Clinical presentation, viral kinetics and management of human monkeypox cases from New Delhi, India 2022

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Case Report

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Abstract

We describe the clinico-demographical, virological follow-up and management of five confirmed Monkeypox cases from New Delhi, India without any international travel history. The viral load kinetics and viral clearance was estimated in oropharyngeal swab (OPS), nasopharyngeal swab (NPS), EDTA blood, serum, urine and various lesion specimens at every fourth day of follow-up ranging from 5-24 post onset day (POD) of illness. All the five cases presented with mild to moderate grade intermittent fever, myalgia and lesions on the genitals, groins, lower limb, trunk and upper limb. Four cases had non-tender firm lymphadenopathy. No secondary complications or sexually transmitted infections were recorded in these cases except for HBV in one case. All the cases were mild and had good recovery. The high viral load was detected at POD 14 in lesion fluid, followed by lesion roof at POD 5, lesion base at POD 14, while in urine, OPS and NPS at POD 5. The MPXV DNA was detected from 5 to 24 POD. These Monkeypox cases suggests the under diagnosed monkeypox infection in the community. This emphasizes the need for active surveillance of MPXV in high-risk population such as Men having sex with men (MSM) and female sex workers (FSW).

Introduction

Monkeypox virus (MPXV) is an emerging *Orthopoxvirus* causing infection in humans post smallpox eradication. Since its first identification in human from Democratic Republic of Congo in 1970, numerous sporadic outbreaks have been reported across the globe.[1,2] The increased human-to-human transmission could be due to a “vulnerable” population following the cessation of smallpox vaccination which provides cross protection against MPXV. The disease was endemic to African countries until the first infection reported from United States with importation of infected rodents and exotic animals from Ghana in 2003.[3] Subsequently, travel associated importation of MPXV have been reported in the UK (2018, 2019), Israel (2018), Singapore (2019), and USA (2021).[4] All these outbreaks have linked to travel to the African countries including Nigeria or associated with healthcare or household contacts as observed in the UK.[5] In 2022, multi-country outbreak of Monkeypox was observed affecting 39,434 cases from 94 locations across the globe, affecting all six WHO regions.[6]

The analysis of earlier outbreaks of MPXV (1970-2019) demonstrated significant difference in the case fatality rate between Central African clade (10.6%) and West African clade (3.6%). In 1970 outbreaks, young children were found to be affected unlike the 2010–2019 outbreaks which affected young adults.[7] In contrast to the earlier outbreaks where both genders were almost equally affected the current outbreak seems to have originated from the community transmission of virus with men having sex with men (MSM) and bisexual contacts.[7,8]

The clinical presentation of monkeypox disease closely resembles smallpox disease with an early occurrence of lymphadenopathy in monkeypox. In the earlier outbreaks, it was observed that classical MPXV infection starts with the maculopapular rashes which progresses to vesicles, pustules and then

scabs in the sequential manner after completion of the prodromal febrile phase. The infection persists until the scabs off which usually takes up to 4 weeks. The rashes were primarily affecting the face, arms, trunk and lower limbs. Various other secondary complications involving encephalitis, gastrointestinal, respiratory, and corneal infections have been also observed among the patients.[9] In 2022, Bragazzi *et al*. carried out clinical analysis of Monkeypox cases reported in the ongoing outbreak compared to the previous outbreaks. The study demonstrated unusual and atypical clinical presentations characterized by ano-genital lesions and rashes on the face and extremities with fever, inguinal lymphadenopathy and exanthema were the common signs and symptoms.[5] The rashes observed in the current outbreak, had shown pleomorphic presentations with lower number of lesions which differ from the earlier outbreaks.[2,5] The World Health Organization has recently designated the former Congo Basin (Central African) clade as Clade one (I) and West African clade as Clade two (II) with two sub-clades IIa and IIb.[10] There are two simultaneous MPXV outbreaks occurring worldwide with A.2 and B.1 sub-lineages.[11]

With the emergence of MPXV globally, a threat was looming over India, the second highest populated country, connected with huge number of daily flights across the globe. In last two decades, importations of cases with high-risk pathogens have been seen from other countries to India i.e., Ebola, Crimean Congo hemorrhagic fever and SARS-CoV-2 including its Variants of Concern i.e., Alpha, Beta, and Omicron. On 14 July 2022, India reported its first human monkeypox case from Kerala.[12] Since then ten confirmed case of monkeypox has been identified from Kerala (n=5) and New Delhi (n=5) till 12th August 2022. The cases observed in Kerala had well defined epidemiological linkage with international travel history and contact with suspected cases.[13] Unfortunately, the confirmed monkeypox cases from New Delhi have no travel history to monkeypox endemic or current outbreak areas.

Here, we describe the clinical features, viral kinetics and management of five confirmed monkeypox cases from New Delhi, India.

Methods

The clinical specimens of real-time PCR confirmed MPXV cases (n=5) from New Delhi were collected sequentially every fourth day post isolation and referred to Biosafety level-4 facility of ICMR-National Institute of Virology, Pune, India. The cases were followed up (except case-5) till the lesions were healed and the scabs were fallen off. The specimens including oropharyngeal (OPS) & nasopharyngeal swab (NPS), EDTA blood, serum, urine, lesion samples from multiple sites (lesion fluid, lesion roof, lesion base and lesion crust) were tested to assess the viral kinetics of MPXV using Real time PCR.[13,14] The demographic and clinical information of all the cases was obtained from the hospital. The variables in clinico-demographic data such as age, ethnicity, gender, signs and symptoms, sites of lesions, number of lesions, co-morbidities and other sexual transmitted infections (STIs) of each case were analyzed. Similarly, the hematological and biochemical parameters of the cases were analyzed at the time of admission to understand any change in the vital parameters/abnormalities that could reflect the complications in managing the cases.

Results

Clinical presentations of the monkeypox cases

The confirmed monkeypox cases presented between 5-14 days post onset day (POD) of illness. Of five cases, three were male and two female with mean age of 31.2 years and presented with mild to moderate grade intermittent fever with myalgia. All of them presented to the hospitals with vesicles, pustules with absence of the traditional evolution of the lesions from maculo-papular to crust. The lesions were most commonly observed on the genitals, groins, lower limb, trunk and upper limb and were pruritic (Figure 1). The palms and soles were also involved in Case 2 and 3. The mucocutaneous lesions including oral ulcers were observed in Case 2, 4 and 5. The oral lesions were painful and showed ulceration. The skin lesion severity score for all the cases were moderate (25-99 skin lesions) as per the WHO clinical grading.

The lymphadenopathy was recorded in four out of five cases (Table-1). The sites included bilateral inguinal (n=4), cervical (n=1), submental (n=1), retro-auricular (n=1), submandibular (n=1). The lymph nodes were non-tender and firm. Notably, cases reported dysuria (cases 2 & 4), genital swelling (cases 3 & 4), sore throat (cases 4 & 5), headache (case 1), difficulty in deglutition (cases 4 & 5), and chest pain (case 4). Other symptoms like rectal pain or pain on defecation were not observed in the cases. All the hematological and biochemical findings were in the normal range except for the Cases 1 & 5 which had mild leukocytosis which is the consistent feature seen in Monkeypox infection (Table 1).

Exposure details

Cases 2, 3 & 5 shared the history of heterosexual contact within 21 days of onset of symptoms not under influence of drug or alcohol. The Cases 1 & 4 had denied any sexual contact. All the cases denied a history of same sex contact or bisexual contact. The cases did not report international travel history in last one month from the date of onset of symptoms. The Case-5 had given history of sexual contact with a male partner having similar lesions seven days before onset of symptoms.

All the cases were negative for varicella zoster virus (VZV), human immunodeficiency virus (HIV), hepatitis-C and B viruses, herpes simplex virus (HSV) 1&2, and *Treponema pallidum* (syphilis). Case 2 was also positive for hepatitis B virus. All the cases were not vaccinated against smallpox or monkeypox virus.

Viral kinetics

The cases were confirmed to be positive for Orthopox, Monkeypox and West African clade specific Real-time PCR [Case 1: POD 14; Case 2: POD 7; Case 3: POD 10, Case 4: POD 5, and Case 5: POD 5].

The MPXV DNA was detected in urine (21-35 Ct), lesion specimens (22-38 Ct) of all the cases at first time point [Table-1]. The EDTA blood and serum samples were negative for all cases except Case-4 [33 Ct] at POD 5 suggestive of transient viremia. On the contrary, OPS sample of all cases were positive [27-37 Ct] except Case-1, while NPS of all the cases were positive (27-36 Ct) except Case-5.

The cases were followed every fourth day [Case 1: POD 14-22; Case 2: 7-21; Case 3: 10-24; Case 4: 5-17; Case 5: 5-23] to assess the persistence of the viral DNA in different clinical specimens. In our study, the MPXV DNA was detected from 5th POD until 24th POD.

The distribution of MPXV viral load showed variability in detection at different time points of follow up specimens. The high viral load was detected in lesion fluid (Ct 18 at POD 9), followed by lesion roof (Ct 22 at POD 19), urine (Ct 21 at POD 5), lesion base (Ct 24 at POD 14), lesion crust (Ct 25 at POD 14), OPS and NPS (Ct 27 at POD 5) (Table-1). Viral clearance was observed in all the specimens of Case 1 and Case-5 on 22nd and 23rd POD respectively. While at their recent follow-ups; case 2 (POD 21, lesion crust), case 3 (POD 24, lesion roof), case 4 (POD 17, lesion crust), and cases 5 (POD 19 all lesion samples) showed persistence of viral DNA [Figure-2].

Hospital management and care

All the five cases were isolated in the tertiary care hospital designated for monkeypox cases for reducing the secondary transmission and infection control. The patients were encouraged to wear full sleeves and fully covering clothes to prevent the secondary infections in the lesions. The lesions were covered with the disposal sheet to reduce the exposure of the lesions. Patients were also provided with the surgical masks to reduce the respiratory droplets and fomites. Every eight hourly, vitals were monitored including temperature, blood pressure, pulse rate, respiratory rate, and oxygen saturation. All cases were provided with symptomatic treatment that included antipyretic, anti-allergic, analgesics, broad spectrum antibiotics to prevent secondary infections. The lesions were managed with analgesic ointment, saline compress and soft paraffin gentle massages for pustular, crusted and dry scales respectively.

All the common areas, isolation ward, washrooms were disinfected with the 0.5% freshly prepared hypochlorite solution. Health care workers were designated round the clock duties and used complete personal protective equipment including coveralls, N-95 masks, face shield, double gloves for patient care activities.

Discussion

This report describes the five cases of human monkeypox infection detected from India without any international travel history. The assessment of the viral kinetics on the follow up of cases suggests the presence of the viral DNA from 5-24 POD in the lesion specimens compared to other specimens. The presence of high viral load in the lesion specimens of the cases demonstrates it as the best specimen type for the detection of MPXV DNA. However, OPS, NPS and urine also found to be the other appropriate specimens. Considering the evolvement in the clinical presentation of monkeypox cases [single lesion/other symptoms without lesions/asymptomatic], OPS, NPS and urine samples could be utilized for the MPXV diagnosis. In our study, the Case 1 and Case 5 showed viral clearance on 22nd and 23rd POD respectively. This is in concordance with the already known recovery phase of 4 weeks. Apparently, MPXV viral kinetics follow-up studies are very scarce. A study by Alder et al., demonstrated the longer

persistence of the viral DNA up to 39 days in upper respiratory tract[15] which emphasizes the need for more such studies with large cohort and longer duration.

Apart from absence of lymphadenopathy in Case 1, other clinical features were similar for all the cases. The presence of genital lesions, enlarged inguinal lymph nodes, and sexual contact history suggest a need for in-depth study on the modes of sexual transmission of the MPXV. The cases were infected with West African clade of MPXV and presented with milder infection. All of them were young, immunocompetent with no co-morbidities and had shown good clinical recovery without the administration of any antivirals.

In our study, the cases denied in-depth details of any sexual contact which is primarily due to stigma associated with the disease. This necessitates the counseling of Monkeypox positive cases to alleviate the fear, stigma, anxiety, stress, and depression associated with the infection.

The detection of Monkeypox cases in Delhi without travel history to endemic or affected areas suggest the undetected circulation of MPXV in the community. Such cases could be either asymptomatic or pauci-symptomatic and could be identified with the intensified surveillance involving MSM/FSW/bisexuals community. This could lead to establishment of community transmission also in the vulnerable population such as children, pregnant women and immuno-compromised individuals. In conclusion, an enhanced awareness is required amongst the health care workers specifically working in the STI clinics for understanding the newer presentations of the monkeypox infection. Most of the monkeypox cases show without any complications. This emphasizes the significance of timely differential clinical and laboratory diagnosis and early patient management in healthy recovery of the affected cases.

Declarations

Ethical approval

The study was approved by the Institutional Human Ethics Committee of ICMR-NIV, Pune, India under the project ‘Providing diagnostic support for referred samples of viral hemorrhagic fever and other unknown etiology and outbreak investigation’. Data and clinical images were collected as part of routine care and were anonymized. The written informed consents were given for the use of all clinical images and details of disease progression by all the cases in the study.

Author Contributions

PDY, VR, RRS, AMS contributed to study design, data analysis, interpretation and writing and critical review. VR, RRS, AMS, DYP, KSPS, SM, AC, BLS, MB, SK contributed to data collection, interpretation, writing and critical review. PDY, RRS, DYP, PA, SM, VR contributed to the critical review and finalization of the paper.

Conflicts of Interest

Authors do not have a conflict of interest among themselves.

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Tables

Table-1: Demographic and clinical profile of the confirmed Monkeypox cases from New Delhi, India (n=4)

Variables	Case 1	Case 2	Case 3	Case 4	Case 5
· **Demographic characteristics**					
Age	34	34	35	31	22
Gender	Male	Male	Male	Female	Female
Ethnicity	Indian	Nigerian	Nigerian	Nigerian	Nigerian
Occupation	Data Analyst	Chef	Businessman	Cloth factory worker	Student
International travel history in last 21 days before onset of symptoms	No	No	No	No	No
Sexual contact in last 21 days before onset of symptoms	Denied	Yes (Heterosexual)	Yes (Heterosexual)	Denied	Yes (Heterosexual)
Small pox/Monkeypox vaccination received	No	No	No	No	No
· **Clinical presentation**					
onset day of illness	14	07	10	05	05
of confirmation	June 23, 2022	August 1, 2022	August 3, 2022	August 5, 2022	August 12, 2022
sical symptoms					
Lesion type on presentation	Vesicle, Pustule	Vesicle, Pustule, Crust	Vesicle, Pustule, Crust	Papule, Vesicle	Vesicle, Pustule
No of lesions	20-50	51-100	51-100	20-50	20-50
No of sites	09	10	08	07	07
Sites of typical lesions	Genitalia, bilateral palm, bilateral upper limb, scalp, trunk, and bilateral lower limb	Groin, legs, arms, trunk, back, face, scalp, palm, and sole	Groin, genitals, leg, arm, trunk, face, scalp, palm, and soles	Bilateral arms, trunk, genitalia, face, and scalp	Genitals, perianal, upper limb, trunk, face, lower limb
Mucocutaneous manifestations	None	Two lesions (0.5x0.5cm) with erythematous margin on oral cavity	None	Two Lesions under the mucosa of lower lip	One lesion over right oral commissure
Fever	Yes	Yes	Yes	Yes (associated with chills and rigors)	Yes
Headache	Yes	No	No	No	No
Fatigue/lethargy	No	No	No	No	No
Myalgia	Yes	Yes	Yes	Yes	Yes
Arthralgia	No	No	No	No	No
Back pain	No	No	No	No	No
adenopathy [firm and der]					
Axillary	No	No	No	No	No

Cervical	No	No	No	No	Yes (Bilateral; 2X2 cm)
Inguinal	No	Yes (Right;2x2cm)	Yes (Bilateral; 2x2cm)	Yes (Bilateral; 1.5x2cm)	Yes (Bilateral; 1.5x2cm)
Submental	No	Yes (Bilateral;1x1cm)	No	No	No
Retro-auricular	No	Yes (Bilateral;1x1cm)	No	No	No
Sub-mandibular	No	No	Yes (Bilateral;1x1cm)	No	No
her symptoms					
Chest Pain	No	No	No	**Yes**	No
Rectal pain or pain on defecation	No	No	No	No	No
Sore throat	No	No	No	**Yes**	**Yes**
Penile swelling	No	No	No	N.A	N.A
Scrotal swelling	No	No	**Yes**	N.A	N.A
Vaginal swelling	N.A	N.A	N.A	**Yes**	No
Dysuria	No	**Yes**	No	**Yes**	No
Difficulty in deglutition	No	No	No	**Yes**	**Yes**
E. Co-morbidities	No	No	No	No	No
· **Other Sexually transmitted Infections**					
HIV antibodies	Negative	Negative	Negative	Negative	Negative
Hepatitis B virus surface antigen	Negative	**Positive**	Negative	Negative	Negative
HCV RNA	Negative	Negative	Negative	Negative	Negative
Syphilis	Negative	Negative	Negative	Negative	Negative
HSV-1 and 2 DNA	Negative	Negative	Negative	Negative	Negative
VZV DNA	Negative	Negative	Negative	Negative	Negative
· **Laboratory diagnosis on clinical specimens (Ct values)**					
OPS	POD 14 (Negative), POD 18 (Negative), POD 22 (Negative)	POD 7 (37.27), POD 11 (Negative), POD 17 (Negative) POD 21 (Negative)	POD 10 (31.71), POD 15 (Negative), POD 20 (Negative) POD 24 (Negative)	POD 5 (27.37), POD 9 (38.72), POD 13 (Negative) POD 17 (Negative)	POD 5 (31.85), POD 9 (31.81), POD 13 (Negative) POD 19 (Negative) POD 23 (Negative)
NPS	POD 14 (34.78), POD 18 (Negative), POD 22 (Negative)	POD 7 (35.74), POD 11 (33.90), POD 17 (Negative) POD 21 (Negative)	POD 10 (31.71), POD 15 (31.47), POD 20 (36.24) POD 24 (Negative)	POD 5 (27.37), POD 9 (37.71), POD 13 (37.03) POD 17 (Negative)	POD 5 (Negative), POD 9 (32.92), POD 13 (35.28) POD 19 (Negative) POD 23 (Negative)
EDTA blood	POD 14 (Negative), POD 18 (Negative),	POD 7 (Negative),	POD 10 (Negative),	POD 5 (33.19),	POD 5 (Negative),

	POD 22 (Negative)	POD 11 (Negative), POD 17 (Negative) POD 21 (Negative)	POD 15 (Negative), POD 20 (Negative) POD 24 (Negative)	POD 9 (Negative), POD 13 (Negative) POD 17 (Negative)	POD 9 (Negative), POD 13 (Negative) POD 19 (Negative) POD 23 (Negative)
Serum	POD 14 (Negative), POD 18 (Negative), POD 22 (Negative)	POD 7 (Negative), POD 11 (Negative), POD 17 (Negative) POD 21 (Negative)	POD 10 (Negative), POD 15 (Negative), POD 20 (Negative) POD 24 (Negative)	POD 5 (Negative), POD 9 (Negative), POD 13 (Negative) POD 17 (Negative)	POD 5 (Negative), POD 9 (Negative), POD 13 (Negative) POD 19 (Negative) POD 23 (Negative)
Urine	POD 14 (Not tested), POD 18 (Negative), POD 22 (Negative)	POD 7 (29.74), POD 11 (32.93), POD 17 (35.71) POD 21 (Negative)	POD 10 (34.52), POD 15 (33.11), POD 20 (Negative) POD 24 (Negative)	POD 5 (21.6), POD 9 (27.35), POD 13 (Not done) POD 17 (Negative)	POD 5 (30.23), POD 9 (Negative), POD 13 (Negative) POD 19 (Negative) POD 23 (Negative)
Lesion base	POD 14 (34.87), POD 18 (Negative), POD 22 (Negative)	POD 7 (26.26), POD 11 (not collected), POD 17 (35.12) POD 21 (Negative)	POD 10 (26.63), POD 15 (30.49), POD 20 (32.70) POD 24 (Negative)	POD 5 (24.76), POD 9 (30.72), POD 13 (36.88) POD 17 (Negative)	POD 5 (29.5), POD 9 (26), POD 13 (29.17) POD 19 (36.62) POD 23 (Negative)
Lesion fluid	POD 14 (22.06), POD 18 (Negative), POD 22 (Negative)	POD 7 (27.28), POD 11 (not collected), POD 17 (32.47) POD 21 (Negative)	POD 10 (30.02), POD 15 (28.03), POD 20 (24.71) POD 24 (Negative)	POD 5 (38), POD 9 (20.98), POD 13 (36.12) POD 17 (Negative)	POD 5 (Negative), POD 9 (17.74), POD 13 (25.58) POD 19 (36.62) POD 23 (Negative)
Lesion roof	POD 14 (25.56), POD 18 (33.03), POD 22 (Not collected)	POD 7 (26.99), POD 11 (26.9), POD 17 (27.73) POD 21 (31.3)	POD 10 (not collected), POD 15 (27.36), POD 20 (31.08) POD 24 (35.3)	POD 5 (26.9), POD 9 (29.77), POD 13 (30.52) POD 17 (Negative)	POD 5 (33.58), POD 9 (22), POD 13 (31.82) POD 19 (Negative) POD 23 (not collected)
Lesion crust	POD 14 (25.44), POD 18 (26.42), POD 22 (Negative)	POD 7 (not collected), POD 11 (26.28), POD 17 (28.81)	POD 10 (27.75), POD 15 (29.18), POD 20 (29.93)	POD 5 (26.77), POD 9 (27.25),	POD 5 (30.68), POD 9 (23.54), POD 13 (32.98) POD 19 (32.97)

		POD 21 (28.1)	POD 24 (Negative)	POD 13 (not collected) POD 17 (37.14)	POD 23 (Negative)
· **Haematological and Biochemical findings (normal range)**					
Haemoglobin (11.6-15.5 g/dl)	15.4	14.4	15.6	11.3	12.3
TLC (4000-10000/µL)	11,700	8,900	7,500	7,300	12,100
Differential count [Neutrophils/Lymphocytes /Monocytes/Eosinophils]	50/37/21/5	89/61/21/13	48/33/10/6	65/19/29/15	55/38/6/1
Platelet (150000-450000/ µL)	3.87 lakhs	2.57 lakhs	1.34 lakhs	1.6 lakhs	2.2 lakhs
Haematocrit (35.5-48.6 %)	44.1	41.6	45.6	34.5	35
Serum urea (17-49 mg/dl)	25	30	19	15	22
Serum creatinine (0.6 to 1.2 mg/dl)	0.85	0.76	0.5	0.8	0.65
Serum sodium (136-146 mmol/L)	142	140	136	133	136
Serum potassium (3.5-4.5 mEq/L)	4.6	5.7	5.3	5.2	4.3
AST(24-40 U/L)	31	32	32	34	25
ALT (44-80 U/L)	30	31	38	31	22
ALP (50-130 U/L]	82	88	92	102	90
Total bilirubin (0.1-1.2 mg/dl)	0.57	0.6	0.5	0.3	0.4
Direct bilirubin (upto 0.5 mg/dl)	0.30	0.2	0.28	0.16	0.16
RBS (<200 m/dl)	143	100	102	98	110
ne	Recovered without complications	Recovered without complications	Recovered without complications	Recovered without complications	Recovered without complications

TLC- Total Leucocytes count, AST- Aspartate aminotransferase, ALT- Alanine aminotransferase, ALP- Alkaline phosphatase, RBS- Random Blood Sugar, HIV-Human Immunodeficiency Virus
HBV- Hepatitis B virus, HCV- Hepatitis C Virus, HSV- Herpes Simplex Virus, VZV- Varicella Zoster Virus, OPS- Oropharyngeal swab, NPS- Nasopharyngeal swab, Ct- Cyclic Threshold (cut off- 40), NA- Not applicable, RNA-Ribose Nucleic Acid, DNA- Deoxy Ribose Nucleic Acid

Figures

Figure 1

The images depicting the lesions of the confirmed monkeypox cases at the time of hospitalization

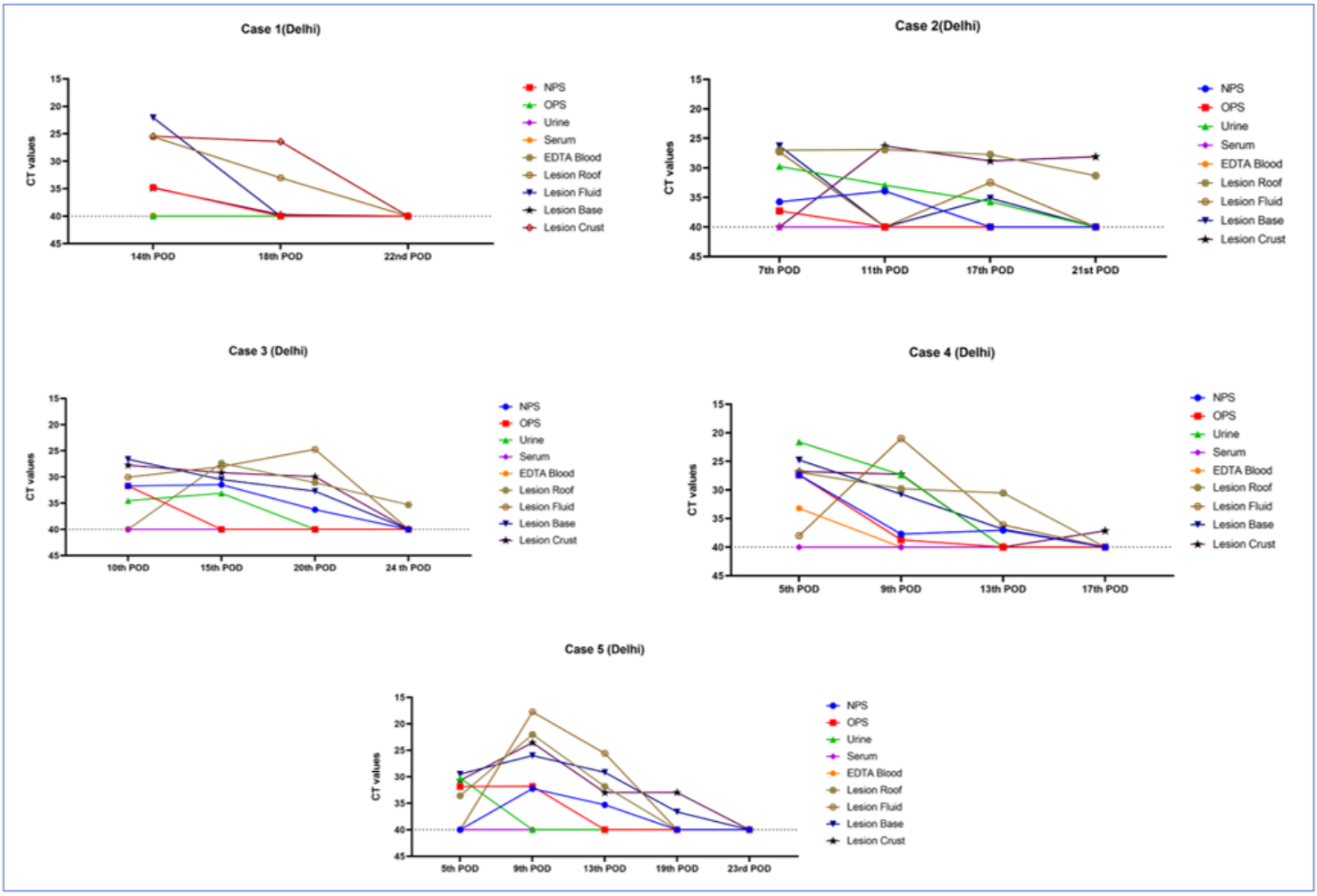

Figure 2

The viral kinetics of five MPXV cases at different time intervals