Journal of Clinical Case Reports Online

J Clin Case Rep On

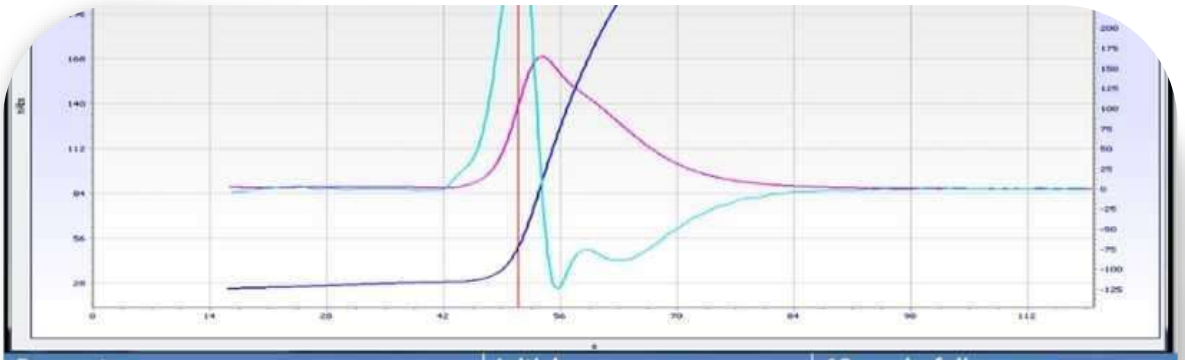
2021

Volume 1, Issue 1

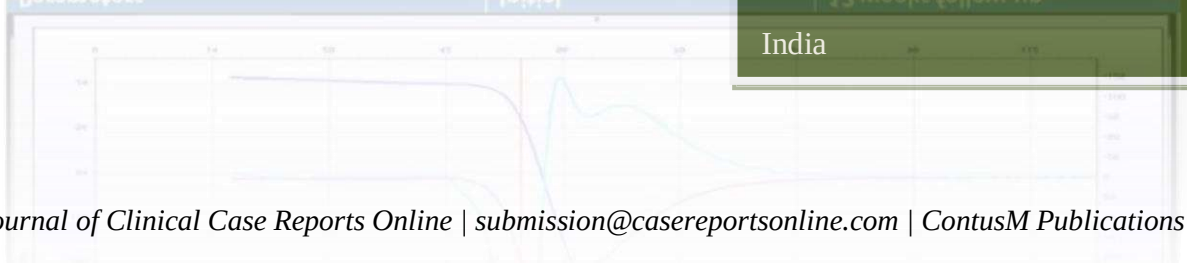
Article ID: JCCRO-1010

Short Communication

Recurrent Hemorrhagic Bullae on the Tongue: A Rare Hemorrhagic Manifestation of Primary Antiphospholipid Syndrome



Parameters	Initial	12 weeks follow-up
APTT (seconds)	60.7	54.4
Maximum velocity (mabs/sec)	241.8 (Lab mean-163)	193.5 (Lab mean-163)
Maximum acceleration (+mabs/sec2)	1280.8 (lab mean- 1326)	1932.6 (lab mean 1326)
Maximum deceleration abs/sec2)	541.1 (lab mean- 521.8)	614.8 (lab mean- 521.8)



Dr. Sabina Langer

Department of Hematology,

Sir Ganga Ram Hospital,

India

Recurrent Hemorrhagic Bullae on the Tongue: A Rare Hemorrhagic Manifestation of Primary Antiphospholipid Syndrome

Aditi kundoo[1], Ananya Kumar[2] and Sabina Langer[1*]

[1]Department of Hematology, Sir Ganga Ram Hospital, India

[2]Bharati Vidyapeeth Deemed University, India

***Corresponding author:** Sabina Langer, Department of Hematology, Sir Ganga Ram Hospital, New Delhi-110060, India, E-mail: sabinapost@yahoo.com

Received Date: May 27, 2021; Published Date: July 21, 2021

Citation: Aditi kundoo, Ananya Kumar and Sabina Langer. Recurrent Hemorrhagic Bullae on the Tongue: A Rare Hemorrhagic Manifestation of Primary Antiphospholipid Syndrome. J Clin Case Rep On. 2021;1(1):1010

Short Communication

Primary antiphospholipid syndrome is diagnosed based on clinical and lab criteria which commonly included repeated abortions or increased thrombosis in both arterial and venous channels. It does not commonly come in differential diagnosis of patients chiefly presenting with haemorrhage. High level of suspicion and correct diagnostic algorithm can help us reach the final diagnosis.

A 29-year-old man belonging to sindhi community presented to the haematology OPD with history of recurrent haemorrhagic bulla on tongue associated with acute pain (Figure 1). Patient had one episode of nose bleed 4 months back which resolved on its own. Past history of chicken pox was present. The patient was non-smoker/non tobacco chewer. No significant medical or family history was present. On examination the vitals of the patient were stable. No other mouth lesion/ulcer was seen and oral hygiene was good. The CBC showed Hb- 14.5g/dl, WBC-6890/microlitre, Platelet-2,55,000/microlitre. The Prothrombin Time (PT) was 12.5 seconds and Activated Partial Thromboplastin Time (APTT) was 48 seconds. Thrombin time was 15.3 seconds (Normal-10.3-16.6 seconds). The patient was then worked up for coagulopathies outside. Fibrinogen levels were 2.33g/L. VWF was 114.4%; VWF: RCo/VWF ratio of 0.7(normal->0.7); VWF: RCo-98.5% (Normal: 60.8-239.8) and VWF: Ag was 146 (Normal: 66.1-176.3). Factor VIII levels were 114.4% thus indicating that the prolongation of APTT was not because of fallacy in coagulation factors. Further work up was then done for determination of elevated APTT in our laboratory. APTT Mixing study showed a correction of 41.2% which was less than lab cut off of 58% indicating presence of inhibitors. The following tests were then done for detection of Lupus Anticoagulant (LAC) and Anticardiolipin (ACL) antibodies (Table 1).

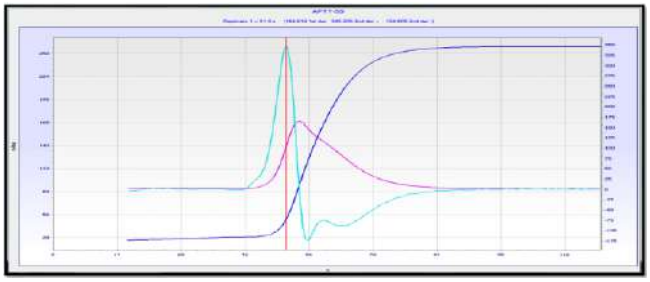


Figure 1: Haemorrhagic bullae on dorsal aspect of tongue.

Tables 1: Test results of the patient.

Test	Patient	Reference range
dRVVT screen	53.9 seconds	24.4-49.0 seconds
dRVVT screen ratio	1.47	<1.2
dRVVT confirm	26.7 seconds	23.3-33.5 seconds
dRVVT confirm ratio	0.94	<1.2
Normalized dRVVT ratio	1.56	1.2-1.5- LA weekly + 1.5-2.0-LA moderately + >2.0- LA strongly +
dRVVT screen (1:1 mix)	52.5 seconds	24.4-49.0 seconds

dRVVT screen ratio (1:1 mix)	1.43	<1.2
dRVVT confirm (1:1 mix)	28.2 seconds	23.3-33.5 seconds
dRVVT confirm ratio (1:1 mix)	0.99	<1.2
Normalized dRVVT ratio (1:1 mix)	1.86	1.2-1.5- LA weekly + 1.5-2.0-LA moderately + >2.0- LA strongly +
SCT screen	105.8 seconds	33.0-60.6 seconds
SCT confirm	29.9 seconds	24.0-38.8 seconds
SCT ratio	2.37 seconds	>1.16-Positive
SCT screen (1:1 mix)	73.3 seconds	33.0-60.6 seconds
SCT confirm (1:1 mix)	34.3 seconds	24.0-38.8 seconds
SCT ratio (1:1 mix)	2.13 seconds	>1.16-Positive seconds
Anticardioplipin antibodies IgG	6.5 GPL U/ml	<12: Negative 12-18: Equivocal/doubtful >18: Positive
Anticardioplipin antibodies IgM	32.0 MPL U/ml	<12: Negative 12-18: Equivocal/doubtful >18: Positive
β2 GPI IgM	10.70 AU/ml	<12: Negative 12-18: Equivocal/doubtful >18: Positive
β2 GPI IgG	<3.00 AU/ml	<12: Negative 12-18: Equivocal/doubtful >18: Positive

The interpretation was moderately positive LAC with presence of IgM anticardiolipin antibodies. The patient was then further worked for detection of secondary causes of Antiphospholipid Syndrome (APS). Antibodies to ds DNA were negative (<10.0 IU/ml) and the antinuclear antibody profile was also negative. Thus, the final diagnosis of primary APS was considered and no evidence of any thrombotic events was found when the patient was worked up. The patient was started on oral steroids. Repeat testing was done three months later and was positive confirming the diagnosis of primary APLA syndrome with unique presentation of recurrent haemorrhagic bullae.

Retrospectively, we analysed the clot waveform of APTT of the patient and compared it to the mean normal control of our lab which depicted the increase in Max 1 and Max 2 values (Figure 2).

Parameters	Initial	12 weeks follow-up
APTT (seconds)	60.7	54.4
Maximum velocity (mabs/sec)	241.8 (Lab mean-163)	193.5 (Lab mean-163)
Maximum acceleration (+mabs/sec2)	1280.8 (lab mean- 1326)	1932.6 (lab mean 1326)
Maximum deceleration (-mabs/sec2)	541.1 (lab mean- 521.8)	614.8 (lab mean- 521.8)

Figures 2: Clot wave form pattern of the case.

Haemorrhagic blisters on the tongue can be seen commonly in the ENT practice and cause can be attributed to vague steroids use which is commonly seen in ENT practise [1]. Angina Bullosa Hemorrhagica (ABH) is a rare benign disorder characterized by sudden onset of painless, blood-filled, blisters of the oral cavity that quickly expand and rupture spontaneously within 24 to 48 hours [2].

The revised Sapporo classification criteria of 2006 subdivide APS into thrombotic and obstetric subtypes [3]. However, there are no classification involving haemorrhagic manifestations of APS even though the therapeutic approach is in contrast to Vitamin K antagonists usually prescribed in APS. Thrombocytopenia is one of the common clinical features of APS [4] however, bleeding and haemorrhagic

manifestations in the APS are highly uncommon including even catastrophic APS [5]. Causes of bleeding in APS can be due to thrombocytopenia, thrombocytopathy, acquired coagulopathies or rarely non neutralising antibody against prothrombin leading to Hypoprothrombinaemia (HPT). The HPT in APS can cause both decreased prothrombin activity and antigen levels [6]. In our case, patient had a normal platelet count as well as normal factor VIII and IX activity, thus the most likely the recurrent haemorrhagic bullae formation can be attributed to HPT. However, it wasn't tested due to lack of resources. In most of the haemorrhagic cases of APS, symptoms resolve itself and only rarely blood transfusion or steroids are prescribed. In the APS cases with low platelet count (<30,000) and haemorrhage are treated with steroids similar to ITP treatment [7].

First case of haemorrhagic presentation in APS was reported in a 17-year-old girl [8]. Only few cases are reported in the literature presenting an acute bleeding manifestation in adult patients. The usual haemorrhagic symptoms are gum bleeding, epistaxis, diffuse muscular haemorrhage, brain haemorrhage and gastrointestinal bleeding. The recurrent haemorrhagic bullae on tongue although commonly seen in ENT practice is reported first time in a case of primary APS to the best of our knowledge. Interestingly, according to Cervera et al. [9] haemorrhagic manifestations of APS are more commonly seen in secondary APS (41%) in comparison to primary APS (20%) [9], although in our case, result of workup of autoimmune disease was negative.

Because of haemorrhagic manifestation of our patient, doctor refrained from prescribing anticoagulants and the patient was started on high dose glucocorticoid (20 mg, Omnacortil). The corticosteroids impair the phagocytic activity of macrophages and thus lead to increased prothrombin activity by slowing the clearance of the antigen antibody complexes. It has been studied that the corticosteroids reduce the aPT titers and LA activity but has no effect on aCL and B2GPI levels [10], thus the repeat testing post 12 weeks as mandated by Revised 2006 guidelines can still be done.

However, as briefly mentioned earlier, there are several limitations in these guidelines such as non-inclusion of haemorrhagic or even neurological manifestations in the diagnostic criteria. Other limitations are exclusion of IgA isotypes of aCL/β2GPI from the diagnostic criteria although numerous studies have already proven its significant association with thrombosis and it has also been included in the Systemic Lupus ICC classification criteria of SLE [11]. Also, APL antibodies are known to decrease post therapy and even single baseline LAC confers 50% increased risk of thrombosis but a second/repeat negative test will omit the patient from the diagnostic criteria of APS leading to improper treatment and follow-up [12].

There is now introduction of new parameters for assessment of haemostasis in APS patients such as Activated Protein C (APC) resistance, Endogenous Thrombosis Potential (ETP), complement levels, annexin A5 resistance and domain 4/5 specific B2GPI auto-antibodies which can be studied and standardised for increasing the sensitivity and specificity of diagnosis as well assessment of risk of thrombotic/haemorrhagic manifestations. There is a dire need to revise the 2006 guidelines to counter all the aforementioned limitations.

Conclusion

Even though the thrombosis and obstetric manifestations of the APS are well classified and documented rare haemorrhagic manifestations such as in our case should be kept in mind while ruling out the causes of raised APTT especially when the inhibitors and factor deficiencies have been ruled out.

References

1. Yamamoto K, Fujimoto M, Inoue M, Maeda M, Yamakawa N, Kirita T. Angina bullosa hemorrhagica of the soft palate: report of 11 cases and literature review. J Oral Maxillofac Surg. 2006;64(9):1433-6.
2. Paci K, Varman KM, Sayed, CJ. Hemorrhagic bullae of the oral mucosa. JAAD Case Rep. 2016;2(6): 433-5.
3. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement

on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost. 2006;4(2):295-306.

4. Cervera R, Boffa MC, Khamashta MA, Hughes GR. The Euro-Phospholipid project: epidemiology of the antiphospholipid syndrome in Europe. Lupus. 2009;18(10):889-93.
5. Finazzi G, Brancaccio V, Moia M, Ciaverella N, Mazzucconi MG, Schinco PC, et al. Natural history and risk factors for thrombosis in 360 patients with antiphospholipid antibodies: a four-year prospective study from the Italian Registry. Am J Med. 1996;100(5):530-6.
6. Bajaj SP, Rapaport SI, Fierer DS, Herbst KD, Schwartz DB. A mechanism for hypoprothrombinemia of the acquired hypoprothrombinemia-lupus anticoagulant syndrome. Blood. 1983;61(4):684-92.
7. Uthman I, Godeau B, Taher A, Khamashta M. The hematologic manifestations of the antiphospholipid syndrome. Blood Rev. 2008:22(4):187-94.
8. Rapaport SI, Ames SB, Duvall BJ. A plasma coagulation defect in systemic lupus erythematosus arising from hypoprothrombinemia combined with antiprothrombinase activity. Blood. 1960;212-27.
9. Cervera R, Boffa MC, Khamashta MA, Hughes GR. The Euro-Phospholipid project: epidemiology of the antiphospholipid syndrome in Europe. Lupus. 2009;18(10):889-93.
10. Forastiero Rocardo. Bleeding in the antiphospholipid syndrome. Hematology. 2012;17 Suppl 1:S153-5.
11. Yelnik CM, Laskin CA, Porter TF, Branch DW, Buyon JP, Guerra MM, et al. Lupus anticoagulant is the main predictor of adverse pregnancy outcomes in aPL-positive patients: validation of PROMISSE study results. Lupus Sci Med. 2016;3(1):e000131.
12. Somers E, Agder LS, Petri M. Antiphospholipid antibodies and incidence of venous thrombosis in a cohort of patients with systemic lupus erythematosus. J Rheumatol. 2002:29(12):2531-6.