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Drug-induced aseptic meningitis

SHORT CASE REPORT

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Drug-induced aseptic meningitis is a rare but serious condition that should be suspected in patients with meningitis who test negative for a microbiological agent. The medical history is presented here of a woman with recurrent urinary tract infections where meningitis symptoms arose after repeated exposure to a frequently prescribed drug.

A woman in her fifties had been prescribed trimethoprim 160 mg × 2 for a urinary tract infection by her GP. After the first dose of trimethoprim, she developed chills, fever, vomiting and loose stools, and she was admitted to hospital due to her worsening condition despite treatment with oral antibiotics. On arrival, she was febrile (tympanic temperature 38.8°C) and tachycardic (heart rate 122 beats/min). Other vital parameters were normal, and the patient was awake, alert and oriented. Blood tests showed CRP 16 mg/L (reference range 0.0–4.0) and leukocytes 8.1×10^9/L ($3.5–10 \times 10^9$). Urinalysis was negative. A urine culture was taken, and a wait-and-see approach was taken to antibiotic treatment as there were few clinical signs of infection. On

the day of admission, the patient was experiencing increased neck stiffness, reduced responsiveness, headache and light sensitivity. CRP was slightly elevated (34 mg/L), while the leukocyte count remained normal. CT head showed no relevant pathology. Following a lumbar puncture and blood cultures, empirical treatment was initiated for meningoencephalitis with cefotaxime 3 g × 4 intravenously and aciclovir 600 mg × 3 intravenously. The cerebrospinal fluid examination showed findings compatible with meningitis, with no indication of microbiological agents (Table 1).

Table 1

Key results from analysis of cerebrospinal fluid and serum from the various hospital admissions. Elevated leukocyte counts in cerebrospinal fluid and no indication of microbiological agents are consistent with aseptic meningitis – protein levels may be elevated, while glucose levels are often normal (1). CSF = cerebrospinal fluid, EV = enterovirus, FilmArray = multiplex PCR with meningitis/encephalitis panel that tests for 14 different microbiological agents, HSV = herpes simplex virus, TBEV = tick-borne encephalitis virus, VZV = varicella-zoster virus.

Analysis	1st hospital admission	2nd hospital admission (eight months after 1st hospital admission)	3rd hospital admission (one year after 2nd hospital admission)
Cerebrospinal fluid			
Leukocytes, $\times 10^6$/L (ref. range: $< 5 \times 10^6$)	139 (24 % polymorphonuclear cells)	832 (47 % polymorphonuclear cells)	226 (65 % polymorphonuclear cells)
Protein, g/L (ref. range: 0.15–0.50 g/L)	0.366	0.620	0.520
Glucose ratio (CSV/serum)	0.8 (3.4/4.3)	0.7 (3.6/5.2)	0.6 (4.9/7.7)
Microscopy	Negative	Negative	Negative
Culture	Negative	Negative	Negative
FilmArray		Negative	Negative
EV, HSV and VZV PCR	Negative		Negative
HSV and VZV antibody		Negative	Negative
Bacterial PCR	16S-rDNA: Negative *Neisseria meningitidis*, *Listeria monocytogenes*, *Streptococcus pneumoniae*, *Escherichia coli* and *Haemophilus influenza* PCR: Negative	16S-rDNA: Negative *Staphylococcus aureus*-PCR: Negative	16S-rDNA: Negative

Analysis	1st hospital admission	2nd hospital admission (eight months after 1st hospital admission)	3rd hospital admission (one year after 2nd hospital admission)
Borrelia burgdorferi antibody	IgG and IgM: Negative	IgG and IgM: Negative	IgG and IgM: Negative
TBEV PCR		Negative	
Serum			
Treponema pallidum antibody	Negative		
Borrelia burgdorferi antibody	IgG and IgM: Negative	IgG and IgM: Negative	IgG and IgM: Negative
HSV antibody		HSV IgM: Negative HSV IgG: threshold HSV IgG, 2nd test: Negative	HSV IgG: Negative

Prior to the admission in question, the patient had been hospitalised twice in the last two years with meningitis with no indication of microbiological agents from a cerebrospinal fluid examination (Table 1). During the first period of hospitalisation, the patient's urinary tract infection (with E. coli in the urine) and meningitis symptoms were treated with a 14-day course of ceftriaxone 4 g × 1 intravenously and a 4-day course of dexamethasone 10 mg × 4 intravenously. She was not given gentamicin.

After a few days, the patient developed bilateral hearing loss which persisted, and six weeks later she received a right-ear cochlear implant. During the second period of hospitalisation, she received empiric antibiotic treatment in the form of ampicillin 3 g × 4, ceftriaxone 4 g × 1 and aciclovir 600 mg × 3 intravenously for ten days because of the earlier serious complication. The second time, the course of the illness was uncomplicated, and she was discharged in a normal condition after twelve days.

A review of the patient's earlier medical history showed that she had also been given trimethoprim during her previous hospital stays; once in combination with sulfamethoxazole. A literature review showed that trimethoprim can trigger aseptic meningitis, and antimicrobial treatment was discontinued one day after the patient's third admission. The patient quickly improved and was able to go home after five days. At an outpatient check-up a month after discharge, she was completely healthy and back to work full time.

Discussion

The case study illustrates several challenges in the investigation and treatment of meningitis. During the patient's first period of hospitalisation, she received a 14-day course of antibiotics for suspected culture-negative bacterial meningitis

with accompanying hearing loss. During her second and third periods of hospitalisation, she was tested for the most common cause of recurrent meningitis, namely herpes simplex virus type 2 (HSV-2) (2), but this was not found. It was not until she was admitted for the third time that the likely diagnosis was made: drug-induced aseptic meningitis. The diagnosis was made on the basis of a new review of her earlier medical history and the absence of infectious agents during this and previous periods of hospitalisation.

Aseptic meningitis is an umbrella term for all causes of inflammation of the meninges that have negative cerebrospinal fluid bacterial cultures. Viruses are the most frequent cause, of which HSV-2, enterovirus and varicella-zoster virus are the most common agents (1). Bacteria such as *Mycobacterium tuberculosis, T. pallidum* and *B. burgdorferi* and previous antibacterial treatment are bacterial causes of aseptic meningitis, while non-infectious causes are malignant disease, immunological diseases and certain drugs (1, 3, 4).

Drug-induced aseptic meningitis is a diagnosis of exclusion. The pathogenesis of the condition is not fully understood, but the literature describes possible mechanisms such as hypersensitivity reactions and drug toxicity (3). Autoimmune disease is frequently associated with drug-induced aseptic meningitis (4), but this was not found in investigations on our patient. Drug-induced aseptic meningitis should particularly be suspected in patients whose findings and symptoms are consistent with meningitis, but where investigation does not reveal an agent, and where symptoms occur after (repeated) drug exposure (3). The drugs most frequently associated with aseptic meningitis are nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics (particularly sulphonamides and penicillins), immunoglobulins, and monoclonal antibodies. The time from exposure to the onset of meningism can vary from minutes to months (4); in our patient's three episodes this interval varied from a few hours to a couple of days. Patients must be informed of the likely connection and advised against future use of the triggering drug. Norway's national network of regional medicines information and pharmacovigilance centres (RELIS) should also be notified of adverse effects.

The prognosis for drug-induced aseptic meningitis is usually good, and improvement can be expected within two to three days after cessation of the triggering drug (3). This was the case in our patient on all three occasions. Unfortunately, the patient developed irreversible hearing loss with concomitant meningism during the first bout of meningitis. To our knowledge, there is only one published case of hearing loss (transient), and this was in a patient with HIV infection and trimethoprim-induced aseptic meningitis (5). However, several cases of deafness after the use of trimethoprim have been reported in the WHO's VigiAccess database of adverse reactions, but the causal relationship is not clear (Hanne Stenberg-Nilsen, personal communication, October 2022). RELIS South East highlights how the reports in the WHO database are spontaneous reports that stem from normal clinical use of the drugs. It is known that there is extensive under-reporting to this system, and the reports cannot be used in isolation to draw any conclusions about causation or to indicate the frequency of an adverse effect, since the number of unreported incidents is unknown. The patients may also have used other (triggering) drugs, or there may be other factors that have impacted on the

course of events. The WHO emphasises that data extracts from the VigiAccess database do not represent the WHO's official view, and that the data are not homogeneous in terms of collection through the spontaneous reporting system.

The co-occurrence of meningitis and absence of other probable causes makes it reasonable to assume that our patient's hearing loss was a consequence of meningitis triggered by trimethoprim. This suspected adverse effect was reported to RELIS. Several challenges relating to drug-induced aseptic meningitis are illustrated in this case study, and the thorough medical history and repeated exposure to triggering causes with no indication of an infectious agent raised suspicion of the condition.

The patient has consented to the publication of this article.

The article has been peer-reviewed.

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