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A 74-Year-Old Man from Japan With Fever, Nausea and Drowsiness

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Clinical Presentation

History

74-year-old Japanese man is brought to a hospital with a history of fever, joint pain, headache, and nausea over the past 5 days. He has a history of cerebral infarction without neurological sequelae, hypertension and ulcerative colitis. He is taking antiplatelet, and antihypertensive medicine and subcutaneous injection of the TNF-alpha Blocker adalimumab once every 2 weeks.

He lives in a suburb of a city in Kyushu district, south-western Japan and has opportunities to encounter wild animals such as boars and deer. He is retired and does grape farming once in a while.

He does not have any recent history of overseas travel.

Clinical findings

On examination the patient looks unwell and drowsy. His body temperature is 37°C (98.6°F), pulse rate 101 bpm, blood pressure 120/70 mmHg, SpO₂ 96% with 7l oxygen, and respiratory rate 32 breaths per minute. Chest examination is normal. The Glasgow Coma Scale on arrival is 13/15 (E3V4M6). There is livedo reticularis bilaterally on his lower extremities but otherwise no rash is seen. His left inguinal lymph node is enlarged.

Laboratory results

His laboratory results on admission are shown in Table 88.1.

Questions

1. What are your differential diagnosis and diagnostic approach?
2. How would you manage this patient?

Discussion

A 74-year-old man living in south-western Japan presents with fever, arthralgia, impaired consciousness and respiratory

distress. Laboratory results show elevated AST/ALT, LDH, CK and low platelets.

Answer to Question 1

What Are Your Differential Diagnosis and Diagnostic Approach?

Acute fever with respiratory distress and impaired consciousness are signs of sepsis. Pneumonia, meningitis or infective endocarditis need to be investigated as soon as possible. In addition, considering the patient's lifestyle and habitat, tick- and mite-borne infectious diseases should be included in the differential diagnosis. There are two rickettsial infections and one viral infection that are transmitted by mites or ticks, respectively, in Japan: Japanese spotted fever (caused by *Rickettsia japonica*), scrub typhus (caused by *Orientia tsutsugamushi*) and severe fever with thrombocytopenia syndrome (SFTS).

SFTS should be suspected when a patient at risk of tick bite develops acute fever with thrombocytopenia or pancytopenia, abnormal liver function tests, and an elevated serum creatinine kinase. SFTS and rickettsioses are sometimes difficult to

TABLE 88.1 Laboratory Results on Admission

| Parameter | Patient | Reference Range |
|-------------------------------|---------|-----------------|
| WBC ($\times 10^9/L$) | 5.3 | 3.3–8.6 |
| Haemoglobin (g/dL) | 17.7 | 13.7–16.8 |
| Platelets ($\times 10^9/L$) | 90 | 158–348 |
| AST (U/L) | 413 | 13–30 |
| ALT (U/L) | 95 | 10–42 |
| LDH (U/L) | 1025 | 124–222 |
| CK (U/L) | 7442 | 59–248 |
| CK-MB (U/L) | 41 | 0–15 |
| CRP (mg/dL) | 0.1 | 0.00–0.14 |

differentiate from each other because both show similar clinical manifestations and laboratory results. In this case, however, a negative CRP is suggestive of SFTS rather than rickettsiosis.

Diagnosis of SFTS is confirmed by detecting SFTS virus in blood serum by PCR. It is reported that real-time RT-PCR of serum is 98.6% sensitive and 99.1% specific.

Answer to Question 2

How Would You Manage This Patient?

Symptomatic and supportive treatment such as adequate fluid administration and respiratory support play an essential role in management. Vasopressors should be started if the patient develops hypotension. Laboratory results have to be monitored closely because there are risks of worsening thrombocytopenia, disseminated intravascular coagulation, multi-organ failure and haemophagocytic syndrome. Antibiotics should be administered until the PCR result is available and other infectious diseases have been ruled out.

Medical staff should be aware that there is a chance of human-to-human transmission through blood or body fluids. Contact precaution is needed until the SFTS viral load becomes undetectable.

The Case Continued...

The patient was intubated and admitted to the intensive care unit immediately. Meropenem and vancomycin were initiated for possible bacterial sepsis. His blood sample was sent to the reference laboratory, and SFTS virus PCR came back positive. Antibiotics were subsequently discontinued because no bacterial infection was identified.

Despite adequate fluid administration and other supportive therapies, the patient experienced worsening of his respiratory condition and protracted hypotension for a week. Noradrenaline was initiated, and then hydrocortisone 200 mg/day was added for non-responsive septic shock before he started showing gradual improvement. His platelet count decreased to $65 \times 10^9/L$ on day 4 of admission but subsequently recovered to the normal level. His CK was highest on admission and decreased to the normal level on day 7.

He was extubated on day 12 and discharged on day 35 without any sequelae.

SUMMARY BOX

Severe Fever With Thrombocytopenia Syndrome (SFTS)

SFTS is an emerging infectious disease caused by infection with the SFTS virus and transmitted by tick bites. The first case was reported in China in 2009; and since then, cases have been reported in both Japan and Korea. As of 2019, 491 cases had been reported in Japan from when the first case was reported in 2012.

The SFTS virus belongs to the family Bunyaviridae, which also includes the Crimean Congo haemorrhagic fever virus and hantavirus. Its incubation period is 6 to 14 days. Despite being a tick-borne disease, it is reported that an eschar is rarely seen. Clinical manifestations of SFTS include fever, nausea, diarrhoea, arthralgia, myalgia and neurological symptoms. Laboratory results typically show leukopenia, thrombocytopenia and elevated serum AST, ALT, LDH and CK levels. Patients sometimes develop multi-organ failure and hemophagocytic syndrome, which results in a high case-fatality rate.

Supportive treatment is the main treatment strategy. There is no effective antiviral agent against SFTS. Patients require close monitoring of their respiratory condition and blood pressure. Adequate fluid administration, close monitoring and management of thrombocytopenia, haemophagocytic syndrome and secondary bacterial infection are important.

The case-fatality rate has been reported to range from 6.3% to 30% in China and be 23.2% in Japan. Older age, impaired consciousness and high serum LDH and CK levels are associated with high lethality.

Further Reading

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