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An immunosuppressed woman in her sixties with a high fever

EDUCATIONAL CASE REPORT

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Investigation of fever in immunosuppressed patients can be challenging. Rapid and correct microbiological test results are essential for steering the investigation in the right direction. Our patient was eventually diagnosed with a condition that was initially suspected, but the time to reach a laboratory-confirmed diagnosis was unusually long.

A woman in her sixties was admitted to the division of medicine with a high fever and altered mental status in late summer. The fever had persisted for four days and was accompanied by fatigue, feeling of dyspnoea, nausea and joint pain. She had a history of aortic insufficiency, systemic lupus erythematosus, fibromyalgia and non-specific joint pain, and was on daily treatment with prednisolone 7.5 mg and azathioprine 25 mg. She had received 2 doses of the COVID-19 vaccine. On arrival, she was disorientated and had a rectal temperature of 40.1°C (reference range <38.0), blood pressure 122/68 mmHg (<140/90), pulse 88 bpm (50–80) and respiratory rate of 23 breaths per minute (12–20). Auscultation revealed a murmur consistent with the patient's aortic insufficiency and basilar rales over the right lung.

Acute onset of high fever is often a manifestation of new onset bacterial infection. The scoring tool *quick Sepsis-related Organ Failure Assessment* (qSOFA) is used to triage patients in the emergency department. Sepsis should be considered if a patient has a qSOFA score of 2–3 and suspected infection. The patient in this case had increased respiratory rate and altered mental status, and so fulfilled two of the criteria.

After microbiology specimen collection in the form of blood cultures, urine sample and nasopharyngeal sample, intravenous antibiotic treatment for serious infection with unknown focus was initiated in the emergency department with benzylpenicillin 3 g four times daily and gentamicin 360 mg once daily. Chest X-ray revealed no relevant abnormalities, and urine test strip only detected traces of blood and nitrite.

The patient's altered mental status was attributed to her high fever. She reported no headache, neck stiffness or dysuria. Blood tests found CRP 40 mg/L (<5), ESR 39 mm (<30), neutrophils 8.5 × 10^9/L (1.8–7.4 × 10^9/L), lymphocytes 0.5 × 10^9/L (0.9–3.0 × 10^9/L), platelets 216 × 10^9/L (165–387 × 10^9/L) and AST 55 U/L (15–35). Other hepatobiliary parameters, renal function tests and electrolyte status were within reference ranges. Rapid molecular testing for the most common respiratory viral and bacterial pathogens, including SARS-CoV-2, was negative.

When the results of the initial tests came back, suspicion of bacterial infection and sepsis was reduced. Viral infection appeared to be the likely cause, but the empirical antibiotic treatment was continued due to the patient's immunosuppressant treatment.

During the first day of admission, the patient was observed to have a fluctuating fever. In the afebrile intervals, she responded adequately to questions but was notably drowsy and had problems carrying out

instructions. During the fever spikes, she was confused with visual hallucinations. Blood and urine cultures were negative. A rapid IgM antibody test for tick-borne encephalitis virus in serum was negative.
Head CT scan ruled out suspected intracranial bleeding, but the radiologist reported a hypodense lesion in the left basal ganglia. This finding could represent a recent infarction, but was not enough on its own to explain the patient's condition. Due to the joint pain, the rheumatologist on duty was contacted. Several decades earlier, the patient had been diagnosed with systemic lupus erythematosus with secondary Sjögren's syndrome, based on characteristic butterfly-shaped rash, pericarditis, positive test for antinuclear antibodies (ANA) and positive anti-SSA test. Her condition had been stable for a long time, and therefore it was unlikely that the patient's symptoms were manifestations of systemic lupus erythematosus. Antibiotics were changed to cefotaxime 2 g three times daily on the second day of admission due to a perceived failure to control the infection in this immunosuppressed patient.
Fluctuating fever will usually suggest an abscess or other focus of infection, but investigations so far had pointed away from ongoing bacterial infection. The patient had not recently travelled abroad, and tropical diseases seemed unlikely. Repeat blood cultures were negative, and there was low clinical suspicion of endocarditis.

On the fourth day of admission, the patient still had a fever along with altered level of consciousness and impaired cognitive function, consistent with encephalitis. Lumbar puncture revealed moderately abnormal findings, with leukocytes 6 × 10^6/L (reference range <5 × 10^6/L) and slightly elevated protein levels of 0.73 g/L (0.15–0.50). Antimicrobial treatment was changed to empirical coverage of an assumed infection in the central nervous system: intravenous ceftriaxone 2 g once daily, ampicillin 3 g four times daily and aciclovir 10 mg/kg three times daily.
The cerebrospinal fluid was sent for bacteriological culture, and PCR testing was performed for neurotropic viruses, Listeria monocytogenes and Toxoplasma gondii, as well as autoimmune and paraneoplastic antibodies. Serological testing included tick-borne encephalitis virus, Borrelia burgdorferi, Parvovirus B19, HIV, syphilis and hepatitis virus. A repeat rapid IgM antibody test for tick-borne encephalitis virus was negative in both serum and cerebrospinal fluid.
The causative agent remains unknown in the majority of patients assumed to have infectious encephalitis. Herpes simplex virus type 1 (HSV-1) and varicella zoster virus are the most common causative agents detected in Norway and are diagnosed by means of PCR testing of cerebrospinal fluid (1). The incidence of tick-borne encephalitis is increasing in Norway (2), and this condition is diagnosed by detecting specific antibodies in serum (3).

On the fifth day of admission, CT scanning of the chest/abdomen/pelvis was performed with no abnormal findings. Unenhanced head MRI ruled out a recent ischaemic event, but detected low-grade chronic changes as well as high-signal changes in the right thalamus. EEG was described as clearly abnormal with slow basic rhythm but no epileptiform activity, consistent with diffuse encephalopathy.

That same afternoon, the patient had a persistent high fever, became less responsive, developed respiratory failure and was transferred to the intensive care unit for mechanical ventilation. PCR testing for herpes simplex virus and varicella zoster virus was negative, and aciclovir was discontinued on day 9. No IgM or IgG antibodies to Borrelia burgdorferi were detected in serum or cerebrospinal fluid. IgG antibodies to tick-borne encephalitis virus were detected in serum, without IgM antibodies, consistent with previous infection or vaccination. A surprising finding was Toxoplasma gondii DNA in plasma, and treatment with intravenous trimethoprim/sulfamethoxazole 320 mg/160 mg twice daily was initiated on day 9, despite consensus that the finding was of uncertain significance. The result turned out to be a false positive due to a technical error at the laboratory, and therefore the treatment was discontinued after six days.

HSV-1 encephalitis is a very concerning disorder with high mortality. Affected patients usually display confused mental state combined with fever and objective signs of central nervous system dysfunction. Cerebrospinal fluid will generally reveal elevated protein levels and lymphocytic pleocytosis, but a normal cerebrospinal fluid profile has been reported in immunosuppressed patients (4). The diagnosis of HSV-1 encephalitis will generally be supported by focal EEG findings and abnormal MRI findings. Detection of virus in cerebrospinal fluid on PCR testing is the gold standard, and treatment with aciclovir is recommended until negative PCR results are obtained.

Investigations to this point had not detected any causative agent or found anything to support malignancy, vasculitis or an autoimmune disorder as the underlying cause. The patient's spouse confirmed that the patient had received basic vaccination against tick-borne encephalitis virus with three vaccine doses 8–10 years previously.

Another lumbar puncture on day 12 revealed slightly elevated protein levels and moderate mononuclear pleocytosis, 7×10^6/L leukocytes ($<5 \times 10^6$). Treatment for bacterial infection was discontinued. Contrast-enhanced MRI of the head and magnetic resonance angiography detected several new non-specific changes, including decreased diffusion in the left internal capsule, in the right periventricular area and in the right temporal lobe, while the high-signal changes in the right thalamus had fully resolved. On day 14, evidence for the causative agent was finally obtained when a repeat rapid IgM antibody test for tick-borne encephalitis virus was positive in serum. The finding was confirmed with the laboratory's standard method, and intrathecal IgM and IgG antibody production was detected in cerebrospinal fluid in accordance with the manufacturer's instructions.

The patient lives in an area with many reported cases of laboratory-confirmed tick-borne encephalitis. The patient's spouse could not remember a tick bite in relation to this admission, but confirmed that the patient often walked in the woods. The clinical presentation was consistent with a serious case of tick-borne encephalitis, with the patient needing respiratory support for 26 days.

When the patient woke up, she had tetraparesis as well as difficulties with swallowing and speech. She was admitted to the rehabilitation department for a further 71 days, until she was discharged for further rehabilitation in her

local municipality.

Discussion

Tick-borne encephalitis is the most common tick-borne viral infection in Europe. Tick-borne encephalitis virus is a flavivirus comprising three subtypes: European, Siberian and Far Eastern, of which only the European subtype has been detected in Norway (5). Tick-borne encephalitis is a public health problem in parts of Central and Eastern Europe. The incidence in Norway is low, but has been increasing since 2018 (6). Nearly all cases of domestic infections are acquired following tick bites in coastal areas in the counties of Agder and Vestfold and Telemark.

The incubation period varies from days to weeks. Tick-borne encephalitis caused by the European subtype usually has a characteristic biphasic course (7, 8). In the first phase, patients present with flu-like symptoms, such as fever, headache and myalgia. This is usually followed by an afebrile period, before recurrence of high fever combined with symptoms of central nervous system inflammation. Clinically, this phase will present as meningitis (approx. 50 %), meningoencephalitis (approx. 40 %) or, more rarely, encephalomyelitis (7, 9). There are no specific antiviral drugs, and treatment is only symptomatic with organ support.

Diagnostic criteria for a definite case are clinical findings consistent with central nervous system inflammation, presence of pleocytosis ($> 5 \times 10^6$ cells/L), in addition to at least one of four laboratory criteria (i.e. detection of specific IgM *and* IgG antibodies in serum, detection of specific IgM antibodies in cerebrospinal fluid, significant increase in IgG in paired sera or detection of viral RNA in clinical specimens) in a patient who has stayed in an endemic area. Cerebrospinal fluid profile is characterised by normal glucose and lactate levels, moderately elevated protein and mononuclear pleocytosis (9).

Detection of antibodies in serum is central to diagnosis (3, 9). Specific IgM antibodies are absent in the first phase of the disease, but the majority of patients with central nervous system symptoms will have findings of both specific IgM and IgG antibodies. IgM antibodies have the highest sensitivity and are detectable in nearly all patients at the time of admission to hospital (7, 8). An immunochromatographic rapid test is available for rapid diagnosis of suspected cases. Therefore, reaching a diagnosis is not usually challenging, but it does require awareness of the condition as a relevant differential diagnosis.

In our patient, absence of specific IgM antibodies at the time of admission and on the fourth day of admission led to extensive investigations into other conditions. Tick-borne encephalitis in patients who have been previously vaccinated can present as a secondary immune response characterised by an initial sharp rise in IgG and delayed IgM production (10). In case of ongoing clinical suspicion, follow-up samples are recommended after ten days to test for IgM appearance (3). Antibody testing in cerebrospinal fluid is not routinely recommended, but should be performed if infection is suspected despite vaccination.

Vaccination against tick-borne encephalitis virus consists of basic vaccination (three or four doses) followed by booster doses every three/five years based on age and immunocompetence (11). Basic vaccination in line with the recommendations produces 96–99 % protection in people with healthy immune systems, but irregular vaccination, advanced age and immunosuppressant treatment produces a weaker immune response (12–14). In the period 2006–2015, 53 out of 1,004 recorded cases of tick-borne encephalitis in Sweden were attributed to vaccine failure, defined as infection despite at least two previous vaccine doses (15). The majority had received three or four doses of vaccine, had moderate/severe disease and a monophasic course, as in our patient. Eight patients were on immunosuppressant treatment. Advanced age is a known risk factor for severe disease, but knowledge about the disease course in immunosuppressed patients is scarce (15). It is still unclear whether breakthrough infection alone increases the risk of severe disease (10, 15, 16).

In case of suspected viral meningitis/encephalitis, routine PCR testing of cerebrospinal fluid for neurotropic viruses is performed. Tick-borne encephalitis virus is not usually detectable, and therefore PCR testing does not have a role in routine diagnostic work-up. In the first phase, prior to formation of neutralising antibodies, the virus can be detected in serum with reverse transcriptase-PCR (RT-PCR) (3). In practice, RT-PCR is rarely carried out, but should be considered in cases where there is a strong clinical suspicion of the virus in immunosuppressed patients with negative serology (17). In our patient, RT-PCR testing was carried out retrospectively in cerebrospinal fluid and serum from the fourth day of admission, but the result was negative.

The patient's neutrophilia and lymphopenia were probably related to prednisolone, but mildly elevated inflammatory markers and leukocytosis are common at the time of admission (8). MRI has low diagnostic specificity for tick-borne encephalitis, and its sensitivity is probably influenced by the time of the scan. MRI findings are usually localised to the thalamus, basal ganglia, cerebellum and brain stem, and are associated with severe disease (7, 18). Diagnostic testing for rarer tick-borne pathogens, such as *Borrelia miyamotoi* and *Candidatus Neoehrlichia mikurensis,* was not performed, despite publication of a single case report of the latter in Norway (19).

Tick-borne encephalitis virus IgG tests have moderate specificity due to cross-reactivity with other flaviviruses (3). If only IgG antibodies are detected, it is important to find out about previous exposure to flaviviruses, such as Japanese encephalitis, dengue and yellow fever viruses, for the correct interpretation to be made. The patient's spouse was able to confirm that the patient had been vaccinated against tick-borne encephalitis virus.

An increasing incidence of tick-borne encephalitis has been observed in Norway. The majority of patients have detectable IgM antibodies at the time of admission and are correctly diagnosed in good time. Diagnosis can be more challenging in breakthrough infections, as illustrated by our patient.

The patient has given consent for the article to be published.

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