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

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Received 11 November 2012; received in revised form 9 January 2013; accepted 17 January 2013

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 Rous 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 dissection with false lumen. To explore the cause of renal dysfunction and macroscopic haematuria, the patient was tested for AASV. Antimyeloperoxidase antibodies (MPO)-ANCA and antiprotease 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 corticosteroid 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 dissection 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 persisted longer than any of the other symptoms, but also resolved after 1 year. It meant that ANCA-AASV may have mainly contributed to the haemolytic anaemia.

DISCUSSION

Haemolytic anaemia is a rare complication for patients undergoing surgical treatment for aortic disease. It is usually associated with severe aortic stenosis or kinked prosthetic graft. Aortic prosthesis and subvalvular stenosis are reported to induce intravascular 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 syndrome had haematuria. To investigate the genesis of microscopic and 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 clue 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 multisystem disease. Among these, AAV is a distinct subclass involving antineutrophil cytoplasmic antibody as the common pathogenesis. Kidneys are the most common involved organ in these vasculitides. Renal involvement is characterized histologically by crescentic glomerulonephritis. Because warfarin was used as anticoagulant therapy, a renal biopsy was not taken. AAV is a rare form of such vasculitis in patients with Marfan syndrome with pauci-immune glomerulonephritis rapidly progressive 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 anastomosis (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 dissection (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.

Funding

This study was supported by Guangdong Provincial Science and Technology Foundation (No. 2012B031800164 and 2011B031800303) and Guangzhou City Science and Technology Project (No. 2012J4300084 and 2012Y2-00028).

Conflict of interest: none declared.

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