

# Splenectomy as an effective treatment for macrothrombocytopenia in Takenouchi-Kosaki syndrome

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## Abstract

Takenouchi-Kosaki syndrome (TKS) exhibits clinical features represented by macrothrombocytopenia, developmental delay, dysmorphic facial features, and deafness. There is little information on the treatment for macrothrombocytopenia in TKS. Splenectomy has been a contraindication for inherited thrombocytopenia. In the case of autoimmune haemolytic anaemia (AIHA) with TKS that we previously reported, AIHA initially resolved with prednisolone; however, it gradually became resistant to drug therapy. We performed splenectomy, and post-operatively, both anaemia and macrothrombocytopenia improved. This is a novel effect of splenectomy for thrombocytopenia in TKS, which suggests that splenectomy could be a treatment option for thrombocytopenia in TKS.

## Introduction

Takenouchi-Kosaki syndrome (TKS) is a rare congenital disease caused by a de novo heterozygous mutation, NM.001039802.2:c.191A>G:p.(Tyr64Cys) in the *CDC42* gene, a gene known to play a pivotal role in cell cycle regulation.<sup>1,2</sup> *CDC42* functions in multiple organs in the cardiovascular, genitourinary, respiratory, nervous, and immune systems. This explains the following clinical features of TKS: macrothrombocytopenia, developmental delay, dysmorphic facial features, deafness, and other medical conditions, such as hypothyroidism, immunodeficiency, lymphedema, and camptodactyly, depending on the case.<sup>3-6</sup> Previously, we reported a case of autoimmune haemolytic anaemia (AIHA) with TKS,<sup>5</sup> which was the first reported comorbid case. Little is known about treatment for macrothrombocytopenia associated with TKS,<sup>7</sup> and therefore, thrombocytopenia has been treated with platelet transfusion only when patients exhibit severe hemorrhage. Splenectomy has been a contraindication for treating inherited thrombocytopenia<sup>8</sup>; however, in this case, we decided to perform splenectomy to break the vicious cycle of intractable hypersplenism and AIHA, which required repetitive red blood cell transfusions.

After splenectomy, we unexpectedly observed an improvement in thrombocytopenia in addition to AIHA, which is a novel effect of splenectomy for thrombocytopenia in TKS.

## Results(Case Description)

A case of a 15-year-old female patient with warm type AIHA and TKS was previously reported.<sup>5</sup> Besides anaemia, she exhibited severe developmental delay, dysmorphic facial features, deafness, camptodactyly, and chronic macrothrombocytopenia ( $60 \times 10^3/\mu\text{L}$ ). A computed tomography (CT) scan showed splenomegaly (160 mm craniocaudally).

AIHA was initially improved with intravenous prednisolone (2.0 mg/kg/day) for 24 days, followed by oral prednisolone, as previously described.<sup>5</sup> Anaemia improved, and the dose was reduced gradually. However, AIHA relapsed when the dose of oral prednisolone was reduced to 0.19 mg/kg every other day, requiring treatment with high-dose prednisolone. AIHA relapsed every time the dose was reduced, and gradually the required amount of prednisolone increased. After anaemia became uncontrollable with prednisolone, rituximab (375 mg/m<sup>2</sup>/week, four times) was added. She had a transient response to rituximab, but again, relapsed during prednisolone tapering.

AIHA was resistant to prednisolone and rituximab, and over time, she required frequent red blood cell transfusions. In addition, the follow-up CT scan showed an exacerbation in splenomegaly (190 mm cranio-caudally). Uncontrolled AIHA worsened the anaemia, which led to hypersplenism. In turn, hypersplenism worsened the anaemia (5.4 g/dL at the lowest) and thrombocytopenia ( $26 \times 10^3/\mu\text{L}$  at the lowest), and enhanced autoantibody production, making AIHA even more uncontrollable (**Figure 1**). The vicious cycle resulted in the anaemia becoming drug-resistant, and the thrombocytopenia to gradually exacerbate. As her general condition worsened because of the edema and thoracoabdominal fluid production caused by both pathologies, we decided to perform splenectomy to treat the refractory AIHA.

Post-operatively, the haemoglobin gradually normalized to 11–15 g/dL and we were able to taper prednisolone (**Figure 1**). She no longer required red blood cell transfusion or hospitalization even after discontinuation of prednisolone, although direct antiglobulin test results remained positive. Platelet counts also normalized to  $230\text{--}400 \times 10^3/\mu\text{L}$  (**Figure 1**), and the numbers of large platelets ( $< 8 \mu\text{m}$ ) increased.

## Discussion

Two impressive facts were indicated in this case, namely, splenectomy resolved intractable AIHA in TKS, and chronic macrothrombocytopenia was unexpectedly resolved.

This case suggests that refractory AIHA can be improved by splenectomy. Splenectomy is performed in 15% of the AIHA patients in our country (25%–57% in western countries), and its short-term effectiveness is 60%. The first-line therapy for warm type AIHA is prednisolone. For patients who are resistant or require high-dose prednisolone treatments, rituximab is selected as a second-line therapy.<sup>9</sup> Splenectomy is positioned as another option for second-line therapy, and is thought to be the most effective conventional treatment for AIHA to be proposed for patients unresponsive to prednisolone.<sup>10</sup> In this case, the patient was resistant to prednisolone and rituximab, and the uncontrollable AIHA pathology exacerbated hypersplenism. Increased splenic sequestration of platelets and red cells led to severe anaemia and thrombocytopenia, and therefore, splenectomy was performed as the next second-line therapy. After splenectomy, intractable anaemia improved, never requiring red blood cell transfusion until the present time.

Chronic macrothrombocytopenia also was improved by splenectomy. Generally, inherited thrombocytopenia is caused by the impaired production of platelets from megakaryocytes.<sup>11</sup> Giant platelets in TKS suggest disturbance of platelet production,<sup>11</sup> but pathophysiology of macrothrombocytopenia in TKS still remains insufficiently elucidated. Previous studies revealed a possible relationship between Wiskott-Aldrich syndrome (WAS) and TKS, as CDC42 directly interacts with the WAS protein.<sup>5,7,12</sup> Thrombocytopenia in WAS is caused by an increased clearance of platelets by the reticuloendothelial system and a premature, ectopic release of platelets in the bone marrow<sup>8</sup>; TKS may be suggested to have a common pathology, but to clarify the mechanisms of macrothrombocytopenia in TKS, further studies are required. Splenectomy has been believed to be contraindicated for treating inherited thrombocytopenia, but the recovery of platelet counts after splenectomy in our patient suggests that an increase in platelet destruction in the spleen contributed to thrombocytopenia. The observations in our patient may provide a novel option for the treatment of TKS. Furthermore, our results might propose a revision of treatment options for inherited thrombocytopenia.

Our case report concludes that splenectomy resolved both refractory AIHA and chronic macrothrombocytopenia. Splenectomy can be suggested as a treatment option for not only refractory AIHA, but also for macrothrombocytopenia in TKS. As this is still the first case, further studies are required to conclude the efficacy, safety, and effects of splenectomy in these cases.

## Authors' contributions

AI (both Iguchi and Ishiguro), TU, and SK contributed to the conception and supervised the study; TK and KY performed genetic analysis; SY and KI drafted the manuscript and figures with contributions from both AIs and AS. All authors reviewed and approved the final manuscript.

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## Compliance with ethical standards

This study was approved by the Ethics Committees of the NCCHD in May 2018 (#1818). Informed consent for this report was obtained from the patient and her parents.

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**Declaration:** The authors declare no conflicts of interest associated with this manuscript.

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## Figure legends

**Figure 1.** Trends of haemoglobin levels and platelet counts before and after splenectomy. Hypersplenism caused by the exacerbation in splenomegaly spurred anaemia (5.4 g/dL at the lowest) and thrombocytopenia ( $26 \times 10^3/\mu\text{L}$  at the lowest). The relationship between splenomegaly and anaemia is shown. In order to overcome treatment-resistant haemolytic anaemia, we decided to perform splenectomy. After splenectomy, the haemoglobin gradually normalized to 11–15 g/dL and platelet counts also normalized to  $230\text{--}400 \times 10^3/\mu\text{L}$ . The left vertical axis indicates both the length of the spleen edge from the costal margin (cm, gray area), and haemoglobin levels (g/dL, blue closed triangles and dotted line). The right vertical axis indicates platelet counts ( $\times 10^3/\mu\text{L}$ , purple closed circles and straight lines). Red arrows represent red blood cell transfusions.

Figure 1

