Case Report

Takayasu's Arteritis and Liver Transplantation: Association and Implications

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ABSTRACT

We present a 37-year-old lady who had liver transplantation for hepatitis B cirrhosis and was on immune suppressive treatment consisting of mycophenolate mofetil (MMF) and tacrolimus. She presented with undue fatigue and recurring pain in both arms. The diagnosis of Takayasu's arteritis was made, supported by angiographic findings of significant stenosis of the left subclavian and both renal arteries. She was managed by adjusting the immune suppressive medications and underwent a successful percutaneous transluminal balloon angioplasty (PTBA).

Key Words: Angioplasty, immunosuppression, liver transplant, Takayasu's arteritis, vasculitis

Received: 16.04.2015, Accepted: 06.06.2015
How to cite this article: Alokaily F, Bzeizi K, Al-Nori R, Alqahtani S. Takayasu's arteritis and liver transplantation: Association and implications. Saudi J Gastroenterol 2015;21:337-40.

Takayasu's arteritis (TA) is a form of large vessel granulomatous vasculitis that affects the aorta and its major branches (pulseless disease). TA is a relatively rare disease characterized by chronic inflammatory vasculitic changes of the aorta and its major branches. It usually affects women under 40 years of age, particularly of Asian descent, and it may present as an acute and/or chronic illness. Fever, arthralgia, and skin rashes are the common manifestations during the acute phase of the disease. The significant complications that appear during the chronic phase include limb claudication due to subclavian artery stenosis and systemic hypertension secondary to renal artery stenosis. The disease can also lead to cerebral, coronary, or mesenteric ischemia with devastating effects.[1,2]

Magnetic resonance angiography (MRA) and computed tomography (CT) angiography are widely used to diagnose TA; however, the gold standard test is angiography.[2]

TA may precede or appear in patients with existing autoimmune disorders. There have been numerous reports of its association with Crohn's disease, sarcoidosis, spondyloarthropathies, and systemic lupus erythematosus (SLE). The role of autoimmunity in TA, however, is yet to be determined.

To our knowledge, this is the first reported case of TA post liver transplantation in the English literature.

Access this article online

Quick Response Code:

Website: www.saudijgastro.com

PubMed ID: ***

DOI: 10.4103/1319-3767.166201

CASE REPORT

We present a case of 38-year-old female patient who underwent liver transplant in July 2001 for decompensated hepatitis B cirrhosis. The patient was followed up in the Transplant Clinic at Prince Sultan Military Medical City, Riyadh, Kingdom of Saudi Arabia. She is currently on mycophenolate mofetil (MMF) 1 g twice daily, prednisolone 5 mg once daily, tacrolimus 1.5 mg twice daily, lamivudine 100 mg once daily, and immunoglobulin and hepatitis B human Immunoglobuline injection 400 U given intramuscularly (IM) once a month. She was initially treated with cyclosporin, hepatitis B virus immunoglobulin, and lamivudine to prevent recurrence of hepatitis B virus. Her immunosuppressive treatment was modified by replacing ciclosporin with tacrolimus, following an episode of acute graft rejection in 2007. MMF was added following the second episode of rejection that was confirmed histologically in June 2011. Her liver function tests have normalized.

She was also diagnosed to have hypertension in 2008 and was treated with amlodipine 5 mg and enalapril 5 mg. It was later changed to valsartan 160 mg once daily.

She gradually developed pain and claudication in both hands and arms in the last 3 years. She has a history of fatigue and headache, but no weight loss, fever, or rashes. Cardiovascular evaluation showed loss of radial and brachial pulses in the left upper limb. The lower limb pulses were normal. Blood pressure was 165/79 mmHg in the left upper limb and 115/60 mmHg in the right upper limb, and there was a bruit over the right subclavian artery. Abdominal examination showed Mercedes scar with no organomegaly. Respiratory and neurological examinations were unremarkable. A psychiatric evaluation was also satisfactory.

Hematological examination revealed normal complete blood count: WBC, Haemoglobin, and platelets. Serum electrolytes were normal. Other findings were: Urea 8.2 (2.0–6.7) mmol/l, creatinine 94 (87–108) mmol/l, gamma-glutamyl transpeptidase (GGT) 301 (7–32) U/l, total bilirubin 7 (2–22) mmol/l, albumin 43 g/l, alkaline phosphatase 104 U/l, alanine transaminase 52 (2–40) U/l, and FK-506 7.5 (4.0–20) µg/l. Erythrocyte sedimentation rate (ESR) was normal, extractable nuclear antigens was negative, dsDNA was negative, anti-nuclear antibody was 1/80, and C-reactive protein (CRP) level was 1 mg/l. Echocardiography showed normal ventricular function, normal aortic arch, normal valves, and no cortication. Chest radiography and ECG were both normal.

The patient had magnetic resonance imaging (MRI) [Figure 1] which demonstrated smooth narrowing of the short segment of the right subclavian artery by 30%, where it crosses between the first right rib and the right clavicle. The origin of the proximal left subclavian artery with marked stenosis of 99% was not visualized. In addition, there was bilateral renal artery stenosis of approximately 50% on the right side [Figure 2], but was not significant on the left side. The patient was diagnosed to have TA based on American College of Rheumatology (ACR) criteria 1990, since she met all the criteria. She received prednisolone 60 mg/day (increased from 10 mg/day), which was gradually tapered after 1 month. The dosage of cellcept was doubled to 1 g twice daily and the tacrolimus level was titerated to maintain a trough level of 5 ng/ml.

She underwent balloon angioplasty for the left subclavian artery, which resulted in excellent recanalization [Figure 3]. She also underwent balloon angioplasty of the right renal artery, which also resulted in good recanalization [Figure 4].

In addition to the angiographic recanalization of the stenotic lesions, the steroid dose was increased to 60 mg daily that was tapered after 1 month.

DISCUSSION

TA is a chronic inflammatory disease that affects aorta and its major branches. The exact etiology is unknown. The diagnosis is made clinically according to the ACR1990 criteria to diagnose TA, which depends on the presence of at least three criteria of the following six criteria: 1. age of onset less than 40; 2. claudication of extremities; 3. absence of brachial pulse; 4. blood pressure difference of 10 mmHg between the two arms; 5. bruit over the subclavian artery; and 6. abnormal angiogram. Our patient showed all these criteria. Autoantibodies against aortic endothelial cells were found to have a role in its pathogenesis.[1] In another study, TA patients demonstrated CD36 deficiency (CD36d). The human CD36 antigen is a multifunctional membrane glycoprotein that belongs to the class B scavenger receptor family. It is expressed on monocytes, platelets, and endothelial cells, and contributes to myocardial fatty acid transport. In patients with CD36d, myocardial I-15-(*p*-iodophenyl)-3-(*R*, *S*)-methyl pentadecanoic acid (BMIPP) uptake was absent.[3]

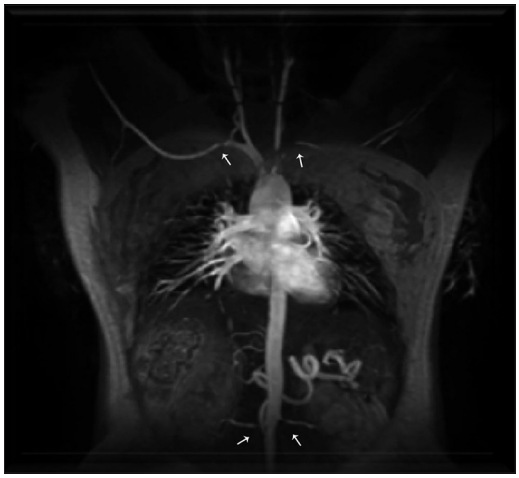

Figure 1: MRA showing 99% stenosis of the left subclavian artery and 30% stenosis on the right side (arrows)

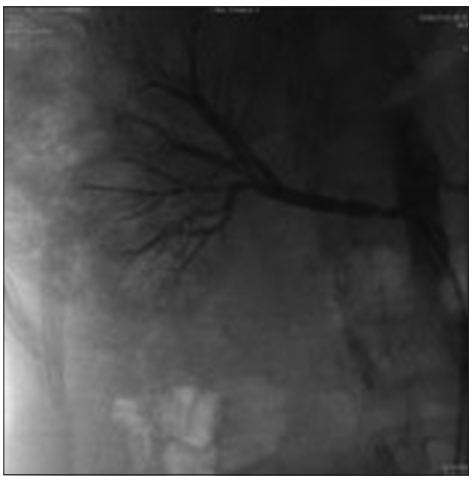

Figure 2: Right renal artery with 50% stenosis

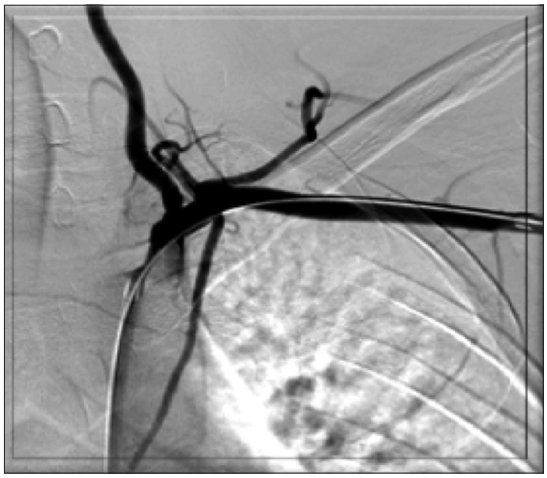

Figure 3: Angiography showing left subclavian recanalization

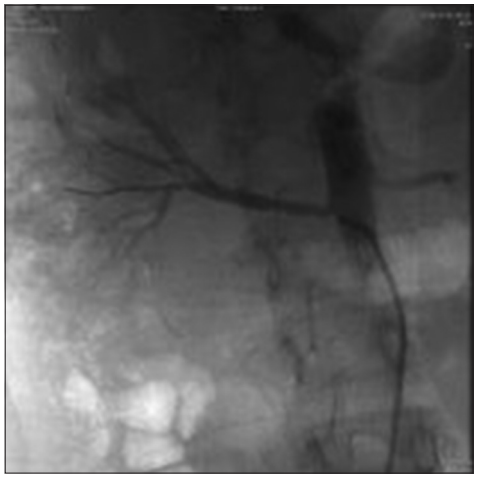

Figure 4: Right renal artery post-ballooning with good response

Human leukocyte antigen (HLA) associations have also been identified, of which the frequently reported were HLA-A10, B5, Bw52, DR2, DR4, B21, and B22. Many of these, however, remain unconfirmed and are variable across different ethnic groups.[3] HLA typing was not performed in this patient. It is our understanding that it was not required for the diagnosis. Also, there is no evidence that it has any bearing on the management plan or disease monitoring.

TA has been reported in association with other autoimmune disorders such as Crohn's disease,[4] SLE,[5] sarcoidosis, and spondyloarthropathies, either as the primary disease or secondary to an existing autoimmune disorder.[6]

The diagnosis in our patient was carried out 2 years after the onset of the first symptoms. This is not surprising as the delay in diagnosing this condition is common with an average latency of 18 months. The immunosuppressive drugs might have masked some of the symptoms. Our patient had liver transplantation over 10 years ago and was maintained on cyclosporin for 6 years after which it was replaced with tacrolimus following an episode of acute rejection. Both drugs have been used to treat TA and have shown good results, and so it is plausible to believe that her symptoms and the arteritis activity were partially controlled with this treatment. The counter argument is that TA may manifest itself in patients who are well covered with immune suppressive treatment. The severe form of the disease can be refractory to high doses of corticosteroids and conventional immune suppressive medications such as azathioprine, methotrexate, and cyclophosphamide.

Tacrolimus was reported in early animal studies, particularly in dogs, to induce arteritis.[7] However, we are not aware of similar reports in humans, except for only report on a single case of cerebral vasculitis associated with neurotoxicity in a liver transplant patient treated with tacrolimus.[8]

This patient was transplanted for hepatitis B cirrhosis, a known association with arteritis such as polyarteritis nodosa, however, there areno reports of any link between hepatitis B and TA disease. The fact that this patient remained negative for both HbsAg and HBV-DNA throughout the post-transplantation period further rules out the association of these two conditions.

The difficulty in managing TA patients lies in the setting of the liver transplantation, the choice of treatment, and absence of reliable disease activity markers. Inflammatory markers like ESR and CRP may be normal even when the disease is very active. They have 72% sensitivity and 56% specificity. Other tests used to monitor TA activity are imaging modalities like digital subtracting angiography (DSA) and computed tomography angiography (CTA). These tests are used in screening, diagnosis, and in interventional treatment. MRI may also help to visualize the vessel wall stenosis and thickening and using T2 imaging, active inflammation of the vessel wall manifested by wall edema can be visualized. Ultrasonography (US) is another test that is cheap and convenient in diagnosing any structural wall abnormalities, but will not be able to detect disease activity. Positron emission tomography with radiolabeled glucose (FDG-PET) can highlight the region of inflammation with a sensitivity of 92% and specificity of 100%. It is more sensitive than MRI in detecting vascular involvement in early TA and it is helpful in monitoring response to treatment. It is however expensive and not widely available.[9] Corticosteroids remain the mainstay of medical treatment and appear to be effective in 20–75% of patients. Immune suppressive agents that include methotrexate, cyclophosphamide, and azathioprine may be effective. MMF has recently been introduced to treat TA. In a recent study, MMF was found to be a safe and effective steroid-sparing agent in treating patients with TA.[7]

The main treatment for TA is immune suppression, which is parallel to the treatment of patients post liver transplantation. The most widely used immune suppressives for TA such as steroids or mycophenolates are widely used post liver transplantation, and therefore, there is no concern with regard to graft rejection or hepatotoxicity. Selection of a therapeutic agent depends largely on the side effect profile, as the data remains limited on the treatment of choice of TA. Biological treatment with agents such as anti-tumor necrosis factor (anti-TNF), etanercept, and infliximab had been tried in refractory TA, and the response was variable. Anti-IL-6 has also been used in a few cases that were resistant to conventional immunosuppressant therapy, and anti-TNF-α and was found to be effective.[10]

Surgical vascular reconstruction of the involved vessels used to be carried out in the past in the form of bypassing a stenotic segment, graft anastomosis, or end arterectomy. Recently, percutaneous transluminal angioplasty has emerged as the treatment of choice for stenotic lesions.

CONCLUSION

In conclusion, this is the first report of TA post liver transplantation in the English literature. The immunosuppressive drugs might have reduced severity of the disease, but are not effective in preventing it. The standard measures for early diagnosis of this condition and other vasculitic disorders are not adequate in immune suppressed patients and a higher index of suspicion is needed.

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Source of Support: None of the authors received any fund for producing this article, **Conflict of Interest:** No one has any commercial associations that might cause a conflict of interest in relation to the submitted article.