Africa, and Asia. The occurrence of paragonimiasis has decreased significantly in Japan, so it is now extremely rare, but a few cases are still reported.³ Cerebral paragonimiasis may not be included in the differential diagnosis due to its rarity in developed countries including present Japan. We report an extremely rare case of cerebral paragonimiasis, via brain tissue, finally diagnosed by histological examination of brain tissue, after misdiagnosis as eosinophilic granulomatosis with polyangiitis (EGPA) and steroid treatment.

CLINICAL SUMMARY

A 48-year-old female was admitted to our hospital with right-hand convulsion. The patient complained of right-hand numbness, sputum, and fatigue. Disturbance of consciousness did not accompany the convulsion. Her consciousness level was clear and neurological examinations revealed no abnormalities except for right upper limb motor palsy (3/5 manual muscle testing [MMT]). Chest radiography and computed tomography (CT) demonstrated

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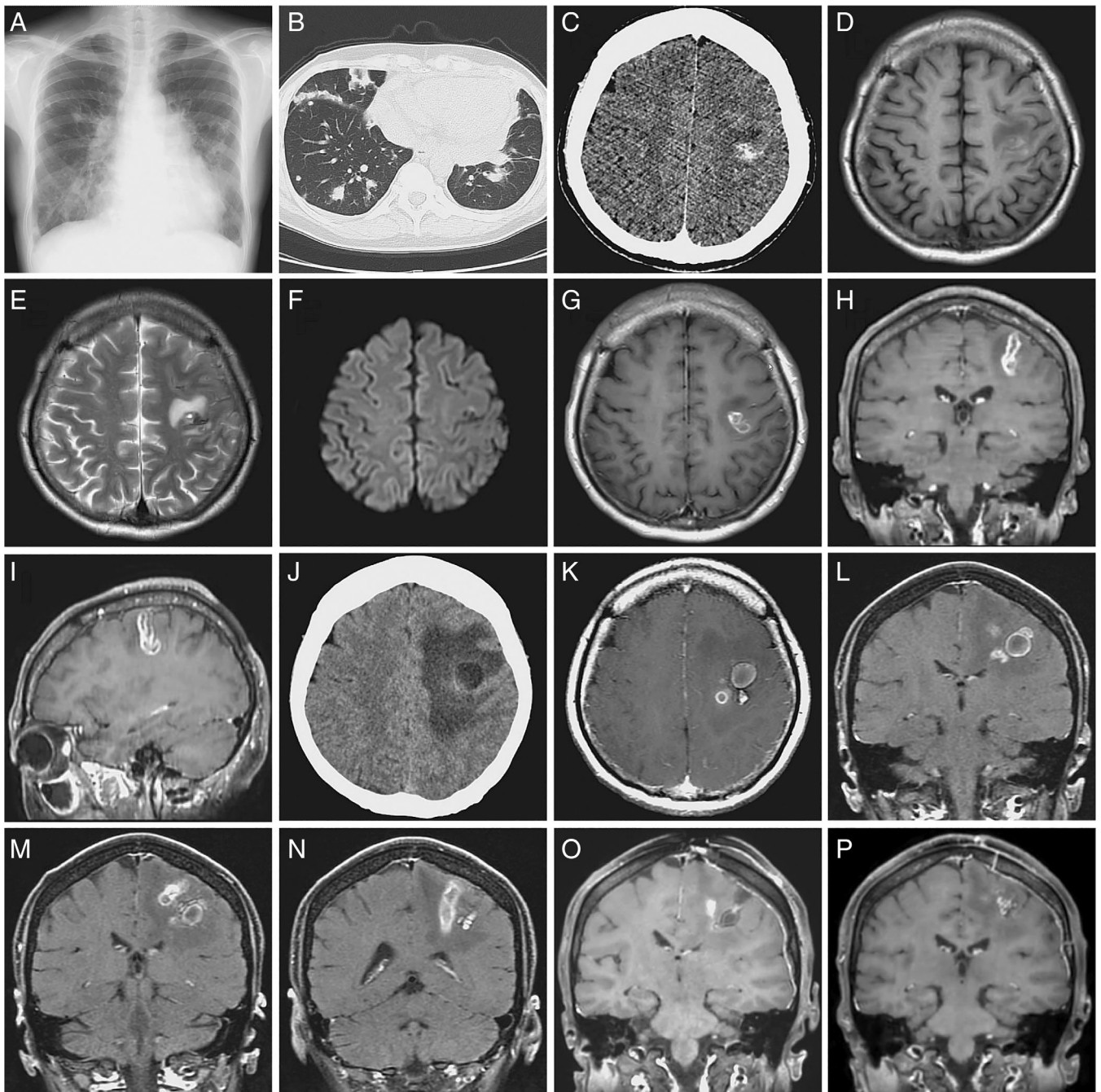


Fig 1 Chronological imaging findings. Initial chest radiograph (A) and CT scan (B) demonstrating multiple nodular lesions in the lung field, and head CT scan (C) demonstrating a high-density area suggesting a hemorrhagic lesion in the left frontal lobe motor area. Initial axial T1-weighted (D), T2-weighted (E), diffusion-weighted (F), axial (G), coronal (H), and sagittal (I) gadolinium-enhanced T1-weighted MRI revealing multiple small ring-shaped lesions with surrounding edema in the same place as CT. Preoperative head CT scan (J) and axial (K) and coronal (L–N) gadolinium-enhanced T1-weighted MR images demonstrating new hemorrhagic lesions and exacerbation of brain edema. Postoperative coronal gadolinium-enhanced T1-weighted MRI taken immediately after the surgery (O) revealed removal of the lesion, and the lesions remain stable after praziquantel therapy (P).

multiple nodular lesions (Fig. 1A, B). Head CT revealed a high-density area in the left frontal lobe, which was considered to be a hemorrhagic lesion (Fig. 1C). Magnetic resonance imaging (MRI) revealed multiple small ring-shaped

lesions with surrounding edema (Fig. 1D–I). These lesions appeared as high and/or iso intensity on T1- and T2-weighted imaging and low intensity on diffusion-weighted imaging, with ring-shaped contrast enhancement

after gadolinium injection (Fig. 1D–I). Head CT angiography demonstrated no vascular abnormality. Laboratory evaluations found peripheral eosinophilia of 11 000 cells/mm³ white blood cells with 47% eosinophils, elevation of C-reactive protein (3.2 mg/dL), immunoglobulin G4 (1990 IU/mL), and soluble interleukin-2 receptor (1070 IU/mL). Serine proteinase 3-antineutrophil cytoplasmic antibody and myeloperoxidase-antineutrophil cytoplasmic antibody were negative. These laboratory examinations suggested EGPA or immunoglobulin G4-related disease. The rheumatologist considered the intracerebral lesion as a different disease from EGPA or immunoglobulin G4-related disease, but we wanted to avoid a cerebral lesion biopsy since the lesions were localized in the motor cortex. Therefore, we selected steroid treatment as a diagnostic therapy for suspected EGPA.

Prednisolone was started at 60 mg/day and gradually tapered after administration of 1000 mg methylprednisolone for three days. The eosinophil count rapidly decreased with steroid treatment, and brain edema also improved with glycerin infusion therapy. Her motor palsy improved, but postcontrast MRI revealed no change. Follow-up CT (Fig. 1J) and subsequent MRI (Fig. 1K–N) revealed a new mass lesion four months after starting steroid therapy. The number of ring-shaped lesions had increased, and there seemed to be new occurrences of multiple hemorrhagic lesions with capsular formation (Fig. 1K–N). At the same time, motor paralysis of the right upper limb was worsening (MMT 3/5), and right lower limb motor palsy newly appeared (MMT 4/5). The patient underwent craniotomy surgery for mass reduction, decompression under motor-evoked potential and somatosensory evoked potential (SEP) monitoring. First, the central sulcus was detected as phase reversal of the SEP (Fig. 2A). The surface lesion was first approached (Fig. 2B). The lesion included reddish-brown fluid similar to that found at surgery for the chronic subdural hematoma (Fig. 2D, E). Next, the deep lesion (Fig. 2C) was approached. The lesion included yellow fluid similar to that in abscesses or old hematoma (Fig. 2F–J). Those cavities demonstrated clear, normal brain wall after careful washing, and minimum biopsy specimens were taken for the pathological diagnosis. Postoperative MRI revealed removal of the target mass (Fig. 1O).

We established the final diagnosis based on the pathological findings of trematode eggs. A detailed life history taken after diagnosis revealed that the family often ordered and consumed mitten crabs from China. Serum anti-parasite antibody was positive, and *Paragonimus westermani* antigen was also detected. Based on the diagnosis of cerebral paragonimiasis, treatment with praziquantel (75 mg/kg/day) was started for three days, and this protocol was repeated three times every two

weeks. After starting oral treatment of praziquantel, no new hemorrhagic lesions have appeared (Fig. 1P), and her right upper limb motor palsy has mildly improved with rehabilitation.

PATHOLOGICAL FINDINGS

Multiple calcified eggs were found in the brain tissue containing infiltration of inflammatory cells, which were mainly lymphocytes and plasma cells (Fig. 3). The trematode eggs were oval, 50–75 µm in length, 25–50 µm in width, and had an operculum (Fig. 3). The trematode eggs were encapsulated by a double shell, and the shell became thicker at the end to the operculum, as shown previously.⁴ These findings were detected from the deep lesion and not the surface lesion.

DISCUSSION

Cerebral paragonimiasis often manifests with similar clinical symptoms and imaging findings to cerebral stroke.^{5,6} Cerebral paragonimiasis frequently appears as a large mass consisting of multiple ring-shaped lesions with surrounding edema on MRI.⁷ The mass appears as an isodense or hypo-dense lesion with extensive hypodense areas of perilesional edema on CT, and contrast-enhanced MRI often reveals lesion enhancement combined with adjacent meningeal enhancement.⁷ Several cases of cerebral paragonimiasis with cerebral hemorrhage have been reported within the past 20 years,^{3,4,8–11} and the present case is typical of cerebral paragonimiasis with similar clinical and/or imaging findings to previously reported cases. Furthermore, the findings of laboratory examinations are more characteristic than the imaging findings. An elevated value of peripheral eosinophils is very characteristic of cerebral paragonimiasis and aids in the diagnosis.^{2,5,6} Cerebral paragonimiasis can be diagnosed via detection of *Paragonimus westermani* from the serum with enzyme-linked immunosorbent assay.¹² The presence of parasitic disease can be determined by the reaction to serum anti-parasite antibody. Cerebral paragonimiasis can be treated with praziquantel with a good prognosis, as shown by the present and previous cases.^{3,4,9,13} Therefore, if we considered cerebral paragonimiasis in the differential diagnosis in the early stage of the present case, craniotomy surgery could be avoided and targeted treatment begun earlier. However, we did not consider cerebral paragonimiasis in the differential diagnosis since we had no clinical experience of cerebral paragonimiasis at our institution.

Eosinophilic granulomatosis with polyangiitis is associated with intracranial hemorrhage^{14–18} but is extremely rare. We wanted to avoid a cerebral lesion biopsy if possible since the lesions were localized in the motor cortex. Therefore, we chose to start steroid treatment as a

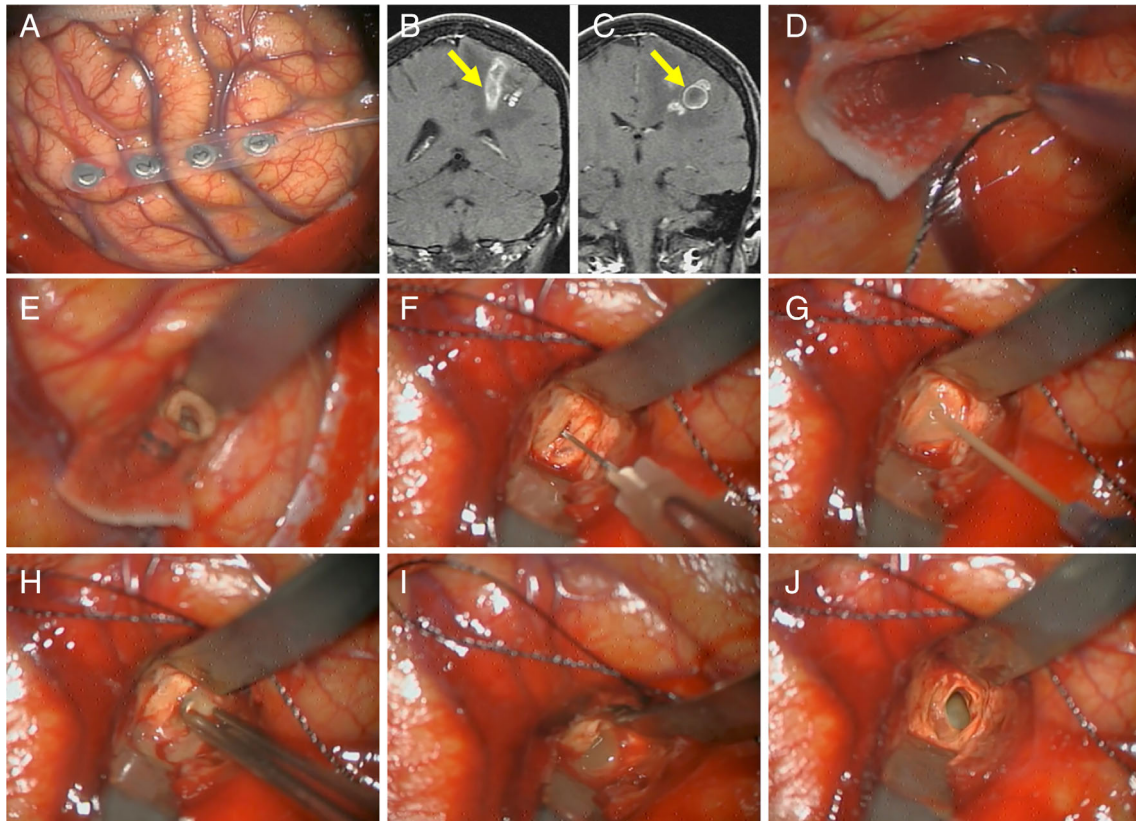


Fig 2 Intraoperative findings. (A) Brain mapping via SEP. (B) Preoperative coronal gadolinium-enhanced T1-weighted MRI revealing the surface lesion (yellow arrow). (C) Preoperative coronal gadolinium-enhanced T1-weighted MRI revealing the deep lesion (yellow arrow), which was approached second. (D, E) Intraoperative findings from the surface lesion in (B). (F–J) Intraoperative findings from the deep lesion in (C). The lesions were capsular (F), and the content of the cystic lesions was reddish-brown (D) or yellow fluid (G). Those cavities demonstrate a clear normal brain wall (E, J).

diagnostic therapy. Histological diagnosis of EGPA via biopsy of intracranial lesions is difficult, if not impossible after steroid treatment is begun. This concern also delayed the timing of the intracranial lesion biopsy. In the present case, the intracranial lesion was also considered to be hemorrhage from EGPA. The steroid treatment was continued since a decrease of eosinophils and temporary stabilization of the general condition were obtained by the steroid treatment. This improvement both delayed the diagnosis and treatment of cerebral paragonimiasis and also resulted in unnecessary steroid administration.

In the present case, a biopsy should have been obtained from the pulmonary nodules, not from the cerebral lesions, to establish the diagnosis. However, craniotomy surgery was performed to decompress the mass effect of the hematoma and prevent deterioration of the neurological symptoms. We collected a minimum amount of tissue to eliminate the possibility of any unexpected pathological conditions, such as parasitic disease, but we initially did not expect to obtain the diagnosis from the biopsy tissues. We would have performed biopsy of the pulmonary lesions much earlier had we considered the possibility of

parasitic disease preoperatively. Although the initial imaging and blood test findings were typical for parasitic disease, we did not consider this possibility preoperatively due to our lack of experience and knowledge of parasitic disease. Rheumatologists suspected EGPA based on the pulmonary imaging and eosinophilia and considered the brain lesions to be from another unrelated disease. Conversely, neurosurgeons assumed that the brain lesions were also caused by EGPA and did not consider the possibility of parasitic disease based on the epidemiological rarity since the patient had a high standard of living in a developed country.

Samples of trematodes are difficult to obtain for pathological diagnosis, so morphological identification of the eggs of trematode species is very important.⁴ The eggs of *Paragonimus westermani* have an oval shape with opercular ridges or shoulder at one pole.^{4,9,19} The egg is encapsulated by a double shell and exhibits three distinct histopathological forms: the meningoencephalitic form, the granulomatous form, and the organization-calcification form.^{4,20,21} A pathological diagnosis for cerebral paragonimiasis is often difficult to establish because most

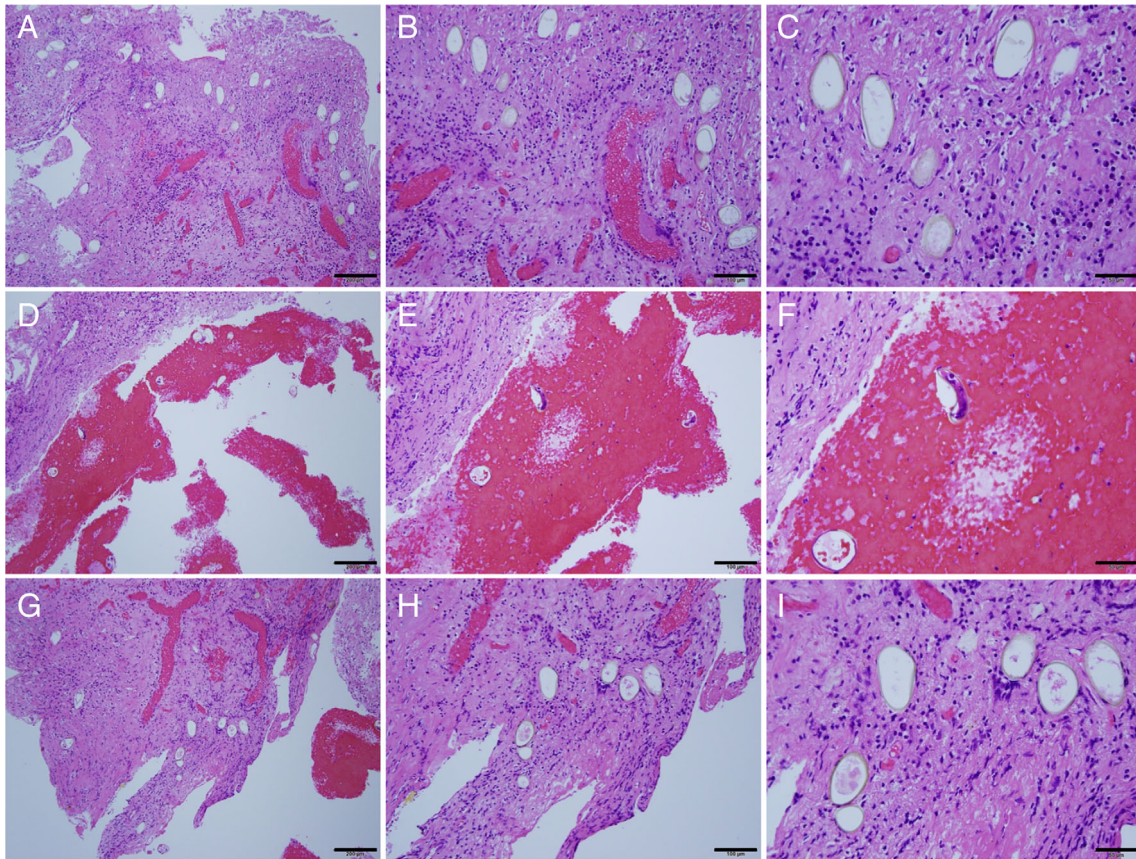


Fig 3 Pathological findings obtained from the deep lesion in Figure 2C. The trematode eggs were detected from three samples in (A–C), (D–F), and (G–I). Multiple calcified trematode eggs surrounded by inflammatory cells were detected in the brain tissues. The eggs were oval shaped with operculum and were encapsulated by a double shell. Scale bars = 200 μ m (A, D, G), 100 μ m (B, E, H), 50 μ m (C, F, I).

surgical specimens do not contain trematode eggs.⁴ This was especially true in the present case since only minimal tissue could be collected due to the lesion location in the motor cortex. We were very fortunate to find eggs in the very small amount of sample, as the incorrect treatment would have continued otherwise. In the present case, the pathological examination revealed the typical morphology of trematode eggs. Therefore, the diagnosis of paragonimiasis would have been relatively easy for the pathologist had a parasitic disease been considered in the differential diagnosis. However, the pathologists examined the specimens without considering parasitic disease since the neurosurgeon submitted preoperative clinical information detailing suspicion of EGPA vasculitis or hemangiomas. In addition, the specimens were from brain lesions, not pulmonary lesions, which also made diagnosis difficult. The morphological examination could have considered parasitic disease since the submitted specimen was not normal brain tissue, vasculitis, or tumor. Furthermore, periodic acid-Schiff staining and/or immunostaining cannot assist with parasitic disease diagnosis, unlike fungal,

bacterial, and/or viral infection. Only hematoxylin and eosin staining can identify trematode eggs. Therefore, in the absence of suspicion of parasitic disease, if the pathologists do not consciously search for trematode eggs, there is a risk of misdiagnosis. In the present case, the neurosurgeons had no suspicion of parasitic disease. Overlooking the possibility of a pathological diagnosis would have resulted in a very poor prognosis for the patient. Recognition of the possibility of this parasitic disease and sharing the experience of pathological diagnosis is very important for both neurosurgeons and pathologists. In addition, the present case suggests that the parasitic disease could be diagnosed via neurosurgical findings, not from investigation of the common location in the lung.

In conclusion, cerebral paragonimiasis is an extremely rare disease in developed countries, including present Japan. However, presentation with atypical intracranial hemorrhage and/or peripheral eosinophilia should prompt consideration of cerebral paragonimiasis as part of the differential diagnosis. Furthermore, we were strongly reminded of the importance of including rare diseases and

detailed medical history, including eating habits, in making a differential diagnosis.

DISCLOSURE

The authors have no conflicts of interest to disclose.

ETHICAL CONSIDERATIONS

Approval of the research protocol: N/A.

Informed Consent: The patient has given informed consent and signed our hospital format consent form for clinical research.

Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

Research involving recombinant DNA: N/A.

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