64

A 40-Year-Old Woman from Thailand and Her Brother-in-Law With Severe Headache

CAMILLA ROTHE AND JURI KATCHANOV

Clinical Presentation

History

A 40-year-old Thai woman presents to an outpatient clinic in Germany with a history of severe headache for the past 8 days. The headache was of gradual onset and did not respond to any painkillers. There is no fever and no chills. She denies any visual problems, any weakness of her limbs or memory problems.

Ten days earlier she had returned from a 4-week journey to north-east Thailand, where she visited friends and relatives. During her visit she ate traditional regional dishes, including freshwater fish, seafood, snails and frogs. She reports that her brother-in-law, with whom she had shared several traditional meals, has also fallen ill with a severe headache.

She presented to a municipal hospital 3 days earlier. A CT scan of her brain was performed and reported to be normal. Her blood count was also normal. A differential white cell count has not been done.

Her past medical history is unremarkable. The patient is married, she is a housewife and has lived in Germany for the past 13 years.

Clinical Findings

On examination, she is afebrile, her neck is supple and Lasègue's sign (straight leg raise) is negative. Pupils are equal, round and react to light and accommodation, and there are no cranial nerve palsies. The remainder of the neurological examination, including the assessment of higher cortical functions such as language, memory and praxia, is unremarkable. There is no rash, no oral thrush and there are no subcutaneous swellings. Cardiopulmonary examination is normal. Liver and spleen are not enlarged, and there is no lymphadenopathy.

Laboratory Results

Her laboratory results at presentation in the clinic are shown in Table 64.1.

Questions

1. What is your presumptive diagnosis?
2. Which investigation would you perform to substantiate your diagnosis?

Discussion

A 40-year-old Thai woman presents with a history of severe intractable headache after a stay in north-east Thailand where she enjoyed traditional regional dishes. Her brother-in-law in Thailand is suffering from the same severe headache.

TABLE 64.1 Laboratory Results at Presentation in the Clinic

Parameter (units)	Patient	Reference
WBC ($\times 10^9$/L)	12.3	4–10
Eosinophils ($\times 10^9$/L)	2.34	<0.5
Haemoglobin (mg/dL)	11.7	12–14
MCV (fL)	70	83–103
Platelets ($\times 10^9$/L)	330	150–350
ESR (mm/h)	20	≤10
IgE (U/mL)	944	<100
Creatinine (μmol/L)	62	<80
ALT (U/L)	28	<30
GGT (U/L)	35	<40
C-reactive protein (mg/L)	<5	<5

On examination, she is afebrile with no meningism and no focal neurological deficits. Her blood results reveal peripheral eosinophilia and elevated IgE levels. A CT scan of her brain done elsewhere showed no abnormalities.

Answer to Question 1

What is Your Presumptive Diagnosis?

The most likely diagnosis is a food-borne parasitic infection of the meninges. The key points from the history which support a food-borne infection are: (1) temporal relationship with travelling to north-east Thailand, where food-borne nematodes are prevalent; (2) consumption of traditional Thai food, including raw or undercooked freshwater fish, seafood, snails and frogs; and (3) the occurrence of similar symptoms in a relative who participated in the same meals (cluster).

Headache is a typical symptom of meningitis, therefore infestation of the meninges is very likely. The diagnosis of a parasitosis is strongly supported by the presence of considerable blood eosinophilia and elevated IgE levels in serum.

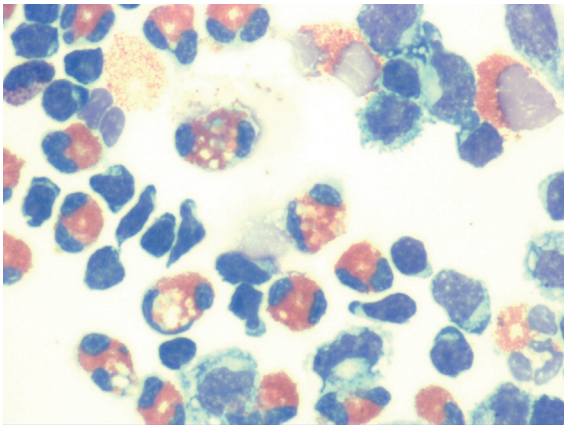
Answer to Question 2

Which Investigation Would You Perform to Substantiate Your Diagnosis?

Parasitic infection of the meninges typically results in eosinophilic meningitis. The next investigation to perform is a lumbar puncture to confirm meningitis and to look for a possibly eosinophilic profile of inflammation. Eosinophilic meningitis in an otherwise healthy person with positive history of exposure to helminths and features of an outbreak is almost always attributable to a parasitic infestation.

The main differential diagnoses are fungal meningitis with *Coccidioides immitis* (in North and Central America), lymphoma, eosinophilic leukaemia, sarcoid and idiopathic hypereosinophilic syndrome.

It is important to measure the CSF opening pressure. If it is elevated, serial spinal taps might relieve the symptoms.



• **Fig. 64.1** Romanowski–Giemsa stain of the CSF sample revealing large numbers of eosinophils with red (eosinophilic) cytoplasm. (Courtesy Prof. Thomas Schneider)

The Case Continued…

A lumbar puncture was performed. The cerebrospinal fluid showed 1877 leukocytes/μL (reference value <5), with 42% eosinophils, 39% lymphocytes, 18% monocytes and 1% neutrophils (Fig. 64.1). CSF protein levels were elevated at 1.59 g/L (reference value <0.45), glucose was 1.85 mmol/L (reference range: 2.2–3.9).

On microscopic examination of the CSF, no larvae could be detected. Ziehl–Neelsen stain as well as cryptococcal antigen were negative. There were no suspected malignant cells. CSF culture did not yield any bacterial or fungal growth. Urine and stool microscopy did not show any ova of *Schistosoma* species. *Taenia solium* serology was negative, as were *Fasciola hepatica* and *Paragonimus* serologies. *Toxocara canis* serology was weakly positive but did not show any change of titre on follow-up. HIV serology was negative.

The initial CSF opening pressure was elevated, at 34 cmH_2O (reference range 12–20). Lumbar puncture relieved the patient's headache and was therefore repeated

TABLE 64.2 Main Causes and Characteristics of Parasitic Eosinophilic Meningitis

Pathogen	Incubation Period	Source of Infection	Geography	Clinical Features	Serology
Angiostrongylus cantonensis	2–35 days	Consumption of infected crustaceans, snails, prawns, crabs, frogs, and/or contaminated vegetables	South-east Asia, Pacific basin, Australia, Caribbean	Paraesthesia of trunk, limbs, or face	Western blot of antibodies against 31 kD antigen*
Gnathostoma spinigerum	Days to months	Consumption of infected poultry or fish, snakes, frogs	South-east Asia (mainly Thailand), emerging in sub-Saharan Africa	Migrating subcutaneous swellings, creeping eruption, sharp radicular pain at onset	Western blot of antibodies against 24 kD antigen*

*Serology can be negative in acute state and a paired convalescence sample should be taken after 4 weeks.

twice, whereupon the patient felt markedly better. No further specific treatment was prescribed. She received iron tablets for a mild microcytic anaemia. The patient was discharged significantly improved after a 1-week hospital stay. After her discharge, serology results came back and Western Blot showed specific antibodies against 31kD *Angiostrongylus cantonensis* antigen. Since the patient hat no symptoms any more no further treatment was prescribed. At 4-week follow-up she had fully recovered and her peripheral eosinophil count had returned to normal.

SUMMARY BOX

Eosinophilic Meningitis

Eosinophilic meningitis is defined as the presence of ten or more eosinophils per microlitre of CSF, or eosinophilia of at least 10% of the total CSF leukocyte count. Invasion of the central nervous system by the food-borne nematodes *Angiostrongylus cantonensis,* and less frequently, *Gnathostoma spinigerum,* are the most common causes (Table 64.2). Rarely, neurocysticercosis, neuroschistosomiasis, paragonimiasis, fascioliasis, toxocariasis, baylisascariasis and trichinellosis can be associated with eosinophilic meningitis; however, the meningeal involvement is usually not prominent.

Angiostrongylus cantonensis, the rat lungworm, is the most common infectious cause of eosinophilic meningitis. Humans are infected by ingestion of *Angiostrongylus* larvae in intermediate hosts such as fresh water snails and slugs; or transport (paratenic) hosts, such as prawns, crabs and frogs; or salad and vegetables contaminated with slime of infected snails. Once ingested, the third stage larvae (L3) penetrate the intestinal wall, reach the portal vein and from there enter the systemic circulation. *A. cantonensis* is a truly neurotropic helminth. Humans are dead-end hosts, the larvae die in the human subarachnoid space, causing an eosinophilic inflammatory response.

To date, no standard of care treatment regimen for CNS angiostrongyliasis exists. Mild cases may be managed symptomatically with serial lumbar punctures and analgesics. More severe cases may be treated with corticosteroids alone or in combination with anthelmintic drugs. Corticosteroids (eg prednisolone 1 mg/kg/day) reduce the duration and intensity of headache. The use of antiparasitic drugs (eg albendazole) is controversial and the benefit of antipararasitic treatment compared to steroid use alone is marginal. If antiparasitic drugs are administered, they should be given with steroid cover.

Further Reading

1. Heckmann JE, Bhigjee AI. Tropical neurology. In: Farrar J, editor. Manson's Tropical Diseases. 23rd ed. London: Elsevier; 2013 [chapter 71].
2. Graeff-Teixeira C, da Silva AC, Yoshimura K. Update on eosinophilic meningoencephalitis and its clinical relevance. Clin Microbiol Rev 2009;22(2):322–48.
3. Wang QP, Lai DH, Zhu XQ, et al. Human angiostrongyliasis. Lancet Infect Dis 2008;8(10):621–30.
4. Martins YC, Tanowitz HB, Kazacos KR. Central nervous system manifestations of Angiostrongylus cantonensis infection. Acta Tropica 2015;141:46–53.
5. McAuliffe L, Ensign SF, Larson D, et al. Severe CNS angiostrongyliasis in a young marine: a case report and literature review. Lancet Infect Dis 2019;19:e132–42.