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# Immunoadsorption therapy for Klinefelter syndrome with APS in a patient : A case report

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**Abstract**

BACKGROUND

Klinefelter syndrome is a genetic disease of male sex chromosome malformations that affects sperm production and reduces testosterone production. There're currently more than 10 cases of Klinefelter syndrome combined with antiphospholipid syndrome were reported.

CASE SUMMARY

Here, we describe a 31-year-old male patient with chromosome 47, XXY type who suffered deep vein thrombosis of lower limbs, accompanied by abnormal antiphospholipid antibody, lupus anticoagulant, factor VIII. After treated with immunoadsorption therapy, glucocorticoid, cyclophosphamide, intravenous immunoglobulin and anticoagulant therapy, the patient showed symptomatic improvement dramatically. During the follow-up, the patient did not develop new thrombotic events.

CONCLUSION

Immunoadsorption combined with glucocorticoid and cyclophosphamide shock comprehensive treatment had achieved significant results for patient with Klinefelter syndrome combined with antiphospholipid syndrome.

**Key Words:** Klinefelter syndrome; antiphospholipid syndrome; immunoadsorption; glucocorticoid; cyclophosphamide; bone morphogenetic protein receptor type-2

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**Core Tip:** we describe a 31-year-old male patient with chromosome 47, XXY type who suffered deep vein thrombosis of lower limbs, accompanied by abnormal antiphospholipid antibody, lupus anticoagulant, factor VIII. After treated with immunoadsorption therapy, glucocorticoid, cyclophosphamide, intravenous immunoglobulin and anticoagulant therapy, the patient showed symptomatic improvement dramatically. During the follow-up, the patient did not develop new thrombotic events.

## INTRODUCTION

Klinefelter Syndrome (KS) patients are prone to hypercoagulability state due to sex glucocorticoid disorders in the body. The relationship between KS and thrombosis was first reported in 1993[1]. A follow-up study of 412 male KS patients found that the risk of thrombosis was significantly increased, and the prevalence of venous ulcers was 20-50 times higher than general population[2].

Regarding the case of KS combined with Antiphospholipid syndrome (APS), it is currently relatively rare in the world. There are about 10 cases reported, and the venous thrombosis accounts for the majority. Ayli and Ertek(2009)[3] reported a 26-year-old man with KS combined with type 2 diabetes had severe venous thromboembolism, heterozygous factor V Leiden and prothrombin G20210A mutations. Lapecorella *et al*(2003) presented that severe venous thromboembolism in a young man with Klinefelter's syndrome and heterozygosis for both G20210A prothrombin and factor V Leiden mutations[4], Recurrent deep vein thrombosis and pulmonary embolism in a 21-year-old man with Klinefelter's syndrome and heterozygous mutation of MTHFR-677C>T and 1298A>C was described by Angel *et al*[5].

This case we presented in the department of rheumatology was due to recurring deep vein thrombosis in the lower extremities. To our knowledge, it is noteworthy that in our case for the first time that immunoadsorption (IAS) combined with glucocorticoid (GCs) and cyclophosphamide (CTX) shock comprehensive treatment had achieved significant results in patient with Klinefelter syndrome combined with antiphospholipid syndrome.

## CASE PRESENTATION

### *Chief complaints*

Left lower extremity deep vein thrombosis event for 4 years, New onset of right lower extremity deep vein thrombosis for 10 days

***History of present illness***

+ADw-html+AD4APA-p+AD4-The patient first developed left lower extremity deep vein thrombosis 4 years ago without obvious incentives. After the thrombus was removed, rivaroxaban 20 mg once a day was started and stopped after half a year. Deep vein thrombosis of the right lower extremity occurred again 10 days ago. Among the clinical symptoms, except for the lower extremity edema caused by venous thrombosis of the right lower extremity, the patient had no rash, Raynaud's phenomenon and other autoimmune diseases symptoms when he was admitted to the rheumatology department.+ADw-/p+AD4APA-/html+AD4-

***History of past illness***

The patient was diagnosed with Klinefelter syndrome when he was 28 years old, and his karyotype was 47 XXY, 15 sites of AZFa, AZFb and AZFc showed no deletions detected by Polymerase chain reaction.

***Personal and family history***

The patient was diagnosed with Klinefelter syndrome when he was 28 years old, and his karyotype was 47 XXY, 15 sites of AZFa, AZFb and AZFc showed no deletions detected by Polymerase chain reaction. It was discovered at the age of 33 that both the patient and his father were heterozygous mutations in bone morphogenetic protein receptor type-2 (BMPR2).

***Physical examination***

Obvious edema of the right lower extremity, no obvious abnormality was found in the rest of his body.

***Laboratory examinations***

Serological examination revealed many abnormalities in rheumatic immunological indicators, which were manifested in the obvious increase of anticardiolipin antibodies, lupus anticoagulants and FVIII:C%, and the autoimmune antibodies (antinuclear antibodies was nuclear homogeneous Type 1: 320, anti-SS-A antibody, anti-dsDNA antibody, anti-nucleosome, anti-histone). Glucocorticoids levels examination showed the increase of luteinizing glucocorticoid, follicle stimulating glucocorticoid, and pituitary prolactin, the decrease of corticotropin and dehydroepiandrosterone levels, and the progesterone, estradiol, testosterone, human growth glucocorticoid, and pancreatic islet function was normal.

*Imaging examinations*

During the imaging examination, the patient had multiple arteriovenous thrombosis throughout the body, the most typical of which was pulmonary embolism, as shown in Figure 1A.

## FINAL DIAGNOSIS

Due to the patient's recurrent thrombotic events and abnormal autoimmune antibodies, he was diagnosed with APS, which was initially thought to be caused by abnormalities in coagulation caused by KS.

## TREATMENT

Considering that the patient's antiphospholipid antibodies are extremely elevated, combined with multiple thrombosis throughout the body, there is a tendency for catastrophic antiphospholipid syndrome. If the antibody titer is not lowered as soon as possible, serious consequences may occur in the short term. Finaly, we decided to use blood purification technology to quickly reduce antibody titers in a short period of time. Considering the poor selectivity of ordinary plasma exchange separation technology and greater side effects, we finally chose the IAS.

## OUTCOME AND FOLLOW-UP

A month or so after his second VTE event, he accepted the first of IAS. Fortunately, the original pulmonary embolism miraculously disappeared (Figure 1B)

It is worth noting that after the first use of IAS, he experienced a significant drop in platelets. At this time, we urgently suspended IAS and added sufficient GCs and intravenous immunoglobulin (IVIG) therapy. His platelets quickly returned to normal.

Anticoagulant therapy was used throughout the entire course of the disease by rivaroxaban 20 mg once a day. The dose of glucocorticoid was gradually adjusted according to his condition, from 40 mg once a day to the current 14 mg once a day. CTX impulse therapy was given 4 times during the one-year follow-up. The treatment plan is shown in Figure 2.

After comprehensive treatment of IAS, GCs, CTX injection and IVIG once, his conditions had been significantly improved. During the one-year follow-up, no more thrombotic events recurred with him. In addition, the APL-IgG titer and lupus anticoagulant showed a significant decline during the follow-up of the past year, performance in his cardiolipin antibody-IgG titer dropped from 1071.4CU to 116.7CU and beta2 glycoprotein antibody 1-IgG titer dropped from 5870.7 CU to 444.6 CU. (as shown in Figure 3), dRVVT screening/confirmation in lupus anticoagulant (LAC) decreased from 2.19 to 1.8, SCT screening/confirmation decreased from 4.17 to 1.7 (as shown in Figure 4).

## DISCUSSION

There is no direct evidence to prove the relationship between KS and APS. Some hypotheses explained why KS patients were prone to hypercoagulability. The level of testosterone in patients with KS are decreased, and the low testosterone levels increase the synthesis of plasminogen activator inhibitor-1(PAI-1). Elevated levels of PAI-1 can inhibit the activity of tissue-type plasminogen activator (t-PA), prevent the degradation of plasminogen into plasmin, and induce thrombosis[6]. There was also a hypothesis that the higher ratio of β-thrombin in patients with KS is the part of the reason of underlying

hypercoagulable state of KS[7]. In recent years, some scholars stated that the increase of Factor VIII(FVIII) and high platelet aggregation will increase the risk of individual thromboembolism[8]. In this case, the apparent increase in his FVIII: C% serological level also supports this conjecture.

He has a family of BMPR2 mutations, and pulmonary embolism can be explained by this, but it is not clear whether BMPR2 mutations will affect the formation of multiple thrombosis throughout the body.

During the one-year follow-up, the patient did not reappear deep vein thrombosis in the lower extremities. Currently, IAS has not been used for 10 mo, and his overall condition has stabilized. Combined with previous case analysis, the first thrombotic event in this type of patient usually occurs earlier, mostly between 20-30 years old, and patients often have multiple thrombotic events repeatedly. It is particularly important to assess their coagulation function in their lifetime. The focus of treatment in such patients is to reduce thrombotic events, and the anticoagulation therapy become very important. In the past reported cases in the world, intravenous or oral anticoagulants were widely used. Our patient did not take anticoagulants regularly after the first thrombosis event, and deep vein thrombosis of the lower extremities occurred again after three years. Therefore, we recommend that he should take anticoagulants for a long time or even for life. Oral anticoagulants should be started when the first thromboembolic event occurs. The time of anticoagulation treatment should be determined based on individual conditions. If thromboembolic events occur repeatedly during the course of the disease or APL-Ab is significantly increased, short-term IAS combined with GCs therapy can be used under close monitoring.

Due to repeated deep venous thrombosis in our patient, much high titers of anticardiolipin antibodies and lupus anticoagulant, imaging exam revealed multiple arteriovenous thrombosis throughout his body, which belongs to the acute stage of the disease. To avoid recurrence of thrombotic events, we consider using blood purification technology to quickly reduce antibody titers in a short period of time. Considering the poor selectivity of ordinary plasma exchange separation technology and greater side

effects. we selected IAS, which therapy programs is known internationally as the first case. In this case, IAS has shown a good effect.

According to the timing and dosage of GCs usage in Klinefelter, syndrome is still unclear, considering his high autoantibody titers at the initial diagnosis, we decided to use methylprednisolone on a trial basis. Then gradually adjust the dosage of methylprednisolone according to the antibody titer. During the GCs reduction period, in order to avoid recurrence, short-term supplementary CTX impulse therapy was applied.

In addition, testosterone replacement therapy (TRT) is also a treatment method for patients with KS combined with autoimmune diseases whose androgen levels are reduced and gonadotropins are raised[9]. In the long-term follow-up process, their autoantibody has a certain downward trend[10]. However, it does not reduce the incidence of venous thrombosis and thrombotic mortality in patients with KS. The degree of androgen level decline in the patient we describe is not obvious, so TRT is not recommended.

## CONCLUSION

We will continue to track the patient's prognosis and evaluate the long-term effectiveness of this treatment programs. Through this is a rare case, we have clarified the exact efficacy of IAS combined with glucocorticoids and immunosuppressants on patients with KS and APS. This patient is only an occasional case, and our treatment experience is limited. We report this case only to hope to provide a successful experience and provide a basis for earlier identification of the same type of patients in the future.

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