INFLAMMATION AND FEVER AFTER BOTHROPS SNAKEBITE: A BRIEF CLINICAL-EPIDEMIOLOGICAL REVIEW THROUGH CASE REPORT AND INFRARED THERMOGRAPHY FOLLOW-UP

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Resumo: — A Termografia Infravermelha (IRT) é um método capaz de delinear visualmente a extensão de um processo inflamatório. Relatamos o caso de um jovem picado por serpente do gênero Bothrops que experimento febre ao longo de 4 semanas de internação (37,8 ºC ±0,67, IC 95%) com rastreamento laboratorial para infecções negativos. Considerou-se crer que os fenômenos pró-inflamatórios locais e sistêmicos foram a fonte de um fenômeno inflamatório atípico desencadeador da febre persistente. **DISCUSSÃO:** a ação do veneno das serpentes do gênero Bothrops é caracterizada por diversos fenômenos, especialmente proteolíticos e pró-inflamatórios que parecem promover um quadro inflamatório persistente em sua fase aguda associado ou não com febre persistente. O esclarecimento desta condição, assim, se mostra essencial na decisão de se introduzir antibióticos profiláticos ou terapêuticos perante sua elevada morbidade. **CONCLUSÃO:** A IRT parece ser um recurso útil para avaliar a extensão de processos inflamatórios e seguimento clínico em casos de ofidismo, elucidando visual e indiretamente a extensão da lesão inflamatória por meio da intensidade/topografia da radiação infravermelha. A febre pode não representar um processo infeccioso, mas inflamatório ou imunomediado, sendo um importante diferencial etiológico considerando que, não raramente, antibioticoterapia de largo espectro é precocemente introduzida nesses casos.

Palavras-chave: febre; *Bothrops*; inflamação; termografia; antibiótico

Abstract: Infrared Thermography (IRT) is a method capable of visually delineating the extent of an inflammatory process. We report the case of a young man who was bitten by a Bothrops snake who experienced fever during 4 weeks of hospitalization (37.8 ºC ± 0.67, 95% CI) with laboratory screening for infections negative. It was considered that local and systemic proinflammatory phenomena were the source of an atypical inflammatory phenomenon triggering persistent fever. **DISCUSSION:** The venom action of Bothrops snakes is characterized by several phenomena, especially proteolytic and proinflammatory that seem to promote a persistent inflammatory picture in its acute phase associated or not with persistent fever. The clarification of this condition is thus essential in the decision to introduce prophylactic or therapeutic antibiotics in view of their high morbidity. **CONCLUSION:** IRT seems to be a useful health resort for assessing the extent of inflammatory processes and clinical follow-up in cases of ophidism, visually and indirectly elucidating the extent of the inflammatory lesion through the intensity / topography of infrared radiation. Fever may not represent an infectious but inflammatory or immunomediated process, being an important etiological differential considering that, not infrequently, broad spectrum antibiotic therapy is introduced early in these cases

Keywords: fever; *Bothrops*; inflammation; thermography; antibiotic

INTRODUÇÃO

In 2017, the Brazilian Ministry of Health reported 105 deaths caused by venomous snakes among about 27000 reports[1]. From 2000 to 2017 there were about 1900 deaths with such characteristics, despite the extensive public health network enabled for the treatment with antivenom serotherapy[2]. Of the total number of notifications, about 85% of accidents are caused by *Bothrops* snakes, with the delay in specialised care being one of the main factors for death[3] and high morbidity due to the action of its venom[4]. With extensive proteolytic activity (caused by the presence of metalloproteinases and serine proteinases)[5], procoagulant (determined by the action of the thrombin-like venom fraction and other substances capable of activating prothrombin and factor X)[3], paradoxically haemorrhagic (attributed to haemorrhaging factors and metalloproteinase fractions)[3,6] and proinflammatory (resulting from activation of cellular immune response in tissue degradation)[7], *Bothrops* venom generates local disturbances (pain, oedema, bruises, blisters , local necrosis, gangrene, and compartmental syndrome)[8,9] and systemic, such as gingivorrhagia, epistaxis, haematuria, acute renal failure, haematemesis, hypotension, and even shock[4,10].

A condition present in the bothropic accidents and the reason for this report is the occurrence of possible persistent fever during the recovery of the patient[11]. Not rarely, in the clinical context, fever is presumably associated with secondary infections either due to the inoculation of bacterias thru the snakebite or due to the bacterial colonisation existing in the patient's skin. However, in this context, it is necessary to consider that the macrophages activated after the inoculation of the venom and consequent biological action release a broad spectrum of mediators that play an important role in the generation of fever, especially cytokines such as IL-1, IL-6 and TNFa[7,12,13].

Infrared thermography (IRT) is a method that quantifies the infrared radiation of the surface of a body expressing it in terms of temperature and creates a digital image based on a colour scale called thermogram. This colour scale represents the surface temperatures of the skin[14]. The IRT has been used to study diseases in which the skin temperature may reflect the presence of inflammation in the underlying tissues, or those in which the blood flow is increased or decreased due to a clinical or neurological abnormality[15].

It is widely known that venom of venomous animals are capable of inducing localized reactions involving inflammation and pain[16]. One of the challenges clinicians face when treating snakebite victims is the lack of adequate clinical tools for accurate evaluation of local and distant effects caused by different venoms. The IRT has great potential for use as a clinical tool, because it is a non-invasive, non-ionizing method that does not have any biological side effects, does not require sedation or anaesthesia and can be repeated as desired for the clinical follow-up[14,15,17]. The physiological basis for the use of IRT in medicine lies in the fact that the distribution of the skin temperature depends on complex relationships that determine heat exchange processes between the local vasculature, the metabolic activity, the cutaneous tissue, the internal tissues and sympathetic and parasympathetic regulation in the maintenance of homeostasis[17,18] and the external environment. The skin, in this case, is the place of heat exchange between internal metabolic equalization and externally available heat, and vascular and behavioural processes can assist in this exchange and, thus, be observed by a methodology that measures the intensity

of radiation. Therefore, the skin becomes a visual summary of the heat transfers of part of the body or its observed totality. In general, the thermal asymmetry between the opposite sides of the body of up to 1 ºC in comparison to the regions of interest (ROI) has been considered indicative of dysfunction[17,18].

CASE REPORT

Male patient, 23 years old, resident of a riverside community in Oriximiná / PA - Brazil (1° 45'57.0 "S, 55° 51'57.0" W), bitten by a *Bothrops* snake on his right leg - distal third laterally. Admitted to an emergency care unit of the municipality after about 4 hours of the accident and ensuring that it was a "jararaca" snakebite. On arrival, he had severe pain with bruising and oedema at the bite site, with no evidence of coagulation disorder or acute nephropathy. It was classified as a moderate snakebite event according to the protocol of the Brazilian Ministry of Health and was administered six ampoules of pentavalent heterologous antivenom, remaining under medical care in clinical hospitalisation.

During the first week of care, the patient remained in good condition, with no symptoms or signs of coagulopathy or nephropathy, with analgesia based on piroxicam and dipyrone, and prophylactic antibiotic therapy with chloramphenicol + oxacillin was introduced. The appearance of necrotic lesion at the bite site was evident after about 5 days, with serous exudate and fibrin-purulent with deep, whitish background. In the first week, the patient presented persistent axillary hyperthermia around 37.67 ± 0.19°C (95% CI), with a maximum peak in the period of 38°C.

About 7 days after admission, the anti-inflammatory drug was discontinued, and the antipyretic was maintained if necessary, using mild opioid analgesia with tramadol 50mg three times per day. Careful clinical examination was performed daily to identify early signs of compartment syndrome, noting that severe pain is one of the early symptoms of this syndrome, which contraindicates the use of strong painkillers. After ceasing the use of anti-inflammatory and antipyretic, to better understand the behaviour of fever thru a thermal curve, the elevation of the patient's axillary temperature was observed in the next day, reaching peaks of up to 39.2 °C, maintaining temperature management with dipyrone as prescribed (if necessary). During this period, thermograms - all with explicit authorisation from the patient for assistance in their clinical follow-up and eventual use for educational and scientific purposes - were collected. An infrared camera brand/model FLIR/C2 (FLIR Systems AB, Taby, Sweden) was used. Results were analysed using the RAIN colour scale, with white/red as "higher temperatures" and blue/purple/black as "lowest temperatures". The acquisition, selection of regions of interest (ROI), thermal analysis and image storage were performed with FLIR TOOLS + ® software (V5.3.18031.2002, 2015, FLIR Systems AB,

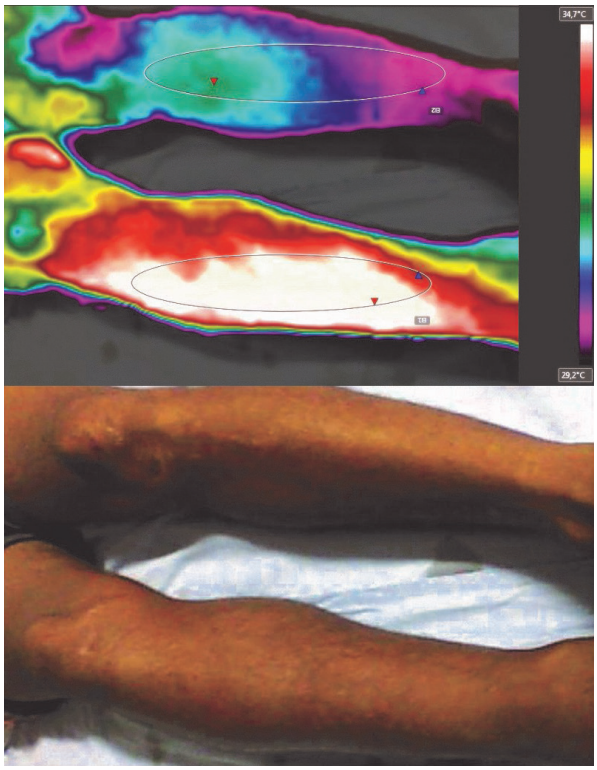

Figure 1- The first thermogram obtained in the middle of the second week of medical care

Danderyd, Sweden). The emissivity of the skin was assumed to be 0.98, which is the most suitable for the human body (19). All wards of the health service in which the patient was hospitalised were acclimatised at about 24 ºC, being considered adequate for the collection of images. In Figure 1, is possible to observe the first thermogram obtained in the middle of the second week of medical care. A wide zone of high temperature was evidenced in the injured leg (right leg). The mean ROI in comparison to the contralateral (anterior) leg one day after the removal of the anti-inflammatory reached 4.2 ºC (ΔTmax = 4.3 ºC).

On the following day, a new thermogram (Figure 2) revealed a mean ROI in comparison to the contralateral (anterior) leg of 1.6 ºC (ΔTmax = 2.1 ºC), which suggested good thermoregulation without anti-inflammatory drugs.

In subsequent days, a series of precautions were taken to ensure that the fever was not from a detectable infectious process - given the presence of persistent febrile peaks. Biochemical tests were performed, including routine blood count, CRP (C-reactive protein), renal function and coagulation test, as well as blood culture, urine culture and even plasmodium research, remembering that the patient's region of origin is an endemic zone for malaria: all were negative for detection of infections, without leukocytosis in any of the blood counts collected, but with mild to moderate elevation of CRP.

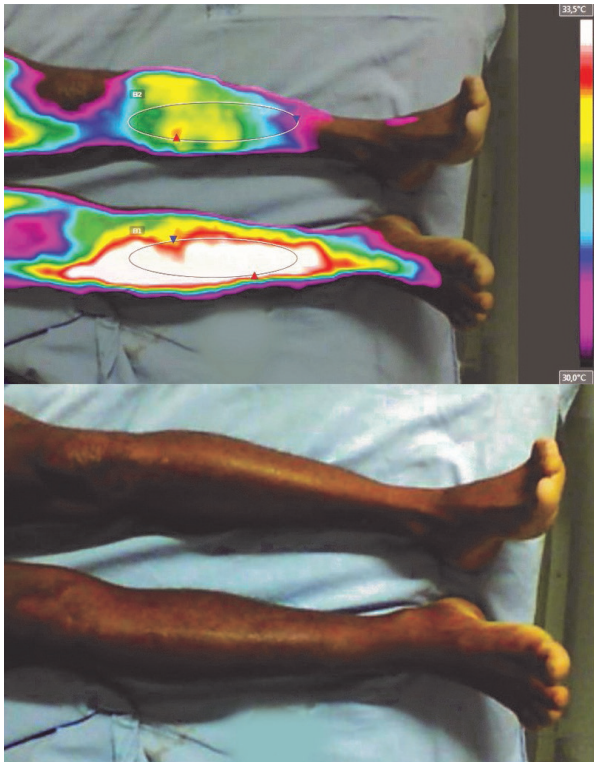

Figure 2 - The second thermogram, obtained in the next day of the first thermogram

Nursing interventions were instituted for wound care to minimise the risk of secondary infections, using dressing according to the phase and characteristics of the lesion, as well as the increased protein-caloric intake provided by the clinical nutrition team. In the third week of follow-up of the hospitalised patient, fever was a relevant factor given its persistence.

The twenty-four axillary temperature samples measured throughout hospitalisation (one sample per day) followed a statistically normal distribution. The average temperatures throughout the hospitalisation period were 37.84 ± 0.67 °C (95% CI), ranging from 36.6 °C to 39.2 °C (Figure 3).

All febrile episodes during hospitalisation were controlled according to medical prescription.

At the end of the third week of hospitalisation, a third thermogram was collected (Figure 4), also revealing extensive inflammatory lesion of the entire lower limb (posteriorly), presenting an average ΔT of ROI compared to the 3.4 °C posterior contralateral thigh (ΔTmax = 2.7 ºC) and mean ΔT of ROI compared to the posterior contralateral leg of 3.9 ºC (ΔTmax = 2.7 ºC). Clinical examination showed good muscle mobility, no apparent venous thrombopathy, and good peripheral perfusion.

In the third week of hospitalisation and with lower perception of local pain, the patient was stimulated in a neuromotor

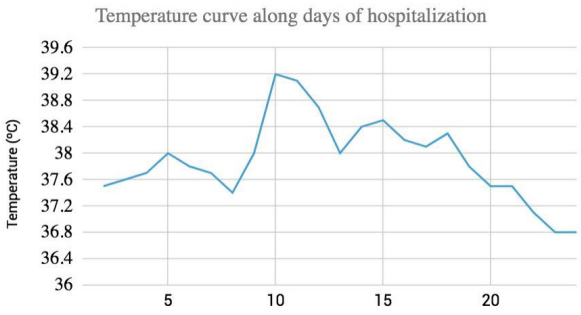

Figure 3 - Graphic representing the temperatures throughout the hospitalization period

rehabilitation programme with the physiotherapy team, with progressively positive evolution of movement and recovery of ambulation. Progressively lower levels of pain and even axillary temperature were already observed. The patient maintained prophylactic antibiotic therapy until the middle of the third week of hospitalisation. The patient was discharged from hospital in the fourth week of follow-up, walking well and without help, with guidance on wound self-care and outpatient follow-up.

Figure 4 - The third thermogram, obtained at the end of the third week of hospitalisation

Discussion

Male patient, 23 years old, resident of a riverside The monitoring of the inflammatory process resulting from Bothrops bite by infrared thermography (IRT) provided a new dimension in accidents with venomous snakes, as also observed by Medeiros et al.[17]. The consequent persistent fever in this case has gained a new meaning and goes beyond infectious processes and other immune-mediated processes, such as Serum Disease.

Not rare, the prophylactic antibiotic therapy is instituted early in cases of bothropic accidents[20]. However, the routine use of antibiotics, especially in the prophylactic context, remains controversial[21] and antimicrobial regimens for prevention or treatment of infections secondary to snake-bites are not based on good evidence from randomised controlled trials[22,23].

While some recommend the prophylactic use of routine antibiotics after snake bites[24,25], others argue that antibiotic use should be initiated only after clinical evidence of infection, such as necrosis or local tissue gangrene[25,26], abscess formation[27] or blisters[28].

Accident studies involving snakes of the Bothrops genus mainly describe factors associated with systemic complications, such as coagulopathy, acute renal failure and death, especially in extreme age groups, and complications regarding the time of initiation of medical care and treatment[30,31,32]. However, there is little information about local complications. This is relevant information because prophylactic measures for late disability could be applied early if well clarified.

Conclusion

Infrared thermography, even with low thermal definition, proved to be a good instrument to identify persistent acute and subacute inflammatory processes in bedside evaluation. In bothropic accidents, this information may play a relevant role in the differential diagnosis of persistent fever - a fact that sets a new dimension in the clinical decision to initiate (or not) antibiotic therapy - as well as allowing the stratification of the actual extent of venom action and preventing possible late disabilities. As it was a propaedeutic evaluation, this report did not intend to impose greater methodological rigours. However, it was revealing of an insufficiently explored gap in public health, especially as regards the secondary and tertiary prevention strata.

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