

Cutaneous Manifestations of Chikungunya Fever: Observations from an Outbreak at a Tertiary Care Hospital in Southeast Rajasthan, India

Abstract

Background: Chikungunya fever is caused by chikungunya virus which is transmitted by the bite of infected *Aedes aegypti* and *A. albopictus* mosquitoes. **Aims:** To study the various mucocutaneous manifestations in suspected cases of chikungunya fever. **Materials and Methods:** The patients who attended our outpatient department from July 2016 to October 2016 and fulfilled the criteria for “suspect cases” of chikungunya infection stipulated by the National Institute of Communicable Diseases, Directorate General of Health Services, Government of India, were included in the study prospectively. A total of 112 patients (62 males and 50 females) with mucocutaneous manifestations of chikungunya fever were enrolled in the study. **Results:** Mucocutaneous manifestations were found more in males than females. Serological immunoglobulin M enzyme-linked immunosorbent assay (IgM ELISA) test for chikungunya virus was positive in 62 (55.3%) patients. Generalized erythematous maculopapular rash (53.5%) was the most common finding. Genital pustular rash with aphthae (4.4%), oral and intertriginous aphthae, red lunula, subungual hemorrhage, localized erythema of the ear pinnae, erythema, swelling, and eczematous changes over the preexisting scars and striae (scar phenomenon) were the other interesting findings. Various pattern of pigmentation (37.5%) were observed including striking nose pigmentation in a large number of patients, by looking at which even a retrospective diagnosis of chikungunya fever could be made. There was flare-up of existing dermatoses like psoriasis and dermatophytic infection. **Conclusions:** Wide varieties of the mucocutaneous manifestations were observed in our study, but the striking nose pigmentation was present irrespective of age and this peculiar pigmentation may be considered as a specific clinical marker of chikungunya fever. Chikungunya fever must be suspected in any patient with painful oro-genital and intertriginous aphthous-like lesions associated with febrile polyarthralgia with rash.

Keywords: “Chik sign,” chikungunya, genital ulcer, melanophages

Introduction

Chikungunya virus is a mosquito-transmitted alphavirus that belongs to the Togaviridae family.^[1] It causes chikungunya fever, a febrile illness associated with severe arthralgia, myalgia, and skin rash. Chikungunya is a Makonde word (Bantu language) meaning “the one which bends up” referring to the stooped posture of the affected patient acquired due to severe pain in the joints.^[2] The arthropods remain infected throughout their life. Its transmission to humans is mainly through *Aedes* species mosquitoes.^[3] An Indian study reported transmission of chikungunya virus by *Anopheles stephensi* too.^[4] The Indian Ocean outbreak is caused by transmission by *Aedes* only.^[1] The incubation period of chikungunya fever ranges from 3 days to 7 days.

Following inoculation with chikungunya virus through a mosquito bite, the virus directly enters the subcutaneous capillaries, with some viruses infecting susceptible cells in the skin, such as macrophages or fibroblasts and endothelial cells. Local viral replication seems to be minor and limited in time, with the locally produced virus probably being transported to secondary lymphoid organs close to the site of inoculation. Chikungunya virus spreads rapidly in the body after initial infection. Virus dissemination occurs through the blood and pathological events develop.^[5,6]

The pathological events associated with tissue infection are mostly subclinical in the liver (hepatocyte apoptosis) and lymphoid organs (adenopathy), whereas in the muscles and joints are associated with very excruciating pain. Symptoms

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of chikungunya virus infection include high grade fever, rigors, headache, and a maculopapular or petechial rash. “Silent” infections do occur but are rare, being observed in around 15% of infected individuals.^[7]

Materials and Methods

The patients who attended our institute outpatient department from July 2016 to October 2016 were prospectively included in the study if they fulfilled the criteria for “suspect cases” of chikungunya infection stipulated by the National Institute of Communicable Diseases, Directorate General of Health Services, Government of India.

“Suspect cases” have been defined as patients presenting with an acute illness characterized by the sudden onset of fever, with several symptoms such as joint pain, headache, backache, photophobia, and eruption during an epidemic of chikungunya fever and in the absence of confirmatory serological tests.^[8] A total of 112 patients (62 men and 50 women) who satisfied the above criteria were enrolled for the study. Due to paucity of resources, immunoglobulin M enzyme-linked immunosorbent assay (IgM ELISA) specific for chikungunya virus was done only in 76 cases. Skin biopsy was done from selected patients. Routine investigations were done in all cases while rheumatoid factor was done in relevant patients.

Results

Out of the 112 patients, 62 (55.35%) were males and 50 (44.64%) were females. The youngest patient was a 1 month old neonate and the oldest was a 77-year-old man. Maximum patients (66; 58.92%) were in the 20–40-year age group, with the mean age being 30.18 years.

Cutaneous lesions are shown in Table 1. Patients presented with either a single lesion or a combination of lesions. The most common skin lesion was a maculopapular rash [Figure 1a] in 60 (53.5%) patients. Rash was distributed predominantly over trunk, face, and extremities and associated with severe pruritus. Most of the skin lesions developed during the acute phase of the disease, 2–3 days after the onset of fever in 90 (80.3%) patients



Figure 1: (a) Maculopapular rash (b) Bullous lesion (c and d) Milian's ear sign (e) Scar phenomenon

while along with fever observed in 22 (19.7%) cases. Vesicles and bullae were seen in two patients of which one was a female child [Figure 1b]. Localized erythema and swelling of the pinnae mimicking the Milian's ear sign of erysipelas [Figures 1c and d] was an interesting observation in 5 (4.4%) patients. Similarly, erythema and edema of preexisting post-traumatic scars and striae resembling the “scar phenomenon” of sarcoidosis [Figure 1e] were seen in four (3.6%) patients. Skin lesions subsided without any sequelae in the majority, except pigmentation in 42 (37.5%) patients, desquamation in 10 (8.9%) cases and xerosis. Various types of pigmentation were observed [Table 2], the most common site being the nose followed by face, trunk, neck, and palms [Figure 2a-c]. Purpuric lesions were seen in four patients. Multiple painful aphthous-like lesions were seen in 18 (20.2%) patients over various sites [Figure 3a-d].

Oral mucosal involvement was found in 18 (16.07%) patients in the form of multiple aphthae, erosions, and cheilitis. Angular cheilitis were also seen in 4 (3.6%) patients. Mucosal lesions subsided completely without any sequelae except hard palate pigmentation in few patients.

The peculiar nail findings noted in our study were red lunule, black lunulae, periungual ulcers, subungual hemorrhages, periungual exfoliation, and diffuse and longitudinal melanonychia [Figure 4a-c]. Serum IgM ELISA specific for chikungunya virus was done in 76 (67.8%) cases. It was positive in 62 (55.3%) cases while negative in 14 (13%) cases. Decreased white blood

Table 1: Cutaneous manifestations of chikungunya

Skin lesions	Number of patients	Percentage
Maculopapular rash	60	53.5
Vesicles and bullae	2	1.7
Genital aphthae	5	4.4
Oral/lip aphthae	11	9.8
Axillary pustules and ulcers	2	1.7
Desquamation	2	1.7
Urticaria/angioedema	4	3.5
Hemorrhagic/Purpuric	4	3.5
Palmar rash	2	1.7
Acquired ichthyosis	3	2.6
Flare-up of tinea	1	0.8
Seborrheic dermatitis-like rash	1	0.8
Flare-up of psoriasis	2	1.7

Table 2: Sites of pigmentation in chikungunya

Site	Number of patients
Nose	30
Face	6
Trunk	2
Flexures/cubital fossa	2
Palmar creases	2
Mucosa (palate)	2



Figure 2: Various types of pigmentation, (a) Facial pigmentation and hand edema (bilateral) (b) Facial and palmar pigmentation (c) Nose and lip pigmentation in a neonate



Figure 3: Various aphthae, (a) Oral aphthae (b and c) Aphthae at male and female genitalia (d) Aphthae at axilla



Figure 4: (a) Red lunula with purpura. (b) Subungual hemorrhages. (c) Black lunula

cell count was observed in 6 (5.3%) cases. No other hematological abnormality was noted.

Discussion

Chikungunya fever is a re-emerging viral infection clinically characterized by an acute febrile illness associated with polyarthralgia, sore throat, conjunctivitis, and skin eruptions. It is usually self-limiting.^[9] Although actual reasons are not clear, but globalization of trades and increased international travel, the abundance of potential vectors like the *Aedes* mosquitoes, poor vector control, absence of herd immunity, and viral mutation may be reasons for the re-emergence of chikungunya fever in the Indian subcontinent.^[10] Chikungunya fever may be seen in all age groups and both sexes. In our study, males outnumbered females similar to other studies,^[11,12] while both sexes were equally affected in another study.^[13]

The most common cutaneous lesion described in chikungunya fever is erythematous maculopapular rash affecting the trunk, limbs, and face^[10] Erythematous maculopapular rash was the most common presentation in our study which developed abruptly after the first 2–3 days of fever and subsided within 5–7 days. Skin manifestations have been reported in 77% of patients during the first week by Hochedez *et al.*^[14] which spared the face and involved mainly the trunk and limbs with islands of normal skin. Morbilliform rash involving the upper extremity was the most common type in another study.^[13] Majority of our patients had generalized lesions, except in 10% who had localized erythema of the face, nose, palms and soles, upper extremities, and ear lobules. Transient nasal erythema has been reported in another study.^[12] Recurrent crops of lesions can occur as a result of intermittent viremia.^[10] These exanthems were associated with edema of hands and feet similar to the observation by others.^[14] Pruritus has been reported in 80.8% of patients,^[15] whereas it was present in 87 (77.6%) of our patients. Pruritus was intractable, not completely controlled by oral antihistamines. The initial manifestation in any viral exanthem is attributed to viremia and dissemination of virus into the skin resulting in a direct cytopathic effect leading to epidermal, dermal, or dermal capillary endothelial injury. It may be due to a combination of direct cytopathic effect and immunological factors.^[16]

Hemorrhagic manifestations have been reported to be 11% in chikungunya fever, but the severity is much less. In a series by Inamdar *et al.*, multiple ecchymotic patches and subungual hemorrhages were noted in six children and three adults.^[12] Purpura was noted in four of our patients which is similar to the study by Kannan *et al.*^[15], but one 77-year-old patient developed purpura fulminans. The purpuric lesions may be due to thrombocytopenia induced by the virus or viral replication in the capillary endothelium causing a direct vascular damage or by a type 3 immune reaction.^[17] No abnormalities of bleeding time or clotting time were observed in our patients.

Multiple painful aphthae-like lesions affecting oral cavity, intertriginous areas, axillae, and scrotum have been documented in various studies.^[9,10,12,13,15,18] Aphthae-like erosions, ulcers, and cheilitis were observed in 18 (20.2%) of our cases. Tender, discrete, and oval aphthae-like ulcers of 0.5–1.5 cm size, with irregular margins on the scrotum and adjacent thighs (kissing ulcers), inner aspect of prepuce, shaft of penis, glans, and labia were observed in six patients, whereas it was the predominant finding in other studies.^[12,19] Bacterial culture from the ulcer did not grow any organism. Tzanck smear was negative for giant and acantholytic cells. These oral aphthae subsided within 3–5 days while scrotal and intertriginous lesions took 7–10 days for complete healing without scarring.

Various patterns of pigmentary changes have been described in chikungunya fever. Similar to other studies,^[20,21] nose was the most common site affected in our study. Nose pigmentation was also present in a 1 month old neonate. Pigmentation was macular, and a few of them had pinpoint (confetti-like) macules. Other patterns of pigmentation were melasma-like over the face, lichen planus pigmentosus-like over neck and flexures, periorbital hypermelanosis, irregular and flagellate patterns on the trunk, and an Addisonian type of palmar pigmentation. Mechanism of pigmentation could be postinflammatory.^[10] An increased intraepidermal melanin dispersion/retention triggered by the virus had been postulated as a cause for pigmentation.^[12] Histopathology was done in selected patients. The hyperpigmented lesions showed increased basal pigmentation, pigmentary incontinence, and melanophages [Figure 5a] while in psoriatic erythroderma, melanophages and dermal

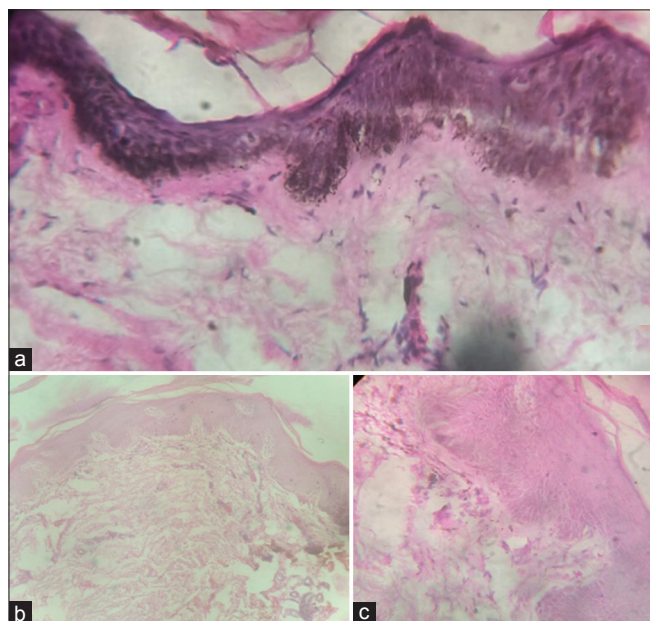


Figure 5: (a) Increased basal pigmentation with melanophages in pigmented macule (H and E \times 10) (b and c) Melanophages in upper dermis with chikungunya (H and E \times 10, \times 40)

edema without increased basal pigmentation was revealed [Figure 5b-c].

Nail changes may be secondary to inflammation of the nail matrix, reduced adrenocortical activity secondary to infection.^[19] In further studies, serum cortisol level in chikungunya fever patients associated with nail and cutaneous pigmentation could be evaluated.

Exacerbation of existing dermatoses has been well documented in chikungunya fever.^[12] One psoriatic patient who was free of the disease developed erythroderma while another patient had guttate exacerbation. In the erythroderma patient, characteristically flexures were spared. Stasis eczema was aggravated following chikungunya fever in three patients. However, there are differences in mucocutaneous manifestations in chikungunya fever in various Indian studies which is shown in Table 3.^[5,11-13,22]

One patient noticed the suspected site of mosquito bite. On dermatologic examination it was an inflamed papule with central puncta over left ankle area. It increased in size as fever subsided and rash appeared then gradually decreased in size and healed with slight hyperpigmentation in 7–10 days [Figure 6a-c]. It could be compared with the eschar of tick bite in typhus fever. It was an interesting new finding which should be evaluated in further studies.

Serology was positive for IgM antibody in 62 (55.3%) of cases while negative in 14 (13%) cases, probably because the blood samples were sent too early. In humans, chikungunya virus produces disease about 48 h after mosquito bite followed by high viremia in the first 2 days of illness.^[10] Viremia declines by 3–5 days followed by the appearance of hemagglutination inhibition (HI) and neutralizing antibodies (NAs). Protection and recovery from chikungunya fever in humans are thought to be mainly mediated by NA response directed at the envelope glycoprotein. Positivity of IgM chikungunya fever antibodies has been reported in 40.13% of patients.^[13]

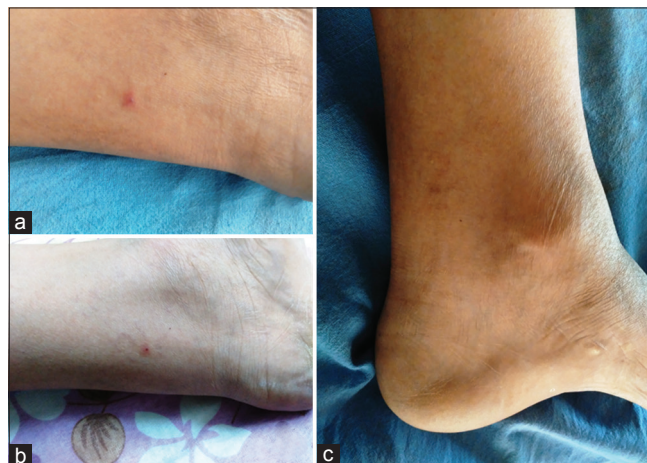


Figure 6: (a-c) Evolution of papules at the mosquito bite site

Table 3: Comparison of studies done in India on cutaneous manifestations of chikungunya fever

Variable	Our study (n=112)	Inamadar <i>et al.</i> ^[12] (n=145)	Prashant <i>et al.</i> ^[5] (n=115)	Bandyopadhyay <i>et al.</i> ^[13] (n=26)	Riyaz <i>et al.</i> ^[11] (n=162)	Seetharam <i>et al.</i> ^[22] (n=52)
Year/place	2016, Kota, Rajasthan	2006, Bijapur, Karnataka	2006, Hyderabad	2007, Kolkata	2009, Calicut, Kerala	2009-10, Guntur, Andhra Pradesh
M:F ratio	1.2:1	1.8:1	1.3:1	1:1	1:1.5	1:1.1
Hyperpigmentation	44 a) Nose 30 b) Face 6 c) Trunk 2 d) Mucosal 2	61 a) Centrofacial 44 b) Diffuse 13 c) Flagellate 2 d) Mucosal 1	17 a) Centrofacial 12 b) Face, trunk 5	3	62 a) Nose 52 b) Trunk 9 c) Face 6	27 a) Diffuse 18 b) Macular 9
Maculopapular rash	60	48	41	21 (m.c. morbilliform)	55 (m.c. erythematous macules) 32	14
Onset of rash						
a) With fever	22	106	Majority cases	6	23	Mostly 2-3 days after onset of fever
b) After fever	90	39	Few cases	20	120	
Vesicles and bullae	2	4	ND	ND	21	16
Symptom (Itch)	87 (77.6%) intractable in most cases	Mild/moderate itch, stinging sensation (few cases)	asymptomatic in 80%	Mostly asymptomatic, 19% intense itching	70%	ND
Apthous-like ulcer						
a) Genital	5	28	27	ND	2	ND
b) Oral/lip	11	1	7	4	22	ND
c) Axillary	2	2	ND	ND	ND	ND
Desquamation	2	1	ND	7	7	ND
Exacerbation of existing dermatosis	Psoriasis (2) Scar phenomenon (4) Stasis eczema (3)	Psoriasis (2) Type 1 lepra reaction (1) Melasma accentuation (1) Acne lesion darken (1)	Psoriasis (6) Lichen planus (4)	ND	Psoriasis (14) Scar phenomenon (4) LP, stasis eczema, Hansen's disease with type 1 reaction and pemphigus vulgaris	Psoriasis (4) Lichen planus (2) Guttate psoriasis de novo (2)
Other/Rare type lesions	Urticarial/angioedema 4 Hemorrhagic/Purpuric 4	Vasculitic (2) Hemorrhagic/Purpuric (6)	EM- like (2) EN-like (3) Urticarial/angioedema (2)	Hemorrhagic/Purpuric (1) Urticarial/angioedema (2)	Vasculitic (2) EM- like (1) TEN-like (7) Hemorrhagic/Purpuric (6) Urticarial/angioedema (6)	Hemorrhagic/Purpuric (4)
Systemic features	100%, lesser degree in pediatric cases, ARF (1) with PF	100%, lesser degree in children ARF (2), Meningo encephalitis (1),	100%	100%, Myalgia (46%), Fatigue (73%)	Seizures (1.6%) and loose stools (0.8%)	100%, seizures (3) Meningo encephalitis (1)
Histopathology	basal pigmentation, pigmentary incontinence and melanophages	Intact basal layer, diffuse epidermal hypermelanosis, sparse perivascular infiltrate, intraepidermal bullae	ND	ND	Both intra and subepidermal cleavage, periadnexal infiltrate, melanophages,	Intraepidermal bullae

Contd...

Table 3: Contd...

Variable	Our study (n=112)	Inamadar <i>et al.</i> ^[12] (n=145)	Prashant <i>et al.</i> ^[15] (n=115)	Bandyopadhyay <i>et al.</i> ^[13] (n=26)	Riyaz <i>et al.</i> ^[11] (n=162)	Seetharam <i>et al.</i> ^[22] (n=52)
Hematological abnormality	Leucopenia (6)	Within normal limit	ND	Leucopenia (2), Thrombocytopenia (1)	Monocytosis (13 infants)	Lymphopenia (5)
Chik IgM ab (+)	62 (55.3%)	100%	100%	40.13%	97%	100%

EM-like: Erythema multiforme-like, EN-like: Erythema nodosum-like, TEN-like: Toxic epidermal necrolysis-like, ARF: Acute renal failure, PF: Purpura fulminans, ND: Not described

Serum IgM antibody may be detectable from 5 days after onset of symptoms and persist for 2–6 months. Virus isolation is possible during the period of viremia (2–10 days) by inoculation of serum on vero or mosquito cells and identification by immunofluorescence. Reverse transcription polymerase chain reaction (RT-PCR) using nested primer pairs is used to amplify several chikungunya virus specific genes from whole blood, generating millions of copies of genes in order to identify them. By RT-PCR, diagnostic results can be available in 1–2 days.

The first reported outbreak of chikungunya in India was from Calcutta in 1963 and in South India in 1964.^[23] Chikungunya fever has an interesting epidemiological trend. Several patterns in the epidemic of chikungunya fever are evident. First, human movement has been crucial for the international spread of chikungunya virus. Second, the incidence of chikungunya is following seasonal patterns. In the South-East Asia Region, chikungunya virus is maintained in the human population by a human-mosquito-human transmission cycle. Chikungunya fever epidemics display cyclical and seasonal trends. There is an interepidemic period of 4–8 years (sometimes as long as 20 years). Outbreaks are most likely to occur in post-monsoon period because the vector density is very high at that time and accentuates the transmission. Human beings serve as the chikungunya virus reservoir during epidemic period while during interepidemic periods, a number of vertebrates have been implicated as reservoirs in African region. These include monkeys, rodents, and birds. However, the reservoir status in South-East Asia region has not been documented yet. Third, in areas with little preexisting immunity, transmission is intense.^[24,25]

Conclusions

To conclude, wide varieties of the mucocutaneous presentations were observed in our study. These includes nose pigmentation, erythema, and edema of preexisting scars and striae resembling “scar phenomenon of sarcoidosis,” erythema and swelling of the pinnae mimicking the Milian’s ear sign of erysipelas, various nail changes, and aphthous-like oro-genital lesions. Out of these, we are unable to find out this striking nose pigmentation in any other viral exanthem. Nose pigmentation was present irrespective of age, even in 1 month old neonate. Hence, we support Riyaz *et al.* for the peculiar pigmentation to be

considered as specific clinical marker of chikungunya fever and the name “chik sign” for this. Although, there is no vaccine against chikungunya virus, vector control measures and use of insect repellents, mosquito nets, full-sleeved clothes may help in minimizing the transmission.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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