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CASE REPORT

Osteonecrosis of Femoral Head with Antiphospholipid Syndrome and Acquired Subclinical Hemophilia A

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SUMMARY

Background: **Osteonecrosis of the femoral head is a common orthopedic disease, usually caused by traumatic and non-traumatic factors. Antiphospholipid syndrome (APS) is an autoimmune disorder marked by the persistent presence of antiphospholipid antibodies (aPL). Acquired subclinical hemophilia A is a subset of acquired hemophilia A. The content of factor VIII often drops to the subclinical range due to the inhibitor of factor VIII produced by certain autoimmune diseases. Here, we report a rare case of osteonecrosis of the femoral head with APS and subclinical hemophilia A.**

Methods: **The patient was diagnosed with bilateral femoral head necrosis according to clinical symptoms and imaging findings. APS and subclinical hemophilia A were diagnosed based on a coagulation function test, APTT correction experiment, antiphospholipid antibody detection, thromboelastogram and coagulation factor activity and inhibitor detection.**

Results: **The above test results confirmed the presence of both antiphospholipid antibodies and factor inhibitors in the patient, which is rare clinically. The diagnosis of femoral head necrosis with antiphospholipid syndrome and acquired subclinical hemophilia A was established.**

Conclusions: **Such cases are extremely rare, relevant experimental results are complex, and misdiagnosis and mistreatment are common clinically. We report this case to remind clinicians and blood transfusion department staff to focus on coagulation experiments and related diseases, avoid misdiagnosis and delayed diagnosis, and provide timely, standardized treatment to improve patient prognosis.**

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KEYWORDS

osteonecrosis of femoral head, antiphospholipid syndrome, acquired subclinical hemophilia A, diagnosis

INTRODUCTION

Osteonecrosis of the femoral head is a common orthopedic disease, usually caused by traumatic and non-traumatic factors. Antiphospholipid syndrome (APS) is an autoimmune disorder marked by the persistent presence of antiphospholipid antibodies (aPL), thromboembolic events in arteries, veins, or small vessels, pathological pregnancy, and/or non-thrombotic manifestations like thrombocytopenia [1,2]. APS-related thrombosis can af-

fect vascular beds of various sizes, including arterial and venous systems. Lower extremity deep veins and cerebral circulation are the most common sites for venous and arterial thrombosis respectively [3]. Acquired subclinical hemophilia A is a subset of acquired hemophilia A. The content of factor VIII often drops to the subclinical range due to the inhibitor of factor VIII produced by certain autoimmune diseases. There has been no report on femoral head avascular necrosis associated with APS and acquired subclinical hemophilia A. Here, we report a case of osteonecrosis of the femoral head with APS and subclinical hemophilia A. Such cases are extremely rare, relevant experimental results are complex, and misdiagnosis and mistreatment are common clinically. We report this case to raise awareness of clinicians about such cases.

CASE PRESENTATION

The patient was a 40-year-old man of medium build. He denied having hypertension, diabetes, a history of trauma, alcohol consumption, or a family history of genetic disorders. One year ago, due to thrombocytopenia, positive platelet and antiphospholipid antibodies, the patient was diagnosed with idiopathic thrombocytopenic purpura and treated with 30 mg/day oral prednisone. This time, he was hospitalized for three months due to bilateral hip pain. Double hip joint CT showed bilateral avascular necrosis of the femoral head, so hip replacement was planned. The preoperative examination showed the patient had abnormal coagulation and low platelet count. The surgeon then ordered a plasma infusion. The transfusion physician noted that the patient had a significantly prolonged APTT and a positive history of antiphospholipid antibodies. The physician communicated with the surgeon, recommending additional coagulation-related lab tests and determining whether the patient required plasma infusion based on the test results. Based on the above test results, the transfusion physician assessed the patient's bleeding as low-risk, determined that no plasma transfusion was necessary before surgery, and diagnosed antiphospholipid syndrome with acquired subclinical hemophilia A. The patient had a successful surgery, received no blood products during the perioperative period, and was prescribed cyclosporine and anticoagulation therapy.

Laboratory tests

Blood tests showed PLT 78 x 10^9/L with platelet reduction. All laboratory test results are presented in Table 1. The patient's coagulation routine showed APTT 50.1 seconds, which was significantly prolonged. The coagulation factor activity test revealed that factor VIII activity was 39.9%, well below the lower limit of the reference value. The activity of factor XII is 46.9%. Factor XII activity is generally low in the Chinese population. Given the reference range, this is not suitable for the Chinese population. The remaining factors include II, V, VII, IX, X, XI activity without significant abnormalities. The APTT correction experiment results were as follows: APTT2 was 33.8 seconds, APTT5 was 35.1 seconds, APTT1 was 87.3 seconds, APTT3 was 84.6 seconds, APTT4 was 89.4 seconds, APTT6 was 112.1 seconds, APTT7 was 100.1 seconds, and Rosner index was 58%. These findings suggest that the presence of antiphospholipid antibodies and/or factor inhibitors in the patient's decreased coagulation factor activity. Antiphospholipid antibody tests showed a lupus anticoagulant dRVVT screening test ratio of 3.52, a lupus anticoagulant dRVVT confirmation test ratio of 1.63, a lupus anticoagulant dRVVT normalized ratio of 2.15, an anticardiolipin (aCL) antibody level of 95.5 U/mL, and an anti-β_2 glycoprotein I (β2GPI) antibody level of 182.97 U/mL. These values were significantly elevated, indicating the presence of antiphospholipid antibodies in the patient. The thromboelastogram test checks for the presence of factor inhibitors in the patient's body simultaneously. The thromboelastogram detection reagent contains sufficient phospholipids. If the patient's plasma has no factor inhibitor, factor activity is normal and the R value is within the normal range. If a factor inhibitor is present, factor activity decreases and the R value prolongs. Thromboelastogram showed an R value of 11.6 minutes, longer than the normal upper limit, indicating that the co-existence of factor inhibitors in the patient reduced coagulation factor activity. The detection of coagulation factor inhibitors revealed that the factor VIII inhibitor content was 0.8 BU, and the vWF antigen content was 108.9%, within the normal range. This ruled out the possibility of decreased vWF caused by insufficient factor VIII protection.

In summary, laboratory test results confirmed the presence of both antiphospholipid antibodies and factor inhibitors in this patient, a rare finding in clinical practice. According to the 2006 revised APS classification criteria in Sydney, the patient met one clinical criterion (low platelets) and one laboratory criterion (persistent positivity for anti-β2GPI antibody and aCL antibody). Thus, the patient's APS diagnosis was established. In addition, as the patient has reduced factor VIII and a 0.8 BU factor inhibitor, and no history of joint bleeding or hematoma, the patient is considered to have acquired hemophilia A. The factor VIII activity is in the subclinical range, and the patient shows no clinical bleeding manifestations. Thus, the patient is diagnosed with acquired subclinical hemophilia A. The imaging evidence for the patient's diagnosis of femoral head osteonecrosis is sufficient, and the diagnosis of femoral head osteonecrosis associated with antiphospholipid syndrome and acquired subclinical hemophilia A is established.

DISCUSSION

Bone necrosis pathogenesis involves ischemia from reduced blood flow perfusion, causing bone and marrow cell death and eventually loss of bone mechanical prop-

Table 1. Laboratory test results.

Laboratory test	Test item	Result	Reference interval
Coagulation function test	PT(s)	13.6	9.4 - 12.5
	INR	1.24	0.85 - 1.14
	APTT(s)	50.1	25.1 - 36.5
	TT(s)	14.7	10.3 - 16.6
	TT(s)	2.98	2.38 - 4.98
	DD (ng/mL)	365	0 - 500
Coagulation factor activity test	factor II activity (%)	84.6	70.0 - 120.0
	factor V activity (%)	76.3	70.0 - 120.0
	factor VII activity (%)	103.1	70.0 - 120.0
	factor VIII activity (%)	39.9	70.0 - 150.0
	factor IX activity (%)	78.7	70.0 - 120.0
	factor X activity (%)	98.2	70.0 - 120.0
	factor XI activity (%)	65	70.0 - 120.0
	factor XII activity (%)	46.9	70.0 - 150.0
APTT correction experiment	APTT1 (second)	87.3	25.1 - 36.5
	APTT2 (second)	33.8	25.1 - 36.5
	APTT3 (second)	84.6	25.1 - 36.5
	APTT4 (second)	89.4	25.1 - 36.5
	APTT5 (second)	35.1	25.1 - 36.5
	APTT6 (second)	112.1	25.1 - 36.5
	APTT7 (second)	100.1	25.1 - 36.5
	Rosner index (RI%)	58	10-15
Antiphospholipid antibody test	lupus anticoagulant screening test 1 (LA1) (second)	125.6	31.0 - 44.0
	lupus anticoagulant screening test 2 (LA 2) (second)	57.7	30.0 - 38.0
	lupus anticoagulant dRVVT screening ratio	3.52	< 1.28
	lupus anticoagulant dRVVT confirmation ratio	1.63	< 1.14
	normalized ratio of lupus anticoagulant dRVVT	2.15	< 1.20
	anticardiolipin antibody (aCL) (U/mL)	95.5	< 20.00
	glycoprotein (β2GPI) antibody (U/mL)	187.9	< 20.00
Thromboelastogram	R (minute)	11.6	5 - 10
	K (minute)	3.8	1 - 3
	MA (mm)	51.9	50 - 70
	LY30	0.3%	-7.5%
	CI (second)	-7.1	-3 - +3
Factor VIII inhibitors	VIII inhibitor (BU)	0.8	0 - 0.6
	vWF antigen (%)	108.9	50.0 - 160.0

Factors VIII, XI, and XII are results of 16-fold dilution, while factor IX is the result of 8-fold dilution. APTT1 - Patient plasma, APTT2 - Normal mixed plasma, APTT3 - Detect immediately after 1:1 mixing, APTT4 - The patient's plasma was incubated for two hours prior to detection, APTT5 - Normal mixed plasma incubation was performed after 2 hours, APTT6 - Mix 1:1 and incubate for 2 hours, APTT7 - 1:1 mixed assay following two-hours.

erties. This process typically progresses gradually, often leading to joint destruction over months to years. In the US, bone necrosis accounts for about 10% of total hip arthroplasty surgeries, and is more common in the femoral head [4]. Multiple traumatic and non-traumatic factors are linked to bone necrosis. Glucocorticoids and ex-

cessive alcohol use are associated with over 80% of non-traumatic cases [5]. The incidence of bone necrosis in SLE patients is 3% - 44%, with SLE patients on glucocorticoids most at risk [6]. Data on the role of antiphospholipid antibodies in SLE are inconsistent, some suggest a link to bone necrosis. The etiology of femoral head necrosis in this patient is unclear. Given the patient had no femoral head fracture, no alcohol use, no weight-bearing or diving work, and was not obese, non-traumatic factors likely caused the femoral head necrosis. Although not an SLE patient, this man had a clear APS diagnosis, positive antiphospholipid antibodies, and a history of hormone use. Thus, his femoral head ischemic necrosis may relate to APS and hormone intake. As the patient had sufficient diagnostic evidence of femoral head necrosis with obvious clinical manifestations, joint preservation was not possible, and total joint replacement was needed.

APS is a clinical autoimmune syndrome affecting young and middle-aged people. It is characterized by one or more clinical manifestations and persistent laboratory evidence of aPL [7]. This middle-aged male patient has a chronic disease course. Last year, platelet antibodies and antiphospholipid antibodies were positive. The current laboratory test shows positive antiphospholipid antibodies, and 12 weeks have passed since the last detection. Based on the 2006 revised APS classification criteria in Sydney, the patient can be diagnosed with APS. With a male-to-female ratio of 1:9 and a low incidence in APS, inexperienced clinicians may easily miss the diagnosis. Also, due to positive platelet antibodies and low platelet counts, APS may be misdiagnosed as ITP.

CONCLUSION

Femoral head necrosis is easily diagnosed by clinical imaging. However, the combination of APS and acquired subclinical hemophilia A is relatively rare and prone to misdiagnosis and missed diagnosis. Overall, the patient's bilateral femoral head necrosis surgery went smoothly. However, the cause of avascular necrosis of the femoral head is unknown and may be related to antiphospholipid antibodies produced by APS and oral hormone use. This case also indicates that clinicians still have a blind spot in understanding and diagnosing APS. Moreover, it is more challenging to rediagnose acquired coagulation factor deficiency based on APS. Clinicians and blood transfusion department staff are reminded to study coagulation experiments and diseases, prevent patient misdiagnosis and delayed diagnosis, and provide timely, standardized treatment to improve patient prognosis.

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The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki and approved by the Regional Ethics Committee of Bazhong Central Hospital of Sichuan Province.

Data Availability Statement:
The datasets used during the current study are available from the corresponding author on reasonable request.

Declaration of Interest:
The authors have no conflicts of interest to declare.

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