

CASE REPORT OLGU SUNUMU

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Scrub Typhus and Influenza B Virus Co-Infection in a Child

Çocukta Çalılık Tifüsü ve İnfluenza B Virüsü Koenfeksiyonu

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ABSTRACT Scrub typhus is one of the most common, yet under diagnosed, re-emerging and most neglected tropical diseases. Timely diagnosis and initiation of appropriate treatment can significantly reduce the complications and case fatality. The influenza B (IFB) virus, responsible for nearly 30% of seasonal influenza cases, can also cause serious illness, especially in children. In tropical countries, infectious diseases are still one of the leading causes of mortality in children. There is often co-infection between scrub typhus and viral agents such as IFB virus due to overlapping endemicity and seasonal patterns. Both scrub typhus and influenza can present with non-specific flu-like symptoms that are not specific, making early clinical differentiation difficult. We report a child of scrub typhus who developed severe febrile thrombocytopenia and cough, and was found to have concurrent IFB virus infection, as detected by polymerase chain reaction (reverse transcription polymerase chain reaction) on a nasopharyngeal swab.

ÖZET Çalılık tifüsü, en yaygın fakat yeterince tanı konulmayan, yeniden ortaya çıkan ve en çok ihmal edilen tropikal hastalıklardan biridir. Zamanında tanı konulması ve uygun tedaviye başlanması, komplikasyonları ve ölüm oranını önemli ölçüde azaltabilir. Mevsimsel grip olgularının yaklaşık %30'undan sorumlu olan influenza B (IFB) virüsü de özellikle çocuklarda ciddi hastalıklara yol açabilmektedir. Tropikal ülkelerde, çocuk ölümlerinin önde gelen nedenlerinden biri hâlâ enfeksiyon hastalıklarıdır. Çalılık tifüsü ile IFB virüsü gibi viral ajanların birlikte enfeksiyonları sık görülür; bunun nedeni, endemik bölgelerin ve mevsimsel döngülerin örtüşmesidir. Hem çalılık tifüsü hem de influenza, spesifik olmayan grip benzeri belirtilerle seyredebileceğinden erken klinik ayırım yapmak güçtür. Çalışmamızda, yüksek ateşli trombositopeni ve öksürük geliştiren bir çalılık tifüsü olgusu bildiriyoruz. Bu hastada, eş zamanlı IFB virüsü enfeksiyonu da nazofaringeal sürüntü örneğinde polimeraz zincir reaksiyonu (ters transkripsiyon polimeraz zincir reaksiyonu) ile saptanmıştır.

Keywords: Co-infection; scrub typhus; influenza B virus

Anahtar Kelimeler: Koenfeksiyon; çalılık tifüsü; influenza B virüsü

The World Health Organization (WHO) has recognized scrub typhus as one of the most neglected tropical diseases of public health importance in the Asia-Pacific region.¹ Scrub typhus is a re-emerging, under diagnosed and one of the most common vector-borne diseases caused by *Orientia tsutsugamushi*.^{2,3} Approximately 18,781 confirmed cases have been reported in the last decade.³ However, a major drawback is the non-availability of affordable, rapid, specific diagnostic tests.¹

According to the WHO, each year, seasonal influenza affects approximately one billion individuals

globally.⁴ Influenza contributes to nearly 6,50,000 deaths annually. Influenza B (IFB) virus, which is known to cause serious illness, especially in children, accounts for 30% of seasonal influenza cases.^{4,5}

In regions like India, where scrub typhus is endemic and seasonal, patients are often prone to co-infections with other infectious diseases.² Both scrub typhus and influenza can present with non-specific flu-like symptoms.² These concurrent infections can make diagnosis challenging for the physician. We report a child of scrub typhus who presented with high-grade fever, cough, and severe thrombocytopenia.

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IFB virus was confirmed by a positive nasopharyngeal swab polymerase chain reaction [reverse transcription polymerase chain reaction (RT-PCR)].

CASE REPORT

A 3-year-old boy presented with a history of high-grade fever for 5 days and mild cough for a day. The fever was continuous but without chills and rigors. There was no history of hurried respiration, vomiting, loose stools, rashes or convulsions. Clinical examination revealed a temperature of 104 °F, respiratory rate of 32/minute, pulse rate of 140/minute, capillary filling time of 2 seconds, oxygen saturation of 98% and a blood pressure of 90/62 mm of Hg. He had puffiness of the face, and an eschar was noted in the left inguinal region. Abdominal examination showed hepatomegaly of 2 cm and a just palpable spleen. Other systemic examination was unremarkable. In view of eschar and puffiness of the face, scrub typhus was considered the first differential diagnosis. Facial puffiness due to plasma leakage is a manifestation of dengue fever and scrub typhus. Other differentials like dengue fever and enteric fever were also considered. The child was started on oral doxycycline, intravenous ceftriaxone, oral paracetamol, and intravenous fluids. Given the presence of cough and the ongoing influenza outbreak in India, a nasopharyngeal swab for influenza RT-PCR was also sent at admission. Initial laboratory investigations revealed haemoglobin 7.8 g/dL, total leukocyte count 11,970/mm³, and platelet count 20,000/mm³. Investigations are depicted in Table 1.

On the 2nd day of hospitalisation, though the other vital parameters were normal, the child continued to have a fever of 100.4 °F. Cough had worsened, although the respiratory rate and auscultation were normal. Scrub typhus immunoglobulin M (IgM) antibodies detected by enzyme-linked immunosorbent assay were strongly positive (91.56 IgM units; normal = <9 IgM units). Serology for dengue (NS1) and human immunodeficiency virus were negative. Abdominal ultrasound revealed hepatosplenomegaly, ascites, gall bladder wall thickness of 4 mm with oedema, and bilateral pleural effusion supporting the diagnosis of scrub typhus. His chest X-ray was normal. The nasopharyngeal swab

TABLE 1: Biochemical, microbiological and radiological investigations

Investigations	At admission	At 12 hours of admission	At 24 hours of admission	At discharge
Hemoglobin [g/dL]	7.8		8.0	8.1
PCV	23.6		24.2	25.3
TLC [cells/mm ³]	11,970		9,370	
DLC	62%, 34%, [N, L, E, M, B] %			
Platelet count [cells/mm ³]	20,000	48,000	96,000	1.92 lakhs
CRP [U/L]	61			
ESR in 1 st hour	50		40	
SGOT (U/L)	90			
SGPT (U/L)	39			
Serum albumin [mg/dL]	2.7			
Serum creatinine [mg/dL]	0.3			
Blood urea [mg/dL]	16			
Serum sodium [mEq/L]	128			
Serum potassium [mEq/L]	4.3			
CK-NAC [U/L]	103			
Serum albumin [mg/dL]	2.7			

Scrub typhus IgM antibodies detected by ELISA (91.56 IgM units; normal = <9 IgM units); nasal swab RT-PCR detected influenza B virus; Influenza A and H1N1 virus not detected; Serology for dengue (NS1), HIV and weill-felix are negative; blood and urine cultures were sterile; chest X-ray normal.

Sonography: Liver enlarged in size 12.3 cm; spleen enlarged in size; gall bladder wall edema present; gall bladder wall thickness 4 mm; ascites present and bilateral pleural effusion present.

PCV: Packed cell volume; TLC: Total leukocyte count; DLC: Differential leukocyte count; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; SGOT: Serum glutamic-oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase; CK-NAC: IgM: Immunoglobulin M; ELISA: Enzyme-linked immunosorbent assay; RT-PCR: Reverse transcription polymerase chain reaction; HIV: Human immunodeficiency virus

RT-PCR detected IFB virus infection, and oral oseltamivir was started.

On day 4 child became afebrile, and all vital signs normalised. Blood and urine cultures remained sterile. His platelet count improved to 1.92 lakhs/mm³. He was discharged on the 5th day with advice to complete 7 days of oral doxycycline and 5 days of oral oseltamivir. Informed consent was taken from the parents to report the case.

DISCUSSION

Scrub typhus, caused by *O. tsutsugamushi*, presents with a wide spectrum of clinical symptoms like fever, headache, cough, nausea, vomiting, rash, and myalgia/flu-like symptoms.¹ However, these clinical features are often found in other infections like dengue fever, chikungunya, typhoid, influenza and coron-

avirus infections.¹ Although scrub typhus and influenza frequently have non-specific flu-like symptoms, skin rash and the presence of an eschar, which has a high specificity of 98.9% are the hallmark of scrub typhus.^{2,6} The child described in our case had a well-formed eschar in the left groin region.

IFB virus is responsible for causing seasonal influenza cases with mild to moderate respiratory illness in children.^{4,5} The common clinical features include sudden onset of fever, cough, rhinorrhea, headache, and musculoskeletal pain.⁴ However, it can occasionally lead to complications such as pneumonia and multisystem involvement.⁵ Out of 56 IFB virus-infected children, upper respiratory tract infection occurred in 44 (78.5%) cases, pneumonia in 11(19.6%) and severe pneumonia in 1 (1.7%) child.⁵

The present child presented with fever and cough, both of which are common symptoms of scrub typhus and IFB virus. The presence of an eschar in the groin pointed towards scrub typhus, but in view of the outbreak of influenza, RT-PCR was done for influenza, which was positive IFB virus. This confirmed the co-infection of IFB with scrub typhus. Although respiratory symptoms are not the main complaints in scrub typhus, they are well recognised.⁶ Nearly 40% of patients can present with a non-productive cough and even community-acquired pneumonia.⁶

Thrombocytopenia can occur in both scrub typhus and IFB virus infection. Severe thrombocytopenia (platelet count of 20,000/mm³) in our case may be attributed to the synergistic effect of both infections.

Various co-infections with scrub typhus have been reported, including malaria, dengue fever, chikungunya, typhoid fever, leptospirosis and coronavirus disease-2019.² Hence, there may be a delay in the diagnosis of scrub typhus, as the nonspecific clinical features of scrub typhus (other than the eschar) often overlap with other co-infections.^{2,6} Delayed diagnosis and initiation of appropriate therapy in scrub typhus can significantly worsen disease severity, leading to increased morbidity and a case fatality rate as high as 30%.³

The clinical symptoms and signs overlap between scrub typhus and influenza, making the detection of co-infection difficult.⁶ Yamamoto et al. reported scrub typhus and influenza A virus co-infection in a 74-year-old

TABLE 2: Summary of the previously published articles on scrub typhus and influenza virus co-infection

Yamamoto, et al. ²	74 years old from forest area presented with respiratory symptoms diagnosed as influenza A and treated with oseltamivir.
Japan	Fever persisted and developed respiratory failure and liver dysfunction. She had skin rashes and eschar was present; positive for scrub typhus serology. She was treated with minocycline and improved.
Jhuria L, et al. ⁶	30 year old presented with acute respiratory distress syndrome. She had eschar over the groin and crackles on chest auscultation.
India	Investigations revealed leucopenia, thrombocytopenia, and elevated transaminases. She was positive for both scrub typhus and influenza. She responded for oseltamivir and azithromycin by 2 days.
	23 year old presented with fever, cough and breathlessness for 7 days and positive for H1N1. Treated with oseltamivir for 5 days but fever persisted.
	No eschar, but positive for scrub typhus serology and responded to doxycycline.
	A 28-year old primigravida presented with fever, dry cough and sore throat. No eschar. Her liver enzymes were elevated. She was positive for both scrub typhus and influenza.
	She responded to oseltamivir and azithromycin treatment by 2 days.
Ahn, et al. ⁷	53 year old presented with fever and cough; positive for H1N1; oseltamivir and zanamivir started. But fever continued. eschar present along with thrombocytopenia and deranged liver function tests.
Korea	Recovered after treatment with doxycycline.
Sahu, et al. ⁸	44 year old presented with fever, cough and breathlessness. Started on azithromycin and piperacillin-tazobactam.
India	On 2nd day patient deteriorated with decreased in oxygen saturation and delirious mental state.
	On examination, eschar was found. scrub typhus serology positive and doxycycline started and sent for H1N1 in view of respiratory system involvement which was also positive.
	He had thrombocytopenia and deranged liver function tests. He improved with oseltamivir.

woman from Japan.² Jhuria et al. reported 3 adult cases of co-infection of H1N1 influenza with scrub typhus from India.⁶ Ahn et al. reported a similar co-infection of H1N1 with scrub typhus in a 53-year-old female from Korea.⁷ Sahu et al. reported a case of co-infection with H1N1 influenza and scrub typhus, which also had central nervous system involvement.⁸ Table 2 depicts the summary of the previously published articles on scrub typhus and influenza virus co-infection.⁸ Even though a few cases of H1N1 co-infection with scrub typhus are reported in the literature, this is probably the first documented case of pediatric co-infection with scrub typhus and IFB virus.

Some of the clues for high index of suspicion of co-infections include: persistence of fever despite doxycycline/oseltamivir, eschar, multisystem involvement, thrombocytopenia and deranged liver function tests. Knowing the local habitat conditions and seasonal influenza trends can aid in clinical decision-making.

A study from North India observed dual infections in 16 acute undifferentiated febrile illness patients. Among them, 10 had co-infection of scrub typhus and dengue, 3 had scrub typhus with leptospirosis, one case each of scrub typhus with vivax malaria, scrub typhus with dengue and malaria and dengue with chikungunya.⁹ This highlights the burden and diversity of co-infections in tropical regions.

In Asia, both scrub typhus and influenza share seasonal peaks, commonly occurring during the post-monsoon and winter months. The cool and moist environment enables chigger activity (the vector of scrub typhus). Meanwhile, the influenza transmission also increases during cooler seasons.¹⁰ This seasonal overlap may explain the co-infection in our case. The main importance of this case report lies in the fact that although both infections are indistinguishable in signs and symptoms and are commonly overlooked, they have a therapeutic divergence. Scrub typhus requires doxycycline, while influenza mandates antiviral therapy with oseltamivir.

In a country like India, where several endemic diseases such as dengue, scrub typhus, leptospirosis, and typhoid are common, seasonal epidemics of influenza coexist with them. There is often an overlap of clinical features posing as a diagnostic dilemma. Careful clinical examination (especially looking for eschar), awareness of local disease epidemiology, seasonal pattern of epidemics and timely investigations are critical for accurate diagnosis and management. Persistent fever despite appropriate antibiotics or antivirals, presence of eschar, thrombocytopenia, liver dysfunction, and multisystem involvement should prompt suspicion of co-infection.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Kalenahalli Jagadish Kumar, Jawahar Reddy Dwarsala, Harshitha Thammanna, Nandish Huchavanahalli Rudrappa; **Design:** Kalenahalli Jagadish Kumar, Jawahar Reddy Dwarsala, Harshitha Thammanna, Nandish Huchavanahalli Rudrappa; **Control/Supervision:** Kalenahalli Jagadish Kumar; **Data Collection and/or Processing:** Jawahar Reddy Dwarsala, Harshitha Thammanna; **Analysis and/or Interpretation:** Kalenahalli Jagadish Kumar, Nandish Huchavanahalli Rudrappa; **Literature Review:** Jawahar Reddy Dwarsala, Harshitha Thammanna; **Writing the Article:** Kalenahalli Jagadish Kumar, Nandish Huchavanahalli Rudrappa; **Critical Review:** Kalenahalli Jagadish Kumar, Nandish Huchavanahalli Rudrappa; **References and Findings:** Kalenahalli Jagadish Kumar; **Materials:** Kalenahalli Jagadish Kumar, Nandish Huchavanahalli Rudrappa.

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