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Case Report

A mysterious hematochezia in an adolescent boy: atypical presentation of childhood systemic lupus erythematosus

Abhik Paul, Sandeep Ghosh*, Saherin Jesmin, Sananda Pati

Department of Paediatric Medicine, Institute of Post Graduate Medical Education and Research, Kolkata, India

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***Correspondence:**
Dr. Sandeep Ghosh,
E-mail: sandeep.ghosh027@gmail.com

ABSTRACT

Thrombosis is a well-known entity in presence of antiphospholipid antibody (APLA) associated with systemic lupus erythematosus (SLE) as a hematological complication. Bleeding manifestations instead of thrombosis is hardly found in literature in presence of APLA seromarkers in SLE. Since these can range from minor bleeding like epistaxis to major life-threatening intracranial bleeding, early diagnosis and prompt treatment is essential to manage such condition. We report a 12 years old boy with no significant past history presented with hematochezia and epistaxis along with pallor requiring blood transfusion. Hematological investigations were normal except for elevated PT, aPTT and INR. Common causes of coagulopathy were ruled out. Upon suspecting systemic diseases, the investigations were carried out which revealed ANA 4+ along with high titre of dsDNA, low C3 and C4 complement and positive anti-β2 glycoprotein, anticardiolipin antibody and lupus anticoagulant. Diagnosis of SLE was made according to ACR-EULAR criteria with no renal involvement. Immunological basis was considered for coagulopathy in this child. He was started on oral prednisolone, hydroxychloroquine and methotrexate. He is now under close monitoring of the coagulation profile for titration of steroid dose. We want to create awareness about the uncommon hematological manifestation of SLE presenting as bleeding diathesis instead of thrombosis through this case report and that can be life threatening too if not treated promptly. A high index of suspicion and careful follow-up may help in preventing adverse outcome of the disease.

Keywords: SLE, LAHS, Hypoprothrombinemia, Lupus anticoagulant, Bleeding

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem chronic autoimmune disease that manifests differently according to involvement of various organs. The hematological manifestations generally present as mild leukopenia, thrombocytopenia and anemia. Other hematological manifestation includes thrombosis, seen in 10-15% of SLE patients in presence of lupus anticoagulant.[1] On the other hand the bleeding manifestation is uncommon in SLE. It may be due to thrombocytopenia or clotting factor deficiency, most frequently prothrombin (clotting factor II).[2] As this bleeding manifestation mainly attributed to immunologic cause, immunosuppressant therapy is the key for management. This case report describes a young adolescent boy presented with bleeding manifestation in form of hematochezia and epistaxis, later found to have systemic lupus erythematosus.

CASE REPORT

A 12 years old boy, second born, out of a nonconsanguineous marriage, presented to our institute with the chief complaints of hematochezia for 3 days and two episodes of blood tinge vomitus. He was treated conservatively with two units of packed red blood cell at a local hospital for severe pallor. He had no history of yellowish discolouration of eyes, any drug intake, rash, hematuria, hemarthrosis, prolonged bleeding from minor cut. On examination, he was afebrile, moderately pale and anicteric. There was no rash or cutaneous bleeding Blood

pressure was 106/70 mm of Hg (between 50th-90th percentile according to height and age). He had a body-weight of 32 kg (-1.39 Z-score for age) and height of 149 cm (-0.36 Z-score for age). Systemic examination was normal.

During hospital stay, he had epistaxis without any history of trauma. His mother was also complaining of an intermittent low grade (100.6ºF-100.9ºF) fever with myalgia, arthralgia. No other bleeding manifestations, features of arthritis, rash were found.

Management and outcome

In view of recurrent bleeding manifestation, the possibility of acquired coagulopathy due to chronic liver disease and hematological malignancy was considered. The laboratory investigations showed anemia with normal reticulocyte count, total leucocyte and platelet count along with normal ESR and CRP. Peripheral blood smear revealed microcytic hypochromic RBCs with no blast cells. The liver function and kidney function profile were normal except borderline low serum albumin level. The coagulation profile showed raised prothrombin time (PT), activated partial prothrombin time (aPTT) and INR though thrombin time was normal (Table 1). The patient had deranged coagulation profile persistently even after parenteral vitamin-K therapy. Abdominal ultrasonography showed normal liver echotexture. Upper gastrointestinal endoscopy and colonoscopy were also non-contributory.

It seemed to be a case of coagulopathy, but the initial differentials were not consistent with laboratory parameters. He was evaluated for connective tissue disorders in view of fever, arthralgia, myalgia and pallor. The Anti-Nuclear antibody (ANA) test showed 4+ with homogenous pattern along with low complement -C3 and C4 level. The anti-dsDNA antibody was also positive at high titre along with anti-nucleosome and anti-histone antibody. In view of the deranged coagulation profile, the APLA panel was done which came positive for anti-β2 glycoprotein IgM and anticardiolipin IgM and IgG along with lupus anticoagulant. A diagnosis of SLE was made according to ACR-EULAR criteria. 24-hour urinary protein excretion was within normal range with normal kidney function profile, so kidney biopsy was not considered. Serosal involvement was also ruled out.

He was started on oral prednisolone at 1 mg/kg/day along with hydroxychloroquine at 4 mg/kg/day and methotrexate at 15 mg/m^2/week with folic acid supplementation. Serial coagulation profile (Figure 1) showed normalisation of PT and INR, but persistently elevated aPTT. No further episode of bleeding manifestation occurred. He is now under close monitoring of the coagulation profile for titration of steroid dose.

Table 1: Trends of laboratory parameters.

Parameter	At admission	Day-7	Day-28	Day-90	Reference range
Hemoglobin	9.6	9.8	10.8	12.1	10.5-14.0 g/dl
TLC	6400	6900	9000	9200	6000-14000/mm^3
Platelet	3.3	3.6	3.5	2.8	1.5-4.0 lakh/mm^3
Total bilirubin	0.5	0.6	0.4	0.3	0.2 -1 mg/dl
Serum protein	5.4	5.6	5.2	6.4	6.1-7.9 g/dl
Serum albumin	3.3	3.4	3.7	4.5	3.5-5 g/dl
ALT/AST/ALP	53/41/77	55/45/88	45/42/92	37/26/90	12-45/22-63/145-230 U/l
Urea/creatinine	26/0.7	32/0.6	34/0.6	44/0.6	20-40/0.03-0.50 mg/dl
PT/aPTT	24.5/81.5	29/78.5	19/64.5	12.9/53.3	10-13/24-36 s
INR	2.02	2.39	1.56	0.91	
Factor VIII/IX activity	84%/99%	-	-	98%/109%	50-150%
ANA	4 + Homogenous	-	-	-	
DsDNA	1040	-	-	55.00	<100 U/ml
C3 / C4	37.4/7.63	-	-	136/25.7	90-180/10-40 mg/dl
Anti B2-GP IgM/IgG	77.14	-	-	14.7/4.87	<20 RU/ml
Anti cardiolipin IgM/IgG	21.85/85.36	-	-	<2.0/8.75	<12 PL-U/ml
Lupus anticoagulant	Present	-	-	Present	
Urine RBC	0–1	1–2	0–1	Nil	<5/hpf
24-hour U. protein	176	-	-	214	<500 mg/day

TLC: total leucocyte count, ALT: alanine aminotransferase, AST: aspartate aminotransferase, ALP: alkaline phosphatase, PT: prothrombin time, aPTT : activated partial thromboplastin time, INR: international normalised ratio, ANA: antinuclear antibody

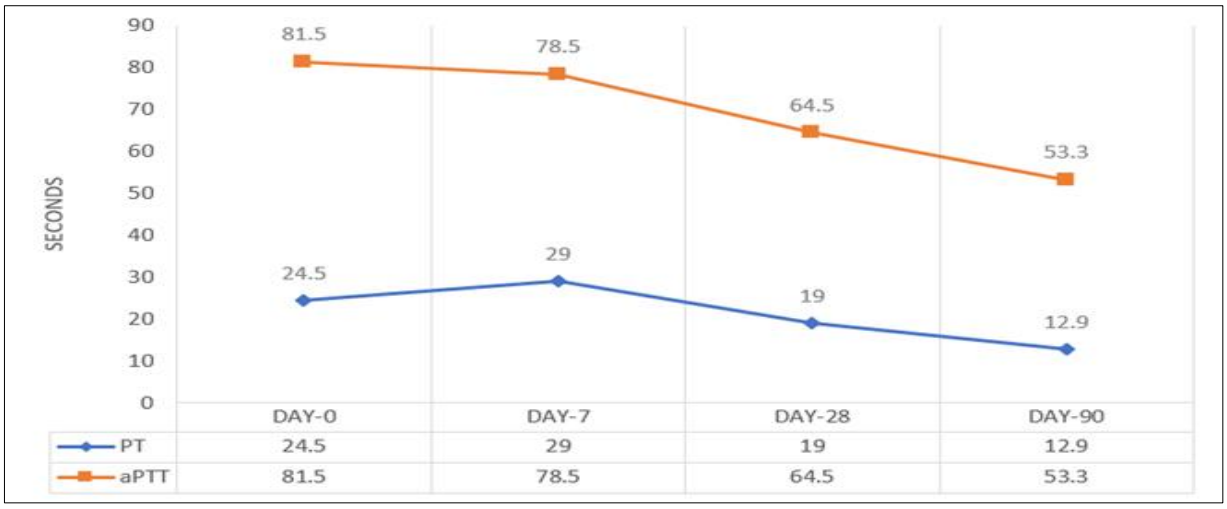

Figure 1: Trends of PT, aPTT over time and medications.

Pred: Prednisolone, MTX: methotrexate, HCQS: hydroxy chloroquine

DISCUSSION

SLE is a chronic multisystemic disease with presence of autoantibodies against self-antigens. The hematological manifestation of SLE can be leucopenia, thrombocytopenia, anemia. Addition to this thrombosis can be seen in about 10-15% of SLE patients. Bleeding is an uncommon feature in SLE but when it is present, the patient should be investigated for thrombocytopenia, severe uremia and presence of lupus anticoagulant with antibody against the clotting factors, more commonly factor-II.[1] Anti-phospholipid antibody (either lupus anticoagulant or anticardiolipin antibody or anti–β2 glycoprotein I antibody) may be positive in around 11-87% pediatric SLE patients.[3] Lupus anticoagulant is commonly recognised to be associated with thrombosis rather than bleeding manifestation.[4] Acquired deficiency of factor-II is the most well-known among the all coagulation factor deficiencies in presence of anti-phospholipid antibodies and this condition is known as lupus anticoagulant hypoprothombinemia syndrome (LAHS).[5] This deficiency of factor-II is attributed to the presence of antibody against the prothrombin which leads to bleeding manifestations.

The association between presence of lupus anticoagulant and antibody against prothrombin may be attributed to cross-reactivity between antiphospholipid antibodies and the epitopes on prothrombin molecule. The hypoprothombinemia due to antibodies become clinically evident only when the prothrombin/prothrombin-antibody complex clearance is accelerated. The accelerated clearance actually explains the pediatric predominance of this condition as children have more rapid hepatic clearance mechanism as compared to adults.[2] LAHS is more common in children with more than 50% of the reported cases are below 16 years of age.[3] Few case reports have been summarised in Table 2.

Table 2: Review of literature of children with SLE-LAHS.

Author, year Geographical area	Age (years)/ gender	PT/aPTT Platelet count/ factor assay	Lupus antico-agula-nt	Bleeding manifestation	Treatment given	Follow-up and outcome
Punnen et al, 2021, Tamil Nadu, India[6]	10/F	31/159.9/2.2 lakh/mm^3/low factor II level (4.6%)	Positi-ve	Hematuria, epistaxis	Oral pred at 1 mg/kg/day slowly tapered over 3-month, oral HCQS	After 3 months: no bleeding normalisation of PT, still prolonged aPTT
Bhowmick et al, 2020, Tamil Nadu, India[4]	7/M	26.7/139.7/5.9 lakh/mm^3/low factor II level (8.6%)	Positi-ve	Epistaxis, oral cavity bleeding	Oral pred @2 mg/kg/day	After 2 weeks: normalisation of PT and INR and no further bleeding
Pilania et al, 2018, Chandigarh, India[3]	7/M	25/60/3.26 lakh/mm^3/low factor II level (3.7%)	Positi-ve	Gum bleeding, ecchymoses, hemoptysis	IV MP followed by oral pred, MMF, HCQS	After 4 months: normalisation of factor II level and no further bleeding episode

Continued.

Author, year Geographical area	Age (years)/ gender	PT/aPTT Platelet count/ factor assay	Lupus antico-agula-nt	Bleeding manifestation	Treatment given	Follow-up and outcome
Kim et al, 2014, Korea[7]	15/F	28.6/>120/19000/mm^3/ low factor II level (3.3%)	Positi-ve	Skin bruises, pulmonary hemorrhage	IV MP and IVIg	Died
Favier et al, 2012, France[8]	11/F	18.7/116/84000/mm^3/low factor II level (5%)	Positi-ve	Petechiae, persisting bleeding from tooth extraction, hematuria	FFP, IVIg, IV MP, IV CYP and maintenance on MMF	After 2 years: no further bleeding
Yacobovich et al, 2001, Israel[9]	12/F	68/high aPTT/2.82 lakh/mm^3/low level of factor II (5%), factor IX (17%), factor XI (29%)	Positi-ve	Bilateral intramuscular hemorrhage of gastrocnemius muscle	Oral pred at 2 mg/kg/day and HCQS followed by gradual tapering	After 1 year: asymptomatic, off-pred, normal factor II level

Pred: Prednisolone, HCQS: hydroxychloroquine, MP: methyl-prednisolone, MMF: mycophenolate mofetil, IvIg: intravenous immunoglobulin, CYP: cyclophosphamide

In our case, the boy presented with bleeding manifestation without thrombocytopenia led us to think about possibility of acquired coagulation factor deficiency secondary to autoantibody. The factor-II deficiency leading to LAHS should be suspected as it is more common and well known to be associated with lupus anticoagulant positivity. The main clue toward our diagnosis is prolongation of PT and aPTT. As prolonged PT could not be caused by lupus anticoagulant, hypo-prothombinemia can explain the prolongation of both PT and aPTT.[2] Unfortunately, we could not do the factor-II activity assay in our patient due to financial constraints.

The coagulopathy is attributed to immunologic mechanism, hence the main goal of the treatment is immunosuppression. The initial management is supportive treatment with fresh frozen plasma, platelets, factor concentrate and packed red cell transfusion to stop any active bleeding along with immunosuppressant medication (steroids with or without combination of azathioprine, cyclophosphamide, mycophenolate mofetil, IVIg or Rituximab). There is no standardised management recommendation exists for LAHS.[3] Monotherapy with corticosteroid is efficient in most cases.[5] In our case, he is being treated with oral prednisolone along with hydroxychloroquine and methotrexate. He showed response in form of normalisation of PT with no further bleeding episode during follow-up, implying resolution of prothrombin deficiency state. But, aPTT is still high that can be explained by the presence of lupus anticoagulant. Since the risk of thrombosis is still there due to presence of antiphospholipid antibodies, both the risk for bleeding and thrombosis should be carefully evaluated during treatment and follow-up and if required the bleeding cessation therapy should be counterweighted by antithrombotic therapy.[5]

CONCLUSION

We want to create awareness about the uncommon hematological manifestation of SLE presenting as bleeding diathesis instead of thrombosis in presence of APLA seromarkers. Early diagnosis and prompt treatment ameliorates fatal hemorrhagic complications. Close follow up is essential to balance the life threatening hemorrhagic and thrombotic tendencies.

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