Case Report: Multiple Schistosomiasis Japonica Cerebral Granulomas without Gastrointestinal System Involvement: Report of Two Cases and Review of Literature

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Abstract. Most schistosomiasis japonica cerebral granulomas reported in the literature have been single and located in the cerebellum, and multiple lesions located in the cerebral hemisphere are uncommon and often misdiagnosed as metastases or gliomas. We describe two rare cases of multiple schistosomiasis japonica cerebral granulomas. Laboratory examinations and cerebrospinal fluid were normal. Parasite eggs were not detected in the stool. No positive findings were detected in the abdominal ultrasonography or chest radiography. Magnetic resonance revealed two intensive patchy lesions in the cerebral hemisphere and surrounded by a large area of edema in both of our patients. Both were misdiagnosed as glioma or metastatic carcinoma before operation. Pathological examination confirmed that the diagnosis was schistosomiasis japonica cerebral granuloma. Praziquantel and dexamethasone were administered. Both patients are alive, symptom-free, and without evidence of recurrence. Combining our data with other literature reports, we summarize the possible mechanism, reasons for misdiagnosis, radiological characteristics, surgical treatment, and postoperative management of schistosomiasis japonica cerebral granuloma, which can be used for clinical reference and to improve our knowledge of schistosomiasis japonica cerebral granuloma.

INTRODUCTION

Schistosomiasis is a parasitic disease caused by trematode blood flukes of the genus *Schistosoma*. It is one of the most common helminthic infections and affects public health worldwide. It is estimated that over 200 million people are infected with schistosomiasis and that nearly 800 million people are at risk of infection.^{1,2} Five species of schistosomiasis infect human beings: *Schistosoma mansoni*, *Schistosoma japonicum*, *Schistosoma haematobium*, *Schistosoma intercalatum*, and *Schistosoma mekongi*.³ Among these five species, only *S. japonicum* has been found in China.⁴

Neuroschistosomiasis is one of the most severe presentations of the disease. Cerebral infection is caused primarily by *S. japonicum*, whereas spinal cord infection is usually caused by *S. mansoni* and *S. haematobium*.^{5,6} Schistosomiasis granuloma is a chronic form of neuroschistosomiasis that is rarely encountered in neurosurgical practice.^{6,7} Most schistosomiasis japonica cerebral granulomas reported in the literature have been single and located in the cerebellum, whereas multiple lesions located in the cerebral hemisphere are uncommon and often misdiagnosed as metastases or glioma.^{4,8–11}

In the present study, we describe two cases of multiple schistosomiasis japonica cerebral granuloma. Combining our findings with other literature reports, we summarize the pre-operative diagnosis and postoperative management of this kind of patient.

CASES REPORT

Case 1. A 61-year-old man was admitted to our department with a complaint of headache and weakness of the right limbs for 1 week. He had no vomiting, convulsion, fever, or any other clinical symptoms. He had no special medical history. He

worked as a fisherman until 4 years earlier in the Anhui section of the Yangtze River, where there were some scattered reports of schistosomiasis decades earlier. Physical examination showed that the muscle strength of his right limbs was grade 4. No positive results were noted in laboratory examinations. The cerebrospinal fluid (CSF) examination revealed normal levels of glucose, protein, and chloride. No parasite eggs were detected in the stool. The results of abdominal ultrasonography and chest radiography were also normal. Cranial computed tomography (CCT) scan showed some small, slightly higher and equal-density nodules, which were distributed in the left temporal lobe and basal ganglia, surrounded by a large area of low-density finger-like edema. The mass effect was obvious, and the adjacent ventricle was compressed. The cerebral sulci were shallow, and the midline was shifted to the right side by approximately 0.9 cm (Supplemental Figure 1). Magnetic resonance (MR) was performed and revealed a large range of finger-like edema in the left thalamus and the left temporal lobe, and no substantial lesions were observed. After intravenous administration of gadolinium, the lesion of the temporal lobe presented as a cystic ring with nodular enhancement, which contained multiple small enhanced punctuate nodules with well-defined borders. Dark spots could be seen in the small nodules. Another patchy enhancement lesion in the left insular was observed (Figure 1). A diagnosis of glioma or metastatic carcinoma was taken into consideration before operation. The patient underwent a left frontotemporal craniotomy in November 2014. After opening the dura mater, we first removed part of the lesion in the temporal lobe and sent it for frozen pathological examination. Pathologic examination of the frozen specimen revealed granulomatous inflammation with a multinucleated giant cell response, and it was filled with schistosomiasis japonica eggs and necrosis (Figure 2). The diagnosis was confirmed. The residual mass in the temporal lobe and the mass in the insular were subsequently removed. A post-operative CCT examination showed that the edema was significantly relieved compared with pre-operation, and the midline shift was retracted (Supplemental Figure 2). The patient was treated with praziquantel (20 mg/kg/day) for six

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FIGURE 1. Preoperative magnetic resonance images of case 1. (A and B) T1- and T2-weighted images of the lesion in the left temporal lobe. The lesion close to isointensity cannot be clearly identified; only a large area of edema in the temporal lobe can be observed. (C) Gadolinium enhancement of the lesion in the left temporal lobe. Multiple, small, enhanced punctuate nodules with well-defined borders were noted; dark spots can be seen in the small nodules. (D) T1-weighted image of the lesion in the left temporal lobe and insula. (E) T2-weighted image of the lesion in the left basal ganglia. (F) Gadolinium enhancement of the lesion in the left basal ganglia; the lesion presented as patchy enhancement.

consecutive days and dexamethasone (10 mg/day) for 14 consecutive days after operation. The muscle weakness of the right limbs was recovered to normal. The patient was discharged without any other physical or mental disorder at

2 weeks after operation. No residual lesions were noted in the follow-up MR examination (3 months after surgery) (Figure 3). He is alive without evidence of recurrence for 57 months after the initial operation.

FIGURE 2. Histopathological examination of case 1. (A) Granulomatous inflammation with multinucleated giant cell response (hematoxylin-eosin staining (HE) $\times 100$). (B) Necrosis (HE $\times 100$). (C) Schistosomiasis japonica eggs (HE $\times 100$). (D) Enlarged eggs (HE $\times 400$). This figure appears in color at www.ajtmh.org.

Case 2. A healthy 68-year-old man, without a remarkable medical history, presented to our department with a complaint of mild headache and dizziness for 2 weeks. The headache was mainly on the forehead and became stronger 3 days earlier. He also complained of a generalized tonic-clonic seizure 3 months earlier, which lasted for 2 minutes with temporary disorder of consciousness. He could not recall the experience of the seizure, which was described by his wife. He had no vomiting, fever, or any other clinical symptoms. Three years before admission, he worked in Xuancheng, Anhui Province, for a few months. In his spare time, he had been swimming several times in the local river, which is a branch belonging to the Anhui section of the Yangtze River. Physical examination revealed that his left eye could not move down and left, and he occasionally had double vision. Laboratory examinations and CSF were normal. Parasite eggs were not detected in the stool. No positive findings were detected in the abdominal ultrasonography or chest radiography. Magnetic resonance revealed that the left temporal lobe had a large area of edema without substantial lesions. After gadolinium enhancement, an intensive patchy lesion was seen in the temporal pole and uncus, and some dark spots could be seen in the lesions (Figure 4). Combining these findings with laboratory examinations, we diagnosed this disease as glioma before operation. The patient underwent left temporal craniotomy with total resection of the lesion. Pathologic examination suggested granulomatous inflammation with a multinucleated giant cell response containing schistosomiasis japonica eggs. No adult worm was observed in the specimen (Figure 5). The final diagnosis was schistosomiasis japonica cerebral granuloma. The patient was given praziquantel at a dose of 20 mg/kg/day for six consecutive days and dexamethasone at a dose of 10 mg/day for 14 consecutive days after operation. No residual lesion was observed in the postoperative CCT scan (Figure 6). The patient was discharged without any other discomfort or clinical symptoms. So far, the patient has been alive and symptom-free for 9 years after the initial operation and without evidence of recurrence.

DISCUSSION

Cerebral schistosomiasis is mainly caused by *S. japonicum* infection.^{5,6} *Schistosoma mansoni*^{12–16} and *S. haematobium*¹⁷ infection caused cerebral schistosomiasis have also been reported in several studies. No matter the kind of schistosomiasis infection, the mechanism by which *Schistosoma* eggs travel to the brain is still controversial. The following potential mechanisms have been proposed: 1) Adult schistosomes ovulate and settle in the intracranial blood sinus to form an infection focus. 2) Schistosome eggs lodge into the portal venous system, followed by systemic circulation through the portosystemic ramus anastomoticus, and finally are carried to the brain. 3) Schistosome eggs are passed to the brain via the vertebral vein or left ventricle. 4) Anomalous migration of the adult schistosome, which produces eggs that enter into the brain via the main blood circulation after passing through the lungs.^{4,10,12,18} Among these mechanisms, in situ egg deposition following the anomalous migration of adult worms appears to be the only viable mechanism of entry into the central nervous system (CNS).¹⁸

Cerebral schistosomiasis is divided into acute and chronic phases. The acute phase occurs a few weeks after exposure to schistosome-infected water.¹⁹ At this stage, patients are usually asymptomatic or manifest with allergic and toxic meningitis.^{4,6,9,20} As schistosome eggs accumulate, they form a granuloma, which enters the chronic phase. The formation of this stage often takes 3 months or more.⁹ In our first case, this fisherman did not have contact with the infected water again after he retired 4 years earlier. In our second case, this patient was not exposed to the infected water again for 3 years. It is quite rare for this disease to occur several years after infection. A previous study reported a cerebral schistosomiasis case that occurred 4 years after exposure to *S. mansoni*.¹⁴ The clinical manifestations of the chronic phase are divided into three categories^{4,7,8}: 1) Symptoms of increased intracranial pressure, such as headache, dizziness, and vomiting. The headache is usually persistent and severe. 2) Seizures, which occur in 57% of the patients with cerebral schistosomiasis. All types of seizures can occur in these patients according to a

FIGURE 3. Follow-up MR examination of case 1 (A and B). No evidence of the lesions recurrence were observed.

FIGURE 4. Preoperative magnetic resonance examination of case 2. T1-weighted image (A) and T2-weighted image (B) revealed a large area of brain edema; the lesion manifested isointensity in both T1 and T2 images which cannot be clearly identified. After gadolinium enhancement, an intensive, patchy lesion was seen in the temporal pole and uncus, respectively; some dark spots can be seen in the lesions (C).

previous study.²¹ 3) Focal neurological deficit, which occurs according to the location of the lesion and can manifest as muscle weakness, sensory impairment, altered mental status, visual abnormalities, and speech disturbances. These clinical manifestations are similar to the symptoms of brain tumors and do not have the value of differential diagnosis.

Both patients in our study were misdiagnosed as gliomas or metastases before operation. There are several reasons for misdiagnosis: 1) History of contact with schistosome-infected water is an important clue for diagnosis.^{8,19} Although the two patients were exposed to water in one of the infected areas of schistosomiasis, they are not high-risk areas, and with the application of anti-schistosomiasis drugs, there have been no reports of schistosomiasis infection for many years. 2) Most of the schistosomiasis japonica cerebral granulomas were single and located in the cerebellum.^{4,8-11} Both of our patients had multiple lesions located in the supratentorial brain tissue.

3) Changes in CSF contents, eosinophilia on blood tests, and parasite eggs in stool can assist in diagnosis. However, these examinations have certain limitations because there are usually no positive findings in the chronic phase of cerebral schistosomiasis.²²⁻²⁴ As in our two cases, as well as other literature reports, these tests are all negative.^{8,10,25} 4) Atypical radiological examination also contributed to misdiagnosis.

Computer tomography and magnetic resonance imaging images usually show a nonspecific tumor-like lesion that is surrounded by finger-like edema. The lesion is usually heterogeneous contrast enhancement and accompanied by an apparent mass effect. The shape of the enhanced lesion is often irregular and without a clear boundary.^{4,6,7,26} Some studies have suggested that arborized linear enhancement circled by multiple enhanced punctuate nodules internally is a clue for diagnosing schistosomiasis cerebral granuloma.²⁶⁻²⁸ However, these characteristics can also be seen in other

FIGURE 5. Histopathological examination of case 2. Granulomatous inflammation with multinucleated giant cell response (A, HE $\times$ 100; B, HE $\times$ 400). Schistosomiasis japonica eggs (C, HE $\times$ 100; D, HE $\times$ 400). This figure appears in color at www.ajtmh.org.

FIGURE 6. Postoperative cranial computed tomography examination of case 2. The lesions were completely resected. Midline shift and brain edema were disappeared.

inflammatory granulomas in the CNS.²⁸ In our first case, the lesions manifested close to the schistosomiasis cerebral granuloma on MR as previously described, but unfortunately, we did not diagnose it correctly before surgery. Between our cases and other reports, there may exist other clues on MR that can assist in diagnosing schistosomiasis cerebral granuloma: 1) The lesion contains multiple small, enhanced, punctuate nodules, 1–3 mm in diameter, with well-defined borders. 2) These small nodules are clustered together, but not fused into patches. 3) Dark spots can be seen in the small nodules.^{7–9,26} When the lesion has these characteristics, a diagnosis of schistosomiasis cerebral granuloma should be taken into consideration. A definitive diagnosis can be confidently reached if histopathological examination demonstrates granulomas and schistosome eggs.^{6,29}

Surgical treatment should be carried out when schistosomiasis cerebral granuloma leads to a mass effect and increased intracranial pressure.^{20,30} The surgical indications have been proposed as follows: 1) Intracranial hypertension uncontrollable by medicine. 2) Severe brain edema and/or mass effect leading to brain hernia or obstruction of CSF circulation. 3) Recurrent seizures, and anti-epileptic drug treatment being invalid. 4) Cases where high suspicion of cerebral schistosomal granuloma, tumor, or other diseases cannot be excluded.^{4,6–8,10,30} However, there is controversy about the selection of surgical methods. Biopsy of cerebral lesions followed by praziquantel treatment has been considered the standard of reference, and biopsy has the advantage of avoiding additional brain damage caused by resection.^{7,14,25} Others suggested that total resection of the lesions should be performed.⁴ Another study also noted that patients who underwent biopsy or partial resection more often had recurrent symptoms or residual lesions despite anthelmintic therapy,

whereas those who were treated with complete resection followed by anthelmintic therapy tended to have a good prognosis.¹⁵ In our opinion, complete surgical resection is not the goal to pursue, if the lesions involve pivotal structures, such as sensory areas, motor areas, the basal ganglia, or the brainstem, because if these are damaged, patients may suffer sensory or motor disorders, even permanent paralysis. In this situation, we should leave part of lesion residual because anthelmintic treatment can eradicate adult worms living in sites close to the CNS and in other organs, preventing the deposition of eggs, which can effectively prevent further development of the lesion. Therefore, for patients with high suspicion of schistosomiasis cerebral granuloma, we recommend that frozen pathological examination be routinely performed before making the decision.

Postoperative management of schistosomiasis cerebral granuloma patients is also very important. Although praziquantel and corticosteroid are recommended as the standard drugs for the treatment of cerebral schistosomiasis, the recommended doses vary between studies.^{4,7–10,12,17,25} Both of our patients received praziquantel at a dose of 20 mg/kg/day for six consecutive days and dexamethasone at a dose of 10 mg/day for 14 consecutive days after operation. This dosage was consistent with previous reports from our country.^{4,8} Both patients were symptom-free and without evidence of recurrence. Another critical issue is to instruct patients to avoid contacting schistosome-infected water again.

In summary, we described two rare cases of multiple schistosomiasis japonica cerebral granuloma without other system involvement. Combining our findings with other literature reports, we summarized the possible mechanism, reasons for misdiagnosis, radiological characteristics, surgical treatment, and postoperative management of schistosomiasis japonica cerebral granuloma, which can be used for clinical reference and to improve our understanding of schistosomiasis japonica cerebral granuloma.

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