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Case Report

Gastrointestinal Bleeding in Lupus Anticoagulant-Hypoprothrombinemia Syndrome with Atypical Chronic Myeloid Leukemia, BCR-ABL1-Negative

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Abstract

A 78-year-old man was transported to our hospital with dyspnea and melena. He had been administered hydroxycarbamide for Atypical Chronic Myeloid Leukemia, BCR-ABL1-negative (aCML), and edoxaban for a history of cerebral infarction. Laboratory tests showed severe anemia, prolonged prothrombin time and prolonged activated partial thromboplastin time. Plasma-mixed testing indicated Lupus Anticoagulant (LA), which was confirmed using dilute Russell's viper venom time. Coagulation factor activities were decreased and positive results were obtained for coagulation factor inhibitor activities. Lupus Anticoagulant-Hypoprothrombinemia Syndrome (LAHPS) was diagnosed. LAHPS is mostly associated with systemic lupus erythematosus or infectious diseases in young patients, but concomitant LAHPS and aCML has not previously been reported. This finding suggests that malignant neoplasms might be underlying diseases in elderly LAHPS patients.

Keywords: Lupus Anticoagulant (LA); Lupus Anticoagulant-Hypothrombinemia Syndrome (LAHPS); Atypical Chronic Myeloid Leukemia; BCR-ABL1-negative (aCML)

Introduction

Lupus Anticoagulant (LA) is defined as an immunoglobulin that inhibits phospholipid-dependent coagulation activity [1], and an association with thrombosis has been identified in antiphospholipid antibody syndrome [2,3]. Lupus Anticoagulant-Hypoprothrombinemia Syndrome (LAHPS) is defined as a syndrome of acquired hypoprothrombinemia and LA, and is associated with bleeding events as well as thrombosis [4,5]. LAHPS is a very rare disease, mostly concurrent with Systemic Lupus Erythematosus (SLE) or infectious diseases in young patients [6,7]. Recently, LAHPS has been reported concomitant with hematological malignancies, including malignant lymphoma, in elderly patients [8,9].

Atypical Chronic Myeloid Leukemia, BCR-ABL1-negative (aCML) is a rare hematological malignancy with poor prognosis [10]. The incidence is estimated as only 1–2 aCML cases for every 100 cases of BCR-ABL1-positive Chronic Myeloid Leukemia (CML), and CML has an annual incidence of 1–2 cases per 100,000 population [11]. Although an increased white blood cell count is one of the main clinical characteristics of aCML, the number of blasts is not usually increased, and no characteristic gene abnormality is observed. No standard treatment has yet been established.

Here we report a rare case of gastrointestinal bleeding in an LAHPS patient treated for aCML.

Case Presentation

A 78-year-old man was transferred to our hospital due to dyspnea and melena. He had undergone partial gastrectomy for gastric cancer 20 years earlier, in addition to catheter ablation on two occasions for paroxysmal atrial fibrillation, 3 years earlier and 8 months earlier. He had been referred to the department of hematology because of leukocytosis 2 years earlier, and had been diagnosed aCML with bone marrow aspiration, revealing a normal karyotype and negative results for gene mutation tests (BCR-ABL1, JAK2, and PDGFRA). Treatment with hydroxycarbamide was then started. He had also been receiving edoxaban due to cerebral infarction 3 months earlier. Initial laboratory tests revealed severe anemia, prolonged prothrombin time and prolonged activated partial thromboplastin time, as well as positive results from immunoassay fecal occult blood testing (Table 1). Heart failure was diagnosed and attributed to anemia caused by gastrointestinal bleeding. Computed Tomography (CT) showed

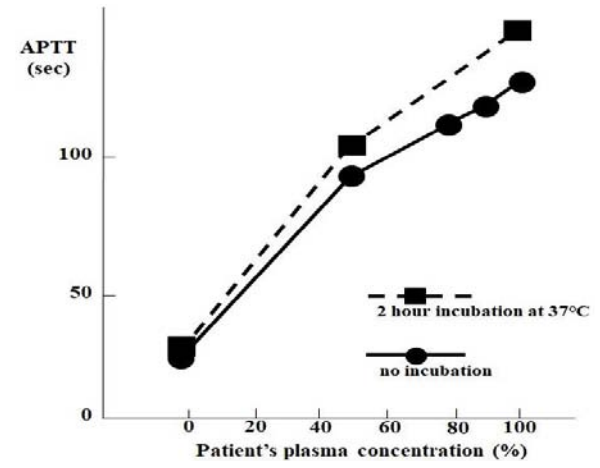

Figure 1: The plasma-mixing test, indicating a lupus anticoagulant pattern.

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Table 1: Laboratory findings at diagnosis.

Complete blood count		Biochemistry		Coagulation	
White Blood Cells	11400/μL (3300-8600)	T-Bil	0.5 mg/dL	PT (%)	43.5% (70-130)
Neutrophil	36%	AST	19 IU/L	PT INR	1.56
Eosinophil	3%	ALT	12 IU/L	APTT	132.5 sec (25-38)
Basophil	2%	LDH	165 IU/L	Fibrinogen	189 mg/dL (170-410)
Monocyte	40%	γ-GTP	26 IU/L	D-dimer	0.5μg/mL (<1.0)
Lymphocyte	19%	TP	6.3 g/dL	FII activity	42% (75-135)
Red Blood Cells	168×10^4/μL (435-555)	Alb	2.9 g/dL	FV activity	40% (70-135)
Hemoglobin	4.9g/dL (13.7-16.8)	BUN	38 mg/dL	FVII activity	44% (75-140)
Hematocrit	14.1% (40.7-50.1)	Cr	1.11 mg/dL	FVIII activity	34% 60-150)
Platelets	13×10^4/μL (15.8-34.8)	Na	137 mmol/L	FVIII inhibitor	2 BU/mL
Reticulocytes	0.40%	K	4.8 mmol/L	FIX activity	5% (70-130)
		Cl	105 mmol/L	FIX inhibitor	2 BU/mL
Immunology		CRP	0.2 mg/dL	FXII activity	9% (50-150)
ANA	40	IgG	2041 mg/dL	VWF activity	199% (60-170)
Anti ds-DNA Ab	<10	IgA	517 mg/dL		
Anti Sm Ab	negative	IgM	177 mg/dL		
Anti CL β2GP1 Ab	<1.2	β2MG	7.62 mg/L		
Anti CL IgG Ab	<8	CEA	3.6 ng/mL		
LA (dRVVT)	2.37 (<1.3)	CA19-9	5 IU/mL		

ANA: Anti-Nuclear Antibody; ds-DNA: Doble-Stranded Deoxyribonucleic Acid; Sm: Smith; CL: Cardiolipin; β2GP1: β2-Glycoprotein 1; LA: Lupus Anticoagulant; dRVVT: Diluted Russell's Viper Venom Time; T-Bil: Total Bilirubin; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; LDH: Lactate Dehydrogenase; γ-GTP: gamma-glutamyl transferase; TP: Total Protein; Alb: Albumin; BUN: Blood Urea Nitrogen; Cr: Creatinine; Na: Sodium; K: Potassium; Cl: Chlorine; CRP: C-Reactive Protein; Ig: Immunoglobulin; β2MG: β2-Microglobulin; CEA: CarcinoEmbryonic Antigen; CA19-9: Carbohydrate Antigen 19-9; PT: Prothrombin; APTT: Activate Partial Thromboplastin Time; F: Factor; VWF: Von Willebrand Factor; BU: Bethesda Unit.
Parentheses indicate normal ranges.

hepatosplenomegaly, but no lesions characteristic of infections such as pneumonia were observed. The plasma-mixing test indicated an LA pattern (Figure 1), which was confirmed using dilute Russell's viper venom time. As a result, LAHPS was diagnosed. Additional blood tests showed decreased coagulation factor activities of factor (F)II, FV, FVII, FVIII, FIX, and FXII, and positivity for coagulation factor inhibitor activities for FVIII inhibitor and FIX inhibitor (Table 1). Red blood cells were urgently transfused, edoxaban was discontinued, and administration of lansoprazole was initiated. Gastroscopy revealed no active bleeding, so the patient resumed eating, and was discharged. As of the time of writing, 6 months later, no obvious gastrointestinal bleeding has recurred.

Discussion and Conclusion

Here we report a case of LAHPS in an elderly aCML patient. To the best of our knowledge, concomitant LAHPS and aCML has not previously been reported, and this case is thus considered very rare. LAHPS is defined in LA-positive individuals showing low prothrombin activity [4,5], and clinical symptoms are basically thrombotic tendencies associated with LA, but severe bleeding tendencies have also been reported. According to reports of 74 LAHPS cases, thrombotic symptoms such as arteriovenous thrombosis were observed in 13%, bleeding symptoms in 89%, and serious bleeding such as intracranical hemorrhage in 51% [4]. In this case, cerebral infarction had occurred 3 months earlier, and might have been a symptom of LAHPS.

In this case, activities of each coagulation factor were decreased, and multiple anticoagulant inhibitor activities were also detected. Prothrombin, FVIII, FIX, and FXI are reportedly significantly reduced in LAHPS cases [4]. Distinguishing LAHPS from acquired hemophilia is particularly important.

LAHPS is a very rare disease, mostly associated with SLE or infectious diseases in young patients [6,7]. In this case, however, the patient was elderly, at 78 years old, and suffered from aCML treated with hydroxycarbamide. Negative results were obtained for autoantibodies associated with SLE such as antinuclear antibody, anti-double-stranded DNA antibody, and anti-Sm antibody. No infectious lesions were observed from CT, and inflammatory reaction was also negative. Recently, cases of hematological malignancies such as multiple myeloma or malignant lymphoma with LAHPS have been reported [8,9]. Chronic myelomonocytic leukemia, a disease in the same category as aCML, has been associated with autoimmune diseases [12]. The patient in the present case also suffered from aCML, so attention must be paid to the possibility of LAHPS concomitant with hematological neoplasms.

In conclusion, we have reported a rare case of gastrointestinal bleeding in an LAHPS patient complicated with aCML. In elderly LAHPS patients, complications of malignant neoplasms should be considered.

References

1. 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: 295-306.

2. de Laat HB, Derksen RH, Urbanus RT, Roest M, de Groot PG. Beta2-glycoprotein 1-dependent lupus anticoagulant highly correlates with thrombosis in the antiphospholipid syndrome. Blood. 2004; 104: 3598-3602.

3. Pengo V, Biasiolo A, Pegoraro C, Cucchini U, Noventa F, Iliceto S. Antibody profiles for the diagnosis of antiphospholipid syndrome. Thromb Haemost. 2005; 93:1147-1152.

4. Mazodier K, Arnaud L, Mathian A, Costedoat-Chalumeau N, Haroche J, Frances C, et al. Lupus anticoagulant-hypoprothrombinemia syndrome: report of 8 cases and review of the literature. Medicine (Baltimore). 2012; 91: 251-260.

5. Ieko M, Yoshida M, Naito S, Ohmura K, Takahashi N. Lupus anticoagulant-hypoprothrombinemia syndrome and similar diseases; experiences at a single center in Japan. Int J Hematol. 2019; 110: 197-204.

6. Erkan D, Bateman H, Lockshin MD. Lupus anticoagulant-hypoprothrombinemia syndrome associated with systemic lupus erythematosus: report of 2 cases and review of literature. Lupus. 1998; 8: 560-564.

7. Knobe K, Tedgård U, Ek T, Sandström PE, Hillarp A. Lupus anticoagulants in two children--bleeding due to nonphospholipid-dependent antiprothrombin antibodies. Eur J pediatr. 2012; 171: 1383-1387.

8. Hara Y, Makita M, Ishikawa T, Saeki K, Yamamoto K, Imajo K, et al. Lupus anticoagulant hypoprothrombinemia syndrome in Bence-Jones protein κ-type multiple myeloma patient with phosphatidylserine-dependent antiprothrombin antibody. Ann Hematol. 2013; 92: 563-564.

9. Koyama D, Hanajiri R, Kanematsu T, Ito R, Yamamoto S, Imoto N, et al. Lupus anticoagulant-hypoprothrombinemia syndrome associated with follicular lymphoma. Rinsho Ketsueki. 2020; 61: 745-749.

10. Orazi A, Bennett JM, Bain BJ, Brunning RD, Thiele J. Atypical chronic myeloid leukaemia, BCR-ABL1-negative. In: Swerdlow SH, Campo E, Harris NL, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th edn. IARC, Lyon, 2017:87-89.

11. Vardiman JW, Melo JV, Baccarani M, Radich JP, Kvashicka HM. Chronic myeloid leukaemia, BCR-ABL1-positive. In: Swerdlow SH, Campo E, Harris NL, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th edn. IARC, Lyon. 2017: 87-89.

12. Elbæk MV, Sørensen AL, Hasselbalch HC. Chronic inflammation and autoimmunity as risk factors for the development of chronic myelomonocytic leukemia?. Leuk Lymphoma. 2016; 57: 1793-1799.