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A 58-Year-Old Woman from Sri Lanka With Fever, Deafness and Confusion

RANJAN PREMARATNA

Clinical Presentation

History

A 58-year-old Sri Lankan woman who resides in a rural area presents to a local hospital with high-grade fever, chills, body aches, non-productive cough and progressive shortness of breath for 10 days. Two days previously she developed tinnitus and hearing loss. One day prior to admission she became increasingly confused.

Clinical Findings

On admission the patient is confused, with a Glasgow Coma Scale score of 13/15 (E4 V4 M5). Her hearing is severely impaired (WHO grade 3). Temperature 39.3°C (102.7°F), heart rate 120 bpm, blood pressure 90/60 mmHg. There are enlarged axillary lymph nodes on the right side. There is no rash and no neck stiffness; Kernig's and Brudzinski's signs are negative. Scattered crackles are audible on auscultation over the bases of both lungs. Her liver is enlarged to 5 cm below the right costal margin and the spleen is just palpable.

Laboratory Findings

Her basic laboratory results on admission are shown in Table 70.1; her cerebrospinal fluid results are shown in Table 70.2.

Her blood cultures grow no organisms; *Leptospira* and *Salmonella* serologies are negative. *Leptospira*-PCR is not available. A thick film for malaria parasites is negative as well.

Further Investigations

Chest radiography does not show any pathological changes. Her ECG shows sinus tachycardia. The EEG reveals widespread slowing; the CT scan of the brain is normal.

TABLE 70.1

Laboratory Results on Admission

Parameter	Patient	Reference
WBC ($\times 10^9/L$)	8.5	4–10
Haemoglobin (g/dL)	12.4	12–16
Platelets ($\times 10^9/L$)	98	150–350
AST (U/L)	74	13–33
ALT (U/L)	68	3–25
ALP (U/L)	126	40–130
Total bilirubin ($\mu\text{mol/L}$)	25.7	13.7–30.8
Blood urea nitrogen (mmol/L)	6.4	2.5–6.4
Creatinine ($\mu\text{mol/L}$)	123.8	71–106
C-reactive protein (mg/L)	48	<6

TABLE 70.2

Cerebrospinal Fluid Results on Admission

Parameter	Patient	Reference
Leukocytes (cells/ μL)	35 (80% lymphocytes)	0–5/ μL
Protein (g/L)	0.64	0.15–0.45
Glucose (mmol/L)	3.25*	50–75% of serum glucose

*Paired random blood glucose 7.17 mmol/L.

Questions

1. What clinical sign will you be specifically looking for?
2. What antibiotic would you include in your empirical regimen?

Discussion

A 58-year-old woman who is a rural resident of Sri Lanka presents in a septic state with confusion and hearing loss. On examination there is a regional axillary lymphadenopathy on the right side. She looks ill and is septic on admission. FBC shows a normal white cell count but slight thrombocytopenia. The liver transaminases are slightly raised, but bilirubin and AP are normal. CSF shows slight lymphocytic pleocytosis, a mildly raised protein and a slightly decreased glucose. Brain CT scan shows no abnormalities.

Answer to Question 1

What Clinical Sign Will You be Specifically Looking for?

Lymphadenopathy in the right axilla was detected on clinical examination of the patient. Her acute presentation with signs of severe sepsis make an infectious aetiology of the regional lymphadenopathy most likely. It is crucial to perform a meticulous examination in order to establish the port of entry of the microorganisms, which should be found in the skin area that drains to the enlarged regional lymph nodes.

In Asia, infection with *Orientia tsutsugamushi*, the causative pathogen of scrub typhus, is a common cause of fever, which is often associated with an eschar at the inoculation site and enlargement of the draining lymph nodes. However, the prevalence of eschar varies in different populations and its absence does not rule out the diagnosis of scrub typhus.

Answer to Question 2

What Antibiotic Would You Include in Your Empirical Regimen?

In Asia, scrub typhus must be considered in every patient presenting with an undifferentiated febrile illness, regardless of the presence or absence of an eschar.

Therefore doxycycline should be added to the empirical regimen to cover for *O. tsutsugamushi* infection. Doxycycline would also cover important differential diagnoses such as other rickettsial infections and leptospirosis.

Chloramphenicol or azithromycin is the accepted alternative treatment if tetracyclines are contraindicated, as is the case in pregnant women or patients with tetracycline hypersensitivity. Children at any age with scrub typhus can be safely treated with doxycycline.

Of note, acute hearing loss or hearing impairment in a febrile patient from Asia should always arouse strong suspicion of scrub typhus. However, no single clinical sign or laboratory test can rule in or rule out scrub typhus; therefore empirical antirickettsial treatment is given based on clinical and epidemiological evidence. A definitive laboratory diagnosis – if at all possible in the particular setting – can be established by demonstration of seroconversion in paired acute and convalescent serum samples or by PCR on pre-treatment buffy coat samples of an eschar biopsy.

The Case Continued...

On day 2 after admission the patient developed coarse tremors of both upper and lower limbs associated with saccadic oscillations of her eyes in all directions with further deterioration of level of consciousness (GCS 8). At this point a careful clinical examination revealed a well-demarcated crater-like lesion in the right axilla hidden within the axillary folds. Doxycycline therapy was commenced and the patient improved over the next 48 hours. She was discharged on day 6 after admission. Her hearing had returned to normal and there were no other neurological deficits.

The patient's *O. tsutsugamushi* IFA-IgG titre came back high (>1:4096), supporting the suspected diagnosis of scrub typhus.

SUMMARY BOX

Scrub Typhus

Scrub typhus is a common cause of pyrexia in large parts of Asia and northern Australia. Its epidemiology has long been considered limited to the Asia-Pacific area but in 2016 was also first described in patients from South America.

Scrub typhus belongs to the tropical rickettsial infections and is caused by *O. tsutsugamushi*. The infection is transmitted by the bite of an infected larva (chigger) of a trombiculid mite.

Infected mite larvae are found in a wide variety of habitats, from scrubs and primary forests to gardens, beaches, bamboo fields and oil palm or rubber estates. Reservoirs of *O. tsutsugamushi* are rodents and the mites themselves, which can maintain the infection by vertical transmission. Humans are accidental hosts.

The incubation period is 6 to 10 days. A painless papule occurs at the site of the bite, which later ulcerates and transforms into a black crust or 'eschar'. Patients present with fever, severe headache and myalgia, regional or generalized lymphadenopathy and, at times, a macular or maculopapular rash. Conjunctival suffusions, vomiting and diarrhoea as well as constipation can occur.

CNS involvement is common in scrub typhus, and presentations with diffuse encephalopathy or a reversible sensorineural deafness are well documented. In contrast, focal neurological signs are rare. Cerebellar, brainstem and extrapyramidal manifestations have been reported, including opsoclonus, myoclonus and parkinsonian tremor. Further complications include myocarditis, interstitial pneumonia, ARDS and renal failure. Immunity is short-lived and strain-specific.

Diagnosis can be challenging and, in many resource-limited settings, remains clinical. The diagnostic gold standard is the documentation of a significant rise in antibody titres in paired acute and convalescent serum samples. However, these serological tests are usually unavailable in resource-poor tropical areas. Despite controversies in sensitivity and specificity, immunochromatographic rapid diagnostic tests have been developed for field use and are being used in the diagnosis of scrub typhus in several endemic countries. ELISA-based tests have a high sensitivity and specificity. PCR-based tests have been developed and are mostly employed in genotypic characterization and for research purposes or as diagnostic tools in high-resource settings. Culture of *O. tsutsugamushi* from the blood takes several weeks and requires a biosafety level 3 facility.

Scrub typhus is very responsive to antibiotic treatment, which should be given empirically once the diagnosis is suspected. Standard treatment is with doxycycline 100 mg bid for 1 week. Alternative options include tetracycline, azithromycin, rifampicin and chloramphenicol.

Further Reading

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3. Weitzel T, Dittrich S, López J, et al. Endemic scrub typhus in South America. *N Engl J Med* 2016;375(10): 954–61.
4. Saraswati K, Day NPJ, Mukaka M, Blacksell SD. Scrub typhus point-of-care testing: a systematic review and meta-analysis. *PLoS Negl Trop Dis* 2018;12(3): e0006330. <https://doi.org/10.1371/journal.pntd.0006330>.
5. Gaillard T, Briolant S, Madamet M, et al. The end of a dogma: the safety of doxycycline use in young children for malaria treatment. *Malar J* 2017;16:148.