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Tomato Flu- an Old wine in New skin!!

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Abstract

This article primarily highlights Tomato flu (TF), a viral epidemic in India and its characteristics. The causative agent is an RNA virus- a novel variant of Coxsackie virus A16. This is a rare, highly contagious, non-life-threatening disease, observed in children below nine years of age. Patients developed influenza like symptoms and extremely painful rash or blisters, all over the body in the shape of tiny tomatoes, hence the name 'Tomato Flu'. TF is a clinical subtype of the Hand, Foot, and Mouth Disease. The first suspected case of the current outbreak was reported from Kollam district, Kerala in May 2022 and later spread to other parts of the state and neighbouring states like Odisha, Tamil Nadu, and Haryana in India with hundred plus cases of tomato flu were reported. An in-depth literature search on the viral replication, epidemiological features and classical symptoms of the illness, disease management and preventive, mitigation strategies were carried out. TF being self-limiting, fatal complications were not observed in the affected children. Currently, there are no specific medications available to treat this infection. Hence, symptomatic and supportive therapy were ensured. Vigilant screening, close surveillance, social and personal sanitary measures, and confinement of confirmed or suspected cases must be adopted to prevent further spread. Raising public awareness and promoting proper hand hygiene among children.

Keywords: Tomato flu, Coxsackie virus A16, Picornaviridae, hand-foot-mouth disease, blisters, myalgia, febrile rash illness.

Introduction

As the global battle against viral triad of COVID-19 variants, Monkeypox and Nipah, continues, a spike of newer threatening viral infections like Tomato flu (TF) or Tomato fever or Tomato influenza seem disturbing. Coxsackievirus A16 (CV-A16) was identified as the primary culprit of the recent viral outbreak of Tomato flu. TF is a non- fatal, communicable infection, febrile rash illness considered as an endemic in India and is generally self-limiting. Based on the clinical presentation, 'Tomato Flu' is currently assumed as viral Hand, Foot, and Mouth Disease (HFMD) with atypical symptomatology and chiefly targets children aged 1–5 years (few cases children aged up to 9 years) and immune-compromised adults [1].

Tomato influenza was initially considered as a sequelae of viral infections like dengue or chikungunya where the classical symptoms of high fever, excruciating joint pains and swelling, body pain, rashes, nausea, vomiting, diarrhoea, dehydration, and extreme fatigue were seen. Small, round, red rashes or blisters (4-6 mm) resembling the vegetable tomato erupt on the skin (hence the name 'tomato flu') that eventually develop an exudative like fluid inside (vesicle) and can enlarge in size. There are currently no specific medications available to treat this infection but is managed using various dosages used for chikungunya and dengue medications [2].

Timeline of Tomato flu epidemic

The first suspected case of the current outbreak was reported from Kollam district, Kerala in May 2022 and later spread to other parts of the state and neighbouring states like Odisha, Tamil Nadu, Haryana in India.

After returning from a family vacation in Kerala, two children in the United Kingdom (UK) who had signs of the Tomato flu were tested and confirmed for enterovirus infection, CV-A16 that caused hand, foot, and mouth disease (HFMD) [3]. It is neither a subtype of influenza nor a recently discovered illness. So far, no cases of "Tomato flu" have been identified in India. It is important to note that less than 100 cases of Tomato flu have been documented since early May 2022 (Fig 1). Apparently, the outbreak seem to be under control [4].

Fig 1: A Timeline of Tomato Flu outbreak across India [5].

Table 1: - Tomato flu vs other viral infections

Characteristic	Tomato Flu/ Hand foot mouth syndrome	Chikungunya	Zika	Varicella/ Chickenpox	Monkey pox	COVID-19	Dengue
Isolation period	5-7 days	2-12 days	3 months – Men, 2 months - Women	5-10 days	3 weeks	2-14 days	2-7 days
Contagious	Less spread	Non transmittable	Communicable	Transmittable	Communicable	More spread	Non contagious
Target of Infection	Children under 10 years.	Any group of age	Any group of age	Any group of age	Any group of age	Any group of age	Any group of age
Treatment options	Drugs used in the treatment of Chikungunya / Dengue	No specific antiviral treatment. supportive care only	Infection is self-limiting, and only supportive treatment is available	Chickenpox vaccine	Brincidofovir (Prodrug of Cidofovir)- FDA approved	Few FDA- approved drugs	No specific antiviral treatment is available. supportive care only
Rash Attributes	Tiny red spots appear progressing to large blisters resembling a tomato on the hands, feet, and buttocks	Diffused erythematous maculopapular rash over trunk and extremities, palms, or soles	Maculopapular dermatitis initiates on the trunk and spreads to the lower extremities.	Erythematous macules on the trunk, face, scalp turns to papules and then to vesicles and pustules.	Monkey pox blisters undergoes various stages before complete healing.	Itchy, tiny red blisters on skin	Flat red spots on the face later moves downward over the body.
Outcome	Non-fatal	Non-fatal	Fatal brain damage in babies and miscarriage or stillbirth in pregnant women.	Non-fatal	Non-fatal	High mortality due to sequelae	Fatal

Table 2: HFMD Emerging strains and their symptoms

1.	CV-A16	Large vesicular rashes
2.	EV-A71	Petechial rashes
3.	CV-A6	Atypical presentations and nail shedding during convalescence

Epidemiology of Tomato flu in South Africa

In 1951, Coxsackievirus A16 was initially isolated in South Africa [6]. Another significant HFMD agent that is frequently used in conjunction with or instead of EV-A71 is CV-A16. Research findings suggest that the co-infection of EV-A71 and CV-A16 exacerbated the severity of the illness [7]. Despite being severe and complex, the condition linked to CV-A16 is typically mild. There have also been reports of HFMD worldwide, including neurological consequences [8–11]. Recently, novel genotypes (D, E, F, and G) were proposed for rare strains, the majority of which were found in central Africa [12], Madagascar [13], and India [14] respectively. Following this, HFMD linked to CVA10 co-transmitted with CVA6 was recorded in Asia, Europe, Africa, and Oceania subsequently

Virology of CV-A16

HEV spread rapidly in the community where children and immunocompromised adults are more susceptible. *Cox Sackie virus* A16 (CV-A16) belonging to genus Human Enterovirus- A (HEV- A) within Picornaviridae family. CV A16 is the causative agent for HFMD. It is single-stranded RNA virus with an icosahedral symmetrical structure, containing about 7400 bases [6]. Similar to other enteroviruses, the genome has three functional regions: structural, non-structural, and non-coding regions (Fig 2). A polyprotein precursor is encoded by the reading frame (structural and non-structural sections) that is translated to structural protein P1 and non-structural proteins P 2 and P3. Virus encoded proteinase processes the P 1 protein to produce the viral capsid subunit proteins VP 0, 1 and 3. VP 0 can also be further broken down to produce VP 2 and 4. VP 1, 2 and 3 are located on outer part of capsid while VP 4 is located internally.

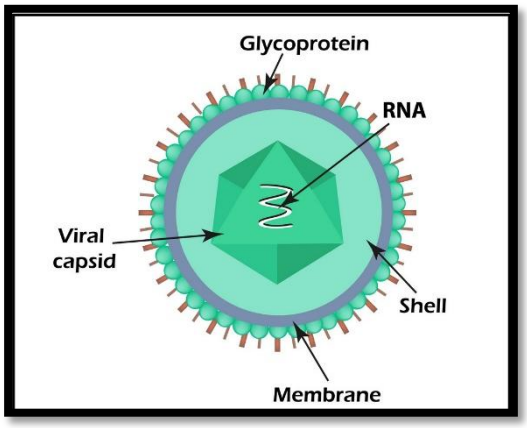

Fig 2: Structure of CV A16

Similar to HFMD, close contact with infected persons, sharing clothes, utensils, their bedding may result in spread of infection [7]. CV-A16 responsible for the current tomato flu epidemic shares genomic sequence with a common ancestor clade from China [8]. The recent tomato flu outbreak signal towards the resurgence of CV-A16 in the subcontinent. Essentially, the molecular knowledge and viral morphology is perquisite for the vaccine development.

Symptoms of Tomato flu:

The disease usually starts with mild fever, poor appetite, malaise, and sore throat for the first 1 or 2 days; following this, tiny red spots appear progressing to large blisters resembling a tomato on the hands, feet, and buttocks [9]. Hand foot and mouth disease (HFMD) associated mouth ulcers (herpangina) may also be seen [2, 10]. TF is self-limiting in most of the cases; rarely it can cause neurological complications like meningitis (0.01%). No deaths due to TF have been reported so far.

Laboratory Diagnosis

Tomato flu diagnosis is based majorly on the clinical symptoms like fever spikes, joint pain, and rash (similar to chikungunya). As part of an outbreak investigation, throat swabs, skin scrapings, stool and CSF samples may be collected in Viral Transport Medium within 48 hours of symptom manifestation [11]. These samples are sent for viral isolation (Gold Standard in HFMD diagnosis), serology (useful for monitoring recovery), or molecular studies to rule out Dengue, Chikungunya, and Zika viruses (Table 1 & 2). Molecular diagnosis with RT-PCR is the preferred mode of laboratory confirmation for TF [12].

Prevention Measures:

As prevention is always better than cure, it is better to maintain proper hygiene and sanitation of surroundings. TF being extremely contagious, isolation should be done for 7-10 days from the onset of any symptom. Parents as well as children must be educated about the modes of transmission. They must be advised not to hug or touch sick individuals with fever or rashes, not to do thumb-sucking or nail-biting and use a handkerchief to cover their mouth while sneezing and not to scratch or rub the blisters. To boost immunity in children, nutritious diet and adequate hydration should be advocated. Supportive measures like using paracetamol for fever, vigorous hydration, warm compress for blisters, regular disinfection of patient belongings, isolation of infected cases and plenty of rest and sleep must be ensured [9].

Primary prevention strategy is mainly by raising public health awareness regarding the disease transmission modes and averting further spread. Early diagnosis, isolation of

suspected and/or confirmed cases and treatment must be considered under secondary prevention (Fig 3).

Treatment of Tomato Flu

TF being self-limiting infectious disease. Alarming symptoms requiring hospitalization are prolonged fever, vomiting, severe weakness, drowsiness, refusal to eat, altered sensorium, convulsions and unstable vitals [13]. No specific vaccination exists to cure it till date. However few are under trial. Though no specific antiviral medication is available for HFMD management, Acyclovir and Oseltamivir have demonstrated efficacy and minimized severity of TF symptoms. Immunoglobulins benefit HFMD treatment by improving clinical signs, symptoms and enhanced recovery as well as decreased mortality.

Fig 3: Tomato Flu in a nut shell

Conclusion

Undoubtedly, CV-A6 and CV-A16 are the root causes for the recent "Tomato flu" endemic in India, with a potential epidemic. Familial and community based health education for risk reduction in young children regarding space sharing during the times of outbreak and adherence to the preventive strategies rolled out the local health authorities must be strictly followed. Appraisal of healthcare providers to promptly identify the various viral rash differentials and be aware of the trending epidemiologic pattern of TF distribution and latest evidence-based treatment guidelines. Drug repurposing and multivalent vaccine development against HFMD related viral outbreaks including CV-A16 may be the most efficacious and

cost effective in TF treatment and mitigation. Continuous monitoring and follow up for serious outcomes and sequelae are needed to understand the disease's evolution and to explore potential treatments of TF.

Early vigilant surveillance, appropriate screening, better diagnostics, stringent personal hand hygiene, and isolation of cases may be the futuristic key steps undertaken by policymakers and health care officials to prevent further outbreaks.

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