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Coxsackievirus A6 (CV-A6) Encephalomyelitis in an immunocompromised child - A case report and brief review of the literature

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Coxsackievirus A6 (CV-A6) has recently emerged as the predominant circulating enterovirus strain causing Hand Foot and Mouth Disease (HFMD) worldwide. CV-A6 is a single-stranded RNA virus; belonging to the family Picornaviridae and genus Enterovirus(1). Enteroviruses such as EV-A71 and CV-A16 are more often associated with neurological manifestations mainly among children below the age of five years (1). Here we report a fatal case of CV-A6-associated encephalomyelitis in a four-year-old child with acute lymphatic leukemia (ALL).

A four-year-old immunocompromised child from North-Kerala presented to the emergency room, of paediatrics department, Kasturba Medical College, Mangalore in the month of December with high-grade fever (39°C). He was a known case of precursor B-cell acute lymphoblastic leukemia without any known cytogenetics markers, since last two years and was on maintenance therapy (MCP-841 protocol). On admission child was febrile, and there was hepatomegaly. The height and weight were 93cm and 13.5kg respectively and were below the third percentile for age. He was appropriately immunized for age. No skin rashes were observed during examination. After collecting serum, throat swab and CSF samples, the patient was initiated on Ceftriaxone. A written informed consent was taken from the patient’s guardian. Within 48 hours, the child developed altered sensorium and was intubated. Early papilledema was observed on fundus examination. On the third day parenteral Piperacillin and Tazobactam were started along with G-CSF (Granulocyte Colony Stimulating Factor). The condition of the child deteriorated and on the fourth day of
admission, and he developed irreversible brainstem dysfunction. Echocardiogram was normal. Child succumbed to death on the 7th day of hospital admission.

Blood examination revealed leucopenia (2600 cells/µL) on the day of admission which dropped to 1000 cells/µL and 500 cells/µL on 3rd and 4th day respectively. There was a decline in the platelet count from $2.5 \times 10^5$/µL on admission to $10^5$/µL on the third day. The cerebrospinal fluid examination revealed normal glucose (50 mg/dl; normal range 45-85mg/dl), normal protein (35.5mg/dl; normal range 15-45mg/dl) and a cell count of 300 cells/µL (60% lymphocytes). CSF gram staining showed only mononuclear cells and the bacterial culture was negative. The liver and renal function tests were normal, and serum samples were tested negative for dengue and malaria.

Throat swab and CSF samples were subjected to virological workup. The nucleic acid extraction was performed using QIAmp Viral RNA Mini Kit (QIAGEN, GERMANY) according to the manufacturer instructions. TaqMan based multiplex real-time RT-CR was carried out in CSF to detect herpes simplex virus 1 and 2 (HSV-1/2), varicella zoster virus, enterovirus, mumps virus and human parechovirus using the primer/probe mix from FTD Viral meningitis kit (Fast-Track Diagnostics, Luxemburg). The amplification was performed using an ABI 7500 real-time PCR instrument (Applied Biosystems®, USA) and the reaction conditions were set as per the manufacturer’s instructions (Fast-Track Diagnostics, Luxemburg). The CSF was tested positive for pan-enterovirus. For typing of enterovirus, CSF sample was subjected to uniplex PCR specific for EV-A71, CV-A16 and CV-A6. The sample was tested positive for the CV-A6 subtype which was further confirmed by sequencing of CV-A6 partial viral protein 1 (VP1) gene using the Big Dye terminator kit (Applied Biosystems, CA, USA) as per the manufacturer’s instructions in a 3500 XL Genetic Analyzer (Applied Biosystems, CA, USA) (2). The sequence was verified by BLAST (https://blast.ncbi.nlm.nih.gov) and was submitted to GenBank under the accession number MG793067. To the best of our knowledge, this is the first report of CV-A6 associated fatal encephalitis case from India.

The enterovirus types that cause neurological manifestations includes, EV-A71, CVA-16, CV-A6 EV-D68, Echovirus 6,7,9,11,13,30, poliovirus 1,2,3, and coxsackievirus B1-B5(3). In majority of the enterovirus cases, neurological presentations have been associated with skin rashes. However, a small proportion of cases demonstrate neurological complications without any skin or oral lesions (4). In enterovirus endemic areas, the possibility of enterovirus infection has to be
considered among children having only neurological manifestations even in the absence of typical skin lesions.

EV associated encephalitis generally carries better prognosis without any neurological sequelae. Fatal EV infections are often observed in infants, children and in patients with immunosuppression (5). In the present case, pre-existing immunosuppression might have led to atypical clinical presentations and greater disease severity. There is no information regarding the circulating enterovirus strains and the epidemiological pattern of the disease in India.

Majority of children with Coxsackievirus A6 usually present with Hand, Foot and Mouth Disease (HFMD) characterized by fever, exanthematous rashes over extremities and mouth extending to the perioral area, buttocks, trunk, knees, elbows, the dorsal and lateral surface of hands, feet, and perianal area. In addition, atypical skin manifestations like widespread mucocutaneous bullous reactions mimicking drug adverse reactions, vesiculobullous erosive eruptions, severe vasculitis-like rash, rash similar to eczema herpeticum or chickenpox, or rash resembling primary immunobullous disease have been frequently described (6,7). Severe and rare manifestations such as aseptic meningitis, encephalitis, and epididymitis have been reported among children (8,9).

From India, Gopal Krishna et al., during the year 2012 published a small cohort of HFMD cases collected from the southern and eastern parts of the country and more than 90% of the infections were attributed to CV-A16 and CV-A6. There were no reports of neurological or pulmonary manifestations among these cases (10).

This case report highlights the fatal neurological complication of CV-A6 infection in an immunocompromised child. Even though most of the children recover without any sequelae, a high mortality rate is often observed among immunosuppressed individuals. In the context of increasing prevalence of neurological complications as a result of non-polio enterovirus infections, further studies are required to analyse the virulence and pathogenicity of these viruses. Usually, EV-A71 and CV-A16 are the main neurotropic viruses causing encephalitis among children and the current vaccine research is focusing on these subtypes. Multicentric laboratory-based surveillance of enterovirus is essential to recognize the type variation in endemic
areas. Even though most of the children recover without any sequelae, a high mortality rate is often observed among immunosuppressed individuals.

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References


