INTERNATIONAL JOURNAL OF MEDICAL AND APPLIED SCIENCES
Earthjournals Publisher
E-ISSN:2320-3137
www.earthjournals.org

CASE REPORT

AN UNUSUAL PRESENTATION OF DISSEMINATED INTRAVASCULAR COAGULATION AS SUBLINGUAL HEMATOMA DUE TO GRAM NEGATIVE SEPTICAEMIA- A RARE CASE REPORT

Alphy Alphonsa Sebastian[1], Auswaf Ahsan[2]

1.School of Dental Sciences, Health Campus,Universiti Sains Malaysia,16150 Kubang Kerian,Kelantan, Malaysia .
2. Professor, Dept of Oral Medicine and Radiology, KMCT DENTAL COLLEGE, MAMPATTA, MANASSERY.P.O, MUKKAM, KOZHIKODE-673602

Corresponding author: Dr.Alphy Alphonsa Sebastian, School of Dental Sciences, Health Campus Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia

ABSTRACT:

Disseminated Intravascular Coagulation (DIC) is a complex clinical syndrome characterized by hypercoagulable state, bleeding diathesis and multiple organ failure. The most common precipitating factor is sepsis. Gram negative sepsis is the most notable infectious cause. The pivotal mediator of activation of coagulation appears to be interleukin-6. This report describes a 60 year old farmer with swelling on the floor of mouth and blisters, non-healing ulcer on the leg which was diagnosed as oral manifestations of disseminated intravascular coagulation secondary to gram negative septicemia. This case represents acute exacerbation of chronic disseminated intravascular coagulation. The main foci of infection for this acute episode arises from the periodontal infection of lower left second molar teeth. The cornerstone of the management of this condition is the treatment of the triggering cause.

Keywords : DIC, Gram negative sepsis, Ludwigs Angina

INTRODUCTION

Disseminated intravascular coagulation is not a specific ailment by itself, it is distinguished by disruption in normal haemostatic mechanisms[1].In healthy individuals, there is equilibrium between the clot formation and fibrinolysis; so that coagulation occurs only on demand. In DIC, the equilibrium is lost; leading to excessive clot formation and bleeding. All the signs and symptoms of the DIC results from the production of two cardinal proteases; thrombin and plasmin.

This article describes a rare case report of sublingual hematoma which developed in a patient with hepatitis B complicated with sepsis induced Disseminated intravascular coagulation.

CASE REPORT

A 60 year old man presented with a complaint of swelling in the floor of the mouth which became painful, about 3 days ago. It was associated with fever and difficulty in deglutition and respiration. The Patient revealed that a sharp end of bamboo had pierced his right leg 2 years

back and has not healed thereafter and also gave a history of similar bilateral swelling of the floor of mouth, involving right lower third of face 1 year back; It was drained and sutured and 47 was extracted at that time and it was uneventful.

Physical examination revealed the following:-

Blood pressure-150/100mm of Hg; Temperature-39^{o}C; Pulse-100 beats per minute; Respiratory rate-20 breaths per minute; Pallor of lower palpebral conjunctiva of both right and left eye; Pedal edema of both right and left leg.

Multiple ulcerated areas were seen on right leg around the ankle with fluid filled blisters seen just above the right ankle of leg (figure 1). Ecchymotic areas were seen on the flexor and extensor surfaces of forearm. Asymmetry of face was present. Right and left submandibular lymph nodes and submental lymph nodes were palpable, tender and movable.

Extraoral examination revealed an irregularly shaped diffused swelling with ill-defined margin and smooth surface extending from right angle to left angle of mandible and superiorly from inferior border of the mandible to 2 cm medial and inferior to inferior border of mandible measuring approximately 6.5cmx7.5cm.

The color overlying the swelling was slight red. Post-surgical scar was found on the right angle of mandible. On palpation, the swelling was tender and firm with slight local rise in temperature.

Intra oral examination revealed a diffuse swelling with ill-defined margin present bilaterally in the floor of mouth extending upto the lingual gingiva with respect to lower right and left posterior region measuring approximately 5.5cm x6.5cm. The color of mucosa was red. Floor of the mouth was elevated and tongue was raised (figure 2). On palpation, swelling about the tongue was firm and tender with drainage of pus from the lower left second molar tooth region. Mouth opening was limited to 2.2cm with Grade 3 mobility of 37. Generalized gingivitis and periodontitis were present. Hence a provisional diagnosis of Ludwig's angina was made.

Orthopantomograph reported periodontal abscess irt 37(figure 3).The affected tooth was removed. Blood cultures obtained from periodontal material irt 37 showed anaerobic gram negative bacilli. According to antibiogram,antibiotic therapy was adjusted to penicillin G Na 4 million units every 6 hours intravenously with metronidazole 400mg every 12 hours intravenously and gentamicin 3mg per kg intravenously every 24hours.The needle compression was performed through left submandibular triangle. Over four days there was marked improvement in his condition.

Routine investigation showed neutrophilia, lymphocytopenia, thrombocytopenia and ESR was elevated. Serology report showed HbsAg positive. In Urine, albumin was present. Microscopically, Pus cells, Epithelial cells, RBCs, Granular casts and Calcium oxalate crystals were found. Peripheral smear showed normocytic and normochromic Erythrocytes. Bleeding time, Prothrombin time, INR and activated partial thromboplastin time were prolonged. Increased D-dimer serum levels and decreased fibrinogen levels were also noted. Liver function test revealed increased serum total bilirubin, serum direct bilirubin and highly elevated SGOT and SGPT. The Blood urea, serum creatinine and C-reactive protein were high. The measured values are given [table1].Purulent bloody fluid was aspirated from the region above the right ankle. It revealed innumerable single rods suggestive of gram negative bacilli infection. Abdominal ultrasonography demonstrated slight hepatomegaly which could be due to hepatitis B

infection. These laboratory findings were consistent with Disseminated intravascular coagulation due to sepsis.

Patient was managed by injection Pencillin, injection Botropase 1ampule I.V. stat,injection Xamic 1ampule IV stat, cold saline wash, injection vitamin K 3 ampule IM stat and 2 units of platelet transfusion. He completed a two months course of antibiotics and weekly follow up revealed gradual normalization of ESR. He also required transfusion of 2 units of fresh-frozen plasma and 10 units of cryoprecipitate. Inspite of all supportive measures and broad spectrum intravenous antibiotics, the patient died of sepsis, when he was transferred for transfusion of fresh frozen plasma.

DISCUSSION

At present, DIC is recognized as a syndrome which manifest fairly acute in situation like septicemia and is also characterized by hemorrhagic symptoms and multiorgan failure[1].The fibrin in DIC is formed as a result of simultaneous occurrence of four different mechanisms such as 1.increased thrombin generation2.Suppression of physiological anticoagulant pathways3.Impaired fibrinolysis and 4.Activation of inflammatory pathways[2].

In DIC, a marked decrease in antithrombin and protein C occurs, which act as the natural anticoagulants of Thrombin. The onset of septicemia is characterized by hyperfibrinolysis. This is followed by rapid release of plasminogen activated inhibitor1, which suppresses fibrinolysis. The fourth mechanism of coagulation in sepsis is due to liberation of inflammatory cytokines[2].

PATHOPHYSIOLOGY

DIC is associated with gram negative bacterial infections but it can also occur with similar gram positive sepsis. The key event is the systemic inflammatory response to the infectious agent. The causative micro-organisms express unique cellular constituents; the Pathogen associated molecular patterns (PAMPs) or microbial associated molecular patterns[3].

Host cell derived factors are generated as ‘danger signals’ during infection or inflammation or stress. Danger signals along with PAMPs are referred to as danger associated molecular patterns (DAMPs). The pattern recognition receptors of our immune system like toll like receptors perceive these components and activates the intracellular pathways, which inturn results in generation of proinflammatory cytokines [3].The latter harmonize with microorganisms and products procured from complement activation initialize the DIC.

In any type of septicemia the micro organisms form fibrin through various mechanisms such as:[3]

1. Up-regulation of procoagulant pathways
2. Down-regulation of physiological anticoagulants
3. Suppression of fibrinolysis.

Up-regulation of procoagulant pathways

Lipopolysaccharides (LPS) are the most high powered tissue factor inducer and have a signature role in gram negative sepsis. But in gram positive sepsis, the causative agents are peptidoglycans, lipoteicoic acid and several exotoxins. Secondly, the cellular interactions, which include the interaction of monocytes with T-lymphocytes, natural killer cells, activated platelets and smooth muscle cells are the powerful tissue inducers.

Activated monocytes and macrophages are the main triggers of blood coagulation during sepsis or endotoxemia. Increased expression of monocyte-macrophage tissue factor has been reported in human beings suffering from septicemia.

Impairment of physiological anticoagulant mechanisms:

Under physiological conditions, Endothelial cell surface acts as the sole source of the deliberate release of certain constituents that has an important role in anticoagulation such as thrombomodulin (TM), endothelial protein C receptor (EPCR), protein S, tissue factor pathway inhibitor and the heparin like Proteoglycan heparan sulphate.

In human sepsis, it is noted that the protein C anticoagulant pathway is down streamed. It is indicated that acquired severe protein C deficiency is associated with early death in individuals with sepsis. The common findings in septicemia are increased levels of EPCR and low levels of PC and PS.

Suppression of fibrinolysis

In sepsis, the deposition of fibrin in the vessels gets easier by an impairment of fibrinolytic system.

TNF, IL-1, LPS and herpes simplex virus are the exclusive factors that decreases t-PA synthesis; while the agents that involved in increased t-PA generation are thrombin and factor Xa. Most of the above stimuli consistently stimulated PAI-1 synthesis, the net effect being antifibrinolytic. In septic patients, a sustained increase in plasma PAI-1 has been consistently reported. In some studies PAI-1 turned out to be a prognostic marker in patients with septic shock. Impaired fibrinolysis is an important factor in the pathophysiology of human sepsis.

Pathogenic mechanisms of multiple organ dysfunction syndrome (MODS)

A MODS is the telltale sign of severe septicemia and leads to high mortality and morbidity. In the *early phase* of MODS overproduction of numerous cell derived cytokines and soluble inflammatory mediators cause widespread activation or dysfunction. In the later phase, the recruited cells in harmony with mast cells and its product cytokine heighten the inflammation.

ETIOLOGY

The etiological factors for DIC is given [table 2][4,5]. Several oral manifestations of DIC were reviewed in the literature. For example, Peters KA et al[6] stated in their study that the oral hemorrhage from extracted tooth socket as the initial sign of DIC caused by multiple thoracic and abdominal aortic aneurysm. Ignacio Duran et al[7] in another literature described a case of Bleeding gums and the diffuse spontaneous ecchymosis as the initial sign of DIC in a patient affected with metastatic prostate cancer. it was documented that 10-15% of patients with metastatic tumors have some evidence of DIC.

Several cases of DIC were reported during or after the surgery of tonsil, tongue carcinoma and also squamous cell carcinoma in relation to lower lip. H.Can[8] described DIC as the very rare complication of neck dissection. patients with early stage and advanced malignancies who developed DIC had inferior survival when compared with their counterparts without DIC.

Juan A et al[9] described gingival bleeding, post oral surgical bleeding and gingival swelling as the outcome of the life threatening coagulopathy accompanying acute promyelocytic leukemia.

DIAGNOSIS

Acute or decompensated DIC is characterized by extensive release of tissue factor within a short period of time, which is seen in situations like severe head trauma, burns, or sepsis. The clinical

signs of this include profuse primary (petechiae, ecchymoses, hematochezia, malena, hematemesis, and hematuria) or secondary in concert with hemostatic disorders. All these distinctive features are due to anemia or multiorgan dysfunction.

However, patients with chronic or compensated DIC may possess subclinical signs and symptoms, and may only be identified through laboratory findings. In this type, destruction and production of coagulation factors and platelets are balanced[11].

The clinical diagnosis is always laborious due to the fact that many pathologic conditions has the similar features of DIC such as fever, hypotension and hemolytic anemia.

Laboratory diagnosis of DIC is also difficult, as none of the current tests are specific for DIC, and no single laboratory test can diagnose DIC with acceptable sensitivity. The paramount of laboratory finding include thrombocytopenia, increased or decreased plasma fibrinogen levels and prolongation of one or more coagulation factors. Therefore, the tests commonly used for assessment of DIC are platelet count, fibrinogen level, fibrin degradation product (FDP) assay, D-dimer assay, prothrombin time (PT) and activated partial thromboplastin time (aPTT). Repeated measurements are necessary as DIC is a dynamic disease[12].The laboratory parameters used in acute and chronic form of DIC is given.[table 3 and 4].

The most reliable test to identify DIC are Profragment 1+2,D-dimer assay, Antithrombin III assay and Fibrinopeptide A and least reliable are Prothrombin time, Activated partial thromboplastin time and Reptilase time[13].

PROGNOSTIC MARKERS

Levels of antithrombin and Protein C have been considered as pathophysiological markers in the blood which parallels with severity of endothelial injury and multiorgan failure. Protein C levels showed a significant difference between survivors and nonsurvivors. Low levels of α2-antiplasmin-plasmin complex and high values of PAI-1 function as markers of aggravating disease. Frequency of organ failure in DIC patients was significantly higher in patients with high levels of soluble TM and PAI-1. Patients with septic DIC also showed high levels of neutrophil elastase, which were associated with low levels of D-dimer and DIC, representing low fibrinolytic activity[13].

MANAGEMENT

The main backbone for the treatment of DIC is the Fresh frozen plasma. The intravascular coagulation is interrupted by a combined approach of blood component therapy and by the administration of heparin. The use of anticoagulants such as unfractionated and low Molecular weight heparin, Danaparoid sodium, Recombinant hirudin, Recombinant nematode anticoagulant protein C 2 and restoration of anticoagulant pathways with antithrombin concentrates, recombinant human activated protein C appeared to be more effective than heparin. The other agents like Antifibrinolytic agents, Antiselectin antibodies, and Recombinant interleukin-10 are also used[13]. Gabexate mesilate (GM) is a synthetic inhibitor of thrombin that has anticoagulant activity even in the absence of antithrombin. But, tranexamic acid and aminocaproic acid are rarely used in DIC.

Table1. LABORATORY INVESTIGATION PARAMETERS OF THE PRESENTED CASE

Parameters	Measured value
Routine Blood Investigation	
C-reactive protein	205mg/l
Hemoglobin	11.5g/dl
Packed cell volume	30 cells/100ml
Mean cell volume	70 femto liters
Mean cell hemoglobin	20 picogram
Mean cell hemoglobin concentration	29 g/dl
Neutrophils	9400 cells/mm^3
Basophils	20 cells/mm^3
Eosinophils	100 cells/mm^3
Monocytes	350 cells/mm^3
Lymphocytes	1000 cells/mm^3
Platelets	66000lakhs/ mm^3
Erythrocyte sedimentation rate	55mm/hour
Bleeding time	12 min
Prothrombin time	> 60 sec
Activated partial thromboplastin time	50 sec
International normalized ratio	4.27
Liver Function Test	
Serum total bilirubin	1.3mg/dl
Serum direct bilirubin	0.5mg/dl
Serum glutamic oxaloacetic transaminase	234IU/L
Serum glutamic pyruvic transaminase	188 IU/L
Blood urea	98mg/dl
Serum creatinine	1.9mg/dl
Metabolic	
Sodium	137meq/L
Potassium	4.9 meq/L
Urine Test	
Albumin	0.2gm/24hr
Pus cells	3-5
Epithelial cells	1-2
RBCs	2-3
Granular cast	3-4/HPF
Calcium oxalate	1.1mmol/24hr
Smear test	
Peripheral smear- Normocyte, Normochromic	
Serological test	
D-dimer serum	3 µg/ml
Fibrinogen	0.10g/l
Creatine phosphokinase	600U/ l
Serum HbsAg	positive

Table 2:Etiology

ETIOLOGY	
1.Infections (sepsis) **a. Bacterial** i.Gram negative bacilli ii.Gram positive bacteria iii.Staphylococcus iv. Streptococcus v. Meningococcus **b.Viral** i. Arbovirus ii.Varicella iii.Variolla iv.Rubella **c.Rickettsial** i.Babesios ii. Rocky mountain spotted fever **d.Parasitic** i. Malaria ii. Kala Azar **e. Mycotic** i. Acute histoplasmosis 2. Trauma a. Serious tissue injury b. Crush injury c. Head injury d. Fat embolism 3.Cancer a. Myeloproliferative disorders b. Lymphoproliferative disorders	4. Obstetical Complications a. Amniotic fluid embolism b. Abruptio placentae 5. Vascular disorders a. Giant hemangioma b. Aortic aneurysm c. Vasculitis 6. Reactions to toxins a. Snake venom 7. Immunologic disorders a. Autoimmune disorders b. Severe allergic reactions c.Hemolytic transfusion reaction d. Transplant reaction 8. Liver disease a. Obstructive jaundice b. Acute hepatic failure 9. Miscellaneous a. Pancreatitis b. Acute glomerulonephritis c. Polycythemia d. Hemolytic uremic syndrome

Figure1: Fluid filled blisters seen just above the right angle of leg

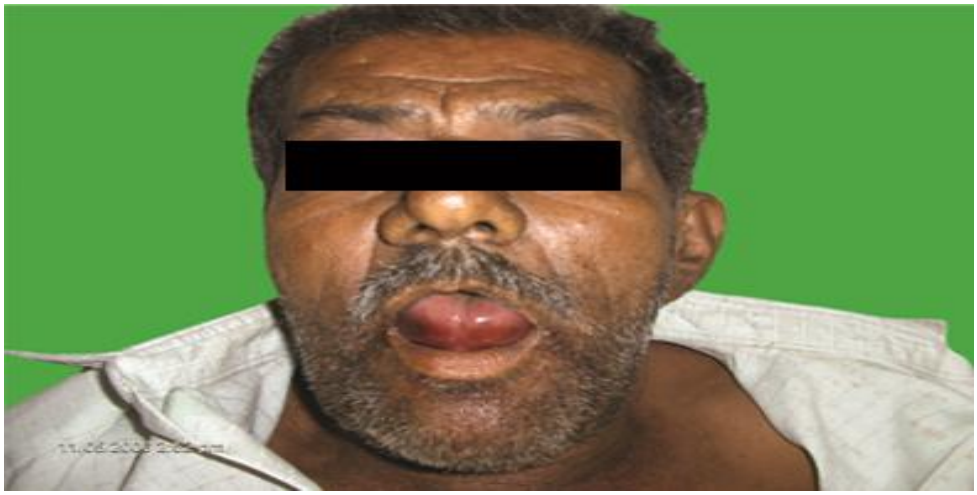

Figure 2: A diffuse swelling in relation to floor of mouth that elevates the tongue.

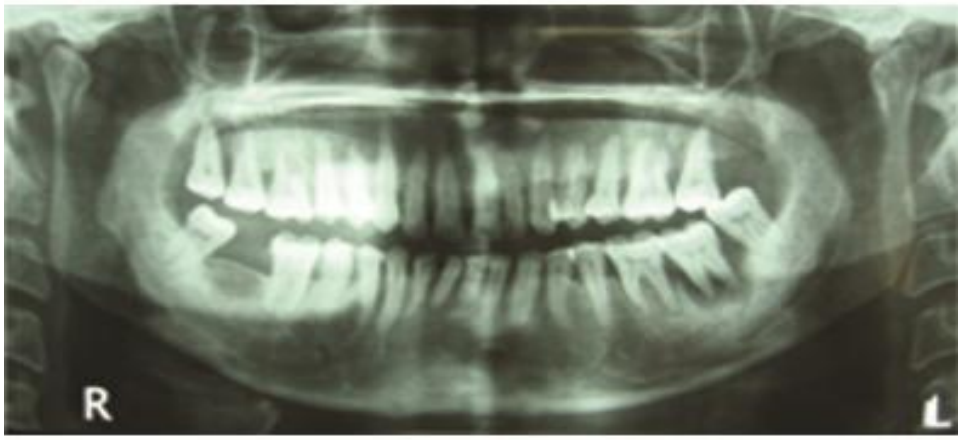

Figure3: Orthopantomograph shows periodontal abscess irt 37

Table 3: Abnormalities of Laboratory Assays in Acute DIC

Increase in	***Decrease in***	***Prolongation of***
Fibrin Split Products (FSP)	Platelet count	Prothrombin time
D-dimer	Fibrinogen	ActivatedPartial Thromboplastin Time
Prothrombin fragment 1+2	Factor V	
Soluble Fibrin Monomer	Factor VIII	
Plasmin		
Fibrinopeptide A and B		
Thrombin-Antithrombin Complex		
Peripheral smear examination:**Schistocytes**		

Table 4: LABORATORY INVESTIGATIONS IN CHRONIC DIC

Prothrombin time Activated Partial Thromboplastin time Thrombin time	Prolonged or normal
Platelet count Fibrinogen	Normal or decreased
Fibrin degradation products D-dimer Fibrinopeptide-A Thrombin antithrombincomplex Antithrombin	Increased

CONCLUSION

To conclude, treatment should be instituted immediately when a diagnosis of DIC is established, or a high index of suspicion exists. In our case, patient died when he was shifted for replacement therapy as a result of bleeding complications and septicemia.

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