Tocilizumab for juvenile Takayasu arteritis complicated with acute heart failure at onset

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Case Report

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Abstract

Background We encountered a 12-year-old girl with Takayasu arteritis (TA) who developed acute heart failure at onset. There have been few reports of specific treatment for acute heart failure (AHF) in TA. We successfully treated her with intravenous methylprednisolone and tocilizumab.

Case presentation The patient developed palpitations and shortness of breath 3 weeks before admission. Her symptoms exacerbated rapidly and she finally entered our hospital intensive care unit due to respiratory distress and tachycardia. Blood pressure values measured on the left arm and bilateral legs were paradoxically lower than values taken on the right arm. Chest X-ray revealed a severely enlarged heart. Contrast computed tomography showed an expanded aorta, aortic aneurysm, meandering, and irregular diameter of the aorta. The left ventricular ejection fraction (LVEF) was 20% on cardiac ultrasound. Laboratory examination suggested acute inflammation and positivity of HLA-B52. Her medical condition was finally diagnosed as TA with AHF. Along with inotropes and diuretics, methylprednisolone pulse therapy was administered for 3 days on the 2nd and 12th hospital day followed by oral prednisolone. Cardiac function was slightly improved. As intravenous cyclophosphamide therapy requires hydration and may exacerbate AHF, we started weekly subcutaneous tocilizumab treatment (162 mg/week) from the 20th hospital day. Inotropes were discontinued on the 51st hospital day and her LVEF had improved to 37.5% on the 63rd day when she was discharged.

Conclusions Tocilizumab could be a significant treatment option for acute heart failure in juvenile TA.

Background

Takayasu arteritis (TA) is a systemic granulomatous large vessel vasculitis affecting the aorta and its branches. TA in adult patients is commonly diagnosed by clinical manifestations due to vascular stenosis, occlusion, and aneurysm[1]. TA in pediatric patients is likely to be diagnosed by general symptoms such as fever and malaise[2]. Chronic heart failure caused by aortic valve regurgitation is a common complication of TA, but fewer than 10% of patients suffer acute heart failure (AHF)[3]. As remission induction therapy, intravenous cyclophosphamide therapy (IVCY) and tocilizumab, an anti–IL-6 receptor monoclonal antibody, have been used particularly for severe TA[4]. However, for prevention of cyclophosphamide-induced hemorrhagic cystitis, aggressive hydration therapy is mandatory following IVCY. As hydration therapy could lead to volume overload and could exacerbate AHF, physicians may hesitate to use IVCY for patients with TA complicated with AHF. Furthermore, gonadal toxicity and carcinogenicity are other concerns. Tocilizumab is an emerging option for refractory TA[5]. Here, we report the case of a girl with TA complicated with severe AHF at onset, who was successfully treated with subcutaneous tocilizumab.

Case Presentation

A 12-year-old girl had developed palpitations and exertional dyspnea 3 weeks before admission. Subsequently, she presented with general fatigue, facial pallor, and orthopnea. AHF was suspected by her

primary physician and she was transferred to our intensive care unit. She had no remarkable history of unknown fever suggesting TA. On admission, she required oxygen (FiO_2: 0.60, high-flow nasal cannula) due to respiratory distress. Consciousness level was clear. Her heart rate was 150/min and her respiratory rate was 50/min. Her blood pressure was 100/60 mmHg on her right arm, but was paradoxically lower (80/50 mmHg) on her left arm and bilateral legs. Capillary refilling time was 2.0 s. Gallop sounds, bilateral moist rales, and coarse crackles were heard. The abdomen was soft and not distended.

Chest X-ray showed significant cardiomegaly, bilateral pulmonary congestion, and marked pleural effusion. Cardiac ultrasound revealed four chambers severely dilated, diffuse decrease of wall motion, moderate aortic regurgitation (AR), and mitral regurgitation (MR). The left ventricular ejection fraction (LVEF) was 20%. Contrast-enhanced computed tomography revealed severely dilated cardiac chambers, aneurysm of the ascending and descending aorta, alternating dilatation and stenosis of the abdominal aorta, and intraluminal thrombi (Figure 1). Laboratory investigation revealed cardiac failure, microcytic anemia, inflammatory findings, renal impairment, and hypergammaglobulinemia. White blood cell count was 9210/μL (51% neutrophils), hemoglobin 7.1 g/dL, mean corpuscular volume 61.5 fL, and mean corpuscular hemoglobin 17.0 pg. Erythrocyte sedimentation rate was 56 mm/hour and C-reactive protein 2.99 mg/dL. Blood urea nitrogen was 28.3 mg/dL, creatinine 0.59 mg/dL; and levels of aspartate aminotransferase, lactate dehydrogenase, and creatine kinase-muscle/brain were normal. Brain natriuretic peptide was 1879.9 pg/mL (reference range: 0.0-18.4 pg/mL) and troponin-T 50-100 ng/L (reference range: <14 ng/L). Serum IgG was 2277 mg/dL, IgA 432 mg/dL, IgM 169 mg/dL, complement component-3 103 mg/dL (reference range: 86-160 mg/dL), complement component-4 9 mg/dL (reference range: 11-31 mg/dL), 50% hemolytic complement 30.5 U/mL (reference range: 25.0-48.0 U/mL), and antinuclear antibodies were negative. We also subsequently found positivity of human leukocyte antigen-B52.

According to radiological findings and laboratory examinations, the patient's disease was diagnosed as TA. The patient was immediately treated with inotropes, diuretics, intravenous heparin, and corticosteroids, including two courses of methylprednisolone pulse therapy (1000 mg/day) on the 2^{nd} and 12^{th} hospital day followed by 30 mg of daily oral prednisolone. However, her cardiac function did not notably improve (Figure 2). For remission induction and further improvement, IVCY was initially considered, but this would require aggressive intravenous hydration for prevention of hemorrhagic cystitis. Such volume overload might exacerbate AHF. We decided to use weekly tocilizumab. Subcutaneous tocilizumab was initiated on the 20^{th} hospital day after obtaining informed consent from the guardian. Her cardiac function gradually recovered. BNP also decreased (Figure 2). Inotropes were discontinued on the 51^{st} hospital day. At discharge on the 63^{rd} hospital day, cardiac ultrasound still exhibited a dilated left ventricle, moderate AR, and trivial MR. However, LVEF had improved to 38% and mural thrombosis in the ascending aorta was reduced in size.

As of this writing it has been two years from onset. She has had no recurrence of TA. Cardiac ultrasound exhibited mild AR and LVEF had improved to 69%. Currently she is being treated with 6 mg of daily prednisolone, 1500 mg of daily mycophenolate mofetil, 12 mg of weekly methotrexate, and 162 mg of weekly subcutaneous tocilizumab. No severe adverse effects of tocilizumab have been observed.

Discussion And Conclusions

TA mainly affects the aorta and its branches, but also frequently demonstrates cardiac involvement. AR is the most frequent cardiac complication. Approximately one-third of adult patients develop AR and one-third of pediatric patients develop cardiac valvular dysfunction[3,6]. These valvular dysfunctions often chronically progress and may result in surgical intervention in some patients[7]. Acute myocardial involvement in TA has not been well investigated. Bechman et al reported only 4 out of 139 registered adult patients with large vessel vasculitis developed acute myocarditis at onset. All 4 patients presented with life-threatening heart failure, but they were successfully treated with IVCY (n=3) or tocilizumab (n=1)[8]. Talwar et al reported clinical and subclinical inflammatory myocarditis in 24 out of 54 patients[9]. They discovered myocardial necrosis and lymphocyte infiltration in myocardial biopsies[9]. In our patient, cardiac magnetic resonance imaging (CMR) was not performed for diagnosis of acute myocarditis, but radiological findings and significant response to glucocorticosteroid and tocilizumab would suggest acute myocarditis. As 10% of adult patients with TA develop ischemic heart disease, early and aggressive intervention may prevent chronic myocardial damage[3]. T-helper 17 (Th17), Th1 cells, and inflammatory cytokines including interferon-γ, tumor necrosis factor-α (TNF-α), IL-6, IL-8, IL-17, and IL-18 are associated with pathogenesis and disease activity in TA[10-14]. In histochemical analysis of vascular tissue, IL-6 and IL-6R were positively stained[14-16]. Tocilizumab may directly act on the lymphocytes infiltrating the myocardium.

Regarding the effectiveness of tocilizumab against TA, Kong et al reported the superiority of tocilizumab to IVCY[10]. However, evidence of the effectiveness of tocilizumab for pediatric TA is quite limited. We chose weekly subcutaneous tocilizumab instead of IVCY and successfully minimized volume overload associated with IVCY treatment. Additionally, IVCY may increase the risks of infertility and carcinogenesis in the future. Therefore, subcutaneous tocilizumab has the advantage of safety and convenience. In conclusion, tocilizumab could be a new therapeutic option for TA with AHF, which can be used for both remission induction and remission maintenance. However, more accumulated evidence and further pathophysiological investigation of AHF in TA is required.

List Of Abbreviations

AHF: acute heart failure

AR: aortic regurgitation

IVCY: intravenous cyclophosphamide therapy

LVEF: left ventricular ejection fraction

TA: Takayasu arteritis

Declarations

Ethics approval and consent to participate

The need for ethics approval was waived, and we obtained consent for participate from the patient and her guardian.

Consent for publication

We obtained consent for publication from the patient and her guardian.

Availability of data and material

Data and materials are available.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

K.K., O.M., and I.S. designed the study; K.K., O.M., I.K., A.I., and I.S. performed data analysis and wrote the paper. All authors read and approved the final manuscript.

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Not applicable

Authors' information (optional)

Not applicable

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Figures

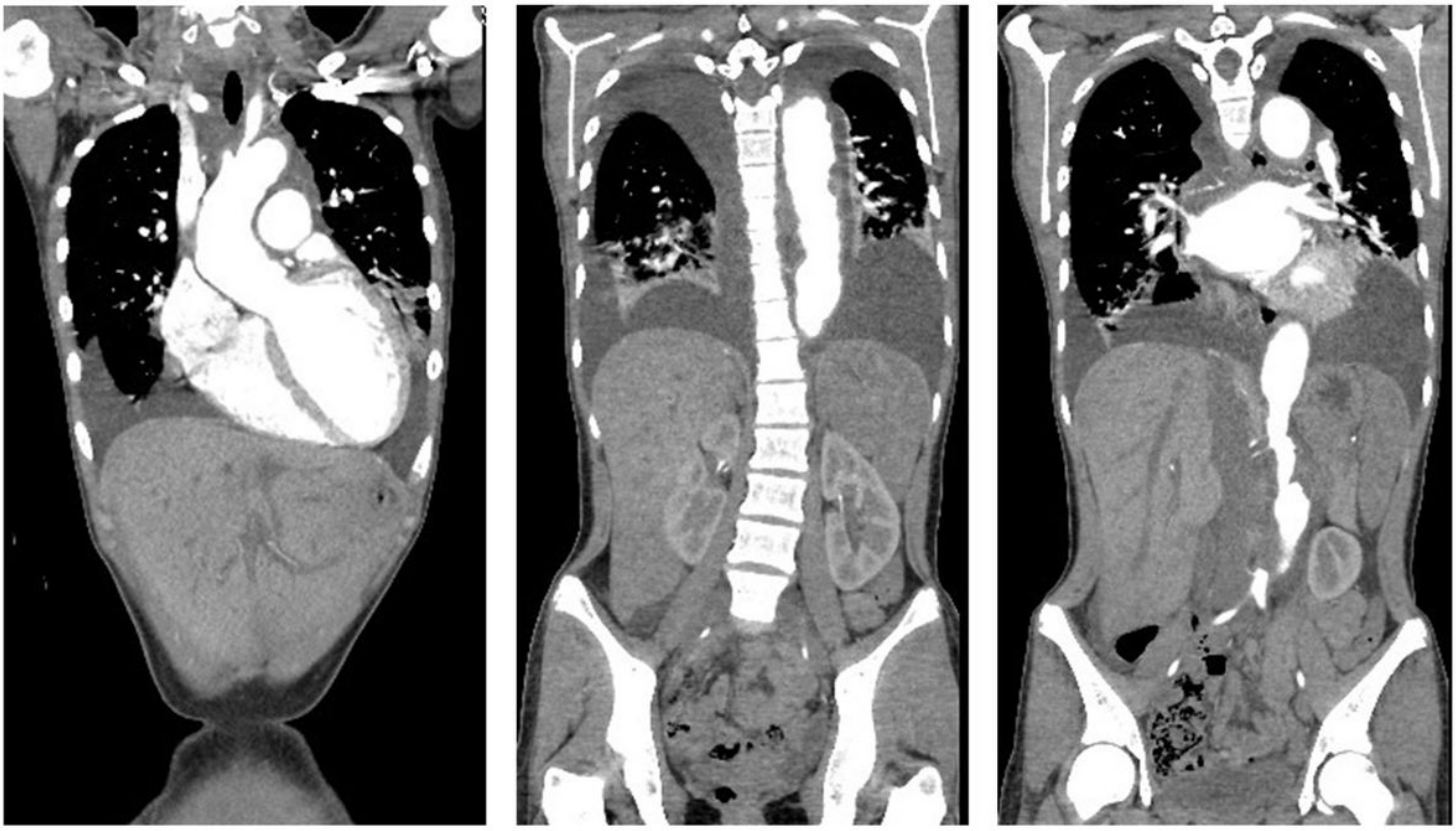

Figure 1

Contrast-enhanced CT imaging at diagnosis Blood vessel lesions are shown by contrast-enhanced CT performed upon admission.

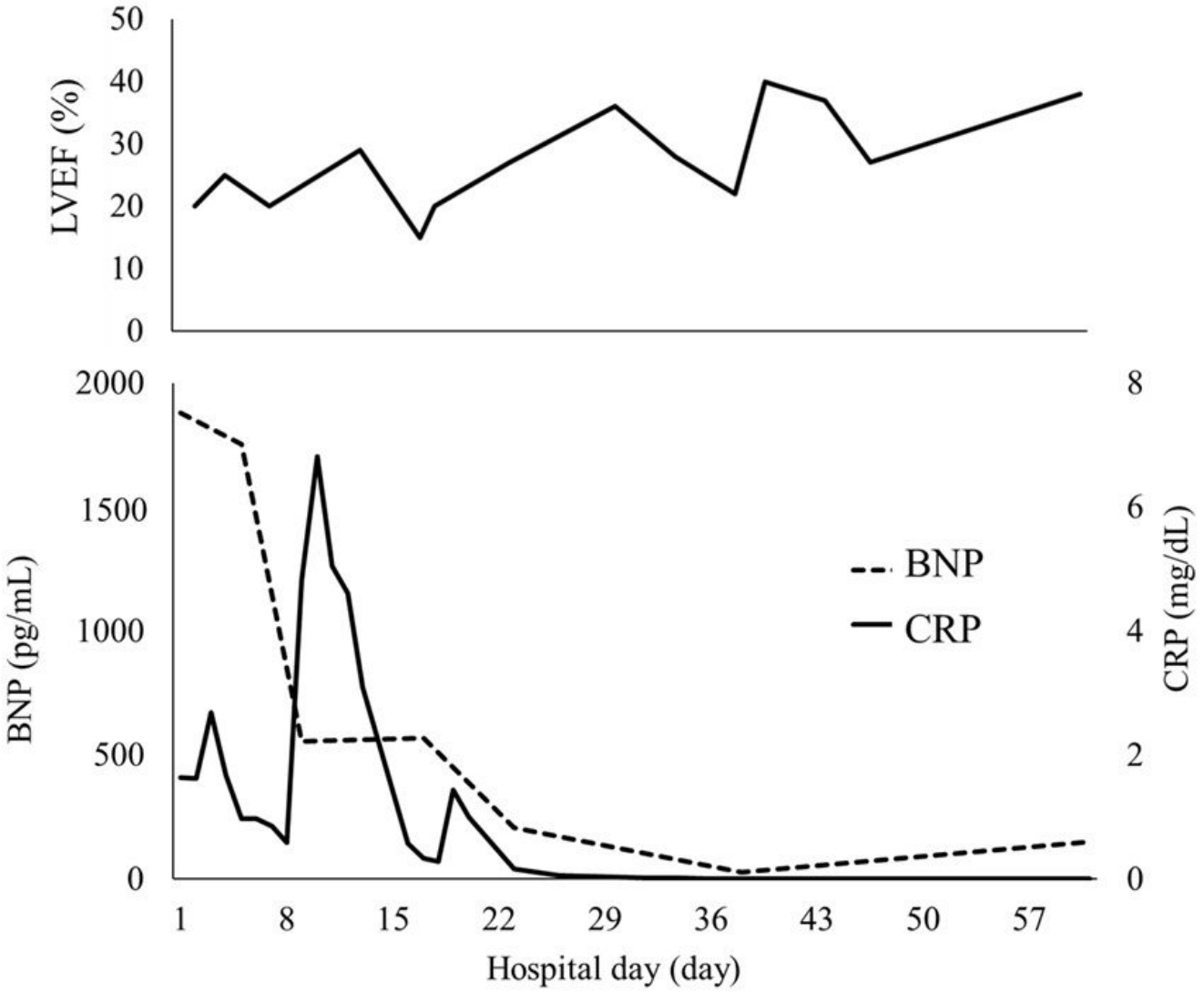

Figure 2

Sequential changes in the left ventricular ejection fraction, BNP, and CRP. The lines in the upper diagram show LVEF and the dotted and solid lines in the bottom diagram show BNP and CRP. The reference range of BNP is 0.0-18.4 pg/mL. BNP, brain natriuretic peptide; CRP, C-reactive protein; LVEF, left ventricular ejection fraction.