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Murine typhus mistaken for COVID-19 in a young man

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SUMMARY

Fever is a widely recognised presenting symptom of COVID-19. Consequently, other febrile illnesses may be difficult to distinguish from COVID-19—leading to delays in diagnosis and treatment. One such illness is murine typhus, a fleaborne illness with worldwide distribution caused by *Rickettsia typhi*. It often presents with fever, headache and myalgia, all of which have been commonly reported with COVID-19. Although the disease is usually mild with a good prognosis, there have been reports of severe illness and death. I present a case of murine typhus in a young male who had 2 weeks of headaches and daily fevers during the COVID-19 pandemic. He was ultimately tested for murine typhus when his occupation as a dog trainer was queried, and he experienced resolution of symptoms after treatment with doxycycline. During this pandemic, clinicians must be vigilant of other febrile illnesses whose symptoms overlap with COVID-19.

BACKGROUND

Murine or endemic typhus is a fleaborne febrile illness caused by *Rickettsia typhi*.¹ Transmission to humans is primarily through fleas from rodents.² While many studies describe cats as domestic reservoir hosts, it can also exist in dogs.³ In the USA, murine typhus is endemic to Hawaii, South Texas and Southern California,⁴ and has been more often reported during warmer seasons.² Because the disease has a non-specific clinical presentation, and often self-limited nature, it may be difficult to diagnose.⁴ As a result—it can be misdiagnosed and under-reported.³ While many cases are mild, there have been reports of death related to murine typhus.⁵ Consideration of this illness, which commonly presents with fever, headache and myalgia, can be overlooked due to symptom overlap with COVID-19. One of the most common symptoms associated with COVID-19 is fever.^{6,7} With the current pandemic, it has become even more important for clinicians to recognise other illnesses that present with persistent fever.^{8,9} The differential diagnoses of persistent febrile illness range from malignancy to infectious diseases to rheumatological conditions. A comprehensive history including occupation, travel or exposure to animals may lead to diagnoses of under-reported febrile illnesses such as murine typhus.

CASE PRESENTATION

A 25-year-old man from Southern California presented virtually by telephone appointment with a 4-day history of headaches, myalgia, chills and fevers up to 39.2°C in July of 2020. On the

day of this initial evaluation, he was tested for SARS-CoV-2—the virus causing COVID-19 by nasopharyngeal and oropharyngeal PCR testing and found to be negative.

One day later, on day 5 of his illness, he presented to the emergency department for persistent symptoms of fever, body aches and headache. He also had vomiting, diarrhoea, cough, congestion, chills and fatigue. He denied any sick contacts, rash, chest pain or shortness of breath. In the emergency department, he was febrile with a temperature of 38.4°C. Comprehensive physical examination was normal. A second PCR test for SARS-CoV2 was negative. He was treated with 600 mg oral Ibuprofen. Given the stability of his vital signs and clinical examination, he was discharged with a diagnosis of presumptive viral syndrome. He was advised to follow up for any worsening symptoms.

On day 8 of his illness, he reported persistent fevers, cough, body aches and vomiting during telephonic follow-up. He reported new back pain and a maximum temperature of 39.9°C. He denied dysuria, rash or shortness of breath. Given his persistent symptoms and repeatedly testing negative for COVID-19, he was advised to pursue further evaluation and work up in urgent care.

At time of arrival in urgent care, he was tachycardic with a pulse rate of 125 and febrile with a temperature of 38.1°C. Physical examination was normal. Serological examination indicated bandaemia of 20.3% and lymphocytopenia recorded at $0.78 \times 1000/\mu\text{L}$. Blood culture was obtained and ultimately showed no growth at 5 days. He was treated with 1 g of intramuscular ceftriaxone, 1000 mg of acetaminophen, 1000 mL of intravenous sodium chloride. He was subsequently discharged with azithromycin for 5 days and precautions to return to the emergency department if he experienced worsening symptoms.

On day 14 of his illness, during another virtual telephone encounter, he endorsed daily and persistent fevers up to 37.9°C. He also reported cough, chills, body aches, headache, dizziness, fatigue and diarrhoea. He was speaking in full sentences on the phone with no audible wheezing and did not appear to be in any distress. On inquiry of his occupation, he reported he was a dog trainer.

INVESTIGATIONS

Retesting for COVID-19 by SARS-CoV-2 PCR was offered and resulted as negative. His case was discussed with haematology oncology, infectious disease and rheumatology. After collaborating with the specialists, extensive workup of his persistent febrile illness was undertaken. Infectious disease



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Case report

specialist recommended further investigation should be guided by epidemiological risk and exposure. As examples, testing for coccidioides should be considered if he had a travel history to Arizona or the Central Valley of California and if the patient was exposed to fleas or animals he should be tested for murine typhus. Given his occupation as a dog trainer, he was tested for murine typhus and titres were found to be above 1:256. Serological evaluation was also notable for an elevated erythrocyte sedimentation rate (ESR) of 25 mm/hour. A blood smear showed mild normochromic and normocytic anaemia with no other significant abnormalities detected. Radiological evaluation with CT scans to exclude malignancy was also recommended.

DIFFERENTIAL DIAGNOSIS

The patient's initial presentation appeared consistent with COVID-19. Given multiple negative PCR tests for SARS-CoV-2 and persistent symptoms for 2 weeks, other aetiologies were explored.

Multidisciplinary discussion with the on-call haematology oncology, infectious disease and rheumatology physicians resulted in more robust differential diagnoses. They suggested an expanded evaluation to include rheumatological, malignant and endemic infectious diseases.

It was ultimately inquiry into the patient's occupational history as a dog trainer that helped reveal his diagnosis of murine typhus.

TREATMENT

The results of abnormal *R. typhi* titres were obtained on day 20 of his illness. He was treated with doxycycline 100 mg two times a day for 2 weeks.

OUTCOME AND FOLLOW-UP

After completing the prescribed course of doxycycline, he subsequently experienced full resolution of his symptoms. He made the decision to cancel the pan CT scans that were ordered as part of his previous workup.

DISCUSSION

Because the symptoms of murine typhus can be nonspecific, it can be challenging to diagnose in a timely manner.^{4 8} This is especially true during the current COVID-19 pandemic where the non-specific presenting symptoms of murine typhus—fever, headache and myalgia—overlap with symptoms of COVID-19. The symptom overlap of fever, reported in over 90% of patients with murine typhus and in 83%–98% of patients with COVID-19, may blind the clinician from exploring the broader differential diagnoses of other febrile illness.^{2 7}

During the pandemic, it is prudent for clinicians to maintain expanded differential diagnoses to COVID-19 so other diagnoses that can mimic it are not overlooked.⁹ With the appropriate history and investigation, clinicians can capture under-reported diagnoses such as murine typhus in a more timely manner.

The 'classic' triad of fever, headache and rash reported in murine typhus is found only in one third of patients.² Chills, malaise, myalgia and anorexia were commonly reported symptoms of the disease. Laboratory abnormalities can consist of elevated liver function tests, elevated lactate dehydrogenase, hypoalbuminaemia, high ESR, thrombocytopenia and hyponatraemia. While common reservoirs of this disease include rats, cats and opossums, dogs have been shown to carry the disease less frequently. The drug of choice to treat murine typhus is doxycycline. Second line therapy can also include azithromycin.¹⁰ In this

particular patient, doxycycline was a superior agent compared with azithromycin in his treatment. Before his diagnosis was made, this patient was incidentally started on azithromycin on day 8 of his illness, however, he still continued to experience fevers on day 14 of his illness—indicating treatment failure for murine typhus with this agent.

In cases where obtaining a timely diagnosis has been challenging, clinicians should not overlook the importance of identifying a patient's occupational history. Inquiring about this patient's work as a dog trainer led me to consider a diagnosis of murine typhus. Because its symptoms are non-specific—it is often misdiagnosed and subsequently under-reported.^{2 3} The disease is primarily transmitted to humans through fleas found on rodents.² While most studies indicate common reservoirs for this disease are rats and cats, there have been reports of serological evidence of the presence of *R. typhi* in dogs.³ There has also been an increased occurrence of murine typhus in warmer seasons.²

Other illnesses related to dog exposure were excluded during the investigation of this patient's illness. Blood smear did not show evidence of either tick borne relapsing fever¹¹ or ehrlichiosis—which is transmitted by the brown dog tick.¹² Blood culture was negative, eliminating a diagnosis of *Capnocytophaga canimorsus* which usually occurs after a bite, scratch or lick from a dog.^{13 14}

Patient's perspective

This experience made me feel like a number rather than a person. I am thankful I was able to recover and my parents did not have to sign the consent form. However, I worry that someone with more than Typhus is out there receiving poor care in the name of COVID-19. While I was sick, I started to lose trust in the medical system. If my step-mother was not a nurse, I would have not have worked so hard to receive care. I did eventually receive care. I am thankful for those doctors and nurses that took the extra time to help me.

Learning points

- ▶ Although murine typhus is often self-limited and mild, there have been reports of serious illness associated with this disease. It presents with nonspecific symptoms and is oftentimes misdiagnosed and under-reported. Prompt diagnosis and treatment can minimise any potential adverse outcomes.
- ▶ Consideration of murine typhus should be made in patients presenting with persistent fever, headache, myalgia and animal exposure in endemic areas. A lack of awareness of murine typhus by clinicians can lead to prolonged symptoms and higher cost of healthcare.
- ▶ Inquiring about epidemiological risk and exposure can help direct investigation of illnesses that are underdiagnosed and under-reported.
- ▶ Dogs can transmit this disease to humans in addition to cats and rats.
- ▶ Clinicians should consider an expanded differential diagnoses to COVID-19 if symptoms are not improving or persist—particularly in those with repeat negative testing. This can be challenging given the wide overlap in symptoms of COVID-19 with other disease processes.

Lack of awareness and inability to differentiate murine typhus from other diseases causing fever such as COVID-19 can lead to delayed treatment and subsequent prolongation of symptoms in addition to higher cost of healthcare.⁴ Although murine typhus has been described as a mild and self-limited illness, there are reports that the disease may be fatal in as high as 5% of patients for whom antibiotic treatment was delayed or not provided.¹⁵ Early recognition of this disease and prompt intervention with doxycycline will result in more favourable outcomes.⁴ During this pandemic, medical providers should develop more comprehensive differential diagnoses in patients who experience persistent symptoms that overlap with COVID-19 and repeatedly test negative for it.

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