

Recurrent Pulmonary Embolism Associated with a New Mutation Site of SLC44A2: A Case Report

INTRODUCTION

Pulmonary embolism (PE) is a potentially life-threatening condition. In recent years, great progress has been made in the etiological diagnosis and treatment of PE. However, some rare causes, like gene mutation, lead to the occurrence and recurrence of PE, in addition, how to guide anticoagulant therapy of these patients is still controversial. In this report, we presented a case of recurrent PE due to SLC44A2 mutation. No such cases have been reported before. The patient was suggested to have an extended anticoagulant therapy to avoid a severe event and required follow-up. So far, the patient has recovered well without recurrence.

CASE REPORT

A 33-year-old male was hospitalized for dyspnea, chest pain, and hemoptysis. A chest computed tomography (CT) scan showed inflammation in the inferior lobe of both lungs and pleural effusion on the left side. After treatment, the patient's symptoms didn't improve, which aroused our suspicion of PE. We arranged for the patient with a computed tomography pulmonary angiography (CTPA), and multiple rounds and irregular filling defects were observed in the bilateral inferior lobe of the pulmonary artery (Figure 1A). Then the patient was diagnosed with PE. The patient's D dimer was elevated, other coagulation indicators were normal, and the number and quality of platelets were normal. We prescribed the patient with low-molecular-weight heparin 1mg/kg every 12 hours for 6 days, then rivaroxaban was given orally at a dose of 15 mg twice a day for 21 days, and then 20 mg once a day last 3 months. Before discharge, the reexamination of the patient's CTPA showed a significant reduction of emboli, especially in the right lung (Figure 1B).

However, 9 months later, the patient relapsed, presenting with chest pain and hemoptysis. The patient's CTPA was detected filling defects in the basilar artery of the right inferior lobe (Figure 1C). The patient was a young healthy male before onset, with no family history and risk factors of thrombosis. We considered that the patient with PE was due to some rare causes. Therefore, the patient was examined for a thrombosis gene mutation test, and the result showed that the SLC44A2 gene with a transition of C to G in exon 16 (NM_020428 c.1585 C>G, p.L529V), which led leucine at 529 site changed to valine. Four bioinformatics tools^{1,2} (MutationTaster, PolyPhen-2, PROVEAN, and SIFT) were all predicted the patient's SLC44A2 mutation as a pathogenic mutation. In addition, to evaluate the presence of a conserved amino acid residue at position 529 in the SLC44A2 protein sequence, ClustalX (1.83) software was used to perform multiple sequence alignment between seven species. The results showed that the amino acid at position 529 was Leu in all 7 species, indicating that the wild-type Leu529 amino acid was highly conserved (Figure 2).

Based on those evidences, we suspected that the patient's recurrence of PE was related to the SLC44A2 mutation. Then the patient was recommended for long-term anticoagulant therapy. The reexamination of the patient's CTPA showed no filling defect in the pulmonary artery (Figure 1D). The patient has been followed up until now, and no recurrence occurred.

CASE REPORT

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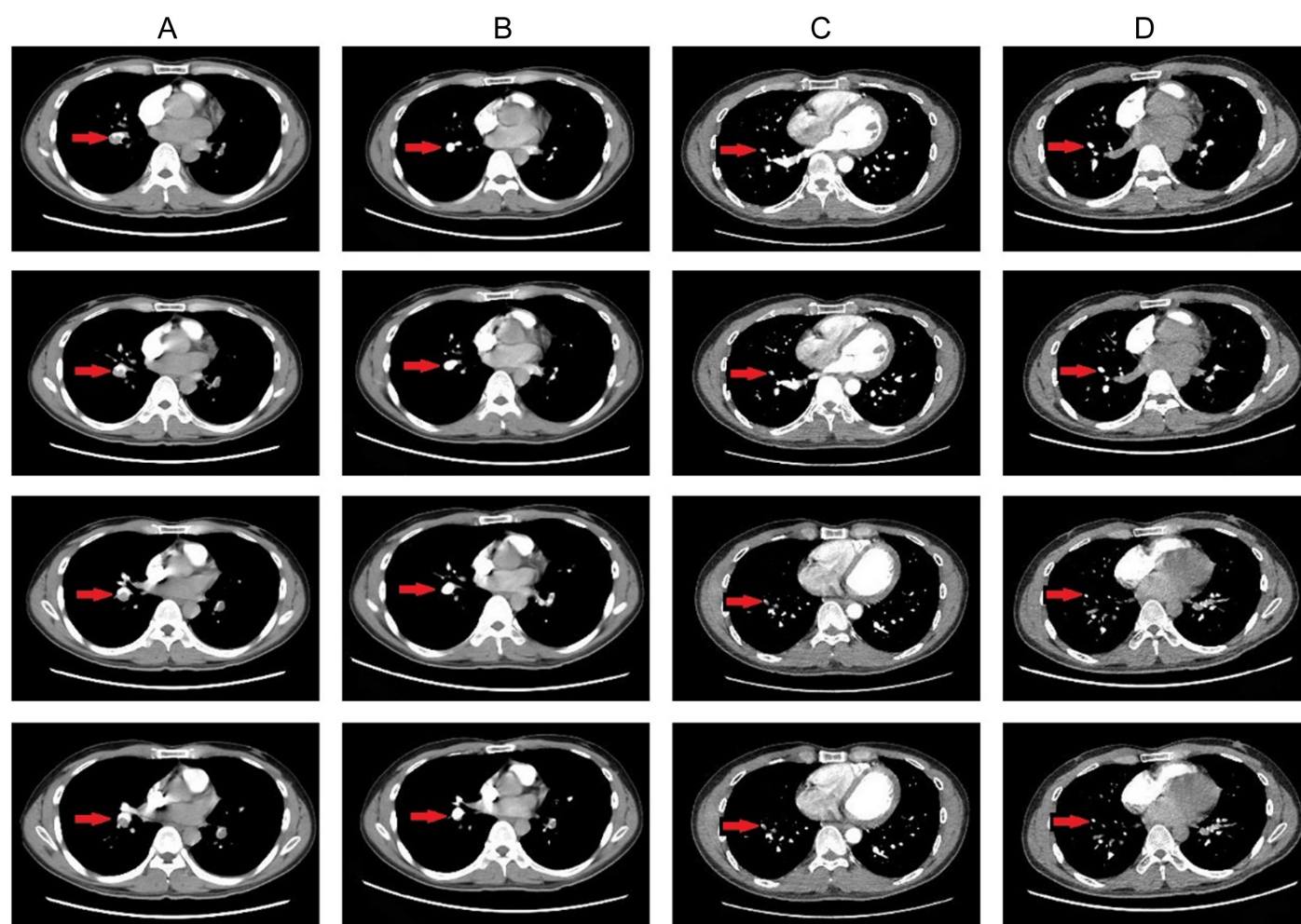


Figure 1. Computed tomography pulmonary angiography images at different phases.

DISCUSSION

It was reported that the polymorphism in SLC44A2 (rs2288904-G/A), which presented in 22% of the population caused an R154Q substitution in an extracellular loop of SLC44A2, protecting against venous thromboembolism (VTE) through severely impairing the capacity of binding to both activated $\alpha\text{IIb}\beta_3$ and VWF-primed platelets.³ In our case, a novel heterozygous missense mutation of SLC44A2 (rs773630712 - c.1585C>G), resulted in the substitution of

Leu529 with VAL529, was found in a patient with recurrent PE. We were the first to report it.

Whether the long-term anticoagulant treatment of recurrent PE was essential has been largely debated. Recently, a meta-analysis showed patients who had no transient risk factor, with the first attack of VTE and completed 3 months of anticoagulant treatment, the risk of recurrent VTE was 10% in the first year after treatment, 16% at 2 years, 25% at 5 years, and 36% at 10 years, with 4% of recurrent VTE events

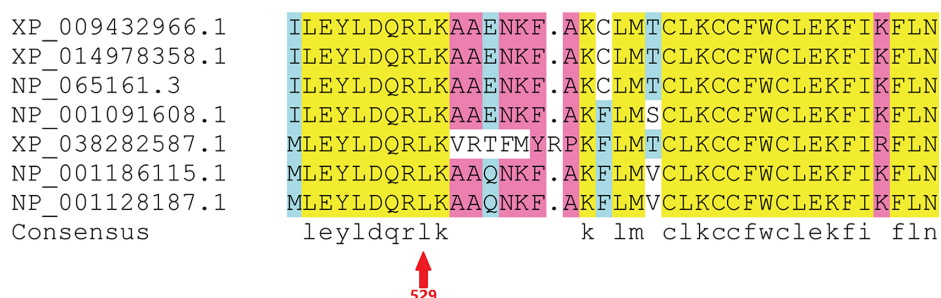


Figure 2. Multiple sequence alignment of the interest site of Leu529 in SLC44A2 protein sequence between 7 species (XP_009432966.1-*Pan troglodytes*; XP_014978358.1-*Macaca mulatta*; NP_065161.3-*Homo sapiens*; NP_001091608.1-*Bos taurus*; XP_038282587.1-*Canis lupus familiaris*; NP_001186115.1-*Mus musculus*; NP_001128187.1-*Rattus norvegicus*).

resulting in death.⁴ These data prompted us that patients with no transient risk factor of VTE were at high potential risk for recurrence, and this should be a guidance for a decision on extended anticoagulation therapy. However, it is uncertain of the optimal duration of anticoagulant treatment. According to the recommendation of the American Society of Hematology, for transient risk factors-induced PE with a history of chronic risk factors or unexplained VTE, or patients with recurrent VTE/PE of unknown cause, anticoagulant therapy should be continued indefinitely.⁵ Consistently, another report suggested that patients with an ongoing strong risk factor or an increased risk of recurrent VTE/PE events should be considered for an extended treatment from 3 months to indefinite.⁶

CONCLUSION

In conclusion, we hypothesized that heterozygous missense mutation of SLC44A2 (rs773630712- c.1585C>G), may result in PE and its recurrence. It is necessary to give the patient who has such genetic mutation with anticoagulant therapy for an extended period. Our data may provide supporting evidence and guidance for implementing an effective therapeutic strategy for similar cases.

Availability of Data and Materials: All data and materials used and/or analyzed are included in this article.

Informed Consent: Written informed consent was obtained.

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