Interdepartmental Conference

Eosinophilic Meningitis Due to *Angiostrongylus cantonensis*

Supathra Tiewcharoen, M.D.*
Anuwat Keerasuntonpong, M.D.**
Praphathip Eamsobhana, Ph.D.*
Kobkunl Danpukdee, M.D.***
Suchart Benjarassamerote, M.D.****

Abstract : **We report a 23 year old female who presented with a history of headache. She was admitted to a hospital in Nakornrachasrima province. Eosinophilic meningitis was diagnosed. However, releasing pressure of cerebrospinal fluid (CSF) by lumbar puncture, supportive and symptomatic treatment were performed resulting in appropriate treatment. The patient was referred to Siriraj Hospital due to the persisted headache. Multidisciplinary investigation such as imaging modalities, cytology and serological test for specific antibodies were carried out. Antibody against an *A. cantonensis*-specific 31-kDa antigen was detected in the serum sample obtained from this patient. In conclusion, *A. cantonensis* is the possible causative agent of headache in this patient.**

เรื่องย่อ : เยื่อหุ้มสมองอักเสบจากพยาธิ *Angiostrongylus cantonensis*

สุภัทรา เตียวเจริญ พ.บ.*, อนุวัฒน์ กีระสุนทรพงษ์ พ.บ.**, ประภาทิพย์ เอี่ยมโสภณา ปร.ด.*, กอบกุล แดนผู้ดี พ.บ.***, สุชาติ เบญจรัศมีโรจน์ พ.บ.****

*ภาควิชาปรสิตวิทยา, **ภาควิชาอายุรศาสตร์, ***ภาควิชารังสีวิทยา, ****ภาควิชาพยาธิวิทยา, คณะแพทยศาสตร์ศิริราชพยาบาล, มหาวิทยาลัยมหิดล, กรุงเทพมหานคร 10700.

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ผู้ป่วยหญิงอายุ 23 ปี มีอาการปวดศีรษะ คลื่นไส้ อาเจียน ตามัว ประมาณ 1 เดือน มารับการรักษาที่โรงพยาบาลแห่งหนึ่ง จังหวัดนครราชสีมา แพทย์ให้การวินิจฉัยว่าเป็น eosinophilic meningitis จากน้ำไขสันหลังของผู้ป่วย จากนั้นได้ทำการเจาะน้ำไขสันหลัง และให้ยารักษาตามอาการหลายครั้ง อาการปวดศีรษะไม่ดีขึ้น ญาติ และผู้ป่วยจึงขอมารับการรักษาที่ รพ.ศิริราช และแพทย์ที่ รพ.ศิริราชได้ทำการตรวจวินิจฉัยหาสาเหตุของ eosinophilic meningitis โดยวิธี imaging CT brain, cytology และตรวจหาแอนติบอดีย์จำเพาะในซีรั่มต่อพยาธิ *Angiostrongylus cantonensis* ผลของ immunoblot analysis พบว่าซีรั่มของผู้ป่วยทำปฏิกิริยากับแอนติเจนจำเพาะของพยาธิ *A. cantonensis* ที่มีขนาดน้ำหนักโมเลกุล 31 kDa สรุปผลการวินิจฉัยพบว่าพยาธิ *A. cantonensis* เป็นสาเหตุของอาการปวดศีรษะในผู้ป่วยรายนี้

Key words **:** *eosinophilic meningitis Angiostrongylus cantonensis*

**Department of Parasitology, **Department of Medicine, ***Department of Radiology, ****Department of Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700.*
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INTRODUCTION

Human infection with the rat lung worm, *Angiostrongylus cantonensis* is still an important public health problems in Southeast Asia and the Pacific Islands[1]. Many cases of human angiostrongyliasis were reported in other parts of the world during 1991-2002, including; Thailand[2-5], Japan[6], America[7-11], England[12], Australia[13-16], Brazil[17], Jamaica[18], Sri Lanka[19-21], China[22]. The infection begins with the accidental ingestion of larvae contained in several species of slugs, snails or land planarians, and includes fish, amphibians, reptiles crustaceans and vegetables. Apparently many gastropods are competent host and the presence of infected rat and primate indicates that there is a reservoir of infection. The lack of host specificity, natural mobility of rats, and expansion of the geographic range of the large African land snail have all contributed to the spread of this infection throughout the tropical and subtropical areas of the world. It is often difficult to identify the specific source of human infection. However, awareness of the various possible hosts may decrease the number of infections.

CASE REPORT

A 23-year-old female presented with bitemporal headache, nausea and vomiting and bluring of vision for six weeks. She was initially seen by a physician at a hospital in Nakornrachasima province. She was diagnosed with acute meningitis. Lumbar puncture was performed. The opening pressure was 30 cmH_2O and the closing pressure was 14 cmH_2O. The cerebrospinal fluid (CSF) showed a white blood cell count (WBC) of 150 cell/mm^3 with 20% eosinophils, a protein of 70 mg/dL and sugar of 60 mg/dL. She was treated with prednisolone 45 mg/day for 7 days with slightly improvement. Her headache then recurred after she was discharged from the hospital. She was subsequently hospitalized on 2 further occasions due to severe headache. Lumbar puncture was performed on each admission to release the intracranial pressure. Because of persistent headache and nausea and vomiting, she was hospitalized for another lumbar puncture. The opening pressure was 20 cmH_2O. The closed pressure was 14 cmH_2O. The CSF revealed a WBC court of 1,200 cell/mm^3 with 80% polymorphonuclear cells. The patient was started on ceftriaxone 2 grams intravenously every 12 hours for possible bacterial meningitis. The patient was then refered to Siriraj Hospital due to persistent headache. The rest of her history was unremarkable except that she occasionally consumed raw snails.

Physical examination revealed a temperature of 37°C, respiratory rate of 16/min, heart rate of 80/min and blood pressure of 120/70 mmHg. Her general appearance was unremarkable. Examination of the nervous system revealed a stiff neck with a positive Kernig's sign. The rest of the examination was unremarkable. The initial laboratory data revealed a hemoglobin of 11.7 g/dL, a hematocrit of 36.3 percent, white blood cell count of 5,900/mm^3 (41% polymorphonuclear cells, 43% lymphocytes, 8.5% eosinophils) and a platelet count of 284,000/mm^3. Blood chemistry showed a creatinine of 0.6 mg/dl. A lumbar puncture performed on the day of admission showed clear CSF with a WBC of 480/mm^3 and differential count of 44% lymphocytes and 55% eosinophils. Biochemical tests on CSF showed protein 57mg/dL, sugar 46 mg/dL (blood sugar 108 mg/dL). CSF for gram stain, cryptococcal antigen and acid bacilli were all negative. The opening pressure was 42 cmH_2O. The closed pressure was 12 cmH_2O. The tentative diagnosis was eosinophilic meningtis.

The patient was given prednisolone 30 mg/day along with a repeat lumbar puncture to release the intracranial pressure. She improved clinically. Both her serum and CSF for antibody against the 31 kDa antigen of *A. cantonensis* were positive. She was discharged home on day 8th of her hospital stay.

Cytology Report and Interpretation

C44-03038 1.5 ml of clear colorless cerebrospinal fluid was submitted. The fluid was spun and smeared and stained with Papanicolaou stain. Cytologic examination of the smear revealed numerous white blood cells. They were predominantly eosinophils, lymphocytes, plasma cells and some neutrophils. Neither parasites nor larvae were seen. No atypical cells were seen. These findings were interpreted as an eosinophilic pleocytosis. The cause

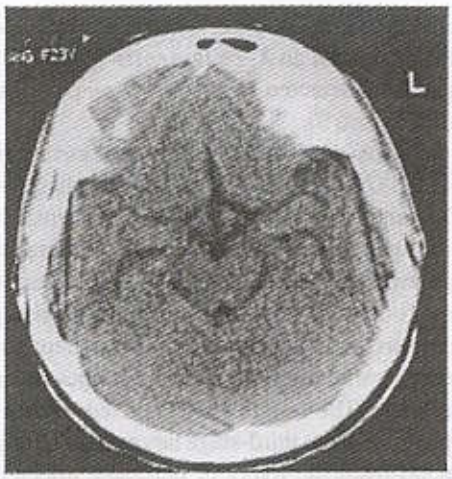

Figure 1. NECT : spliting of the temporal horn of lateral ventricle

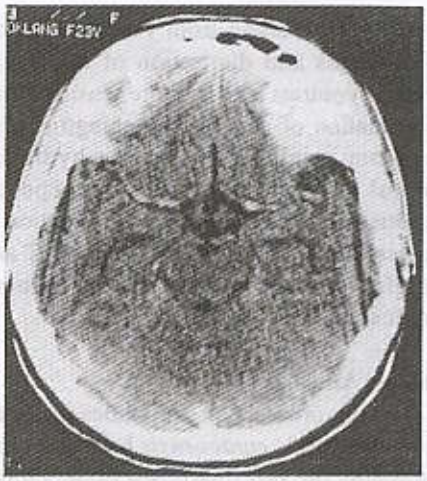

Figure 2. CECT : no evidence of leptomeninges enhancement along the cisterns.

of eosinophilic pleocytosis are mainly parasitic infestation of the CNS. The most common cause of eosinophilic pleocytosis is *Angiostrongyliasis cantonensis* and followed by gnathostomiasis and strongyloidiasis. Definite pathologic diagnosis depend on identification of larvae or parasites in the CSF.

Diagnostic Radiology (Figure 1, 2)

The diagnosis of central nervous system (CNS) discope is established by history, physical examination and laboratory evaluation. Imaging modalities including plain skull film, cranial ultrasound, computed the tomography (CT), and magnetic resonance imaging (MRI) are helpful to confirm the diagnosis or differential diagnosis, to assess severity and for used to evaluate follow-up. These modalities should be used appropriately. A plain radiograp is initial image used to evaluate the cranial abnormality, such as increased intracranial pressure, intracranial calcification and bony destruction. A cranial ultrasound, which is used in neonates for detecting intracranial abnormalities or hydrocephalus is useful due to its' non invasive nature and ability to perform to perform in the neonatal unit. The CT and MRI give more precise and accurate information concerning the brain parenchyma, the meninges and the ventricular system. MRI is superior in multiplanar images and because it was non nephrotoxic contrast medium. The selective of the appropriate imaging study depends on the patient's condition, and was information is needed.

The clinical diagnosis in this patient is meningitis which is the most common form of CNS infection. A CT scan is widely used to assess brain swelling, to exclude brain abscess and ventriculitis, to look at the sinuses and mastoid and to monitor the development of infarction and hydrocephalus.

In this patient, the CT scan shows spliting of the temporal horn of the lateral ventricle and a prominent third ventricle on a non contrast enhanced CT (NECT) and no abnormal meningeal enhancment along the cisterns in a contrast enhanced CT (CECT) which is probably suggestive of a mild degree of increased intracranial pressure when correlated with clinical feathers. In fact, if this is present without any clinical information, its' interpretation is difficult.

The CT findings in meningitis may be normal in the early stages with a mild degree of lymphocytic meningitis[23,24]. It may be continue to look normal if treatment is instituted promtly and adequately[25,26]. A NECT CT shows isodense to hyperdense leptomeminges at the basal cistern and interhemispheric fissure. Intravenous contrast medium (CECT) is necessary to detect abnormal meninges. Abnormal meningeal it enhancement may

be observed, resulting from vascular congestion of the meninges and disruption of the blood brain barrier. A contrast MRI is more sensitive than CT in the evaluation of suspected meningitis. Complications from meningitis including hydrocephalus, subdural collection, ventriculitis, ependymitis, cerebritis or abscess and cerebral infarction are both demonstrated on CT and MRI. Both CT and MRI, are useful to follow up these disease or monitor the complications.

Serologic Analysis (Figure 3)

The presence of antibodies against the 31-kDa antigen of *A. cantonensis* has been reported to be specific for the diagnosis of *A. cantonensis* infection.[27-29] Convalescent-phase serum and cerebrospinal fluid (CSF) from this patient were tested for antibodies against *A. cantonensis* using an immunoblot technique, and crude antigens prepared from male and female worms of *A. cantonensis* recovered from the lungs of laboratory infected rats. Antibody against an *A. cantonensis*-specific 31-kDa antigen was detected in a serum sample from this patient (Figure 3).

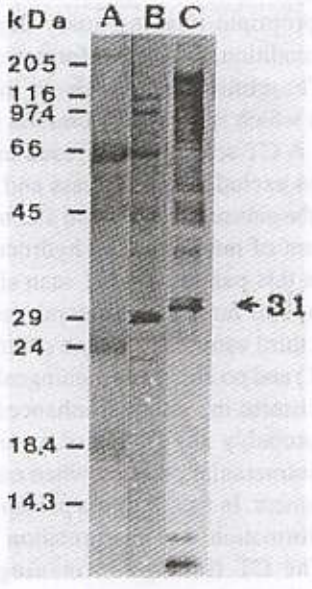

Figure 3. Immunoblot analysis showing reactivity of serum sample from the patient (C) against crude worm extracts of *A. cantonensis*. A and B are low and high molecular weight standards (Sigma). The position of the diagnostic antigen is indicated by the arrow.

Eosinophilic meningitis caused by the nematode *Gnathostoma spinigerum* is also prevalent in Thailand, and specific antibody against the 24-kDa antigen has been documented in parasitologically confirmed cases of *G. spinigerum* infection.[30,31] To exclude this possible cause of eosinophilic meninigitis, serum sample from this patient was also tested by immunoblotting for antibodies against *G. spinigerum*. The crude antigens used in this assay was prepared from third-stage larvae of *G. spinigerum* collected from the livers of naturally infected eels. No antibody against the 24-kDa antigen of *G. spinigerum* was observed in this patient.

DISCUSSION

Eosinophilic meningitis is defined as the presence of greater than 10 eosinophils/mm in the CSF and/ or eosinophils accounting more than 10 percent of CSF leucocytes. Although parasitic infection is the most common cause of eosinophilic meningitis, it can be caused by non-parasitic diseases as well such as tuberculosis and crytococcosis. In Thailand, *Angiostrongylus cantonensis* and *Gnathostoma spinigerum* are the two predominant parasitic infection associated with eosinophilic meningitis. The clinical entities of these two parasite are somewhat different. *A. cantonensis* is inherently neurotropic. Patients usually present with acute severe headache, neck stiffness, nausea and vomiting. Focal neurological findings can also be found but are not common. In contrast to *A. cantonensis*, *G.spinigerum* are not primarily neurotropic but may migrate to subcutaneous, visceral, or neural tissues. Hence, patients with gnathosomiasis can present with not only neurological symptoms but also painless subcutaneous tissue swelling and inflammatory masses in visceral organs. The neurological manifestations of gnathosomiasis which are usually more fulminant than those of angiostrongyliasis include meningoencephalitis, radiculomyelitis, subarachnoid hemorrhage and intracerebral hematoma.

The clinical manifestations in this patient are compatible with *A. cantonensis* which is confirmed by detecting of the serum antibody against *A.cantonensis* antigen in the serum.

A. cantonensis was first reported in 1962 as being found in the brain of a patient from Hawaii who died of eosinophilic meningoencephalitis[32]. Subsequently, there were many reports of eosinophilic meningitis caused by this parasite from other Pacific Islands and Southeast Asia.[33,34] Human infection is usually acquired by consumption of raw infected molluscan intermediate hosts or intervertebrate transport hosts (prawns and crabs).

There is another important issue in this case need to be addressed, the persistence of headache. It is not uncommon for a patient with eosinophilic meningitis to have persistent headache for a month. Punyagupta, et al. reported forty-five out of 436 patients with eosinophilic, meningitis in whom the headache lasted more than 30 days[35]. Another study by Slom, et al. showed eight out of 12 patients with headaches lasting for at least 4 weeks and for 2 of these, the headache lasted for 6-8 weeks[36]. This patient has persistent headache for more than 4 week before she was seen at our institution. Recurrent meningitis in patients with eosinophilic meningitis due to *A. cantonensis* has also been reported[37]. Tsai, et al. showed that two out of 17 cases of eosinophilic meningitis due to *A. cantonensis* had a relapse of meningitis. In one patient, the meningitis recurred on day 55 after eating the snails. The other patient developed recurrent meningitis 29 days after he first became ill[38].

The role of treatment with antihelminthic agents and corticosteroids is still controversial. Punyagupta, et al. found no difference in the duration or severity of illness in patients treated with analgesics alone, analgesics and glucocorticorsteroids[36]. While Chotmonkol, et al. found that the use of a 2-week course of prednisolone helped relieve the headache, shortened the duration of headache and reduced the need for repeated lumbar puncture[38]. Tai, et al. found that using glucocorticosteroids and mebendazole during the first week of symptoms appeared to shorten the duration of illness[38]. However this patient, despite corticosteroid therapy, her headache over persisted for over a month and repeated lumbar puncture was required.

CONCLUSION

We have reported a case of acute eosinophilic meningitis due to *A. cantonensis* who presented with persistent severe headache, despite appropriate management. It is noteworthy that persistent headache from this disease is not uncommon. The role of treatment with antihelminthic agents and corticosteroids remains controversial. Repeated lumbar puncture was necessary.

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