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Letter to the Editor

A case of probable COVID-19 and mononucleosis reactivation complicating the presentation of travel-acquired measles

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Dear Editor,

Here we describe a man in his 30s who traveled from Canada to two large urban areas of India for eleven days who presented upon return with a prolonged viral respiratory syndrome, which may have represented three sequential and separate diagnoses. We summarize the timeline of symptoms and investigations in Fig. 1. Initial symptoms, which occurred two days after landing in India, appeared to be most consistent with COVID-19 infection given retrospectively reported anosmia, dysgeusia, and viral upper respiratory tract infection (URTI) symptoms such as sore throat and rhinorrhea [1]. By the time our patient returned and had negative COVID-19 tests on day 14 and 19 of illness, with rapid antigen test and PCR respectively, he likely did not have ongoing viral shedding.

As per the timeline depicted in Fig. 1, fever and malaise developed upon return to Canada and lasted for at least a week, which is consistent with a post-COVID-19 mononucleosis reactivation syndrome, among other potential common travel-acquired infectious diagnoses such as malaria, enteric fever, and arboviral infections. Epstein-Barr virus (EBV) reactivation after COVID-19 infection has been well-described in the literature, which has documented a six-fold higher chance for active EBV infection in patients with severe COVID-19 compared to controls who do not have COVID-19 infection [2]. A mild biochemical hepatitis and positive monospot test in this patient also suggested potential EBV reactivation.

Four days after fever onset, and one day after taking 1 g of azithromycin orally as self-treatment of typhoid, the patient presented with a polymorphous maculopapular rash across the face, chest, arms, legs, back, and trunk. Erythematous maculopapular rash following azithromycin administration in the setting of mononucleosis has been reported [3]. Three antibiotics that are most associated with rash in the setting of EBV are ampicillin, amoxicillin, and azithromycin [3]. The mechanism of such a rash is proposed to be altered lymphocyte activity and decreased interleukin-10 in the setting of mononucleosis, decreased antigenic tolerance, and a transient and reversible delayed hypersensitivity reaction [3]. Given ongoing fever, systemic symptoms, and clear travel-related exposures, he was treated empirically for typhoid fever on day 19 of illness, at which time additional diagnostic serologies were sent including measles.

The differential diagnosis for this patient's rash, especially given palmar involvement, included drug reaction (in the context of mononucleosis), rickettsial infections such as scrub typhus, secondary syphilis, Parvovirus infection, and measles (Table 1). His rash appeared initially on the hairline and face then spread centrifugally to include the palms, trunk, and extremities which supported a diagnosis of measles [4]. His fever duration of over one week did fit with measles as the prodromal phase is typically two to four days with fever and at least one of conjunctivitis, coryza, and/or cough [4]. His rash developed on the sixth day of fever and while there was some overlap of fever and rash, the time course and pre-test probability did not fit fully with measles exclusively, especially given the positive monospot, suspected drug reaction in the context of viral illness, the reported immunization history, and the absence of high-yield signs such as Koplik spots.

When the measles IgM returned positive on day 26 this was challenging given two alternative possible diagnoses and the potential for a false positive measles serology. Cross-reacting antibodies have been described in cases of measles IgM positivity. In a study investigating patients with febrile exanthems in São Paulo, Brazil from 2000 to 2004, 66 % of patients who had not recently received measles vaccine had a false positive IgM based on lack of seroconversion [5]. Among those patients, 13 % had rubella infection, 30 % had parvovirus B19, and 17 % had HHV-6 infection [5]. In the context of COVID-19, reports have emerged of measles coinfections, which raise the potential of false antibody cross-reactivity. Thus, given the prolonged and atypical clinical time course and the potential for competing diagnoses in our patient, confirmatory testing with measles PCR from nasopharyngeal swab was obtained through our local reference laboratory, which definitively established the diagnosis of measles.

Our patient developed measles infection after travel to India, a country with endemic measles transmission. Additionally, this

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Fig. 1. Timeline of events including dates of travel and symptoms.

individual had no documented record of measles immunization – only reported history - and initial serology was negative for IgG, suggesting lack of vaccination or under-vaccination against measles virus. Although measles is rarely encountered in clinical practice in Canada, the recovery of international travel necessitates consideration of this vaccine-preventable childhood illness. Furthermore, pandemic-related interruptions to public health programming globally have led to measles vaccination rates well below the threshold permissive to community-based transmission in many countries. Prompt consideration of measles in a differential diagnosis should lead to appropriate infection control protocols including airborne isolation, collection of clinical specimens for indirect and direct microbiological testing, notification of

Table 1
Differential Diagnosis for the Rash in our Patient's Presentation.

	Measles	Secondary syphilis	Rickettsioses (scrub typhus)	Drug rash with mononucleosis	Parvovirus infection
Incubation	10–12 days to prodrome; 14 days to rash	Four to ten weeks following primary infection	Six days to 21 days	Six-week incubation period of EBV; antibiotic-induced rash can occur 1 to 4 days after antibiotics initiated	Four to 14 days (can be up to 21 days)
Patho-physiology	Acute viral illness caused by Measles paramyxovirus. Primary site of infection is alveolar macrophages and dendritic cells, followed by spread to regional lymph tissue and distant reticuloendothelial sites. Transmission by respiratory droplets or airborne spread.	Hematogenous dissemination of *Treponema pallidum*. Infection occurs primarily through sexual contact or vertical transmission; less commonly other hematogenous (transfusion, IVDU).	Infection via arthropod vectors; Endothelial infection and inflammation, causing vasculitis; can implicate several organs.	EBV infects B lymphocyte cells and can also infect oral epithelial cells. Most common proposed mechanism for antibiotic-induced rash is transient antibiotic hypersensitivity secondary to immune system alterations to underlying viral illness, with activation of $CD8^+$ T-lymphocytes.	Initial infection of erythroid precursors in marrow. Further pathogenesis depends on organ system involved (see below). Transmission primarily by inhalation of aerosolized droplets; vertical and hematogenous transplant can also occur.
Epidemiologic and risk factors	Unvaccinated and incompletely vaccinated individuals. Hotspots of transmission include health care facilities, travel hubs, and mass gatherings. Highest number of cases in India and Yemen.	Dramatic rise in cases since 2000. Highest rates in MSM and HIV positive. Other risk factors include age <29, IVDU, methamphetamine use, history of incarceration, history of exchanging sex for drugs or money.	North Australia, Asia, Pacific and Indian Ocean islands	Worldwide distribution; primary infection often occurs during childhood or adolescence. EBV reactivation may occur in periods of psychologic stress, malignancy, infection, and autoimmune disease.	Worldwide distribution; acquisition primarily in childhood.
Clinical features beyond rash	Preceded by 2–4 days of high grade fever, cough, coryza, and conjunctivitis. Koplik spots pathognomonic.	Fever, malaise, lymphadenopathy. Other dermatologic features include mucous patches and alopecia. Virtually any visceral organ can be involved (hepatitis and nephritis most common). Early neurosyphilis (meningitis, meningovascular).	Fever, headache, myalgia, shortness of breath, lymphadenopathy, abdominal pain. Multiorgan involvement (hepatitis, renal failure, pneumonitis, ARDS, DIC, myocarditis, meningoencephalitis) can occur in untreated disease.	Symptoms of mononucleosis including fever, pharyngitis, adenopathy, fatigue, tonsillar enlargement or exudate, palatal petechiae	Various organ systems can be involved including renal, hematological (including pure red cell aplasia), central nervous system, and/or placental (hydrops fetalis)
Features of rash	Maculopapular eruption starting at hairline and spreading along neck and face. Rash spreads centrifugally to involve palms and soles.	Generalized rash involving chest, back, palms, and soles. Any combination of macular, papular, squamous or pustular. Usually non-pruritic.	Centrifugal. Eschar at site of arthropod bite is of high diagnostic value if identified.	Erythematous maculopapular rash (described as pruritic or nonpruritic)	Spectrum of rashes include erythema infectiosum often involving bright erythema over cheeks, petechial rash, and/or maculopapular rash of extremities (can have lacy appearance)
Diagnostic testing including turn-around-time	PCR and serology; higher sensitivity if performed on serum or throat swabs compared to oral fluid or dried blood samples	Syphilis serology (positive RPR), including both treponemal and non-treponemal testing. Highest yield in secondary syphilis. RPR reactive except in rare cases of false negative prozone reaction (<2 %).	Acute and convalescent rickettsial serology; sensitivity of 94.2 % and specificity of 93.6 % (turn around time: up to 10 days)	Monospot or heterophile antibody test (not sensitive in first week of illness), EBV viral capsid antigen IgM and IgG, nuclear antigen IgG (only IgM will demonstrate acute infection); turn-around-time 5 days for serology	Parvovirus B19 IgM in the serum and/or parvovirus B19 DNA in the serum or bone marrow aspirate
Treatment	Supportive care	One dose of benzathine penicillin G 2.4 million units IM	Doxycycline. Azithromycin as an alternative agent.	Supportive care; discontinuation of antibiotics	Supportive care
Prevention	Two doses of measles vaccination. Measles vaccination and/or immunoglobulins to exposed, susceptible individuals.	Routine screening for HIV positive, MSM, and pregnant women. Screening indicated for other individuals at high risk of acquisition. Partner notification and treatment. Follow-up of serologic response to treatment. STI prevention including health promotion and counseling, public health surveillance and active case-finding measures.	No vaccine available. Avoid contact with arthropod vectors (avoidance of exposure conditions, high risk areas). Appropriate clothing, insect repellant in areas of potential exposure.	No EBV vaccine available. Antibiotic-induced rash may be prevented by microbiologic confirmation of bacterial pathogens (e.g., streptococcal pharyngitis) before antibiotic prescription.	No vaccine available. Routine infection control measures. Blood and blood product screening.

local Infection Prevention and Control practitioners, and public health surveillance networks. Vaccination and administration of immune globulin to applicable household and other contacts should also be considered [4].

Following resolution of this patient's acute febrile syndrome which included at least a viral URTI followed by measles potentially with an EBV reactivation, we noted serum eosinophilia approximately one month after return to Canada. At a convalescent follow-up appointment, this patient's *Schistosoma* serology returned indeterminate and as such, he was treated with a day of praziquantel, which led to resolution of eosinophilia.

This case illustrates as an important clinical pearl to providers which is that multiple infections, acute and chronic, can co-exist in a patient following travel or migration; as such, maintaining a broad differential is essential in such cases.

Declaration of competing interest

The authors have no commercial or financial interests to declare. Generative AI was not used in the writing of this manuscript. Patient informed consent was received for this report. This work is not under consideration for publication elsewhere, its publication is approved by all authors and, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

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