Review article:

Oral bleeding in dengue fever - Our perspective

Khan Saif[1], Rahman SZ[2]

Abstract:
Dengue fever is one of the major public health problem in the tropical and subtropical countries across the globe with around 50-100 million cases occurring annually**.** It is a mosquito borne disease caused by dengue virus of Flaviviridae family. There are four known serotypes of dengue virus found worldwide. Aedes aegypti mosquito is the principal vector of transfer of dengue virus in humans. Dengue clinically presents with high grade fever, chills, head-ache, retro orbital and severe back ache and sometimes with hemorrhagic manifestations which can occur without plasma leakage and also with plasma leakage as dengue hemorrhagic fever (DHF) and Dengue shock syndrome (DSS). Oral bleeding is one of the important hemorrhagic manifestations of dengue clinically manifesting as petechiaes, ecchymosis, gingival bleeding and hematomas .The dentist is sometimes the first person who encounters these types of cases. Therefore, timely diagnosis and prompt referral can prevent morbidity and mortality. This paper discusses about the clinical and diagnostic perspectives which a dentist should know in order to diagnose a case of dengue fever presenting with oral bleeding.

Keywords: Dengue fever, Oral Bleeding, Thrombocytopenia

Bangladesh Journal of Medical Science Vol. 20 No. 01 January'21. Page : 11-16
DOI: https://doi.org/10.3329/bjms.v20i1.50339

Key Message: Dengue fever is caused by dengue virus which is transmitted by Aedes aegypti mosquito. It is found in the tropical and subtropical areas of the world. Dengue fever is a public health concern. It present clinically as fever, headache, retro orbital pain and back ache. There are also bleeding episodes in more severe form - dengue haemorrhagic fever clinically presenting as epistaxis, oral bleeding likes petechiaes, ecchymosis and gingival bleeding. The dentist is usually the first person who encounters these cases. Prompt diagnosis and timely referral are critical and may reduce morbidity and mortality in these patients**.**

Background

Dengue fever is an arthropod borne viral disease caused by dengue virus, a Flavivirus of Flaviviridae family. There are known four serotypes of dengue viruses (DENV1 to DENV4) found worldwide. The dengue virus is transmitted by Aedes aegypti which is the principal vector of transmission and reservoir of infection are both human and mosquito. The Aedes mosquito also called tiger mosquito due to its big size usually bites humans in the day time and breeds in freshwater collection indoors and around the domestic and peri domestic areas[1,2,3].

It is one of the major public health concerns in about 100 tropical and sub-tropical countries of the world which includes Southeast Asia, South and Central America and Western Pacific. More than 2.5 billion people are affected by this disease. Around 50-100 million cases occur yearly and nearly 500,000 cases developing into fatal dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). Poor public health systems, uncontrolled population, unplanned urban development, poor vector control and travel to endemic areas contribute to the risk of dengue spread [4].

1. Khan Saif, Deptt. of Periodontics & Community Dentistry, Dr Z A Dental College and Hospital, Faculty of Medicine, Aligarh Muslim University, Aligarh,UP, India
2. Rahman SZ, Deptt of Pharmacology, J N Medical College and Hospital, Faculty of Medicine, Aligarh Muslim University, Aligarh, UP, India

Correspondence to: Dr. Saif Khan, Dept. of Periodontics & Community Dentistry, Dr Z A Dental College, Faculty of Medicine, Aligarh Muslim University, Aligarh,UP, India-202002 Email: saifgood@gmail.com

Oral bleeding manifestations ranging from petechiaes, ecchymosis, hematomas, acute gingival bleeding are usually seen the in the oral cavity of dengue patients. The dentist can be the first person to see these patients [5,6].

This review gives an overview of dengue fever patients presenting with oral bleeding and its clinical implications. Sometimes dengue fever can only present with oral or gingival bleeding so the dentists should be aware of dengue fever, its clinical presentations, diagnosis, prognosis and therefore timely referral by the dentist can prevent morbidity and mortality [6]. [Figure 1]

Figure 1: Showing 29 years female clinically

presenting with fever, backache, epistaxis, and oral bleeding with petechiaes, ecchymosis. She had thrombocytopenia (platelet count =14,000/mm^3) and positive NS1 antigen, positive Antidengue IgM antibody serum titers.

The literature was searched using terms "oral bleeding", "gingival bleeding" and "Dengue fever" in Pubmed and Google Scholar and relevant articles were extracted for the clinical and diagnostic relevance of oral and gingival bleeding in dengue fever.

Clinical Presentation

Dengue fever (DF)

It present as acute and abrupt onset of high grade fever (39-40^O C) with chills, head-ache, retro orbital and severe back ache. The fever usually takes few hours to 2 days to subside and then there is second febrile phase for 1-2 days. The span of fever lasts for 5 -7 days. On Physical examination, a typical morbilliform rash is usually seen on the trunk which spreads centripetally to face and extremities, in the second febrile phase. The rash is accompanied by irritation and hyperesthesia and ends up with desquamation of the involved skin. There is also generalized myalgia, arthralgia along with nausea, vomiting and dysgeusia. Clinical signs such as bradycardia and generalized lymphadenopathy are usually seen.

The hematological parameters are marked leucopenia and neutropenia along with thrombocytopenia seen from third to eight day of the presentation.

Sometimes, dengue fever is also associated with hemorrhagic episodes such as petechiaes, epistaxis, gastrointestinal bleeding, haematuria and hypermenorrhea, however in the absence of signs of plasma leakage, a diagnosis of Dengue hemorrhagic fever (DHF) is unwarranted [7].

Dengue hemorrhagic fever (DHF) and Dengue shock syndrome (DSS)

Dengue hemorrhagic fever (DHF) is a severe form of dengue fever which is manifested with hemorrhagic tendencies and can potentially develop into fatal dengue shock syndrome (DSS).

The pathophysiological characteristics of DHF which demarcates it from dengue fever are plasma leakage, increased vascular permeability and abnormal hemostasis. The underlying mechanism causing DHF and DSS are still unknown but evidence points towards intensity of immunological response to dengue virus, leading to pathophysiological cascade which ultimately causes plasma leakage[8].

Oral Manifestations

The oral manifestation of dengue fever range from pinpoint petechiaes, soft tissue hematomas, oral ulcers to acute gingival bleeding.[Figure 1]

The oral bleeding is usually accompanied by cutaneous manifestation like petechiaes, ecchymosis and rashes on trunk, arms and legs[5,6,9,10]. The hemorrhagic episodes usually seen from the third to fifth day after the onset of fever [1]. The oral bleeding is usually seen in patients having platelets counts below 39,000 per cubic milliliter[11].

Ahmed S et al in their study found that around 67.8 % patients with dengue hemorrhagic fever presented with gingival and oral bleeding[10].

In Fiji between January to July 1975, a very severe endemic occurred in which 16 % of patients with dengue fever had some type of bleeding manifestations associated with the disease and

epistaxis and gingival bleeding were the most common hemorrhagic manifestations reported[12].

Another dengue epidemic which occurred again in Fiji between July 1989 to July 1990 where 3686 cases were registered by ministry of health. The majority of cases had classical dengue syndrome and 43% reported to have hemorrhagic manifestations which included epistaxis, gingival bleeding, haematemesis, melena and haematuria[13].

These above studies show that oral bleeding is one of the important clinical manifestations seen in dengue fever and the role of dentist or oral health care professional in diagnosing dengue cases sometimes solely presenting with oral manifestations cannot be overemphasized[5,6].

Pathogenesis

The genome of dengue virus is single stranded RNA which is open reading frame and is translated as a single polypeptide chain. This polypeptide chain is cleaved into 10 viral proteins comprising of 3 structured and seven non-structured (NS) proteins by viral and host proteases[14]. After the mosquito bites human, the viral replication takes place in the dendritic cells of skin . The virus comes into the systemic circulation about 16-18 hours prior to onset of symptoms[15].

The non-specific innate immune system includes skin, cellular and genomic encoded molecules. The innate response to dengue infection is the phase between viral infection and appearance of the clinical signs.

The two major component of innate immune system; Natural IgM antibody and platelets have critical role in the pre illness period of dengue infection[16].

Further, Natural IgM antibodies formed by the CD5+ B cells are component of innate immunity. These circulating nonspecific circulating natural antibodies provide early defense against the dengue infection. They help in antigen uptake, processing and presentation by the B lymphocytes via complement and Fc receptors. Thus, the circulating B cells are the major circulating mononuclear cells infected by the dengue virus. These circulating IgM antibodies can activate complement system through classical pathway and are 1000 times more efficient than IgG antibodies in early recognition and elimination of foreign invaders like bacteria and viruses. Also, hexameric IgM are 15 to 20 times more powerful than pentameric IgM in activating complement. [17,18]

Moreover, IgM antibody forms circulating immune complexes (CIC) with dengue antigen and platelets and these immune complexes have been detected in blood vessels of dermal papillae of the skin rashes[19].

Platelets play crucial role in hemostasis and are an integral component and potent effectors in innate immune system[20,21]. They modulate inflammatory and immune response. During the vascular injury phase platelet rush to the site of injury and form platelet plug and foster hemostasis. One of the key clinical features of dengue infection is thrombocytopenia which is due to both decreased production and increased destruction of platelets[22,23,24]. In dengue infection the platelets form complexes with dengue virus, IgM antibodies. This complex is phagocytosed by macrophages or monocytes via Fcγ receptor. Thrombocytopenia seen in DHF/DSS is due to the destruction of the platelets by the virus either by direct toxicity or indirectly by binding of dengue specific antibodies to virus infected platelets immune complexes[25].

Innate IgM antibodies play significant role in early dengue infection and are detected in the early stage of disease and along with other innate factors such as cytokines, platelets which contribute to the progression of DHF and DSS. In the protective stage of the disease in which fever and viremia has subsided, adaptive immunity induced by dengue virus antigen is provided by antidengue IgG. [16]

The dengue virus is usually found in the peripheral leukocytes particularly mononuclear lymphocytes, lymph nodes, kupffer cells and bone marrow cells. Cytokines such as Tumour necrosis factor-alpha (TNF-α), Interferon-gamma (INF-γ), soluble tumour necrotic factor receptors (sTNFRs), soluble interleukin-2 receptors, soluble CD4, and CD8 are increased. These inflammatory mediators correlate positively with severity of the dengue infection leading to increase vascular permeability, plasma leakage, thrombocytopenia and ultimately leading to hemorrhage (DHF) and shock (DSS)[26,27,28].

The T-lymphocytes remove the viral load and activate immune response. However, sometimes during secondary infection the increase in the low affinity T cells from the previous dengue infection results in an inappropriate immune response and suboptimal clearance of viral load. This phenomenon is called original antigenic sin and it delays the elimination of viral load leading to increased viral reserves and predisposes the patient to more severe form of disease such as DHF and DSS[29,30].

Diagnosis:

The diagnosis is made on basis of the following clinical and laboratory criteria[31].

Clinical Criteria:

- **Fever**: Fever is usually abrupt in the onset and high grade and lasts for 2-7 days. Also, accompanied with two or more of the following symptoms; headache, retro orbital pain, myalgia and arthralgia.
- **Hemorrhage**: Skin petechiaes, purpura, ecchymosis, epistaxis, gingival bleeding, mucosal bleeding, gastrointestinal bleeding; hematemesis and malena
- **Positive tourniquet test**: Elicited when 20 petechiaes with 2.5 cm in diameter appear on the skin surface of the forearm after sphygmomanometer cuff is inflated in the middle between systolic and diastolic pressure for at least five minutes.
- **Hepatomegaly**
- **Clinical signs**: Tachycardia, weak pulse, Narrowed pulse pressure (20mm Hg or less) , and Hypotension

Laboratory criteria

- Decreased platelet count or Thrombocytopenia ($\leq$100,000/mm^3)
- Rise in haematocrit 20% above average for age, sex and race.
- Signs of plasma leakage like pleural effusion.

Dengue hemorrhagic fever (DHF)

The first two clinical criteria (Fever and hemorrhagic manifestations) along with thrombocytopenia and rising hematocrit are sufficient to make diagnosis of DHF.

Dengue shock syndrome (DSS)

DSS encompass all the criteria of DHF along with the manifestation of shock. DSS is characterized by narrowing of pulse pressure (upto 20mm Hg), hypotension and in severe cases undetectable blood pressure and pulse. The duration of DSS is very short and critical. The patient may die within 12-24 hours of DSS or may recover rapidly if appropriate treatment is given during this period.[31]

Differential diagnosis: Viral haemorrhagic fever (Ebola fever, Yellow fever, Lassa fever, chikungunya fever)[31,32] and tropical diseases like malaria[33], rickettsial diseases[33] presenting with fever and bleeding manifestations like oral and gingival bleeding can be considered in the differential diagnosis of these type of clinical presentations.

Conclusion:

Patients presenting with fever, headache, retro orbital pain, backache along with petechiaes, ecchymosis, hematomas, gingival bleeding in the oral cavity should be sent for proper hematological evaluation (haemogram, platelet count, total leukocyte count, haematocrit) and serological investigations (Dengue NS1 Antigen, IgM Dengue antibody and IgG Dengue antibody) to rule out dengue fever and DHF. As timely referral of dengue patient is very critical as far as prognosis is concerned and therefore clinical acumen and knowledge of the dentist plays a vital role in diagnosing serious bleeding disorders which are manifested in oral cavity and proper and prompt referral can avert catastrophes.

Ethical clearance: This article was approved by local ethics committee before submission

Source(s) of support: The study has been supported by author and his institution.

Conflicting Interest : None

Authers' contributions: All authors give their full effort in data gathering and idea owner of this study, study design, writing and submitting manuscript and editing and approval of final draft.

References:

1. Chiu YC, Wu KL, Kuo CH, Hu TH, Chou YP, Chuah SK, *et al* .Endoscopic findings and management of dengue patients with upper gastrointestinal bleeding. *Am J Trop Med Hyg* 2005; **73:**441-4.
2. Guzmán MG, Kourí G. Dengue: An update. *Lancet Infect Dis* 2002; **2**:33-42.
3. Gubler DJ. Dengue and dengue hemorrhagic fever. *Clin Microbiol Rev* 1998;**11**:480-96.
4. WHO Dengue Guidelines for diagnosis, treatment, prevention and control 2009. https://apps.who.int/iris/bitstream/handle/10665/44188/9789241547871_eng.pdf?sequence=1&isAllowed=y (Accessed on 15 January 2020)
5. Pontes FS, Frances LT, Carvalho Mde V, Fonseca FP, Neto NC, do Nascimento LS, Pontes HA . Severe oral manifestation of dengue viral infection: a rare clinical description. *Quintessence Int* 2014;**45**(2):151-6
6. Khan S, Gupta ND, Maheshwari S . Acute gingival bleeding as a complication of dengue hemorrhagic fever. *J Indian Soc Periodontol* 2013; **17**(4):520-2
7. Goel A, Patel DN, Lakhani KK, Agarwal SB, Agarwal A et al. Dengue Fever- A Dangerous foe. *JIACM* 2004; **5**(3):247-58
8. Waidab W, Suphapeetiporn K and Thisyakorn U (2008). Pathogenesis of dengue hemorrhagic fever: From immune to genetics, *Journal of Pediatric Infectious Diseases* 2008; 3: 221–227
9. Setlik RF, Ouellette D, Morgan J, McAllister CK, Dorsey D, Agan BK, Horvath L, Zimmerman MK, Purcell B. Pulmonary hemorrhage syndrome associated with an autochthonous case of dengue hemorrhagic fever. *South Med J* 2004; **97**(7):688-91
10. Ahmed S, Mohammad WW, Hamid F, Akhter A, Afzal RK, Mahmood A. The 2011 dengue haemorrhagic fever outbreak in Lahore - an account of clinical parameters and pattern of haemorrhagic complications. *J Coll Physicians Surg Pak* 2013; **23**(7):463-7
11. Murillo-Llanes J, Soto-Valenzuela H, Flores-Flores P, Peraza-Garay F . Clinical and epidemiological characteristic of dengue. *Rev Med Inst Mex Seguro Soc* 2007; **45**(5):485-91
12. Reed D, Maguire T, Mataika J.Type 1 dengue with hemorrhagic disease in Fiji: epidemiologic findings. *Am J Trop Med Hyg* 1977; **26**(4):784-91
13. AH Fagbami, P J.U. Mataika, M Shrestha, DJ Gubler . Dengue type 1 epidemic with haemorrhagic manifestations in Fiji, 1989-90. Bulletin of the World Health Organization 1995;**73 (**3): 291-297
14. R.J. Kuhn, W. Zhang, M.G. Rossmann et al. Structure of dengue virus: implications for flavivirus organization, maturation, and fusion. *Cell* 2002; **108**: 717–725
15. D.W. Vaughn, S. Green, S. Kalayanarooj et al. Dengue in the early febrile phase: viremia and antibody responses, *J Infect Dis* 1997; **176:** 322–330
16. Noisakran S, Perng GC. Alternate hypothesis on the pathogenesis of Dengue hemorrhagic fever (DHF)/ Dengue shock syndrome (DSS) in dengue virus infection. *Exp Biol Med* 2008; **233**:401-408
17. Davis AC, Roux KH, Shulman MJ .On the structure of polymeric IgM. *Eur J Immunol* 1988;**18**:1001-1008
18. Randall TD, King LB, Corley RB. The biological effects of IgM hexamer formation. *Eur J Immunol* 1990;**20:**1971-1979.
19. Theofilopoulos AN, Brandt WE, Russel PK, Dixon FT. Replication of dengue-2 virus in cultured human lymphoblastoid cells and subpopulations of human of human peripheral leukocytes. *J Immunol* 1976; **117:**953-961
20. Klinger MH. Platelets and inflammation. Anat Embryol (Berl) 1997; 196:1–11.
21. Weyrich AS, Zimmerman GA. Platelets: signaling cells in the immune continuum. *Trends Immunol* 2004;**25**:489–495
22. Phanichyakarn P, PongpanichB, IsrangkuraPB, Dhanamitta S, Valyasevi A. Studies on Dengue hemorrhagic fever. III. Serum complement (C3) and platelet studies. *J Med Assoc Thai* 1977**; 60:**301–306
23. Mitrakul C, Poshyachinda M, Futrakul P, Sangkawibha N, Ahandrik S. Hemostatic and platelet kinetic studies in dengue hemorrhagic fever. *Am J Trop Med Hyg* 1977; **26**:975–984
24. Wang S, He R, Patarapotikul J, Innis BL, Anderson R . Antibody enhanced binding of dengue-2 virus to human platelets. *Virology* 1995**; 213**:254–257
25. Oishi K, Saito M, Mapua CA, Natividad FF . Dengue illness: clinical features and pathogenesis. *J Infect Chemother* 2007**; 13:**125–133
26. I. Kurane, B.L. Innis, S. Nimmannitya, Nisalak A, Meager A, Janus J, et al. Activation of T lymphocytes in dengue virus infections. High levels of soluble interleukin 2 receptor, soluble CD4, soluble CD8, interleukin2, and interferon-gamma in sera of children with dengue, *J Clin Invest* 1991**; 88**: 1473–1480

27. S.J. Gagnon, F.A. Ennis and A.L. Rothman . Bystander target cell lysis and cytokine production by dengue virus-specific human CD4(+) cytotoxic T-lymphocyte clones. *J Virol* 1999; **73**:3623–3629.

28. S. Green, D.W. Vaughn, S. Kalayanarooj et al. Early immune activation in acute dengue illness is related to development of plasma leakage and disease severity, *J Infect Dis* 1999; **179**:755–762.

29. J. Mongkolsapaya, W. Dejnirattisai, X.N. Xu, Vasanawathana S, Tangthawornchaikul N, Chairunsri A, et al. Original antigenic sin and apoptosis in the pathogenesis of dengue hemorrhagic fever. *Nat Med* 2003; **9:** 921–927

30. A.L. Rothman. Dengue: defining protective versus pathologic immunity. *J Clin Invest* 2004; **113 :**946–951.

31. Lakshman Samaranayake, Crispian Scully, Raj G Nair, Stefano Petti. Viral haemorrhagic fevers with emphasis on Ebola virus disease and oro-dental healthcare. *Oral Dis.* 2015;**21**(1):1-6.

32. Athambawa Mohamed Razmy (2014). Clinical features of chikungunya infection in Sri Lanka. *Asian Pac J Trop Dis* 2014; **4(**2): 131-134.

33. Khan S, Zia A, Gupta N D, Bey A. Acute gingival bleeding as a complication of falciparum malaria: a case report. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2012; **113**(5) :e19-e22.

34. Chaudhry D, Garg A, Singh I, Tandon C, Saini, R. Rickettsial diseases in Haryana: not an uncommon entity. *J Assoc Physicians India* 2009; **57**: 334-337