Tick-Borne Relapsing Fever with Severe Jarisch–Herxheimer Reaction

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Tick-borne relapsing fever (TBRF) is an arthropod-borne infection caused by a bacterial spirochete species, *Borrelia*. It is characterized by recurrent acute episodes of high spiking fever. TBRF in Israel is caused by *Borrelia persica* associated with *Ornithodoros tholozani* ticks [1]. The distribution area of *B. persica* in Israel overlaps the distribution area for *O. tholozani*, which covers the entire country, except the southern Negev Desert region. Antimicrobial therapy is highly effective and occasionally can trigger a Jarisch–Herxheimer reaction (JHR), a potentially lethal reaction presenting with sudden fever, rigors, and hemodynamic instability. We describe the case of an Israeli canyoning trainer who suffered from TBRF and developed severe JHR.

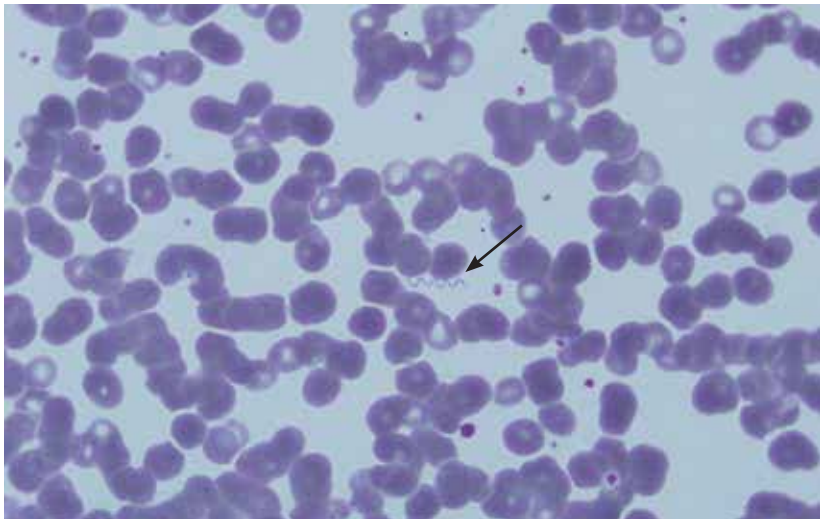
PATIENT DESCRIPTION

A 24 year old man who works as a canyoning and caving trainer presented to the emergency department with a 10 day history of recurrent episodes of high spiking fevers with accompanying headache and myalgias. He mentioned that he entered a cave 10 days prior to the eruption of his symptoms. His past medical history was unremarkable. He mentioned that he was frequently bitten by ticks during his work as a canyoning trainer in the Upper Galilee and Golan areas in Northern Israel. On physical examination his blood pressure was 127/89 mmHg, heart rate of 98 beats per minute, respiratory rate 16 breaths per minute, temperature of 39.6°C, and oxygen saturation of 96% on room air. No other abnormalities were detected during his physical examination. His complete blood count showed a white blood cell count of 6600 cells/μl, hemoglobin level of 14 g/dl, and a platelet count of 160000/μl. The differential count of white blood cells showed: neutrophils (50%), band neutrophils (26%), and lymphocytes (18%). Given his occupational history, a thin blood smear was performed [Figure 1] showing *Borrelia* spirochetes. The patient received oral antimicrobial therapy of doxycycline (100 mg) and was asked to stay in the emergency department for further observation. One hour after receiving antimicrobial therapy his body temperature increased to 40.8°C with accompanying rigors and diaphoresis. A few minutes later his blood pressure dropped to 73/40 mmHg with severe agitation and disorientation for almost 15 minutes. He was treated with intravenous fluids and antipyretics. After 6 hours in the emergency department his condition stabilized and he was transferred to the internal medicine department for observation under continuous electrocardiographic monitoring and vital signs surveillance. By the next day he was afebrile without any complaints. He was given two other doses of doxycycline without any adverse events. The patient was discharged to continue another week of antimicrobial therapy.

COMMENT

The case presented in this article is rather typical of TBRF. Our aim is to increase the awareness of physicians to the possible outcomes of treatment and to consider JHR

Figure 1. A thin blood smear showing helical shaped *Borrelia* spirochete (arrow) measuring nearly 30 microns long



when administering antimicrobial agents to patients with TBRF. JHR is defined as an acute exacerbation of the patient's symptoms possibly occurring upon initial treatment of relapsing fever with an effective antimicrobial therapy. The pathophysiology of JHR has been best studied in louse-borne relapsing fever (LBRF). During this reaction, the spirochetes disappear rapidly from the circulation with massive cytokine release. Symptoms often include hypotension, tachycardia, chills, rigors, diaphoresis, and marked elevation of body temperature. The reaction typically begins within 1 to 4 hours of the first dose of antimicrobial therapy [2].

Mild JHR has been reported among 54% of patients treated for TRBF in one study from North America [2], higher rates were reported from Israel (80%) [1]. Luckily, death from JHR among patients with TBRF has not been reported in Israel or North America, in contrast to JHR in patients with LBRF where mortality rates have reached 5% [2]. JHR has been most commonly reported following spirochetal infections, mainly syphilis, LBRF, leptospirosis, TBRF, and Lyme disease. It also has been rarely reported among many other infections, such as brucellosis, Q-fever, anthrax, and meningococcal infections [3]. The choice of antibiotics used for the treatment of spirochaetal infections was once thought to affect the incidence and severity of JHR. The most common antibiotics were beta-lactams and tetracyclines, while some studies showed that bactericidal drugs (beta-lactams) were more commonly associated with JHR than the bacteriostatic drugs (tetracyclines). Others showed conflicting results with similar or even higher rates of JHR with tetracyclines than beta-lactams [4]. At present, there is no clear evidence suggesting the role of a particular antibiotic class on the occurrence of the JHR.

JHR is a self-resolving condition that can be managed symptomatically by fluids and antipyretics. Currently, there are no effective therapies that can completely prevent its occurrence. The best evidence from randomized controlled trials in prevention of JHR has been with anti-tumor necrosis factor (TNF)-α antibodies, and in some cases steroids. While other pre-medications such as acetaminophen, chlorpromazine, and opioid analgesics may reduce the symptoms or duration of JHR, the reaction itself cannot be prevented [3,4]. Therefore, patients must be warned about its potential occurrence prior to the first dose of antibiotic treatment, and physicians must be aware of its dramatic presentation [3].

TBRF is endemic in Israel. Previous studies indicated that disease incidence has been declining among civilians and increasing among soldiers due to frequent prolonged training in TBRF hyperendemic areas [5]. A post-exposure policy for tick-bite screening and doxycycline prophylaxis among Israel Defense Forces field units training in areas known to be hyperendemic to TBRF proved to be highly efficacious [1].

Prevention of TBRF in Israel is best carried out by avoiding rodent and tick-infested natural sites such as caves. Civilians, and especially those who are occupationally exposed such as canyoning and caving trainers, should be aware of potential infectious hazards and physicians should be aware of JHR before initiating antimicrobial therapy.

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Capsule

Cytoplasmic p53 couples oncogene-driven glucose metabolism to apoptosis and is a therapeutic target in glioblastoma

Cross-talk among oncogenic signaling and metabolic pathways may create opportunities for new therapeutic strategies in cancer. **Mai** and colleagues showed that although acute inhibition of EGFR-driven glucose metabolism induces only minimal cell death, it lowers the apoptotic threshold in a subset of patient-derived glioblastoma (GBM) cells. Mechanistic studies revealed that after attenuated glucose consumption, Bcl-xL blocks cytoplasmic p53 from triggering intrinsic apoptosis. Consequently, targeting of EGFR-driven glucose metabolism in combination with pharmacological stabilization of p53 with the brain-penetrant small molecule idasanutlin resulted in synthetic lethality in orthotopic glioblastoma xenograft models. Notably, neither the degree of EGFR-signaling inhibition nor genetic analysis of EGFR was sufficient to predict sensitivity to this therapeutic combination. However, detection of rapid inhibitory effects on [^{18}F] fluorodeoxyglucose uptake, assessed through noninvasive positron emission tomography, was an effective predictive biomarker of response in vivo. Together, these studies identify a crucial link among oncogene signaling, glucose metabolism, and cytoplasmic p53, which may potentially be exploited for combination therapy in GBM and possibly other malignancies.

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