

# World Journal of *Clinical Cases*

*World J Clin Cases* 2022 January 7; 10(1): 1-396



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**INDEXING/ABSTRACTING**

The WJCC is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, PubMed, and PubMed Central. The 2021 Edition of Journal Citation Reports® cites the 2020 impact factor (IF) for WJCC as 1.337; IF without journal self cites: 1.301; 5-year IF: 1.742; Journal Citation Indicator: 0.33; Ranking: 119 among 169 journals in medicine, general and internal; and Quartile category: Q3. The WJCC's CiteScore for 2020 is 0.8 and Scopus CiteScore rank 2020: General Medicine is 493/793.

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: Lin-YuTong Wang; Production Department Director: Xiang Li; Editorial Office Director: Jin-Lei Wang.

**NAME OF JOURNAL**

*World Journal of Clinical Cases*

**ISSN**

ISSN 2307-8960 (online)

**LAUNCH DATE**

April 16, 2013

**FREQUENCY**

Weekly

**EDITORS-IN-CHIEF**

Bao-Gan Peng

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

**PUBLICATION DATE**

January 7, 2022

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<https://www.wjgnet.com/bpg/gerinfo/204>

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**PUBLICATION MISCONDUCT**

<https://www.wjgnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>



# Acquired coagulation dysfunction resulting from vitamin K-dependent coagulation factor deficiency associated with rheumatoid arthritis: A case report

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**Author contributions:** Huang YJ contributed to the conception and design, and data analysis and interpretation; Chen C and Li J contributed to the administrative support, and data collection and assembly; all authors contributed to the provision of study materials, manuscript writing, and final approval of the manuscript.

## Informed consent statement:

Informed written consent was obtained from the patient for publication of this report and any accompanying images.

**Conflict-of-interest statement:** The authors declare that they have no conflict of interest to disclose.

## CARE Checklist (2016) statement:

The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

**Supported by** the National Natural Science Foundation of China, No. 81803917 and 81904024.

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## Abstract

### BACKGROUND

Rheumatoid arthritis (RA) is a common chronic inflammatory autoimmune disease with the main clinical feature of progressive joint synovial inflammation, which can lead to joint deformities as well as disability. RA often causes damage to multiple organs and systems within the body, including the blood hemostasis system. Few reports have focused on acquired coagulation dysfunction resulting from vitamin K-dependent coagulation factor deficiency associated with RA.

### CASE SUMMARY

A 64-year-old woman with a history of RA presented to our hospital, complaining of painless gross hematuria for 2 wk. Blood coagulation function tests showed increased prothrombin time, international normalized ratio, and activated partial thromboplastin time. Abnormal blood coagulation factor (F) activity was detected (FII, 7.0%; FV, 122.0%; and FX, 6.0%), indicating vitamin K-dependent coagulation factor deficiency. Thromboelastography and an activated partial thromboplastin time mixed correction experiment also suggested decreased coagulation factor activity. Clinically, the patient was initially diagnosed with hematuria, RA, and vitamin K-dependent coagulation factor deficiency. The patient received daily intravenous administration of vitamin K1 20 mg, etamsylate 3 g, and vitamin C 3000 mg for 10 d. Concurrently, oral leflunomide tablets and prednisone were

**Country/Territory of origin:** China**Specialty type:** Rheumatology**Provenance and peer review:**

Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind**Peer-review report's scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

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**Received:** December 12, 2020**Peer-review started:** December 12, 2020**First decision:** July 8, 2021**Revised:** July 21, 2021**Accepted:** November 26, 2021**Article in press:** November 26, 2021**Published online:** January 7, 2022**P-Reviewer:** Abdel Ghafar MT**S-Editor:** Zhang H**L-Editor:** Wang TQ**P-Editor:** Zhang H

administered for treatment of RA. After the treatment, the patient's symptoms improved markedly and she was discharged on day 12. There were no hemorrhagic events during 18 mo of follow-up.

## CONCLUSION

RA can result in vitamin K-dependent coagulation factor deficiency, which leads to acquired coagulation dysfunction. Vitamin K1 supplementation has an obvious effect on coagulation dysfunction under these circumstances.

**Key Words:** Acquired coagulation dysfunction; Rheumatoid arthritis; Coagulation factor deficiency; Vitamin K-dependent; Case report

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**Core Tip:** Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that frequently involves multiple organs and systems, potentially leading to coagulation dysfunction. In this paper, we report the rare case of a patient who was diagnosed with acquired coagulation dysfunction resulting from vitamin K-dependent coagulation factor deficiency associated with RA, and subsequently benefited from vitamin K1 supplementation treatment. This case report may provide some references for diagnosis and treatment of RA patients with coagulation dysfunction symptoms.

**Citation:** Huang YJ, Han L, Li J, Chen C. Acquired coagulation dysfunction resulting from vitamin K-dependent coagulation factor deficiency associated with rheumatoid arthritis: A case report. *World J Clin Cases* 2022; 10(1): 236-241

**URL:** <https://www.wjgnet.com/2307-8960/full/v10/i1/236.htm>

**DOI:** <https://dx.doi.org/10.12998/wjcc.v10.i1.236>

## INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease with the main clinical manifestations of invasive arthritis[1]. The prevalence of RA is estimated to be 0.5%–1.0% globally[2]. The clinical features of blood system damage in patients with RA usually include anemia, neutropenia, thrombocytopenia, and hematological malignancies[3]. RA can also lead to acquired coagulation dysfunction, such as acquired hemophilia. Previous studies indicated that 4%–8% of acquired hemophilia cases were related to RA and that rituximab was effective for acquired FVIII inhibitors in RA patients[4,5]. Compared with healthy people, Dimitroulas *et al*[6] found that RA patients had higher levels of coagulation factors, such as tissue plasminogen activator, plasminogen activator inhibitor, fibrinogen (FBG), prothrombin fragments 1 and 2, and thrombomodulin, indicating that an imbalance of the coagulation and fibrinolysis systems was common in RA, although the underlying mechanism is not fully understood. Nevertheless, cases of acquired coagulation dysfunction caused by RA combined with vitamin K-dependent coagulation factors deficiency are rare. To further explore the possible etiology of coagulopathy in RA patients, we report a case of acquired coagulation dysfunction resulting from vitamin K-dependent coagulation factor deficiency associated with RA.

## CASE PRESENTATION

### Chief complaints

A 64-year-old female patient was admitted to the hospital on November 27, 2019, with a chief complaint of "painless gross hematuria for 2 wk".

### History of present illness

Two weeks previously, the patient had developed painless gross hematuria with no obvious cause. She presented with a whole course of hematuria, including blood clots,

infrequent urination, urgent urination, and urodynia, without pain in the waist or lower abdomen, nausea, or vomiting. At the beginning, the patient was treated at The Fifth People's Hospital of Jingzhou City, Hubei Province, China. A computed tomography scan of the urinary system displayed a soft tissue density in her bladder. A cystoscopy was performed and intravesical blood clots were subsequently removed on November 19, 2019. However, the gross hematuria symptoms recurred after the treatment. Hence, the patient attended our hospital for medical treatment. She was admitted for hematuria of unknown etiology.

### **History of past illness**

The patient had a history of RA for 40 years, with regular treatment of oral indomethacin and prednisone tablets. At the time of admission, the patient had suffered joint pain and stiffness symptoms for several months.

### **Physical examination**

The patient had suffered joint pain and stiffness symptoms.

### **Laboratory examinations**

After admission, laboratory tests revealed the following results: Prothrombin time (PT), 38.6 s; international normalized ratio (INR), 3.97; FBG, 4.85 g/L; activated partial thromboplastin time (APTT), 109.8 s; thrombin time, 16.9 s; and D-dimer, 0.89 µg/mL FEU. The results for blood coagulation factor (F) activity were as follows: FII, 7.0%; FV, 122.0%; and FX, 6.0%. Thus, vitamin K-dependent coagulation factor deficiency was considered. Thromboelastography produced the following findings: R, 10.2 min; K, 3.6 min; angle, 57.4; MA, 76.1 mm; CI, -2.1; and LY30, 0.0%. Routine urine examination showed red blood cells (occult blood), 3+; white blood cells (granular), 3+; nitrite-positive urinary protein, 3+; specific gravity > 1.030; urine glucose, ±; ketonuria, 2+; and urinary bilirubin, 3+. An APTT mixed correction experiment was performed on December 4. The patient's APTT was 55.7 s. Her blood was then mixed with blood from a normal patient in a 1:1 ratio, and the APTT was determined immediately after mixing. The results showed that the mixed blood APTT was 41.4 s (normal control APTT, 37.3 s), and the Rosner index was 7.4 KUA/L, indicating a lack of coagulation factors. The level of rheumatoid factor (RF) was 35.4 IU/mL, RF IgG type was 25.87 RU/mL, RF IgM type was 103.81 RU/mL, and anti-cyclic citrulline polypeptide antibody was 48.4 U/mL. Antinuclear antibodies showed nuclear homogeneous type (1:100), suggesting the presence of trace amounts of antinuclear antibodies. Anti-neutrophil cytoplasmic antibody was positive for perinuclear type. C-reactive protein was 34.2 mg/L, indicating the possibility of infection or inflammation. The disease activity score in 28 joints was 3.7, indicating moderate disease activity.

Routine blood tests showed the following results: Red blood cells,  $3.35 \times 10^{12}/L$ ; hemoglobin, 86.0 g/L; white blood cells,  $5.6 \times 10^9/L$ ; neutrophils,  $3.42 \times 10^9/L$ ; lymphocytes  $1.49 \times 10^9/L$ ; and platelets,  $343.0 \times 10^9/L$ . Liver function tests were: Alanine aminotransferase, < 5 U/L; glutamic oxaloacetic transaminase, 19 U/L; total protein, 62.1 g/L ↓; albumin, 28.8 g/L ↓; globulin, 33.3 g/L; total bilirubin, 5.5 µmol/L; direct bilirubin, 2.9 µmol/L; indirect bilirubin, 2.6 µmol/L; alkaline phosphatase, 96 U/L; γ-glutamyl transpeptidase, 13 U/L; total cholesterol, 3.69 mmol/L; and lactic dehydrogenase, 244 U/L ↓. Other examinations did not show any obviously abnormal values, suggesting that no other disease condition was present.

## **FINAL DIAGNOSIS**

The final diagnosis was hematuria, acquired coagulation dysfunction, RA, and vitamin K-dependent coagulation factor deficiency.

## **TREATMENT**

The patient was given intramuscular injection of vitamin K1 (10 mg) on day 1 after admission. From November 29 to December 8, she received daily intravenous administration of 20 mg of vitamin K1, 3 g of etamsylate, and 3000 mg of vitamin C. Oral leflunomide tablets and prednisone were administered for treatment of RA.

**Table 1 Blood coagulation function test results**

Hospitalization days	PT	INR	FBG	APTT	TT	D-D	FDPs	AT	PTA
2	38.6	3.97	4.85	109.8	16.9	0.89	-	-	19
4	18.4	1.53	5.09	53.9	16.4	0.94	> 4.0	80	54
8	16.9	1.37	4.21	55.7	17.3	0.81	> 4.0	67	62
11	16.4	1.31	4.82	55.5	16.7	1.28	4.2	75	65

Normal reference range: Prothrombin time: 11.5-14.5 s; international normalized ratio: 0.5-1.2; fibrinogen: 2.0-4.0 g/L; activated partial thromboplastin time: 29-42 s; thrombin time: 14-19 s; D-D: < 0.5 µg/mL FEU; FDPs: < 0.5 µg/mL; AT: 80%-120%; PTA: 75%-125%. Hospitalization day 1 was November 27, 2019; day 2: November 28, 2019; day 4: November 30, 2019; day 8: December 4, 2019; day 11: December 7, 2019. PT: Prothrombin time; INR: International normalized ratio; FBG: Fibrinogen; APTT: Activated partial thromboplastin time; TT: Thrombin time; D-D: D-dimer; FDPs: Fibrin degradation products; AT: Antithrombin; PTA: Prothrombin activity.

## OUTCOME AND FOLLOW-UP

During the treatment period, the results of blood coagulation function tests (Table 1), blood coagulation factor activity test (Table 2) and routine urine tests (Table 3) were reviewed. PT, INR, FBG, and particularly APTT were significantly decreased (Table 1), and a trend toward gradual recovery of coagulation function was observed (Figure 1). The results for blood coagulation factor activity are shown in Table 2; FV activity returned to normal, while FII and FX activities did not return to their normal ranges, but did show significant increases compared with the previous results. A routine urine test on December 5 showed: Red blood cells (occult blood), 3+; white blood cells (granular), 1+; urinary protein, 1+; and specific gravity, 1.009. Other indicators were all normal, and the patient's hematuria symptoms had improved considerably. On December 7, the patient's urine color returned to normal. The marked improvement in the patient's symptoms continued, and she was discharged from hospital. Besides anti-rheumatoid therapy, she continued receiving vitamin K1 orally for 3 mo after discharge. The patient was followed for 18 mo, without any hemorrhagic events.

## DISCUSSION

Acquired coagulation dysfunction has a complicated etiology, and can arise secondary to liver diseases, vitamin K-dependent coagulation factor deficiency, pregnancy, neoplastic diseases, autoimmune diseases, and use of certain drugs. The present patient had no family history of hemophilia or severe bleeding tendency during the previous 60 years, or of serious bleeding during pregnancy and delivery. In the previous 2 years, in addition to oral indomethacin and prednisone tablets for treatment of RA, she was prescribed nifedipine sustained-release tablets and insulin to control blood pressure and blood glucose, respectively, with no other suspicious drug usages or toxic exposures. After combining the medical history and other laboratory examinations, the possibility of liver disease or neoplastic disease was ruled out.

The diagnosis was made on the basis of the following clinical features. First, hematuria was the main clinical symptom. Second, increased PT, APTT, and INR indicated coagulation dysfunction. Third, prolongation of the R parameter on thromboelastography suggested that coagulation factor activity was decreased. Analyses revealed that FII was 7.0% and FX was 6.0%, indicating possible vitamin K-dependent coagulation factor deficiency. The Rosner index of 7.4 (< 11) in the APTT mixed correction experiment also suggested a lack of coagulation factors. Finally, after treatment with vitamin K1, the results of routine urine analysis, coagulation function, and coagulation factor activity were significantly improved, and the urine color returned to normal. Therefore, the coagulation dysfunction in this patient may have been due to vitamin K-dependent coagulation factor deficiency, which is usually caused by a lack of vitamin K.

Vitamin K is a coenzyme for many γ-glutamyl carboxylase enzymes[7,8]. When vitamin K is lacking, the γ-glutamyl carboxylases lose their biological activity and ability to synthesize vitamin K-dependent coagulation factors, leading to the disorder of the coagulation function. A previous study found that the serum levels of vitamin K1, menaquinone-4, and menaquinone-7 in patients with RA were significantly lower than those in healthy people[9]. Therefore, RA may be the direct cause of the vitamin

**Table 2 Blood coagulation factor activity test results**

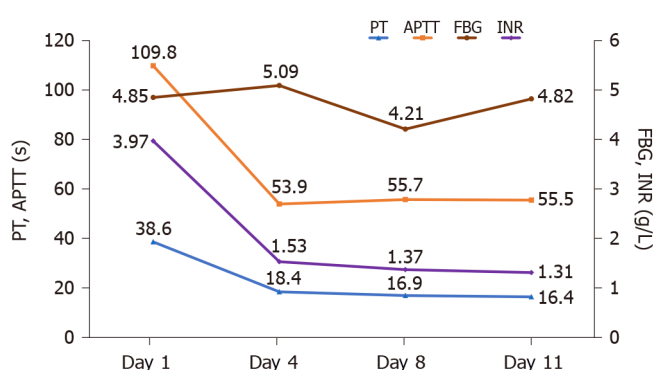
Hospitalization days	II	V	VII	VIII	IX	X	XI	XII
2	7	122	-	-	-	6	-	-
9	36	96	95	168	71	25	86	40

Normal reference range: II: 70%-120%; V: 70%-120%; VII: 55%-170%; VIII: 60%-150%; IX: 60%-150%; X: 70%-120%; XI: 60%-150%; XII: 50%-150%. Hospitalization day 1: November 27, 2019; day 2: November 28, 2019; day 9: December 5, 2019.

**Table 3 Routine urine test results**

Hospitalization days	RBCs	WBCs	Urinary protein	Nitrite	Specific gravity	Ketonuria	Urinary bilirubin	Urine glucose
3	3+	3+	3+	Positive	> 1.030	2+	3+	±
9	3+	1+	1+	Negative	< 1.009	Negative	Negative	Negative

Normal reference range: Red blood cells: Negative; white blood cells: Negative; urinary protein: Negative; nitrite: Negative; specific gravity: 1.015-1.025; ketonuria: Negative; urinary bilirubin: Negative; urine glucose: Negative. Hospitalization day 1: November 27, 2019; day 2: November 29, 2019; day 9: December 5, 2019. RBCs: Red blood cells; WBCs: White blood cells.



**Figure 1 Results for prothrombin time, activated partial thromboplastin time, fibrinogen, and international normalized ratio.** The results showed that the blood coagulation function was gradually recovering. The hospitalization days were: Day 1, November 27, 2019; day 2: November 28, 2019; day 4: November 30, 2019; day 8: December 4, 2019; and day 11: December 7, 2019. PT: Prothrombin time; APTT: Activated partial thromboplastin time; INR: International normalized ratio; FBG: Fibrinogen.

K-dependent coagulation factor deficiency, which in turn caused the coagulation dysfunction in the present patient.

Vitamin K supplementation is the main therapeutic measure for treatment of vitamin K-dependent coagulation factor deficiency[10]. Under such circumstances, patients showed improved coagulation factor activity, PT, APTT, and bleeding symptoms after treatment with vitamin K1[7]. In the present case, the patient's symptoms improved markedly after intravenous administration of vitamin K1, etamsylate, and vitamin C.

The relationship between RA and vitamin K-dependent coagulation factor deficiency has rarely been reported. The present case report provides some references for diagnosis and treatment of RA patients with coagulation dysfunction symptoms. Clinicians should consider investigating vitamin K deficiency in such RA cases. It remains unclear whether the vitamin K-dependent coagulation factor deficiency caused by RA was accidental, or whether there was an internal relationship with autoimmunity. The mechanism for how RA can cause vitamin K deficiency requires further elucidation.

## CONCLUSION

RA can result in vitamin K-dependent coagulation factor deficiency, which leads to acquired coagulation dysfunction. Vitamin K1 supplementation has an obvious effect on coagulation dysfunction under these circumstances.

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