



A man in his sixties from Southern Norway with intermittent fever

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Fever is usually caused by an infection, soft tissue injury, autoimmunity or malignancy. A thorough evaluation of the patient's anamnesis is part of the standard work-up, and is necessary to determine the cause of their illness.

A man in his sixties was admitted to a local hospital at the end of October owing to intermittent fever that had started eight days previously. The fever occurred about once a day and lasted for up to four hours. He had concurrent muscle and joint pain. Prior to

hospitalisation, the patient had attended three consultations with his general practitioner. Blood tests showed increasing CRP levels 90–125–147 (<5 mg/l) and leukocytes 11–8–28.4 ($4\text{--}10 \times 10^9/\text{l}$). The general practitioner performed a thorough examination, including an initial ultrasound of the abdomen, heart and lungs. The only finding was a left-sided pleural effusion of approximately 3 cm. At the first two consultations, the patient was afebrile and in relatively good general condition. At the last check-up, he reported mild asthenia between the febrile episodes. The general practitioner made a preliminary diagnosis of respiratory tract infection and requested hospitalisation before the weekend to clarify the diagnosis.

The patient's medical history included Hodgkin's lymphoma, for which he had received curative treatment with chemotherapy and splenectomy many years earlier. About ten years prior to the current hospitalisation, he had undergone emergency aorto-coronary bypass surgery after myocardial infarction, with subsequent post-infarction heart failure with reduced ejection fraction and recurrent pleural effusion. He was taking Eliquis owing to paroxysmal atrial fibrillation. Other regular medications were Albyl-E (aspirin), Simvastatin, Atacand (candesartan) and Selo-Zok (metoprolol).

The patient was afebrile when he was hospitalised via Acute Admissions. His blood pressure was 114/63 mm Hg, heart rate 83 bpm, rectal temperature 36.7 °C, and he had a respiratory rate of 18 breaths/min and oxygen saturation of 99 %. Blood tests showed leukocytes $22.7 \times 10^9/\text{l}$, CRP 161 mg/l and procalcitonine 17 µg/l (<0.1), but otherwise no significant abnormalities. Urine dipstick analysis was negative, and neither pneumococcal nor legionella antigens were detected in the urine.

Fever and decreased general condition are non-specific symptoms. Elevated inflammatory markers are seen in association with infections, but also with non-infectious conditions such as autoimmunity, soft tissue injury and cancer. The most likely explanation at the outset for the patient's fever was an infection, and empirical treatment with penicillin and gentamicin was initiated on suspicion of infection with unknown focus.

Intermittent fever is characteristic of some parasitic diseases, such as malaria, but the patient did not have a travel history that would lead one to suspect a tropical disease. He had no respiratory symptoms, and examination revealed no other findings that could indicate the focus of the infection. A further review of the anamnesis also failed to reveal other possible causes of the fever. Laboratory tests on the day he was hospitalised had ruled out urinary tract infection as the cause, whereas respiratory tract infection and bacteraemia remained possibilities.

Two days after hospitalisation, the duty doctor was summoned when the patient developed chills, a temperature of 40.3 °C, a fall in blood pressure (75/45 mm Hg), and tachycardia (120). Another blood culture was taken. He had no other new signs or symptoms, and the blood culture taken on arrival still showed no signs of growth. Blood tests revealed a moderate reduction in CRP level (161–142–92) and in leukocytes (22.7–9.3–13.6). A subsequent leukocyte differential count showed predominantly neutrophilia. Respiratory tract samples tested via polymerase chain reaction (PCR) were negative for influenza A and B viruses, Chlamydia pneumoniae and Mycoplasma pneumoniae.

On the basis of the examinations and test results, a respiratory tract infection was now less likely. The patient fulfilled the criteria for sepsis at this point, but his general condition was considered to be relatively good. Due to recurrent febrile episodes, the duty doctor decided to switch the antibiotic therapy to cefotaxime monotherapy. The reasoning behind the choice of antibiotic was not stated in the medical records.

Physical examinations over the following days revealed no new findings. The patient continued to have recurrent episodes of high fever, approximately one episode a day. He had also developed exertional dyspnoea. Computed tomography (CT) of the thorax, abdomen and pelvis revealed an increasing volume of bilateral pleural effusion. There were no other signs of infection or malignancy. Transthoracic echocardiography was performed without any pertinent findings, and cardiac function was described as unchanged relative

to an examination one year previously. No vegetations were seen on the valves, and blood cultures were negative. This argued against endocarditis. Pleurocentesis was performed, and revealed a transudate.

Heart failure in combination with periods of high fever was probably responsible for the increasing pleural effusion that explained his increasing dyspnoea. Upon further review of the anamnesis, it emerged that the patient exercised dogs in fields on the outskirts of town. In this context, he spent a large amount of time in the woodlands along the southern coast of Norway. Two months prior to hospitalisation, he had also been to Sweden to attend a social gathering for dog owners, which had involved exercising dogs in rough terrain. In the absence of a diagnosis, and given information that the patient spent much time outdoors in areas known to contain ticks, it was considered possible that he may have an infectious disease transmitted by tick bites. However, the clinical picture was not seen as typical of the usual manifestations of Lyme borreliosis or tick-borne encephalitis.

The Department of Medical Microbiology at Sørlandet Hospital had recently started to offer testing for more unusual tick-borne bacterial infections. The tick-borne infections tested for can all cause various types of febrile disease. The patient case was discussed with a doctor at the Norwegian National Advisory Unit on Tick-borne Disease, Sørlandet Hospital, who recommended taking a blood sample to exclude rare tick-borne diseases.

PCR tests were performed on the patient's blood for four tick-borne microbes. These were Anaplasma phagocytophilum, Rickettsia spp., Borrelia miyamotoi and Candidatus Neoehrlichia mikurensis. One day later, i.e. day six after hospitalisation, the laboratory reported that a high level of Ca. N. mikurensis DNA had been detected in the blood sample, consistent with neoehrlichiosis.

Based on experience with neoehrlichiosis in Sweden, the antibiotic therapy was changed to doxycycline per os 100 mg x 2 for three weeks. Having previously undergone splenectomy, the patient belonged to a group that is particularly prone to severe infection with *Ca. N. mikurensis*. He also spent a lot of time outdoors and was therefore at increased risk of tick bites. He may have been bitten by ticks either in his own locality in Southern Norway or during his trip to Sweden two months prior to disease onset.

The patient could not recall having been bitten by ticks or having developed any localised rash, and an examination after hospital admission revealed no signs of this either. However, the patient's symptoms including periodic fever, with roughly one febrile episode per day, are highly typical for immunocompromised patients with neoehrlichiosis.

The patient reported feeling better after the first day of treatment with doxycycline, and he became afebrile the following day. After four days he was sent home in relatively good general condition. Further samples were collected on days 6, 14, 28 and 40 after diagnosis. Ca. N. mikurensis DNA was detected in samples taken after six and 14 days with a gradual reduction in the number of copies of microbial genomic DNA. The sample taken after 28 days was not tested because, owing to an error, it did not reach the laboratory. The sample taken on day 40 was negative.

This is the first proven case in Norway of a human infection caused by *Ca. N. mikurensis*. The finding has been verified through sequencing of parts of the 16S rRNA gene at Sahlgrenska University Hospital in Sweden. Correct diagnosis ensured that the patient received targeted antibiotic treatment, which shortened the infection. Nevertheless, more than 14 days elapsed from the first treatment with doxycycline until the microbe could no longer be detected in the blood. The patient later reported having experienced asthenia for several weeks after being sent home, but he had no other symptoms.

Discussion

In Norway, the focus of attention with respect to tick-borne infections is primarily on Lyme borreliosis and tick-borne encephalitis, but sheep ticks may also carry other microbes such as *Anaplasma phagocytophilum*, *Rickettsia helvetica*, *Borrelia miyamotoi* and *Ca. N. mikurensis*. These tick-borne microbes rarely cause severe infections in those with healthy immune

systems.

In Southern Norway, a small percentage of ticks are infected with *Rickettsia helvetica* ($\leq 1\%$), *Borrelia miyamotoi* ($\leq 1\%$) and *Anaplasma phagocytophilum* ($\sim 4\%$) (1) (Box 1). However, a relatively high percentage (2–17%) of ticks in Norway appear to carry *Ca. N. mikurensis* (2) (Box 1). It is therefore reasonable to assume that quite a few persons in Norway are exposed to this bacterium through tick bites. *Ca. N. mikurensis* can also be detected in the blood of about 10% of people who develop symptoms (influenza-like and erythema migrans) following a tick bite, but the significance of this is unknown (3).

Box 1 Overview of bacteria detected in sheep ticks in Norway that may cause human disease, and percentage of ticks that are infected (1, 2)

Borrelia burgdorferi sensu lato 10–30 %

Candidatus Neoehrlichia mikurensis 2–17 %

Anaplasma phagocytophilum $\sim 4\%$

Rickettsia helvetica $\leq 1\%$

Borrelia miyamotoi $\leq 1\%$

Infection caused by *Ca. N. mikurensis* (neoehrlichiosis) has been detected in several countries in Europe (Sweden, Germany, Czech Republic, Switzerland and Poland) and in China (4). Most of the patients in Europe were immunocompromised, but infection has also been detected in a smaller number of individuals with healthy immune systems (4). Diagnostic testing for the infection is not widely available, so neoehrlichiosis is probably significantly underreported. *Ca. N. mikurensis* is thought to be an intracellular bacterium, and has not yet proved possible to culture. There are therefore no serological methods available to detect specific microbial antibodies, and in so doing provide information about the proportion of the population that has been exposed to the bacterium (so-called seroprevalence).

Certain patient groups are particularly vulnerable to severe neoehrlichiosis. These include patients with malignant haematological diseases (malignant lymphoma and chronic lymphocytic leukaemia), autoimmune/rheumatic diseases (rheumatoid arthritis, systemic lupus erythematosus or psoriasis) and those who have recently been treated with chemotherapy or corticosteroids (4). A large proportion of those with severe infections have either undergone splenectomy or treatment with rituximab (a monoclonal antibody against CD20 on B cells) (4). This lends support to the idea that B cell immunity and antibodies may be important in combating the infection.

Reports indicate that in individuals with healthy immune systems, neoehrlichiosis may be either asymptomatic or give rise to febrile disease with a number of different symptoms. In immunocompromised patients, symptoms are often more extreme (5). The patient may develop high fever, with marked fluctuations in temperature throughout the day, and severe muscle and joint pain. Erysipelas or erythema nodosum-like lesions may also occur, along with other more non-specific symptoms of systemic infection. It has been reported that a large proportion of patients with neoehrlichiosis experience thromboembolic events (4). Infection or inflammation of the vascular wall may be one explanation for this. Our patient was probably well protected against thrombosis owing to his treatment with antithrombotic drugs.

Doxycycline is effective for the treatment of infections caused by intracellular bacteria and is used to treat neoehrlichiosis. The recommended dosage is 100 mg x 2 per os for three weeks. Rifampin, 300 mg x 2 per os for two weeks, has been used successfully to treat a patient in whom doxycycline could not be used owing to possible hypersensitivity (4). Doxycycline is also the first-line treatment for tick-borne infections caused by *Anaplasma phagocytophilum*, *Rickettsia helvetica* or *Borrelia miyamotoi*.

Limited awareness of neoehrlichiosis, not only in Norway but also elsewhere in Europe, can

result in patients with severe infections receiving a greatly delayed diagnosis, or no diagnosis at all. Empirical antibiotic therapy will not cover this bacterium, and patients are at risk of thromboembolic events if left untreated. It is important to increase awareness of this type of infection and to be able to diagnose it in order to prevent serious complications.

The Department of Microbiology, Sørlandet Hospital, has therefore established a diagnostic testing service for *Ca. N. mikurensis* using PCR in EDTA whole blood samples. The same type of diagnostic testing is also available for other rare tick-borne microbes such as *Anaplasma phagocytophilum*, *Rickettsia* spp. and *Borrelia miyamotoi*. The tests are indicated in immunocompromised patients with fever of unknown origin, where there is also information to suggest tick bites or time spent in areas where ticks are present.

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