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Acquired Inhibitors to Coagulation Factors in a Male Patient with Systemic Lupus Erythematosus: A Case Report and Review of the Literature

Ozgur ERDEM, Orhan AYYILDIZ, Mehmet AYBAK

[1] Dicle University Faculty of Medicine, Department of Family Medicine
[2] Dicle University Faculty of Medicine, Department of Internal Medicine and Hematology
[3] Dicle University Faculty of Medicine, Department of Physiology, Diyarbakir, TURKEY

ABSTRACT

Acquired coagulation inhibitors are rare but acquired bleeding diathesis caused by autoimmune depletion or dysfunction of coagulation factors can be life-threatening. This occurs most frequently in elderly patients who lack disease associations. Acquired coagulation inhibitors may also arise in association with systemic lupus erythematosus (SLE). The groups of patients who suffer from SLE most frequently are women in their 2nd to 4th decade. In this case, we present a 22-year-old man with systemic lupus erythematosus who developed an acquired inhibitory to factor II, VIII, IX, X and von Willebrand factor (vWF).

Keywords: Acquired Coagulation inhibitors, Systemic Lupus Erythematosus

ÖZET

Sistemik Lupus Eritematozuslu Erkek Bir Hastada Akkiz Koagulasyon Faktör İnhibitör Gelişimi

Akkiz koagülasyon faktör inhibitörleri nadirdir ancak koagulasyon faktörlerinin disfonksiyonu veya otoümmün baskılanma nedenli akkiz kanama diyatezi yaşamı tehdit edebilir. Bu hastalıkla ilişkisiz olarak daha sık yaşlı hastalarda ortaya çıkar. Akkiz koagulasyon inhibitörleri aynı zamanda Sistemik Lupus Eritematozus (SLE) ile ilişkili olarak da meydana gelebilir. SLE, 2. ile 4. dekat arasındaki kadınlarda sıktır. Bu olguda faktör II, VIII, IX, X ve von Willebrand faktör'e (vWF) karşı akkiz inhibitör gelişen 22 yaşında SLE'li bir erkek hasta sunulacaktır.

Anahtar Kelimeler: Akkiz koagulasyon inhibitörleri, Sistemik Lupus Eritematozus

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease, characterised by multisystemic involvement, with a broad spectrum of clinical and laboratory manifestations.[1] Evidence from a broad range of basic science studies indicates that the pathogenesis of this disease is equally complex and may vary from patient to patient. The diverse expression of the common lupus syndrome may result from variable abnormalities in intersecting genetic, immunologic, hormonal, and environmental pathways.[2]

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The group of patients who suffer from SLE most frequently are women in their 2nd to 4th decade.[3,4] Coagulation dysfunctions in the course of SLE usually consist of thrombotic complications caused by the presence of antiphospholipid antibodies. Hemorrhagic events based on the production of antibodies directed against the coagulation factors are rarely observed in SLE.[5]

Acquired haemophilia is a rare but acquired bleeding diathesis caused by autoimmune depletion of factor VIII can be life-threatening. This occurs most frequently in elderly patients who lack disease associations. Acquired haemophilia may also seen with SLE, rheumatoid arthritis, Sjögren's syndrome, other autoimmune conditions, lymphoproliferative malignancy, pregnancy and as a drug reaction.[6,7] Acquired inhibitors to other caogulations factors are very rare.

Here, we describe a male patient with clinically quiescent SLE who developed acquired inhibitors to coagulation factor II, VIII, IX, X and von Willebrand factor (vWF). We also review the literature on acquired coagulation inhibitors associated with SLE.

CASE REPORT

A 22-year-old man, with 3 years history of SLE was admitted to Dicle university hospital due to epistaxis and spontaneous ecchymoses in the elbow, knee and ankle. In addition, in the clinical history there was occasional petechia and subcutaneous ecchymoses on the trunk. On admission he didn't take treatment and SLE had been successfully controlled. No physical signs of SLE exacerbation were detected. He had no family history of bleeding and was diagnosed with acquired coagulation defects.

The laboratory values were as follows: Positive antinuclear antibodies (ANA) 1:160 with homogeneous pattern and lupus anti-coagulant (LAC) screen/ LAC confirm 1.78 (n.v. 0.8-1.2; hemoglobin (Hb), 10.9 g/dl (n.v.12.2-18.1); white blood count, 6.610 /μl (n.v. 4.600-10.200); platelet count, 103x 10^3/μl (n.v 142-424); international normalized ratio (INR) of prothrombin time (PT) 1.82 (n.v. 0.88-1.20); activated partial prothromboplastin time (aPTT), 63.7 s (n.v. 25.00-35.00); FII activity 28.5% (n.v. 50-150); FVII activity 77.2% (n.v. 50-129); FVIII activity 19.5% (n.v. 50-150); and FVIII inhibitor 0.7 Bethesda units (BU)/ml; FIX activity 14.9% (n.v. 65-150); FX activity 73.8% (n.v. 77-131); vWF-Ag 55.8% (n.v. 61-157); C3 complement fraction 60.4 mg/dl (n.v. 79-152); sedimentation rate 19 mm (n.v. 1-7). Neither anti-double-stranded DNA antibodies nor anticardiolipin antibody was detected. Urinalysis failed to reveal any abnormalities. The results of blood chemistry tests are shown in Table 1.

According to anamnesis and laboratory results, acquired inhibitor to coagulation factors was diagnosed. He was treated with oral prednisolone administration (1 mg/kg/day). Three months after treatment, his laboratory date improved; hemoglobin13.9 g/dl (n.v.12.2-18.1); white blood count 12.500 /μl (n.v. 4.600-10.200); platelet count 246x 10^3/μl (n.v 142-424) ; international normalized ratio (INR) of prothrombin time (PT) 1.22 (n.v. 0.88-1.20); activated partial prothromboplastin time (aPTT) 42.3 s (n.v. 25.00-35.00); FVIII activity 45.3% (n.v. 50-150); FIX activity 25.0% (n.v. 65-150). Furthermore oral prednisolone had continued about 6 months. At the and of treatment the laboratory studies disclosed the following values: positive ANA 1:160 with homogeneous pattern and LAC screen/ LAC confirm 1.84 (n.v. 0.8-1.2); hemoglobin 14.5 g/dl (n.v.12.2-18.1); white blood count 14.800 /μl (n.v. 4.600-10.200); platelet count 275x 10^3/μl (n.v 142-424); international normalized ratio (INR) of prothrombin time (PT) 0.97 (n.v. 0.88-1.20); activated partial prothromboplastin time (aPTT) 41.2 s (n.v. 25.00-35.00); FII activity 67.2% (n.v. 50-150); FVII activity 87.7% (n.v. 50-129); FVIII activity 88.7% (n.v. 50-150); FIX activity 105.3% (n.v. 65-150); FX activity 101.9% (n.v. 77-131); vWF-Ag 105.0% (n.v. 61-157). Therefore the clotting tests were become completely normal (Table 2).

DISCUSSION

A multidisciplinary approach is recommended for SLE patients. SLE may begin in any age but especially it seems in 2nd and 4th decades.[8] SLE predominantly affects women with a high incidence and is uncommon in men.[9,10] In some previous studies, the incidence was found as 89% females and 11% males and 92% women and 8% men.[11,12] Antibodies to many clotting factors have been described in patients with SLE, including factors VIII, IX, XI, XII and XIII.[13] Acquired inhibitors to other coagulation fac-

Table 1. The results of blood chemistry tests of the patient.

	Results	Unit of Measurement	Normal Values
Urea nitrogen	39	mg/dl	10-45
Creatinine	0.9	mg/dl	0.6-1.3
Sodium	151	mmol/L	136-145
Potassium	4.1	mmol/L	3.5-4.5
Chlorine	116	mmol/L	98-109
Calcium	8.5	mg/dl	8.4-10.2
Phosphorus	3.7	mg/dl	2.7-4.5
Uric acid	6.1	mg/dl	2.6-7.2
Alkaline phosphatase	81	U/L	40-150
Aspartate aminotransferase	19	U/L	10-40
Alanine aminotransferase	13	U/L	10-35
Lactate dehydrogenase	190	U/L	125-243
Triglycerde	149	mg/dl	50-180
Cholesterol	104	mg/dl	112-200

Table 2. Pre-treatment and post-treatment clotting tests results.

CLOTTING TESTS	Pre-treatment	Post-treatment
ANA*	1:160	1:160
LAC** screen/ LAC confirm	1.78	1.84
Platelet Count	103x $10^3/\mu l$	275x $10^3/\mu l$
INR***	1.82	0.97
APTT****	63.7	41.2
FII activity	28.5%	67.2%
FVII activity	77.2%	87.7%
FVIII activity	19.5%	88.7%
FIX activity	14.9%	105.3%
FX activity	73.8%	101.9%
vWF-Ag	55.8%	105.0%

*ANA: Antinuclear antibodies **LAC: Lupus anti-coagulant

***INR: International normalized ratio

****APTT: Activated partial thromboplastin time

tors, including factors IX, XI, XIII, vWF protein, and the vitamin K-dependent proteins are extremely rare.[7] In patients with acquired FVIII inhibitors, soft tissues and skin hemorrhages are the most frequent symptom. The inhibitory titers do not always correlate with the severity or patterns of bleeding.[14] The underlying causes vary, but it should be noted that the FVIII inhibitory level is not always correlated with underlying disease activity.[24] Acquired inhibitors of FVIII have rarely been reported in the presence of SLE.[22] In our case, acquired hemophilia developed after a long-lasting remission of SLE. There was no evidence of any triggering event able to induce a specific antibody production or unspecific B cell stimulation such as infections as vaccines.

FVIII auto-antibody inhibitors, though rare, may present significant and often life-threatening haemorrhage. The principles of therapy are similar to those which apply to the management of FVIII auto-antibodies. Treatment of patients with acquired FVIII inhibitors varies depending upon the underlying medical condition, the titre of the inhibitory, and the clinical presentation.[7] When reviewing literature, there was no consensus on the treatment of SLE associated with FVIII inhibitors. The aims of treat-

Table 3. Review of reported cases with acquired hemophilia in patients with systemic lupus erythematosus (SLE)

Case no	Author (Reference no)	Age/ sex	APTT* (s) * (s)	FVIII level (%)	FVIII inhibitor (BU**/ml)	SLE activity	Treatment (outcome)
1	Pirner et al.[19]	27/F	77	<3	1.4	Active	Com. Theraphy (improved)
2	Schwartz et al.[20]	40/F	NA	<1	7.2	NA***	Com. Theraphy (improved)
3	Schulman et al.[21]	27/F	42	<1	16	Active	Com. Theraphy (improved)
4	Lafferty et al.[22]	45/F	66	<1	2.8	NA	Com. theraphy (improved)
5	Trotta et al.[23]	19/F	54.6	3	2.8	Active	Com. theraphy (improved)
6	Ishikawa et al.[24] Nishino et al.[25]	24/F	116	2.8	46.5	Inactive	Com. theraphy (improved)
7	Kornfeld et al.[26]	30/F	79	1	7.7	Active	Com. theraphy (improved)
8	Onishi et al.[27]	54/F	77.3	<2	38.7	Inactive	Com. theraphy (improved)
9	Akahoshi et al.[28]	39/F	90.4	<1	1.3	Active	Com. theraphy (improved)
10	Present case	22/M	63.7	19.5	0.7	Inactive	Mono theraphy (improved)

*APTT: Activated partial thromboplastin time, **BU: Bethesda unit, ***NA: not available, Mono therapy: Prednisolone,

Combination therapy: Factor VIII concentrate, Azathioprine, Cyclophosphamide, Ccyclosporine, Intravenous immunoglobulin, Activated prothrombin complex concentrate, Plasmapheresis, Dexamethasone, Methotrexate, Prothrombin complex concentrate.

ment are to eliminate the inhibitory by immunosuppression and to treat the bleeding, which is the most common cause of death in patients with acquired haemophilia.[6] Elimination of the inhibitory is usually achieved through long-term immunosuppression of antibody formation with corticosteroids, cytotoxic agents, such as cyclophosphamide and cyclosporine, or combination therapy, as well as intravenous immunoglobulin therapy and/or plasmapheresis or immunoadsorption.[15,16] To reduce or eliminate FVIII inhibitory, several therapeutic interventions have been tried. Prednisolone and cyclophosphamide are generally used to treat acquired hemophilia. The inhibitory is abolished in up to 70% of patients using prednisolone and cyclophosphamide.[6] Glucocorticoids are recommended as an initial treatment of non-hemophilic patients with FVIII inhibitory[17] and cyclophosphamide is effective as second-line therapy for many of those who are steroid resistant.[15,18,22]

Among previous investigations of acquired hemophilia along with SLE, ten cases (including our case) are available, and the features of these reported cases are summarized in Table 3.[19-28] As reported in other similar cases, a careful follow-up of the clotting tests is important to evaluate the response to therapy and the risk of new hemorrhagic manifestations. In our case normalization of the clotting tests were achieved after 6 month since the start of treatment which was enough monotheraphy with prednisolone, although other nine similar cases were needed combination therapy for controlling the disease.

When we reviewing literature about developing acquired inhibitors to coagulation factors with SLE patients we have found some cases that developing acquired inhibitors to FIX (5), FXI [29] and FXIII [30] with or without FVIII. However, in our case acquired inhibitors developed not only against FVIII but also to FII, FIX, FX and vWF-Ag.

According to our reviewing literature, so far, our case is the only male patient with SLE who developed acquired coagulation inhibitors against to FII, FVIII, FIX, FX and vWF-Ag

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Correspondence

Dr. Özgür ERDEM

Dicle Üniversitesi Tıp Fakültesi

Aile Hekimliği Anabilim Dalı

DİYARBAKIR / TURKEY

Tel: (+90.412) 248 80 01 / 5662

E-mail: dr.oerdem@hotmail.com