

Symptom Resolution in Acyclovir Treated Hand, Foot, and Mouth Disease

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Abstract Background: Hand, Foot, and Mouth Disease (HFMD) is a highly contagious virus primarily affecting young children, but may also impact older children and adults. Initial symptoms typically manifest as fever, malaise, and pharyngitis, followed by eruption of erythematous, papular lesions on the palms and soles. HFMD is typically treated with supportive care, as there is no current gold standard therapy for HFMD. However, based on previous case studies, acyclovir has demonstrated its potential as a viable treatment for HFMD. **Case Presentation:** A 37-year-old female patient presented to the clinic with a two-day history of fever, malaise, pharyngitis, and papulovesicular skin lesions on her hands and feet. A clinical diagnosis of HFMD was made, and the patient was promptly started on oral acyclovir 800 mg, three times daily for seven days. Within two days of acyclovir treatment, the patient's fever subsided, and the skin lesions on the hands and feet were fully resolved. **Conclusion:** Our case report showcases the benefits of acyclovir therapy in treating HFMD. Acyclovir treatment provided our patient symptomatic relief, resulting in defervescence and complete resolution of skin lesions. Symptom duration and severity were lessened significantly within the first couple days of therapy. Acyclovir therapy has shown promising results for potential HFMD treatment, and we encourage additional studies to further evaluate its efficacy.

Keywords: hand, foot, and mouth disease, acyclovir, coxsackievirus, pediatric rash

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1. Introduction

Hand, Foot, and Mouth Disease (HFMD) is a highly contagious virus of the picornoviridae family [1]. The viral infection has an incubation period of 3-6 days accompanied by fever, malaise, and sore throat. The prodromal phase is followed by erythematous, papular or vesicular skin lesions, primarily located on the palms and soles, and painful stomatitis of the mouth. Skin lesions may also be perioral and located on the dorsal and lateral surfaces of the hands and feet [1,2].

The majority of cases of HFMD occur in children, usually younger than seven years old. However, infection is not limited to children, and numerous cases have included older children, adolescents, and adults [3]. Outbreaks regularly involve daycare centers, schools, hospital wards, military installations, as well as larger geographic areas, primarily during the spring and early summer [2,21]. Transmission principally occurs from person to person via fecal-oral route; rarely, transmission may follow vesicular fluid contact, fomites, and oral and respiratory secretions [5].

Complications of the virus may include dehydration, rhombencephalitis, acute flaccid paralysis, aseptic

meningitis, myocarditis, and pancreatitis [6]. Fifteen viral serotypes of HFMD have been noted in medical literature, the most common strains being coxsackievirus A16 and enterovirus 71. The majority of complications is caused by enterovirus 71, with clinical features correlating with viral spread through the reticuloendothelial system and CNS. Other strands of HFMD, including CV-A6 and CV-A10 have also been emerging as important HFMD agents worldwide, with associated outbreaks across Asia, Europe, and in the United States published over the last 15 years. Severe neurologic complications have been observed with CV-A6 and CV-A10, including encephalitis and aseptic meningitis [7].

There are no pharmacologic treatments for HFMD. Current approach is to mitigate viral transmission and prevent complications and death. However, there may be a role in the use of acyclovir as a treatment regimen. Multiple cases have been reported in which acyclovir treatment resulted in symptomatic relief, lesion resolution, and defervescence within days of initial dosing. [7,8,9]

2. Case Presentation

A 37-year-old female patient arrived at clinic with a two-day history of low-grade fever, malaise, and

pharyngitis, accompanied by an aphthous ulcer on the tongue and papulovesicular skin lesions on hands and feet. The patient's son had a fever one week previously. Rapid strep and flu test were negative. She was prescribed oral acyclovir 800 mg, three times daily for seven days and a 'Magic Mouthwash' to be used every four hours for pharyngeal pain.

The patient returned for follow up visit two days after initiating acyclovir therapy. Fever and lesions of hands and feet had fully resolved. Patient was still experiencing mild pharyngeal soreness and aphthous ulcer was present.

3. Discussion

The case presented above is an example of symptomatic reduction in a patient after receiving acyclovir treatment within 2 days after symptom onset. Symptom duration may last as long as 7 to 10 days before full resolution of fever, rash, and oral ulcers [5]. HFMD is infective until complete resolution of skin lesion. Therefore, acyclovir therapy may have shortened symptom presentation, as well as the infectivity of the patient. Currently, treatment is directed toward symptom reduction, prevention, and mitigation of complications.

HFMD may affect entire communities, schools, day care, hospitals, military installations, and entire geographic locations [2]. Outbreaks may infect dozens to tens of thousands of people. A 1998 outbreak in Taiwan affected over 1.5 million, resulting in 400 severe cases [6]. A single outbreak in 2010 in the southern China region resulted in 70,000 infections and nearly 600 deaths [11]. In Sarawak, Malaysia, 10-30% of children infected with the EV-71 serotype developed central nervous system complications, primarily brainstem encephalitis [11]. Europe has also shared outbreaks of similar magnitude involving the EV-71 serotype, which resulted in high case fatality rates [10].

Severe complications of HFMD may include dehydration, brainstem encephalitis, aseptic meningitis, myocarditis, pancreatitis, and onchomadesis. Studies in mice have suggested invasion of the CNS system via retrograde axonal spread along cranial or peripheral nerves [21]. Patients who are immunologically suppressed are particularly at high risk of more severe symptoms [8].

Over 15 serotypes of HFMD exist, with specific strands resulting in greater degrees of severity. Since the early 1990's the EV-71 strand has become the most prevalent cause of HFMD. The EV-71 serotype is also most associated with neurologic complications, particularly encephalitis [7]. Emerging serotypes include CV-A6 and CV-A10, which have been contributing to greater numbers of complications and deaths. A 2012 outbreak in the United States of CV-A6 infected 63 people, resulting in 12 hospitalizations for dehydration and/or severe pain [12].

Four case studies were found on the use of acyclovir as a treatment for HFMD, each with favorable results. The first involved a group of 12 children and 1 adult treated within one to two days of rash onset [12]. Within 24 hours of treatment, all patients had defervescence, lesion involution, and symptomatic relief. In a second study, three children between one and two years old experienced high fevers, widespread vesicular lesions throughout limbs

and trunk, sore throat, and oral erosions [22]. The three patients were described as 'listless' and refused to feed. Patients experienced improvement of their clinical condition within 48-72 hours of starting acyclovir, with reduction in fever, vesicular crusting and resolution, and a return to feeding. The third case was an intra-familial spread of HFMD involving 2, 4, and 37-year-old patients after an outbreak at a daycare center, though which the patients experienced low-grade fevers with papulovesicular eruptions and blisters [4]. Lesions began involution after only a single day of oral acyclovir treatment along with significant reduction in fever and pruritus. Resolution of symptoms were complete after only 3 days of therapy. One further case study involving an immunocompromised adult also had favorable results with the use of acyclovir [8].

Very few clinical compounds have been developed for the treatment of enterovirus infections. There are many molecules which are reported to block enterovirus replication in vitro. However, clinical drug production is hindered by natural barriers to development, including the difficulty of navigating drug development, minimizing adverse drug effects, and investment directed toward lower hanging fruit. In other words, antiviral therapy of diseases of perceived greater urgency with higher allowable harm to benefit ratios, such as hepatitis and HIV, are deemed a priority [13].

Several antiviral candidates for enterovirus have been proposed, including interferons, capsid binders, and proteases. Interferons induce antiviral protein expression, humoral antibody and macrophage proliferation [16]. However, no interferon treatments have demonstrated benefit in established infection [16]. The capsid-function inhibitor pleconaril is the most extensively studied. Pleconaril blocks viral uncoating, thereby inhibiting host cell receptor attachment and viral replication [16]. Pleconaril has been noted to have various efficacy in the reduction of symptoms in multiple randomized control trials for picornavirus infections [14,15]. No trials of pleconaril have taken place for the treatment of HFMD, and it is still unavailable for clinical use. Proteases 2A and 3C have been proposed for halting host cell protein synthesis by cleavage of translated viral polyprotein [17]. Two current drug candidates exist, rupintrivir and SG85, which have demonstrated some inhibitory effects against picornaviridae family [17]. Rupintrivir is in clinical trials and has shown low inhibitory activity towards serotype EV71.

Acyclovir is converted to acyclovir triphosphate via thymidine kinase produced by infected cells. Viral DNA replication is inhibited by action of acyclovir triphosphate strongly binding to viral DNA polymerase [19]. Enteroviruses are RNA viruses, which do not produce the thymidine kinase enzyme, so acyclovir's mechanism of action is not directly influencing the replication of the virus [18]. Acyclovir may indirectly augment the patient's own interferon, leading to antiviral effects demonstrated through symptomatic and severity reduction [5].

Hand, foot, and mouth disease is a highly contagious virus known for significant outbreaks and capable of serious complications. The characteristics of the virus vary unpredictably across geographic location, and practitioners must be prepared to combat its various

effects among different populations. No pharmacological therapies are yet available; nonetheless, acyclovir may prove to be an efficacious tool for the reduction of symptom length and severity when used on patients during early symptom presentation. Based on our case and others presented, acyclovir may prove beneficial for reducing atypical presentation, severe complications, and the contagious nature of HFMD.

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Statement of Competing Interests

The authors have no competing interests.

Compliance with Ethical Standards and Informed Consent

Informed consent was obtained for the publication of this case report.

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