Original Article

Gross and Histopathological Dermal Changes at Sites of Snakebite – Report from Autopsy Series

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Abstract

Background: Snake bite remains a significant cause of accidental death, its occurrence usually underestimated because of under reporting. ***Objective:*** To report on gross and microscopic changes at sites of snakebite in autopsy. ***Methods:*** A cross-sectional, descriptive study was conducted on thirty cadavers of snake bite for study duration of one year based on inclusion and exclusion criteria. Skin was collected from sites of bite. Gross examination was carried out on formalin fixed specimens. Microscopic examination was performed on dermal biopsy of formalin fixed paraffin embedded sections stained with haematoxylene and eosin (H&E). ***Results:*** 53.4% of deceased were in the age group of 41-50 years. Males were predominant in the study (90%) where 63.3% were agriculture workers. Lower limb bite was commonly seen (83.3%) in outdoor locales (90%). Snakes identified were cobra and viper. Death occurred within 48 hours of admission in 80% cases. Bite mark was visualised in ten cases and ulceration in three. Microscopic examination revealed normal epidermis in 53.3% cases. Abnormalities seen included acantholysis in 36.7% and ulceration in 10%cases. Dermal changes were coagulative necrosis (26.7%), fibrinoid necrosis (16.7%), haemorrhagic necrosis (20%), oedema (13.3%). Combination of changes in a particular case also observed. Vascular changes comprised of extravasation (30%), fibrinoid necrosis with microvascular damage (23.4%), vasculitis (13.3%), microvascular damage (26.7%). Perineural fibrosis, subcutaneous gangrenous and haemorrhagic fat necrosis were other observations. ***Conclusion:*** This study highlights histological profile of dermal changes by snake venom at site of bite that can enlighten its pathophysiologic effects on cutaneous tissue.

Keywords: Snakebite, venom, epidermis, dermis, necrosis.

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Introduction

Snake bites are reported as common cause of morbidity and mortality in tropical countries. Globally, snakebite causes at least 18,41,000 envenomation and 94,000 death[1,2]. The mortality due to venomous snakebite in India is estimated between 35,000-50,000 per annum, which is highest in the world. The mortality due to venomous snakebite in India continue to be high due to various social, economic and cultural reasons[3]. A significant gap exists between actual death due to snake bite and official data. Accurate statistics of snake bite incidence, its morbidity and mortality does not exist throughout the world, but it is likely to be much higher than actually documented. This is mainly because even today much of the victims approach traditional healers for treatment and majority of bites occur in remote, inaccessible rural areas where they remain undocumented. India recorded about 1.2 million snake bite deaths in the past two decades[3].

West Bengal is one of the states in India reporting high snake bite incidences besides Tamil Nadu, Maharashtra, Uttar Pradesh and Kerala[4]. Over the years there is an increasing trend in the incidence of both cases and deaths in West Bengal[4]. Among the

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venomous terrestrial snakes, four species of snakes are responsible for deaths, including Russell's viper, Cobra, Common krait and merrem's hump-nosed viper[5]. They are well known to produce swelling, bleeding at local bite site and systemic effects involving coagulation and nervous system[6]. Common krait produces neurotoxic symptoms while Cobra causes neurotoxicity with severe local necrosis. Merrem's hump nosed viper produce severe local swelling with rare progression to renal failure. Haemorrhagic blisters and cellulitis in snakebite wound lesions can cause serious complications[7,8].

The clinical manifestations of snakebite are varying which depend on many factors, including the species of snake, amount and strength of venom injected, location of bite , patient's age, presence of any underlying disease[9]. Among patients bitten by *N. atra*, 65.6% progress to skin necrosis and 42.1% develop necrotizing soft tissue infections[9,10]. Skin necrosis can prevail in patients receiving antivenom therapy. Debridement surgery is usually suggested in such cases three to five days post snake bite. Snake venom produce a variety of pathophysiological effects including local tissue damage and/or systemic effects in the affected individual[11].

Histopathological examination is needed to confirm the mode of death when any morbid gross changes in organs and tissues could be the cause of instability of vital signs of the patient. Limited studies were anticipated while reviewing literature on histopathological changes of skin at sites of snakebite. The aim of current study is to report on gross and histopathological changes of skin at site of snake bite in autopsy specimen. In addition, to compare the differences, if any that might be affected by age or type of venom.

Methods

The study was carried out on autopsy cases where death was due to snake bite on whom medico legal autopsies were performed in one year period. The sampling was conducted using purposive sampling technique based on inclusion and exclusion criteria. The inclusion criteria for the current study were collecting dermal tissue specimens from sites of snakebite in cadavers. Exclusion criteria were pre-existing skin lesions at site of bite, decomposed body and in unknown causes of bite. The skin at sites of snakebite was examined grossly and visualised for bite mark, change in colour, any pigmentation, ulceration, blister, haemorrhage or necrosis. All skin wedge biopsy specimens taken from bite sites in deceased victims were collected from Department of Forensic Medicine and preserved in 10% formaldehyde. After overnight fixation and routine processing of tissue fragment, three to five-micron thick sections made from paraffin embedded blocks and eventually stained with haematoxylene and eosin stain (H&E)[12]. Data for study was documented based on history elicited from relatives, available clinical records and other details received along with the specimens, dermal gross and microscopic findings. Any laboratory investigative procedures available in police inquest was also collected and compiled data tabulated in grand chart in Microsoft word Excel sheet.

The study tools included were consent form, case record form in predesigned proforma, standard autopsy instrument set, usual pathological grossing instruments (scalpel, scalpel blades, forceps, knives, glass vials), 10% formal saline, various grades of alcohol, xylene, paraffin, incubator, Leica Microtome, binocular light microscope, digital camera for photography.

Results

Out of thirty snake bite cases, maximum number were found in the age group of 41- 50 years (n=16, 53.4%) followed by 31- 40 years of age group (n=12, 40.0%). One case each was found in the age group of 20-30 years & 51-60 years respectively. Males were predominant compared to females in the study population. Males were twenty-seven (90%) in number and females were three (10.0%) with a male to female ratio of 9:1. Hindu subjects comprised of twenty- six (86.7%) cases and four (13.3%) cases were Muslim. Based on occupation, nineteen cases (63.3%) were agriculture workers; six were labourer (20.0%); three were housewives (10%) and two cases were fishermen in the study. Most of the cases of snakebite took place in outdoor locations (n = 27, 90%) compared to indoor locations (n = 3, 10%). Site of snakebite was found in lower limb in twenty-five cases (83.3%) and five cases showed bite in the upper limb (16.7%). The time of bite was predominantly during daytime when people were at work in outdoor locales (80%). Bite of cobra and viper snakes found in twelve cases (40%) each, but type of snake could not be identified in six cases (20%). Maximum number of cases died within 48 hours of admission (80%). Death happened within a period of 72 hours in

(6.7%) cases, (13.3%) expired 72 hours post admission, of which a single case died after 15 days. Different gross changes of skin noted, and normal appearance was found in sixteen (53.4%) cases. Normal appearing skin with presence of bite mark was found in ten (33.3%) cases, normal skin with blackish discoloration of underlying tissue was found in only one case (3.3%) and ulceration in skin found in three (10%) cases respectively.

On histopathological evaluation, sixteen cases (53.3%) did not show any epidermal changes. Acantholysis was found in eleven cases (36.7%) and ulceration in three (10%). (Table 1A & 1B). Dermal changes comprised of coagulative necrosis, fibrinoid necrosis, haemorrhagic necrosis, fibrinoid necrosis in the vessel walls, haemorrhagic necrosis with dermal oedema and haemorrhage with coagulative necrosis. Often, it was observed that the changes occurred in combination (Table 1A, 1B, & 2). One case showed profuse haemorrhagic necrosis (3.3%) and no significant dermal change observed in one case (3.3%). (Table 2 and Figures 1,2,3). Vascular changes comprised of extravasation, fibrinoid necrosis in the vessel wall with profuse microvascular damage, microvascular damage only, small vessel vasculitis, thick-walled blood vessel and without any significant vascular change (Table 3 and Figure 4). Other histopathological changes of skin comprised of perineural fibrosis in eight cases, three cases showed suboptimal gangrenous changes in subcutis, two showed haemorrhagic fat necrosis in subcutaneous tissue, and one showed perineural fibrosis with mild oedema in the surrounding zone of infarct. Fifteen (50%) cases had no other changes of skin. The histopathological features were non-specific in relation to time between bite and death of victim. Coagulative necrosis was found in seven cases in cobra bite while haemorrhagic necrosis found in seven cases of viper bite. (Table 1A & B)

Table 1(A): Gross and microscopy of dermal change with snake type and time of death

Patient gender,age	Snake type	Time b/w bite &death	Gross	Microscopy(Epidermal, dermal & vascular Change)
1.M/35yrs	Viper	6hrs	Normal skin , bite mark(+)	Acantholysis,hemorrhagic necrosis, dermal edema, thick walled blood vessel
2.M/38yrs	Viper	11 hrs	Normal skin	Acantholysis,hemorrhagic necrosis, dermal edema, extravasation,fat necrosis
3.M/42yrs	Unknown	48 hrs	Normal skin, bite mark(+)	Acantholysis, hemorrhagic necrosis,extravasation.
4.M/36yrs	Cobra	32 hrs	Normal skin	Perineural fibrosis, mild edema in surrounding zone of infarct
5.M/41yrs	Viper	2hrs	Normal skin with blackish discolouration of underlying tissue	Acantholysis, profuse hemorrhagic necrosis, small vessel vasculitis
6.M/42yrs	Cobra	3hrs	Normal skin	Coagulative necrosis,microvascular damage.
7.M/36yrs	Viper	4dys	Normal skin, bite mark(+)	Fibrinoid necrosis,profuse microvascular damage, gangrenous change in subcutis, perineural fibrosis
8.F/38yrs	Viper	7hrs	Ulceration	Ulceration, hemorrhage & coagulative necrosis,small vessel vasculitis
9.M/42yrs	Cobra	10hrs	Normal skin	Fibrinoid necrosis in vessel wall with profuse microvascular damage
10.M/41yrs	Cobra	9hrs	Normal skin	Fibrinoid necrosis in vessel wall with profuse microvascular damage

Patient gender,age	Snake type	Time b/w bite &death	Gross	Microscopy(Epidermal, dermal & vascular Change)
11.F/28yrs	Viper	2hrs	Ulceration	Ulceration,hemorrhagic and coagulative necrosis, small vessel vasculitis, gangrenous change in subcutis
12.M/55yrs	Viper	72 hrs	Normal skin	Acantholysis,hemorrhagic necrosis, dermal edema, extravasation
13.M/42yrs	Viper	27hrs	Normal skin	Acantholysis,hemorrhagic necrosis,dermal edema, extravasation, fat necrosis in subcutis
14.M/41yrs	Viper	10dys	Normal skin, bite mark(+)	Fibrinoid necrosis in vessel wall with profuse microvascular damage, gangrenous change in subcutis,perineural fibrosis
15.M/36yrs	Unknown	12dys	Ulceration	Ulceration, hemorrhagic and coagulative necrosis, small vessel vasculitis, gangrenous change in subcutis, perineural fibrosis

Table 1(B): Gross and microscopy of dermal change with snake type and time of death

Patient gender, age	Snake type	Time b/w bite &death	Gross	Microscopy (Epidermal, dermal & vascular change)
16.M/47yrs	Cobra	42hrs	Normal skin	Coagulative necrosis,microvascular damage, perineural fibrosis
17.M/43yrs	Cobra	3hrs	Normal skin	Coagulative necrosis,microvascular damage.
18.M/46yrs	Cobra	9hrs	Normal skin	Coagulative necrosis,microvascular damage.
19.M/47yrs	Cobra	10hrs	Normal skin	Fibrinoid necrosis in vessel wall with profuse microvascular damage
20.M/48yrs	Viper	3hrs	Normal skin, bite mark(+)	Fibrinoid necrosis in vessel wall with profuse microvascular damage
21.F/36yrs	Unknown	14hrs	Normal skin, bite mark(+)	Acantholysis, hemorrhagic necrosis, extravasation
22.M/31yrs	Cobra	2hrs	Normal skin	Coagulative necrosis, microvascular damage.
23.M/36yrs	Cobra	2dys	Normal skin	Fibrinoid necrosis in vessel wall,profuse microvascular damage, perineural fibrosis
24.M/38yrs	Viper	12hrs	Normal skin, bite mark(+)	Acantholysis,hemorrhagic necrosis, extravasation
25.M/34yrs	Cobra	10hrs	Normal skin	Coagulative necrosis,microvascular damage
26.M/37yrs	Viper	15dys	Normal skin, bite mark(+)	Acantholysis,hemorrhagic necrosis, extravasation, perineural fibrosis
27.M/42yrs	Unknown	32hrs	Normal skin, bite mark(+)	Acantholysis,hemorrhagic necrosis, extravasation
28.M/46yrs	Unknown	4hrs	Normal skin, bite mark(+)	Acantholysis,hemorrhagic necrosis, extravasation
29.M/47yrs	Cobra	2dys	Normal skin	Coagulative necrosis, microvascular damage,perineural fibrosis
30.M/44yrs	Unknown	1day	Normal skin	Coagulative necrosis, microvascular damage,perineural fibrosis

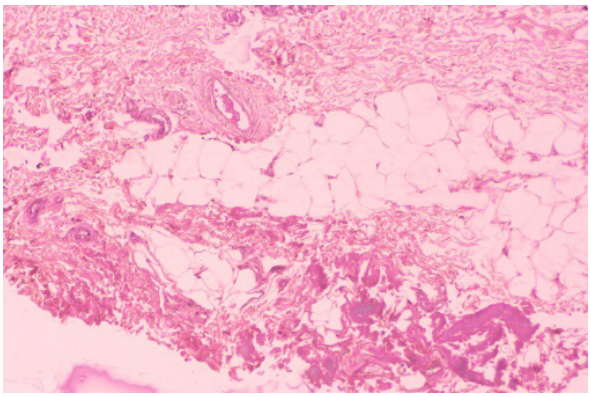

Figure 1: H&E stained section of skin showing thick wall blood vessels, haemorrhagic fat necrosis (×10)

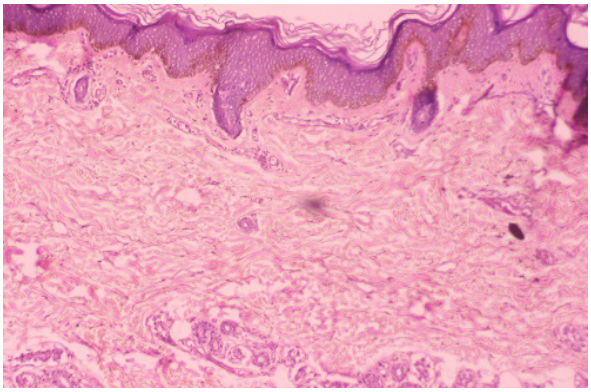

Figure 2: H&E stained section of skin showing dermal oedema (×4)

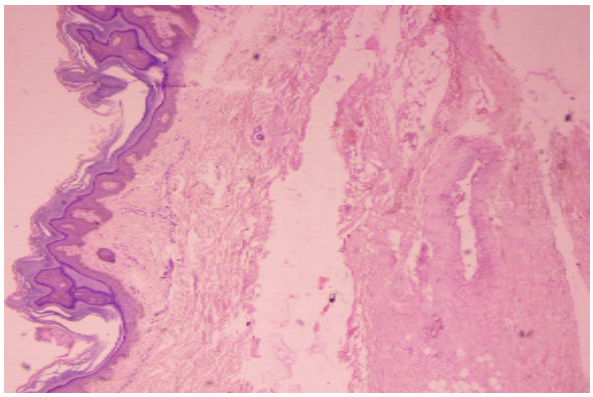

Figure 3: H&E stained section of skin showing dermal oedema, extravasated red blood cell (×4)

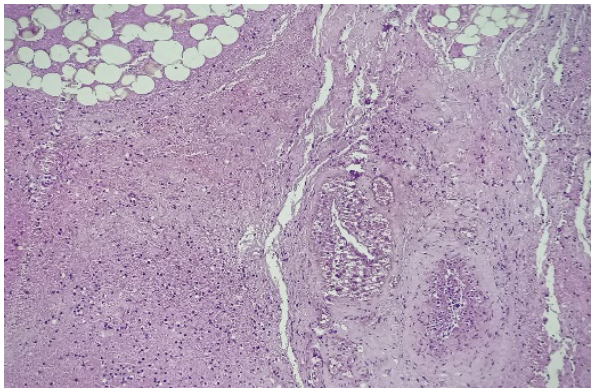

Figure 4: H&E stained section of skin showing microvascular damage and fibrinoid necrosis (×10)

Table 2: Histopathological dermal changes

Dermal change	Frequency	Percentage
Coagulative necrosis	08	26.7
Fibrinoid necrosis	05	16.7
Fibrinoid necrosis in vessel wall	02	6.7
Hemorrhagic necrosis	06	20.0
Hemorrhagic necrosis with dermal edema	04	13.3
Hemorrhagic and coagulative necrosis	03	10
Profuse hemorrhagic necrosis	01	3.3
None	01	3.3
Total	30	100

Table 3: Histopathological vascular changes

Vascular changes	Frequency	Percentage
Extravasation	09	30.0
Fibrinoid necrosis in vessel wall with profuse microvascular damage	07	23.4
Microvascular damage	08	26.7
Small vessel vasculitis	04	13.3
Thick walled blood vessel	01	3.3
Nil	01	3.3
Total	30	100

Discussion

World Health Organization aims to eradicate bite injury due to snake which is a public health problem in tropical areas of the world. Agriculture is the mainstream of employment which accounts for 8,660 mortalities in a year[13]. Histopathological results can be helpful in establishing the cause of death in those snake bite cases where other circumstantial shreds of evidence are lacking[13,14]. Venomous snakes may cause death following

envenomation either by neurotoxin or hematotoxin. In India, snakebites are unnatural deaths that need to be examined at autopsy (medico-legal) according to statutory rules[15].

On the Indian subcontinent, almost all snakebite deaths have traditionally been attributed to the Big Four, consisting of the Russell's viper, Indian cobra, saw-scaled viper, and the common krait. Among 2700 known species of snakes, about 20% are considered to be venomous. Venomous snakes primarily belong to the following families: Viperidae (vipers), Elapidae, Atracta spidae, and Colubridae[16]. Overall, the Colubridae are considered the largest venomous family comprising of nearly 60% of all snakes[17].

The Atractaspidae family, recently classified within the Viperidae, is known for burrowing into the ground and possessing ability to expose their fangs without opening their mouth[18]. The snakes most commonly associated with human mortality in India are cobra (Naja naja), krait (Bungaru scaeruleus), Russell's viper (Vipera russelli) and saw scaled viper (Echis carinatus)[19]. The poisonous snakes are conveniently categorised into haemotoxic (Vipers) and neurotoxic (Cobra and Kraits). Snake venoms are complex mixtures of proteins and peptides, consisting of both enzymatic and nonenzymatic compounds, making up over 90% of dry weight of the venom[20,21].

Ganneru et al. observed peak number of snake-bite cases in the age group of 21-50 years (71%) in their study whereas the age group mostly affected in the present study was in 41-50 years (53.4%)[22]. Deviation from present study was found in Yogesh et al. where majority of snake bite cases were found in age group of 20-39 years (54%) in their study[23]. Males were predominantly higher than female population in the present study with a male to female ratio of 9:1. A previous study by Sharma et al., showed the ratio of 4.25:1, and in a study by Banerjee who conducted a study along similar lines found greater number of males compared to females[24,25].

The present study found agriculture workers as most of the victims (n=19, 63.3%). In a similar study was conducted in Nepal, as Sharma et al. found 74% of the 143 victims were farmers[26]. The present study found 27cases in outdoor (90.0%) location compared to indoor location in three (10.0%). Shetty et al. found a similar distribution, with 25 of the cases involving poisonous snakebites and most of the victims were hard at work in the fields (72.5%)[27]. In the present study, affected area occurred was predominantly in lower limb (n = 25, 83.3%) compared to five cases in upper limb (16.7%).

Sharma et al. and Rao et al. found 27 (45%) of the 60 cases involving lower limbs in their study[26,28]. Results from the present study were consistent with those found in study by Singh et al.[29]. The majority of snakebites (75%) were found in the lower limbs in study by Shetty et al.[27]. The present study shows involvement of Cobra and Viper type of snake responsible for death of victim (n=12, 40.0%).

Wankhede et al. described the bite marks as two puncture wounds in nineteen cases, single puncture wound in three cases, often associated with scratch or laceration deviating the fangs. Additional wounds apart from puncture have been also described. In two cases, there were three fang marks[30]. Metcalfe et al. reported dermal necrosis with two possible reparative scenarios following inflammatory reaction[31]. In some cases, a regenerative process ensues, with re-epithelization and revascularization of the damaged skin associated with lack of fibrotic scar formation. Alternatively, dermal necrosis might be followed by a deficient regenerative process and by formation of a permanent fibrotic scar associated with loss of function[31]. The predominant outcome depends on the balance between profibrotic and pro-regenerative inflammatory cytokines and growth factors which may vary with the anatomical site of skin damage[32].

Rucavado et al. reported case of dermal necrosis due to BaP1, adequate reepithelization occurred in a study of skin damage in the lower limb, with complete restoration of epidermis and dermis with lack of scar formation[32]. Chakrabarti et al. studied endogenous tissue proteinases involved in the pathogenesis of skin damage in other toxic models, such as after administration of the alkylating agent sulphur mustard and in dermal necrosis induced by sphingomyelinase from the venom of spider Loxosceles sp., where matrix metalloproteinase (MMP)-9 plays a role in skin damage[33]. Intradermal injection of certain snake venoms can induce dermal necrosis [33]. The histological features of dermal necrosis following injection of venom of the spitting cobra, Naja nigricollis (family Elapidae) was demonstrated[33]. Chen et al.

demonstrated small focal necrosis, inflammatory infiltrate, and oedema in myocardium due to pit viper toxicity[34]. Benvenuti et al. reported coagulative necrosis, thrombosis and hemorrhage in subcutaneous tissue in a case which happened to be due to the proteolytic, coagulant, and haemorrhagic effects of the venom of Bothrops jararacussu snake[35]. The sample size was small and time period was also less which was major limitation in the current study. Larger sample size with longer time period would have been helpful.

Conclusion

Snake envenomation leads to damage not only kidney, heart, and other endocrine glands but also skin. Cutaneous changes involve epidermis, dermis, vessels and even subcutaneous tissue. A spectrum of histological changes observed at sites of snakebite that can enlighten the pathophysiologic effects of snake venom on cutaneous tissue.

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Author's Contribution: All authors were equally involved in conception, study design, data collection, statistical analysis, writing, editing and final approval of the manuscript.

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