Case report

Digital gangrene caused by vasculitis in a young African female complicated with autoimmune disease and HIV/ hepatitis B co-infection: Case report

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Abstract

Human Immunodeficiency Virus (HIV) is an epidemic in southern Africa. The World Health Organization reports that there are about 25.6 million people in Southern Africa who are infected with HIV. HIV is a disease of immune dysregulation and occasionally, autoimmune disease and vasculitis are seen together in some individuals. Vasculitis among HIV patients is multifactorial. HIV, hepatitis B and hepatitis C are some well recognised infectious causes of secondary vasculitis. In our report, we described a 31-year-old female with digital gangrene in a patient with HIV-hepatitis B co-infection and connective tissue disease. She was HIV positive with a CD4 count of 250 cells/ml and a viral load of <400 copies/ml. She was treated with first-line antiretroviral combination therapy of nevirapine and truvada (tenofovir disoproxil fumarate + emtricitabine) for 4 years before the presentation. She was also a hepatitis B virus-positive with hepatitis B virus DNA<20IU/ml copies. The patient developed digital gangrene initially in upper limbs followed by gangrene in the lower limb digit. Physical examination showed reduced pulsation on radial and dorsalis pedis artery. The laboratory results showed positive serological markers such as ANA, anti-RNP without any cutaneous features of lupus. Angiography confirmed arterial involvement in the limb. Secondary vasculitis mainly secondary polyarteritis nodosa was suspected from the arterial angiographic report. The patient was treated with mycophenolate mofetil with satisfactory clinical improvement. In this case report, we tried to explore the association of the digital gangrene in relation to her multiple coexisting conditions.

Key words: Digital gangrene, Vasculitis, HIV

Introduction

About 36.7 million people are living with human immune deficiency virus (HIV) worldwide, and most of them are believed to reside in developing countries. The WHO reports that there are about 25.6 million people in Southern Africa who are infected with HIV[1].

Digital gangrene is a complication of inadequate peripheral arterial blood flow. Digital gangrene can be a manifestation of large, medium and small vessel diseases[2]. There are multiple causes of gangrene such as autoimmune vasculitis, connective tissue disease, thrombosis, emboli and trauma. Others like smoking, atherosclerosis and diabetes frequently predisposes gangrene[3]. Secondary vasculitis is an important cause of digital gangrene. Secondary vasculitis causes include infectious viral diseases like HIV, hepatitis B and hepatitis C, bacterial infection like mycobacterial infection, syphilis, others like malignancy and drugs[4]. Secondary vasculitis can occur in many rheumatological diseases including rheumatoid arthritis, Systemic Lupus Erythematosus (SLE) and Sjogren's syndrome[4].

We report a case of digital gangrene due to secondary vasculitis involving both upper and lower limb who has HIV and hepatitis B co-infection and lupus or overlap disease.

Case report

A 31-year-old human immune deficiency virus (HIV) positive female presented for the first time with black discolouration of right middle finger, pain and swelling.

She was diagnosed with HIV three years before her presentation. She had been on regular first-line antiretroviral drug- nevirapine and truvada (tenofovir disoproxil fumarate + emtricitabine).

She had been adherent to her antiretroviral. Her CD4+ count was 250 cells/ml and viral load was <400 copies/ml when she developed gangrene. She denied any history of skin tightening. There was no history of Raynauds phenomenon. She did not have mouth ulcers, photosensitive skin rash. There was no weakness in the proximal muscle of the limbs. She was a mother of two children. She had no history of fetal loss in the second trimester during pregnancy and was not taking any other drugs except for her antiretroviral drugs. She also had no history of smoking or taking oral contraceptives. On physical examination, she had reduced peripheral pulsation in upper and lower limb vessels mainly radial artery pulse in the upper limb and dorsalis pedis pulse in the lower limb.

Doppler ultrasonography did not reveal any obstruction of venous and arterial flow. Laboratory investigation was as follows: White blood count-$8.13x10^3/\mu L$, haemoglobin-10.5mg/dl, platelet-$216x10^{3/}\mu L$, aspartate aminotransferase (AST)-30IU/L, alanine aminotransferase (ALT)-51IU/L, creatinine 54µmol/L, Urea 2.3µmol/L, erythrocyte sedimentation rate-130mm/hours, C-reactive protein-184.43mg/dl, Anti-Nuclear Antibody (ANA) 1:640 and anti-U1 RNP was positive but no titre was given. Anti-centromere was positive, Rheumatoid factor- negative, P-ANCA (anti nucleocytoplasmic antibody) negative, C-ANCA- negative, double-stranded DNA (Crithidia)-negative. Lupus anticoagulant-No lupus anticoagulant, no anticardiolipin antibody (IgM-1.70U/ml, IgA-4.5U/ml, IgG-1.60 U/ml -1.6U/ml) no antiB2 glycoprotein (IgG-0.8AEU/ml, IgM-<2.9AEU/ml, IgA-2.5AEU/ml). Creatinine kinase was done a few days after steroid therapy was 63 IU/L. Hepatitis B surface antigen (HBsAg) was positive, hepatitis B virus antibodies were ordered but reports were not available. We also ordered the hepatitis virus DNA level. Hepatitis B virus DNA was <20IU/ml and IgM hepatitis C antibody were negative, cryoglobulin test was not done. Rapid plasma reagent test for syphilis was non-reactive. Triglycerides 1.61mmol/L, cholesterol 6.2mmol/L, LDL cholesterol 3.83mmol/L, HDL-cholesterol 2.33mmol/L. Skin biopsy revealed epidermal necrosis and no overt vasculitis. Urine chemistry –no protein, no glucose. The patient was treated with prednisolone, chloroquine, aspirin and atorvastatin and analgesic.

However, after 5 months she was admitted in the hospital for severe joint pain involving multiple hand joints and knee joints. She was treated with steroid, aspirin and methotrexate.

Two years later she developed similar dry gangrene but this time left the second toe. She required surgical amputation of the affected toe.

CT angiogram showed bilateral thready anterior tibial, irregular right common peroneal which fades off in the mid-leg and left common peroneal fading above the ankle and left posterior tibial thread but right posterior tibial not demonstrated. Aorta, common iliac, external iliac and internal iliac and femoral arteries were normal (Figures 1-3).

Figure 1: Arrow shows fading and thinning of anterior and posterior tibial artery

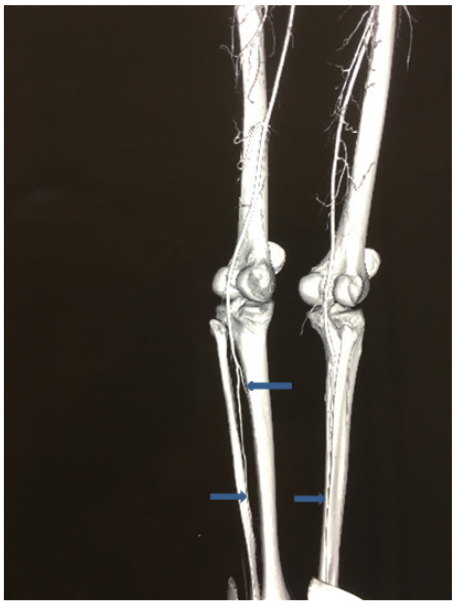

Figure 2: Arrows show contrast enhanced artery in upper part of both legs

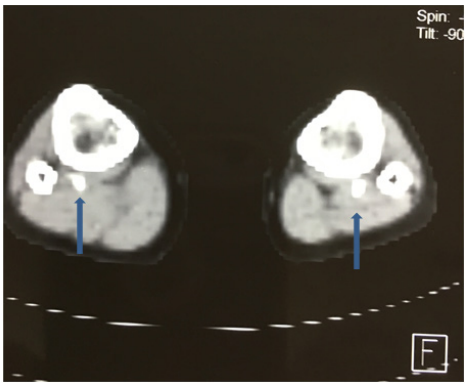

Figure 3: Arrow head shows contrast enhanced artery only in the left

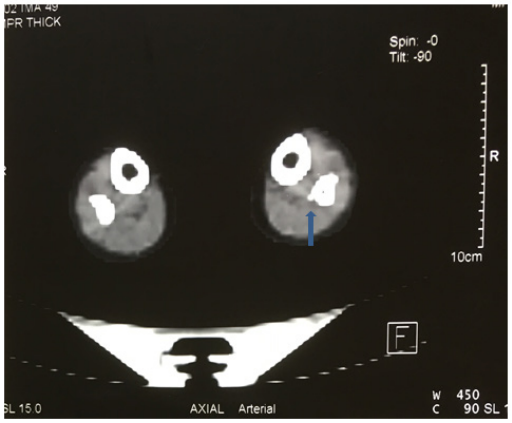

Table 1: Similar reports of digital gangrene published in Journals

Study	Age (years)	Sex	HIV	ANA	Year	Main features
Kakrani *et al*[16]	37	Female	+ve	+ve	2003	Digital gangrene, Angiography: block in artery with collaterals Skin biopsy: PAN-like
Majumder *et al*[17]	42	Male	+ve	-ve	2017	Leg gangrene, Angiography: narrowing of lower limb vessel Skin Biopsy: non –specific vasculitis
Shukla *et al*[18]	21	Male	-ve	-ve	2016	Digital gangrene, Angiography shows lower limb arterial narrowing
Raine *et al*[14]	55	Male	-ve	+ve	2018	Digital ischaemia, U1RNP positive, rheumatoid/limited sclerosis/SLE overlap
This case report	31	Female	+ve	+ve	2020	Digital gangrene, U1 RNP positive, hepatitis B virus positive. Angiography lower limb: Bilateral thready lower limb vessels

She was initiated with mycophenolate mofetil for the suspicion of medium vessel vasculitis along with steroid and chloroquine and vasodilator. Following treatment, her ESR improved to 15mm/hours and C-reactive protein to 18.68mg/dl. Her recent CD4 was 251 cells/ml and viral load was <400 copies/ml.

Discussion

Our reported patient was living with HIV and hepatitis for years and developed digital gangrene when her disease was controlled by antiretroviral treatment. Active inflammation and small to medium vessel vasculitis are the most likely causes of digital gangrene, although histological evidence of vasculitis is lacking in our case. The secondary vasculitis highly considered in our patient is due to one of her multiple co-morbid conditions.

HIV viral disease can mimic many rheumatic diseases like manifestation. HIV infection needs to be distinguished from an associated autoimmune condition. Although the patient can have digital gangrene from multiple causes in HIV such as thrombosis, vasculitis, hypercoagulable state[5]. The peripheral vascular occlusive disease associated with HIV itself can cause gangrene[6]. HIV itself is associated with a wide range of small, medium vessel vasculitis, some are nonspecific and some resembles like classic polyarteritis nodosa[7]. Rarely HIV vasculitis can involve large vessel. Some infections in HIV like cytomegalovirus, herpes virus, tuberculosis, HBV also leads to vasculitis[7].

Hepatitis B is associated with both systemic and cutaneous polyarteritis nodosa. But the association of hepatitis B with cutaneous PAN is very rare[8]. They usually present with livedo reticularis, erythema nodosum, and skin ulcer. It is different from systemic PAN as it does not involve kidney, liver and heart. The case report shows cutaneous polyarteritis nodosa involving small and medium-sized arterial vasculitis can lead to digital gangrene[9]. Our patient was positive for hepatitis HBsAg, she had mild liver enzyme elevation- AST-30U/L, ALT-51 U/L, the patient was on tenofovir based antiretroviral combination therapy which is also used for chronic hepatitis B. Hepatitis B viral DNA was <20IU/ml, which may be attributed to her prescribed antiretroviral drugs with anti-hepatitis B activity. Chronicity of hepatitis disease was suspected but the absence of antibody was a limitation to categorise her appropriately.

In one study in China by Liu *et al*[10], 0.6% of SLE patients developed gangrene. There were multiple aetiological factors associated with digital gangrene in SLE. Vasospasm, antiphospholipid syndrome, vasculitis, atherosclerosis and thromboembolism[10,11]. Vasculitis associated with SLE is attributed to immune complex deposition. Cutaneous vasculitis involving small to the medium vessel is observed in 11%-28%[12]. They present with palpable purpura, livedo reticularis and erythematous plaque and panniculitis. Digital gangrene in SLE is mostly due to Raynaud's phenomena or vasculitis[12]. Vasculitis in SLE involves organs like gastrointestinal tract, kidney, heart, central nervous system and lung. MCTD associated with digital gangrene has been reported infrequently

in case reports[13]. One case report also reveals overlap syndrome associated with digital gangrene[14].

In this case, we found autoimmune disease lupus or possible overlap syndrome complicated by hepatitis and HIV co-infection. The patient had only positive ANA and anti-centromere positive results without any other clinical evidence. Digital gangrene and connective tissue disorder are rarely seen together with HIV, its association has been reported infrequently as case reports[15].

The patient was treated as a case of secondary polyarteritis nodosa after arterial angiographic findings which may be attributable to our patient either hepatitis B or HIV itself.

Conclusion

This case was treated as secondary vasculitis mainly as a polyarteritis nodosa like vasculitis. The diagnosis was supported by angiography findings. It is important to suspect vasculitis as one of a possible cause of digital gangrene in the presence of HIV and hepatitis co-infection. The probable aetiology was difficult to pinpoint as HIV and hepatitis B, lupus and overlap syndrome, all have the potential to cause vasculitis and gangrene.

Ethical consideration: Informed written consent was taken from the patient for publication.

Conflict of interest: Authors do not have any conflict of interest. All authors agree with the final draft.

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