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Infectious Diseases Grand Round

Fever in the returning traveler

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ABSTRACT

Evaluation of febrile illness in a returning traveler is challenging as it requires careful history taking and knowledge of local epidemiology of endemic and epidemic diseases. Incorporating information of host characteristics for susceptibility of infections is also important for endemic mycosis apart from history of tick bites and animal exposures. Laboratory tests directed by clinical and laboratory parameters will help to reach final diagnosis.

1. Case history

A 72-year-old male, medical doctor living in Gujarat with well controlled hypertension and diabetes mellitus presented with the complaint of fever associated with initially chills converted into rigors for last 6 days, along with generalized weakness, body ache, and decreased appetite. Patient described daily two to three spikes of high fever up to 103.6 °F with rigors for last six days. He precisely mentioned that fever started after the boarding the flight to India. During his travel to the USA, the patient stayed in Orlando, Florida, for the entire 2.5 months stay. Patient also described a febrile episode that lasted for three days before nine days of current febrile spikes. He didn't go for hiking, trekking or visited other parts of USA except daily walking in a park with dense vegetations. He described pruritic maculopapular rashes on upper limb while walking in the park. He didn't recall any history of tick bite. He also had transient rashes over medial aspect of right knee. Patient consulted local physician after arrival in India. His initial work up performed by local physician reported normal ultrasound abdomen, negative malarial antigen, Covid, and Influenza RTPCR with elevated CRP - 25.4 (<5 mg/dL). His other baseline reports are described in Table 1 (day 0). Patient consulted infectious diseases clinic after two days as no response to empiric antibiotic (amoxycillin-clavulanic acid) treatment from local physician. He was tachycardic (pulse rate 104/min) with normal blood pressure and no skin rashes on physical examination. Respiratory system revealed right infra and interscapular crepitation. Liver was palpable three finger below the right costal margin and was tender.

High grade fever with chills, transaminitis, hepatomegaly and H/O skin rashes in a returning traveler raised the suspicion of tick born infection like Rickettsial fever, Human Anaplasmosis, Ehrlichiosis, Babesiosis and Lyme Disease.

Lab reports at the clinic were largely unremarkable except transaminitis, elevated CRP 35 mg/dL, and normal WBC counts with 60% lymphocytosis with reactive lymphocytes. (Table 1 column day 3). Scrub Typhus IgM test (Cross react with rock mountain spotted fever) was negative. Lyme serology and blood cultures were pending. Plain CT Thorax reported as bilateral lower lobe bronchiolitis rest normal. Patient denied hospitalization and IV Ceftriaxone and Doxycycline were prescribed to cover tick born infections. Additional tests Cytomegalovirus (CMV)/toxoplasma IgM and IgG and Epstein Barr Virus (EBV) panel were suggested for peripheral blood mononucleosis. Patient got admitted after two days with persistent fever spikes with rigors up to 104 °F. His toxoplasma serology was negative, CMV IgM: 2.16 (>1.0 reactive), IgG: 117.3 (0–6), EBV VCA IgG >750, EBV VCA 61.6 (>40 positive), EBNA IgG >600, EB EA IgG: 16.5 (<10, negative, 10–40 equivocal, >40 positive). Ceftriaxone and Doxycycline were continued along with supportive care. He got daily 2–3 fever spikes with rigors up to 104 °F. His repeat laboratory reports were unremarkable except transaminitis (Table 1, day 5). Patient did not respond to ceftriaxone and doxycycline treatment for more than 72 h. Rickettsia, human anaplasmosis, and ehrlichiosis generally responds well to doxycycline. EBV serology indicated a previous infection, and CMV antibodies were possibly cross-reactive to EBV and false positive. His serial complete blood counts are described in Table 1. We received a clue when we

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Table 1
Serial complete blood counts.

	Day 0	Day 3	Day 5	Day 7	Day 10	Day 14
Hb (gm/dL)	14.6	14	13.7	12.6	14.4	13.7
TC (mm^3)	6900	9240	8930	13,100	14,200	12,800
DC	60/33	37/60	43/50	44/48	44/50	44/49
PLT ($X10^3$ mm^3)	2.32	2.38	2.36	2.36	3.24	4.24
RBC (million/mm^3)	5.36	4.9	4.7	4.47	5.16	4.97
PCV (%)	44.8	41	39.2	37.7	43.3	41.5
SGPT IU/L	143	154	274	215	84	51
SGOT IU/L		136		212	70	60

Abbreviations: Hb: Hemoglobin, TC: Total count, DC: Differential count, PLT: Platelet count, RBC: Red blood cells, PCV: Pack cell volume, SGPT: Serum glutamate pyruvate transaminase, SGOT: Serum glutamic-oxaoacetic transaminase.

compared his available CBCs and noted decrease in Hb, RBC count and pack cell volume.

Asked pathologist to review peripheral smear for Babesia parasites.

Peripheral smear showed RBC infected with babesia parasite with <4% parasitemia (Fig. 1). Repeat malarial antigen test was negative. Tab Azithromycin 500 mg BD and Injection Clindamycin 600 mg q8h added for the treatment of Babesiosis to ongoing doxycycline plus ceftriaxone.

Patient complained of breathlessness and became hypoxic, SpO_2 92–94%. Physical examination revealed regression in the liver, just palpable below right costal margin.

Respiratory system revealed bilateral inter and infra scapular crepitations. His cardiac work up including echocardiography, NT pro BNP, CT pulmonary angiography and bilateral lower limb venous doppler were normal with elevated D-Dimer – 4292 μg/L. Lyme IgM was positive (IgM: 12.5 U/mL, IgG: 2.1 U/mL [< 9 negative, >11 Positive]). Blood cultures remained sterile. After the fifth hospitalization day, the patient began to recover with the above treatment, with a decrease in fever, as well as an improvement in appetite and breathlessness. Patient's laboratory parameters also showed improvement in hemoglobin, RBC counts and PCV with regression in transaminitis (Table 1, day 10 and 14). The patient was given azithromycin for seven days, clindamycin for ten days, and doxycycline and ceftriaxone for fourteen days.

2. Discussion

Malaria, Dengue fever and leptospirosis are described from Florida, USA apart from tick bite infections. Travel to an endemic area within the previous six week is a risk factor for babesiosis. Diagnosis is generally arrived by blood smear examination and polymerase chain reaction (PCR) [1]. Co-infection with other tick-borne illnesses is common. Babesiosis is rarely associated with rash. Concurrent Lyme disease is usually suspected in a patient with skin rashes. About 50% (23%–72%) of *B. microti*-infected patients experience Lyme disease coinfection [2]. Atovaquone 750 mg BID plus Azithromycin 500 mg 7–10 days combination is treatment of choice for babesiosis. Alternative agents are clindamycin + quinine [1]. Marathe A et al. reported Human Babesiosis in patient from Gwalior, India [3]. Bovine babesiosis was reported from 21 states of India with pooled prevalence estimate of 6% (95% CI = 4%–9%) [4]. Zoonotic Babesiosis has been described from Asian countries namely China, Japan, South Korea, Cambodia, Laos and Thailand. Babesiosis pose a potential public health threat in Asian countries [5]. Babesiosis killed 23 Asiatic Lions in the Gir sanctuary in Gujarat in May 2020 [6]. We could be overlooking human babesiosis cases in our clinical practise.

3. Microbiological perspective

It is difficult to distinguish plasmodia species from babesia species in malarial endemic areas. Aside from Babesia PCR, a negative malarial antigen test in peripheral smear showing parasitised RBCs is a useful practical tool for identifying Babesia.

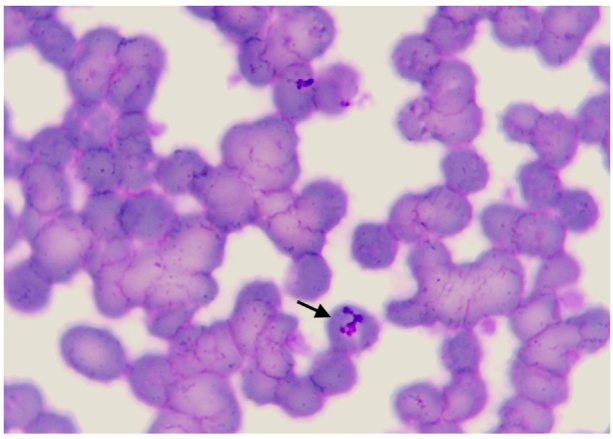

Fig. 1. Peripheral smear showing RBC infected with babesiosis parasite (black arrow).

4. Learning Pearls

A detailed travel history including hiking/trekking, history of tick bites, animal exposures, and exotic food experience while travelling are extremely important in evaluation of fever in the returning traveler. Aside from physical examination, a careful review of laboratory reports is very helpful in fever evaluations.

CRediT author statement

Atul Patel: Conceptualization, writing-Original draft preparation, Supervision.
Kinjal Shah: Data curation, data validation.
Dhaval Patel: diagnosis, manuscript editing.
Deeksha Chhipa: Data curation.
Ketan Patel: Writing- Reviewing and Editing.

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Declaration of competing interest

All the authors have no conflicts of interest to disclose.

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