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Epidemiology, Clinical Presentation, Lab Diagnosis and Outcome of Scrub Typhus Outbreak in a Tertiary Care Center in Southern Rajasthan

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ABSTRACT

Introduction: Scrub typhus is also known as tsutsugamushi disease or bush typhus. It is a mite-borne acute febrile illness caused by Gram-negative intracellular organism called *Orientia tsutsugamushi*, which belongs to the family of Rickettsiaceae. **Aims and objectives:** To study the epidemiological patterns, different clinical manifestations and complications associated with scrub typhus. **Material and methods:** This was a prospective study which was carried out over a period of 12 months from January 2019 to December 2019 in patients of scrub typhus admitted in various medical wards of MB Govt. Hospital and RNT Medical College, Udaipur, Rajasthan. **Observation and results:** All the patients admitted with history of acute febrile illness suspected to be scrub typhus were assessed in the study. All these patients were evaluated by the set protocol in the form of detailed history, physical examination and relevant systemic examination. A total of 3,814 suspected patients of scrub typhus were tested in our microbiology laboratory and 1,340 patients were reported positive. Out of these, only 480 patients who were admitted in our medical wards were enrolled in our study and evaluated. **Conclusion:** We conclude that in rural Rajasthan, any patient who presents with fever, myalgia, hepatosplenomegaly and multiorgan dysfunction syndrome, a diagnosis of scrub typhus should be suspected.

Keywords: Scrub typhus, Rickettsiaceae, tsutsugamushi

Scrub typhus is also known as tsutsugamushi disease or bush typhus. It is a mite-borne acute febrile illness caused by Gram-negative intracellular organism called as *Orientia tsutsugamushi*, which belongs to the family of Rickettsiaceae. Although the disease has a worldwide distribution, most of the cases are reported from the so called "tsutsugamushi triangle", which is a wide area bounded by Pakistan, India and Nepal in the West, Siberia, Japan, China and Korea in the North and Indonesia, Philippines, Australia and the Pacific islands in the South. There is an estimated 1 million new scrub typhus infections each year and over 1 billion people around the world are at risk. In India, the disease was first noted during World War II in the soldiers posted in the tribal regions of Assam and Bengal and in the 1965 Indo-Pak War. This disease is endemic in the hilly areas of India like Himachal Pradesh and Jammu and Kashmir, but from the last few years a large number of cases has been reported from other parts of India, like Kerala, Pondicherry, Goa, Uttarakhand, West Bengal and Rajasthan. Although the illness is endemic to our country, but it still remains underdiagnosed because of the lack of diagnostic tools and awareness among the treating physicians. The disease is primarily seen in the rural populations and majority of cases are reported during the monsoon/post-monsoon season, that is from July to November.

However, it is not uncommon to find cases during the rest of the year because few case reports have been seen in the summer and winter months.

Scrub typhus may present clinically with a variety of symptoms which ranges from mild non-specific febrile illness to a much severe form of disease

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like cardiovascular, renal, hepatic and neurological involvement.

Very few studies are available from India on scrub typhus with fewer reported from Rajasthan where the disease has shown a resurgence lately. Keeping this current situation in minds, our aim was to conduct an observational prospective study on scrub typhus among the adult patients admitted in the Dept. of General Medicine, RNT Medical College and MB Govt. Hospital, a tertiary care institute located in the city of Udaipur in the state of Rajasthan.

AIMS AND OBJECTIVES

To study the epidemiological patterns, different clinical manifestation and complication associated with scrub typhus.

MATERIAL AND METHODS

This was a prospective study which was carried out over a period of 12 months from January 2019 to December 2019 in patients of scrub typhus admitted in various medical wards of MB Govt. Hospital and RNT Medical College, Udaipur, Rajasthan.

All the patients admitted with history of acute febrile illness suspected to be scrub typhus were taken in the study. All these patients were evaluated by the set protocol in the form of detailed history, physical examination and relevant systemic examination. These patients underwent investigations which included complete blood count, platelet count, urine examination, renal function and liver function tests, including hepatitis viral markers, X-ray chest, ultrasonography and electrocardiography. Cerebrospinal fluid examination and magnetic resonance imaging (MRI) of brain were done whenever required. Specific investigations under fever panel were also done in all these patients which included malarial parasite quantitative buffy coat (MPQBC) test for malaria, immunoglobulin M/G (IgM/IgG) and NS1 antigen testing to rule out dengue fever, Typhidot for typhoid fever, enzyme-linked immunosorbent assay (ELISA) test for Chikungunya. For the diagnosis of scrub typhus, we performed ELISA test to detect IgM antibodies against *O. tsutsugamushi* antigens. A total of 3,814 suspected patients of scrub typhus were tested in our Microbiology laboratory and 1,340 patients were reported positive. Out of these, only 480 patients who were admitted in our medical wards were enrolled in our study and evaluated.

Informed written consents were obtained from all the patients enrolled in our study.

Inclusion Criteria

All the admitted patients who were above the age of 18 years and found positive for scrub typhus by IgM ELISA technique were included in the study.

Table 1. Month-wise Distribution of the Cases

Month	Number of patients found positive	Number of patients enrolled in the study
January 2019	0	0
February 2019	1	1
March 2019	1	0
April 2019	1	0
May 2019	1	0
June 2019	2	1
July 2019	35	10
August 2019	173	68
September 2019	281	93
October 2019	320	103
November 2019	343	135
December 2019	182	69
Total	**1,340**	**480**

Table 2. Distribution of the Patients According to the Age, Gender and Rural vs. Urban

Sex/Age groups	18-40 years	40-60 years	>60 years
Male (n = 292)	122 (41.78%)	114 (39.04%)	56 (19.17%)
Female (n = 188)	86 (45.74%)	58 (30.85%)	44 (23.40%)
Total (480)	**208 (43.33%)**	**172 (35.83%)**	**100 (20.83%)**
Distribution			
Rural vs. Urban	Rural: 376 (78.33%)		Urban: 104 (21.67%)

Table 3. Distribution of Patients According to the Signs and Symptoms

	No. of patients	Percentage (%)
Fever	480	100
Headache	402	83.75
Myalgia	437	91.04
Vomiting	287	59.79
Rashes	92	19.16
Jaundice	302	62.91
Oliguria	184	38.33
Eschar	94	19.58
Altered sensorium	59	12.29
Neck rigidity	47	9.79
Bleeding	18	3.73
Hepatomegaly	284	59.16
Splenomegaly	279	58.12
Hypotension	152	31.66

Exclusion Criteria

Patient with known liver disorders, kidney failure and any cerebrovascular events (stroke, meningitis or meningoencephalitis in recent past).

Patient with concurrent infection with malaria, chikungunya and dengue fever.

All these patients were followed-up during their hospital stay and their outcomes were recorded in the form of primary and secondary outcome. Primary outcomes included death or discharge from hospital and secondary outcomes included duration of stay in hospital, need for ventilator and hemodialysis support.

OBSERVATION AND RESULTS

The maximum number of cases were reported in the months from August to December. The highest number of cases were reported in the month of November, i.e., 135 (28.12%) followed by in the month of October [103 (21.45%) cases] (Table 1). Among the 480 patients studied, 292 were male. About 43.33% patients were in the age group of 18-40 years, followed by 35.83% in the 40-60 years age group (Table 2). About 20.83% were above 60 years of age. Majority of patients belonged to the rural setting (Table 2).

Fever was the most common symptom (100%), followed by myalgia (91.04%). Other common signs and symptoms included headache, jaundice, vomiting, hepatomegaly and splenomegaly. Eschar was noted in 19.58% (Table 3).

More than half of the patients with scrub typhus had anemia. About 37.91% had leukocytosis and 36.25% had leukopenia. Nearly 95% patients had total serum

Table 4. Laboratory Findings in Patients of Scrub Typhus

Parameter	No. of patients	Percentage (%)
Anemia (Hb <12)	265	55.20
Leukocytosis (>11,000)	182	37.91
Leukopenia (<4,000)	174	36.25
Thrombocytopenia (<1,50,000)	289	60.2
Bilirubin (>1.1)	324	67.5
Elevated SGOT and SGPT	426	88.75
Elevated ALP	428	89.16
Serum albumin (<2.5 mg/dL)	442	92.08
Serum total protein (<5.5 mg/dL)	456	95.00
Serum LDH (>480 IU/L)	434	90.41
Serum triglyceride (>150 mg/dL)	438	91.25
Serum cholesterol (>200 mg/dL)	430	89.58
Serum urea (>40 mg/dL)	289	60.2
Serum creatinine (>1.1 mg/dL)	339	70.6

Hb = Hemoglobin; SGOT = Serum glutamic oxaloacetic transaminase; SGPT = Serum glutamic pyruvic transaminase; ALP = Alkaline phosphatase; LDH = Lactate dehydrogenase.

Table 5. Outcome Observed in the Patients of Scrub Typhus

Recovery and discharge	431 (89.79%)
Need for mechanical ventilation	58 (12.08%)
Weaned off from ventilatory support	27 (5.62%)
Need for dialysis	42 (8.75%)
Average hospital stay	8 days
Death	49 (10.20%)

protein below 5.5 mg/dL. The laboratory findings in patients with scrub typhus are summarized in Table 4.

Overall, 90% patients recovered and were discharged, 12% needed mechanical ventilation and 8.75% needed dialysis. Average hospital stay was for 8 days (Table 5).

DISCUSSION

Scrub typhus is a potentially fatal infection which affects about 1 million people every year. The disease first came into prominence during the World War II when many from the US, Ceylon and Burma army were infected and ultimately succumbed to the illness due to lack of proper antibiotic treatment.

Although a lot of epidemics of scrub typhus have occurred in India, the literature available on this illness is still limited. *O. tsutsugamushi* is the causative agent. It was first identified and studied in Japan in the year 1930. It is an obligate intracellular bacterium transmitted to humans by the bite of larval mites (chiggers) of *Leptotrombidium deliense*. The incubation period varies from 6 to 21 days with an average of 10 days. These larval mites usually feed on the wild rats of the subgenus Rattus. The organism is maintained by transovarian transmission in mites. Although there are several serotypes of *O. tsutsugamushi*, infection with one species gives only a transient cross immunity to another. After a forest is cleared, scrubs grow on those areas over a period of time. These scrubs later get infested by larval mites. When man gets in contact with these scrubs, he becomes infected. The basic pathologic changes are focal vasculitis and perivasculitis of the

small blood vessels in the involved organs. These arise from multiplication of the organisms in the endothelial cells which line the small blood vessels.

In our study, we used IgM ELISA as the diagnostic tool for establishing the diagnosis of scrub typhus infection. Indirect immunofluorescence test is the gold standard diagnostic test for scrub typhus. Weil-Felix agglutination test is also widely available. Though Weil-Felix agglutination test is not a very sensitive test, it has high specificity and positive predictive value. Due to lack of availability of definitive tests in India, IgM ELISA can be a useful tool when used and interpreted in correct clinical context.

The study was conducted in RNT Medical College and MB Govt. Hospital, Udaipur, Rajasthan from January 2019 to December 2019. A total of 480 patients were enrolled in the study and the following observations were made.

In present study, the maximum number of cases were reported in the months from August to December which was 468 patients (97.5%), with the highest number of cases reported in the month of November i.e., 135 (28.12%) followed by in the month of October 103 (21.45%) cases. A study done in 2017-18 in 160 patients of scrub typhus found maximum patients in the month of September and 78% patients were reported in monsoon and post-monsoon season. The results of our study do not match with this study due to the fact that there may be variation of timing of monsoon and degree of rainfall.

Almost all the outbreaks of scrub typhus seem to occur in the rural population particularly seen among farmers, people involved in animal husbandry and those living close to woods and bushes. In the present study, we observed similar results where 376 (78.33%) patients were from rural population.

In the study, males were more frequently affected [292 (60.84%)] as compared to females [188 (39.16%)]. A study showed that among the 59 patients studied, 59% were males and 41% were females. More number of males affected in our study could probably be because of the reason that more number of males were involved in farming and animal husbandry activities. Among the total number of patients enrolled, maximum belonged to the age group of 18-40 years (208 participants). This is in accordance with the study conducted by Jamil et al in North Eastern India, wherein the investigators found that the maximum number of patients belonged to the age group of 18-30 indicating that these groups are more vulnerable to exposure owing to their involvement in more outdoor and recreational activities. The study conducted by Subbalaxmi et al found the mean age group of the affected population as 41 years.

Scrub typhus can cause a wide variety of symptoms ranging from fever, myalgia, headache, vomiting, loose stools to severe complications like acute renal failure, acute respiratory distress syndrome (ARDS), pneumonia, sepsis, meningitis and even death. Among the symptoms noted in this study, the most commonly observed was fever (100%) followed by headache (83.75%), myalgia (91%), vomiting (59.79%), rashes (19.16%), jaundice (62.91%) and oliguria (38.3%). Serious side effects like hypotension, bleeding and altered sensorium were also seen in less than 10% of the population. The characteristic finding of scrub typhus, that is the presence of eschar, was found in 19.58% of the patients. Hepatomegaly and splenomegaly were seen in 59.16% and 58.12% patients, respectively. This finding is in accordance with a study conducted in Rajasthan wherein the researchers found that fever (100%), headache (81.6%), cough, dyspnea (58.4%) and myalgia (48%) were the most common symptoms. Twenty-six (20.80%) patients had altered sensorium, 6 (4.8%) had gastrointestinal bleed and 6 (4.8%) had opisthotonus posturing with muscle spasms. Eschar was found only in 22% of the total population. Hepatomegaly (22%) and splenomegaly (10%) were also noted. From this, we can conclude that fever is seen almost universally in all the cases of scrub typhus making it an important differential diagnosis of any acute febrile illness.

The most common abnormality found in complete blood count analysis was thrombocytopenia (60.2%) followed by anemia (55.20%), leukocytosis (37.91%) and leukopenia (36.25%). The studies conducted by Subbalaxmi et al, Mathai et al and Wu et al also showed similar results. In the study by Subbalaxmi et al, thrombocytopenia was found in around 30% with leukocytosis in around 24% and leukopenia in 10% of the population. The presence of thrombocytopenia probably explains the bleeding manifestations encountered in scrub typhus.

Scrub typhus is one of the many different illnesses that is almost always associated with hepatitis. Liver function tests of the patients enrolled in our study showed that the abnormalities commonly encountered were raised bilirubin (67%) along with derangements in liver enzymes seen in 88% of the population. This was also associated with decrease in both total protein and levels of albumin seen in around 95% and 92% of the total population, respectively. The study conducted by Vivekanandan et al showed that derangement of liver

function test was seen in 95% of the study group while that of Mathai et al showed derangement in 88% of the study group. Thus, any patient who presents with an acute febrile illness with derangements of transaminase with hypoproteinemia should be evaluated for scrub typhus.

Scrub typhus also leads to derangements in renal function test, as noted in our study. The common findings were raised urea (60.2%) and raised creatinine (70.6%) observed among the patients studied. The study conducted by Mathai et al showed that renal failure was observed in 37% of the population while a similar study by Vivekanandan et al showed the derangement was seen in 13% of the population.

Of the total 480 patients studied, 431 recovered and were discharged from the hospital. Fifty-eight patients needed mechanical ventilation. Among these, 27 were weaned off from ventilator support. Forty-two patients had the need for renal replacement therapy in the form of hemodialysis or peritoneal dialysis. Average number of hospital stay was 8 days and 49 patients died. Similar findings were noted by Saluja et al. Of the total 160 patients included in the study, 12 patients had the need for mechanical ventilation. Average duration of hospital stay was 5.4 days and mortality was seen in 6 patients.

CONCLUSION

Scrub typhus is a disease which clinically mimics infections like dengue viral infection, leptospirosis, malaria and pneumonia. This is because all these infections present with sudden onset fever, mild hepatitis and thrombocytopenia. Whenever there is an associated feature suggestive of a multisystem involvement in the form of associated respiratory involvement, gastrointestinal symptoms, altered sensorium and hepatitis, a physician should always keep the diagnosis of scrub typhus in mind while analyzing the illness. Majority of our patients with scrub typhus are from rural parts. Though eschar is pathognomonic of the disease, it was noted in only less than 20% of the study population. This emphasizes that the absence of an eschar does not rule out scrub typhus. Although fever, headache, myalgia are the most predominant symptoms, serious symptoms like altered sensorium, hypotension and bleeding are also noted. Hepatosplenomegaly was also observed in a significant number of the population studied. Thrombocytopenia, raised transaminases, raised bilirubin and hypoproteinemia are the predominant laboratory abnormalities identified in our study. We conclude that in rural Rajasthan, any patient who presents with fever, myalgia, hepatosplenomegaly, multiorgan dysfunction syndrome and hepatitis, a diagnosis of scrub typhus should be suspected. A delay in treatment may lead to complications and higher mortality. That is why empiric treatment with doxycycline or macrolides may be given in cases where scrub typhus is suspected and if facilities for diagnosis are not available.

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COVID-19: Knowing Viral Load has no Significance

Lescure and colleagues have described the first cases of COVID-19 in Europe, reported in France. The clinical features of 5 patients with COVID-19 are aligned with the quantitative SARS-CoV-2 viral RNA load from nasopharyngeal and other sampling sites.

While the authors make a case for COVID-19 presenting as three distinct clinical patterns, a distinction based on such small numbers seems highly speculative. On the basis of the assumption that viral RNA load correlates with high levels of viral replication, insights need to be gained from this time-course analysis.

Our understanding of the relationship between viral RNA load kinetics and disease severity in patients with COVID-19 continued to be disintegrated. Zou and colleagues had reported that patients with COVID-19 with more severe disease requiring ICU admission were found to have high viral RNA loads at 10 days and beyond, after symptom onset.

Contrary to that, Lescure and colleagues reported the viral RNA kinetics of 2 patients who developed late respiratory deterioration despite the disappearance of nasopharyngeal viral RNA. It would be interesting to know whether viral RNA load in lung tissue, or another sample such as tracheal aspirate, mirrors the reduction in nasopharyngeal shedding. It appears that these late, severe manifestations might be immunologically mediated. This observation has significance for the use of immune-modulatory therapies for this subset of patients. This finding is consistent with recent reports that corticosteroids were beneficial for acute respiratory distress syndrome, and possibly those with COVID-19.

Lescure and colleagues noted the implications for transmission from patients with few symptoms but high viral RNA load in the nasopharynx early in the course of disease. Individuals within the community, policy makers and frontline healthcare providers, particularly general and emergency room practitioners, should remain alert and prepare to manage this risk. The persistently high nasopharyngeal viral RNA load, and the detection of viral RNA in blood and pleural fluid, of the older patient (aged 80 years) with severe multi-organ dysfunction is disturbing. (*The Lancet Infectious Diseases*)

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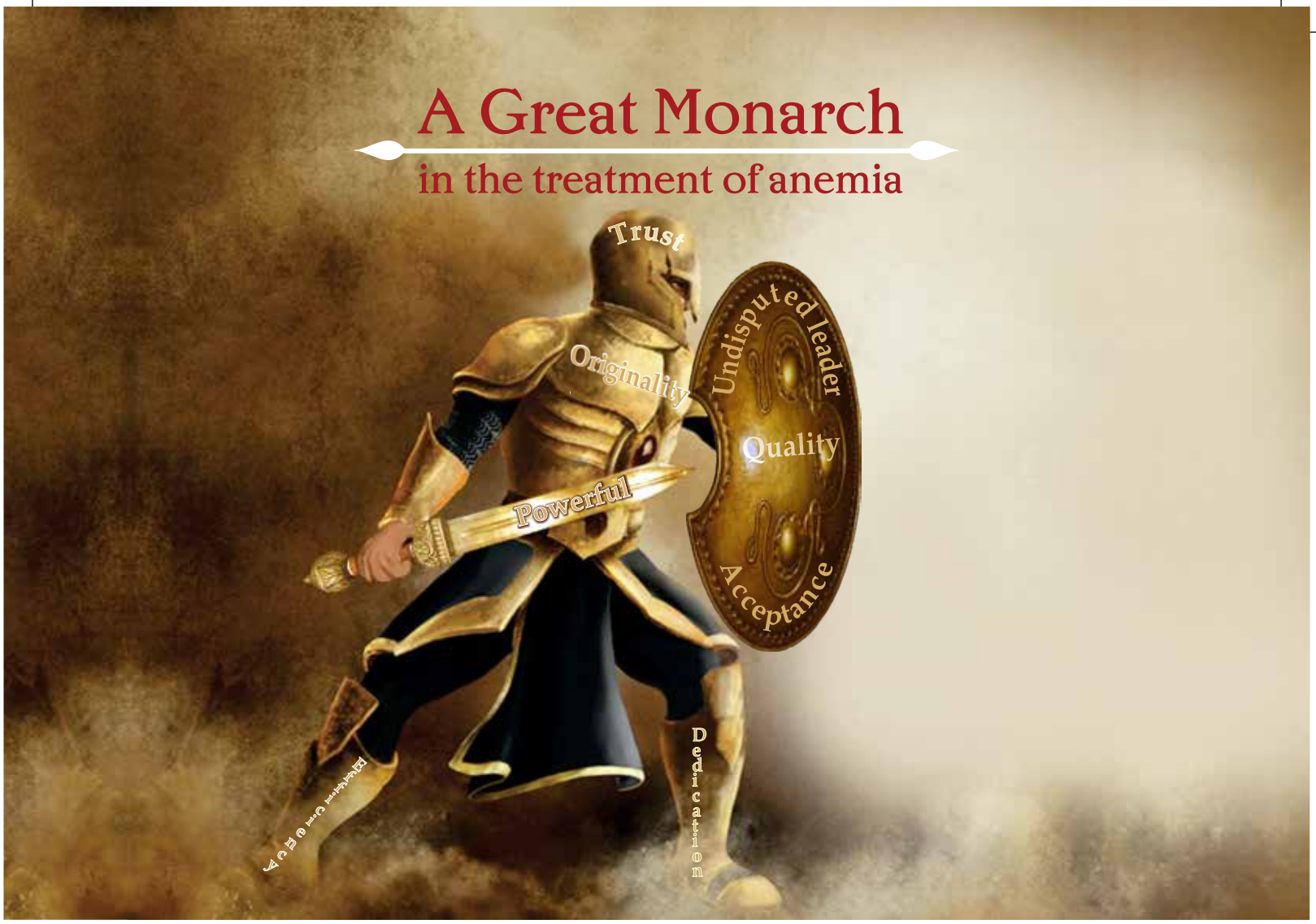

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