Marfan syndrome with antineutrophil cytoplasmic antibody-associated systemic vasculitis presenting as severe anaemia and haematuria after the Bentall procedure

Li Sijia¹, Liu Shuangxin¹, Shi Wei* and Cui Yanhai²

¹ Department of Nephrology, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, China
² Department of Radiology, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, China

* Corresponding author. Department of Nephrology, Guangdong General Hospital, Guangdong Academy of Medical Sciences, 106 Zhongshan Er Lu, Guangzhou, Guangdong 510080, PR China. Tel/fax: +86-02083827812-62027; e-mail: shiw_gh@126.com (S. Wei).

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Abstract

One month previously, a 28-year old male underwent an emergency modified Bentall procedure because of Marfan syndrome with acute aortic dissection Stanford Class A. Computed tomography of the chest did not reveal severe graft stenosis of the anastomosis. To explore the cause of anaemia, renal dysfunction and macroscopic haematuria, the patient was tested for antineutrophil cytoplasmic antibody (ANCA)-associated systemic vasculitis (AASV). Antimyeloperoxidase antibodies (MPO)-ANCA and antiproteinase 3 antibodies (PR3)-ANCA were strongly positive. Corticosteroid therapy was applied, followed by cyclophosphamide and azathioprine. In response to treatment, the MPO-ANCA and PR3-ANCA levels gradually decreased, proteinuria was alleviated and haemoglobin levels returned to normal after 6 months. This is the first report to highlight haemolytic anaemia and AASV with Marfan syndrome after surgery for aortic dissection.

Keywords: Marfan syndrome • Antineutrophil cytoplasmic antibody-associated systemic vasculitis • Anaemia • Haematuria

INTRODUCTION

Haemolytic anaemia is a rare complication of the Marfan syndrome after surgery for aortic dissection. It is usually associated with graft stenosis of the anastomosis, structural deterioration or paravalvular leak [1]. However, rarely, antineutrophil cytoplasmic antibody (ANCA)-associated systemic vasculitis (AASV) can cause refractory anaemia [2]. We describe the case of a patient with haemolytic anaemia, ANCA-AASV and Marfan syndrome who had undergone an emergency Bentall procedure for acute aortic dissection Stanford Class A.

CASE REPORT

A 28-year old male had undergone an emergency Bentall procedure because of Marfan syndrome with acute aortic dissection Stanford Class A at Kiang Wu Hospital in Macao, China, 1 month previously. A modified Bentall procedure was performed, using the 'button' technique, and a 25-mm St. Jude Medical mechanical valved conduit (St. Jude Medical, Inc., St. Paul, MN, USA) was implanted. The proximal end of the conduit was anastomosed to the ascending aorta, distal to the origin of the aortic arch, using neither biological fibrin glue nor a Teflon felt stripe. After completion of proximal anastomosis of the valved conduit, including implantation of both coronary ostia directly to the graft, the circulation was stopped and the brain retrogradely perfused through the superior vena cava. In order to prevent the possible development of late complications at the suture line, the anastomosis between the graft and aorta was tightly wrapped with a Dacron vascular prosthesis, prepared from the residual tube graft. After ascending aorta replacement, the patient received typical anticoagulation medications such as warfarin. Controlling anaemia and haematuria after the procedure proved to be difficult. He had general fatigue with renal dysfunction and macroscopic haematuria and was referred to the nephrology specialists in our hospital. Twenty-four-hour urinary protein and serum creatinine were 5106 mg and 135.3 μmol/l, respectively. His reticulocyte count was markedly high (5.7%), and haemoglobin was markedly low (<6.0 mg/dl). Indirect bilirubin and serum lactate dehydrogenase concentrations were 14.5 μmol/l and 2921 IU/l, respectively, and macroscopic haematuria was seen. The serum iron level was 23.7 μmol/l and showed a discrepancy with the ferritin level (112.5 mg/l). Thus, haemolytic anaemia was suspected. The Roux test was positive, but he had a negative Coombs’ test. A peripheral blood smear revealed numerous schistocytes (7%). White blood cell count, platelet count and clotting factors were all within the normal range. Echocardiography showed that the aortic valve prosthesis had good activity. In order to investigate the cause of haemolytic anaemia, computed tomography (CT) was then performed for a more detailed examination. CT showed that there was no graft
stenosis of the anastomosis and renal artery dissection, but was a residual brachiocephalic artery and descending aorta dissec-
tion with false lumen. To explore the cause of renal dysfunction
and macroscopic haematuria, the patient was tested for AASV.
Antimyeloperoxidase antibodies (MPO)-ANCA and antiprotei-
nase 3 antibodies (PR3)-ANCA were strongly positive
(MPO-ANCA 147.2 RU/ml, PR3-ANCA 120.4 RU/ml, normal
range <19.9 RU/ml). His prognosis was rated as poor, and
methylprednisolone therapy applied, followed by monthly
pulses of cyclophosphamide for 6 months plus oral corticoster-
oid treatment (1 mg/kg day). Cyclophosphamide pulse therapy
followed by azathioprine induces long-term remission in patients
with ANCA-AASV.

In response to treatment, MPO-ANCA and PR3-ANCA levels
gradually decreased, the anaemia was alleviated, the aortic root
was widened, but brachiocephalic and descending aorta dissec-
tion with false lumen were still persistent after 6 months (Figs 1
and 2). Upon hospital discharge, the serum creatinine level had
decreased to 70 μmol/l, haemoglobin levels had returned to
11.4 mg/dl and proteinuria was resolved. The haematuria per-
sisted longer than any of the other symptoms, but also resolved
after 1 year. It meant that ANCA-AASV may have mainly contrib-
uted to the haemolytic anaemia.

DISCUSSION

Haemolytic anaemia is a rare complication for patients undergo-
ing surgical treatment for aortic disease. It is usually associated
with severe aortic stenosis or kinked prosthetic graft. Aortic pros-
thesis and subvalvular stenosis are reported to induce intravascu-
lar haemolysis. In the most recent reports, haemolytic anaemia
was due to stenosis at the site of anastomosis by inverted Teflon
felt strips, which was used to reinforce the aortic stump. Teflon
felt strips have been used to reinforce the anastomosis of the
dissecting aortic wall and to avoid residual dissection and serious
bleeding, but it might be a cause of supravalvular aortic stenosis
at anastomosis site. There are several studies about mechanical
haemolysis after implantation of a ringed intraluminal graft for
Type 1 aortic dissection. They are mainly because of kinking of
the grafts and the resultant high pressure gradient. In the
present case, there is no severe graft stenosis of anastomosis and
without Teflon felt stripe, but there is brachiocephalic artery and
descending aorta dissection with false lumen, the mechanical
element may explain partly the maintenance of haemolytic
anaemia.

Takahashi et al. [3] reported that a patient with Marfan syn-
drome had haematuria. To investigate the genesis of microscopic
dysmorphic haematuria, they undertook a renal biopsy. Light
microscopic analyses revealed the absence of apparent
histological changes in the glomerulus, small artery or arterioles.
Electron microscopic analyses revealed the glomerular basement
membrane to be irregularly thickened, but there was neither
electron-dense deposition nor fibrillar material. It suggested that
the patient with Marfan syndrome had primary glomerular
disease.

Anaemia refractory to conventional treatment is an important
cue to an alternative diagnosis in subjects with prosthetic heart
valves. Accompanying renal involvement during the disease
course suggests a multisystem disease. Small-vessel vasculitis
should be suspected in the patient who presents with the multi-
system disease. Among these, AASV is a distinct subclass involv-
ing antineutrophil cytoplasmic antibody as the common
pathogenesis. Kidneys are the most common involved organ in
these vasculitides. Renal involvement is characterized histologi-
cally by crescentic glomerulonephritis. Because warfarin was
used as anticoagulant therapy, a renal biopsy was not taken.
AASV is a rare form of such vasculitis in patients with Marfan
syndrome with pauci-immune glomerulonephritis rapidly pro-
gressive glomerulonephritis. Serological detection of ANCA is a
useful diagnostic marker not only for renal-limited

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Figure 1: CT of the chest 6 months after the operation showed proximal anas-
tomosis (black arrow), and distal anastomosis (grey arrow) connected with
true lumen at a coronal orientation.

Figure 2: CT of the chest 6 months after the operation showed widening of
the aortic root, distal anastomosis (grey arrow) and descending aorta dissec-
tion (black arrow) at an oblique sagittal orientation.
pauci-immune crescentic glomerulonephritis, but also for microscopic polyangiitis, Wegener’s granulomatosis and Churg-Strauss syndrome. The major value of ANCA testing is to rule out ANCA disease or to increase the suspicion for ANCA disease to a level that will prompt more extensive and rapid diagnostic evaluation [4].

Without therapy, AASV with glomerulonephritis is associated with very poor outcomes. Treatment of AASV consists of the induction of remission followed by its maintenance [5]. The combination of high-dose corticosteroids and cyclophosphamide is widely accepted as the standard therapy for patients with renal involvement and has been reported to improve the short- and long-term outcomes of AASV. The goal of maintenance therapy is to decrease the incidence and severity of relapsing vasculitis. Maintenance-therapy drugs include cyclophosphamide, azathioprine and mycophenolate mofetil (MMF). Because cyclophosphamide is associated with several serious acute and long-term adverse effects (including bone-marrow suppression, infection, infertility, secondary malignancies and haemorrhagic cystitis), azathioprine is the first choice for maintenance therapy in AASV. However, MMF has been recommended for patients who are allergic to or intolerant of azathioprine. According to the response to the treatment, renal involvement with haematuria and haemolytic anaemia are the results of AASV.

As suggested by our case report, haemolytic anaemia is one of the potentially serious complications of aortic disease with surgical treatment. However, anaemia refractory to conventional treatment is an important clue to an alternative diagnosis. AASV should be suspected in any patient who presents with haemolytic anaemia. It is highly probable that the coexistence of AASV and Marfan syndrome had caused haemolytic anaemia and haematuria in this case.

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