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Case Report

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BK Polyomavirus in Patient with Systemic Sclerosis

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Abstract

BK virus (BKV) is a polyomavirus widely present in humans. It mostly manifests as polyomavirus-associated nephropathy in kidney transplant patients and can lead to the loss of the renal allograft in half of the cases. Systemic sclerosis (SSc) is a connective tissue disease, which affects skin, blood vessels, heart, lungs, kidneys, gastrointestinal tract and musculoskeletal system. Involvement of internal organs results in significant morbidity and mortality of patients with SSc. Renal involvement in patients diagnosed of SSc is of about 50%. Involvement includes Scleroderma Renal Crisis (SRC), glomerulonephritis associated with myeloperoxidase-specific anti-neutrophil cytoplasmic antibodies (MPO-ANCA), glomerular filtration rate reduction, and proteinuria. We present a case report of a patient with Systemic Sclerosis and renal involvement, where the anatomopathological exam of urine sample revealed the presence of cytopathic cells change suggestive of BKV infection, confirmed by SV40 immunohistochemistry and molecular biology in urine Polyomavirus (PCR) for BKV.

Keywords

Polyomavirus; Systemic sclerosis

Introduction

BK virus (BKV) is a polyomavirus widely present in humans. Exposure rates for BKV as measured by anti-BKV assays have been reported to be very high in normal adults [1]. In some studies, BKV seroprevalence was positive in up to 98% of the samples [2]. About 30 species of polyomaviruses have been identified in birds and mammals, including 13 species in humans: BK, JC, KI, WU, Merkel cell polyomavirus, H6, H7, H9, H10, H12, STL, trichodysplasia spinulosa-associated polyomavirus, and NJ [3].

BK virus primary infection occurs mostly without specific symptoms or signs in the first decade of life. It is indicated by a shift from negative to positive serostatus in more than 90% of children and young adults worldwide [4,5]. Natural transmission has not been conclusively resolved, and probably occurs through the respiratory fluids [6]. Eventually, following a presumed viremic phase, a state of non-replicative infection is established mainly in the genitourinary tract, but the virus can be located in other locations such as blood, respiratory fluids, skin, liver, stool, and gastrointestinal tract tissues [7]. However, virus can become reactivated in certain immunocompromised disease states. The microenvironment suitable for BKV replication includes an interaction between the virus characteristics, the host's immune system, swelling and/or intrinsic kidney damage. BK virus replication is detected after renal transplantation, and can lead to the loss of the renal allograft in half of the cases [8-11]. Replication is also observed in other solid-organ transplant recipients [12], bone marrow transplant recipients [13,14], human immunodeficiency virus (HIV) patients [15-17] pregnant women [18,19], patients with multiple sclerosis, especially those in treatment with monoclonal antibodies such as natalizumab [20], and other immunocompromised patients. As a consequence of viral reactivation, patients may experience hemorrhagic cystitis, ureteral stenosis, tubulointerstitial nephritis, retinitis, encephalitis and pneumonia [21].

The use of immunosuppressive drugs, including biologics, strongly impacts the host's immune system, increasing the risk for certain opportunistic bacterial, viral, parasitic and fungal infections. In some particular groups of non-transplanted immunocompromised patients, such as those with systemic lupus erythematosus (SLE) and rheumatoid arthritis, treated with anti-tumor necrosis factor (anti-TNF) alpha, the prevalence of BKV is higher than in healthy controls [7,22-25]. However, there are no reports of BKV in patients with systemic sclerosis.

Case Report

A 60 year old male patient with systemic sclerosis diagnosed in 2010 (American College of Rheumatology - ACR - 1980 criteria and ACR/European League Against Rheumatism - EULAR - criteria 2013) with sclerodactyly, swollen fingers, digital ulcers, Raynaud's phenomenon, arthritis, Achilles tendon friction, and anti RNA polymerase III antibody. Antecedents include: hypertension, hiatal hernia with mild antral gastropathy and active smoker for 26 years with 12.5 packages per year. Treatment involved: methylprednisolone 500 mg IV during 3 days at the onset of the disease, followed by prednisone 30 mg in de-escalation, bosentan 62.5 mg BID, methotrexate 20 mg weekly followed by folic acid the next day, 8 acetylsalicylic acid 100 mg QD, pentoxifylline 400 mg BID, losartan 50 mg BID, omeprazole 20 mg QD. Digital capillaroscopy: pathological study with active and tardive systemic sclerosis pattern. PFT (Pulmonary Function Testing) and Echocardiogram evidenced normal results.

In August 2016, patient suffered congestive symptoms of upper respiratory tract over three weeks. At that time, hospitalization was required due to fever and chest pain with bilateral pulmonary infiltrates. It is assumed to be a respiratory infection without germ isolation. He received antibiotic therapy with clinical remission of symptoms. Blood and urine analysis were totally normal. Due to the persistence of bibasal infiltrates in chest high resolution computed tomography (HRCT) scan with findings compatible with nonspecific interstitial pneumonia (NSIP) evidencing incipient signs of evolution towards fibrosis and progression in extension of the ground glass component in bases, fibrobronchoscopy with bronchoalveolar lavage and transbronchial biopsy were performed. In this way, both, opportunistic infection and secondary affectation due to methotrexate were discarded, with possible diagnosis of interstitial lung disease (ILD) without functional repercussion associated to systemic sclerosis. Preventive withdrawal of methotrexate and termination of smoking habit were decided.

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Patient attended consultation on December 2016. He mentioned more accentuated Raynaud's phenomenon with no complications. In blood and urine tests, subject presents: creatinine 1.05 mg/dl (normal range 0.7 to 1.3 mg/dl), elevated erythrosedimentation rate (ERS) 35 mm (up to 20 mm) and C-reactive protein (CRP) 0.68 mg/dl (up to 0.5 mg/dl) with microscopic hematuria of 15-20 red blood cells/high power of field. Therefore, new urine cytology was requested.

By the end of January 2017, subject presented new flu-like state with fever and profuse sweating, general condition compromise, lower limbs myalgia, bilateral retro-orbital pain with ocular accommodation and conjunctival injection. He attended the Emergency Department presenting 96% O2 saturation breathing ambient air and chest x-ray evidenced apparent increase of interstitial lung pattern. Prednisone 60 mg treatment was prescribed for 3 days with rapid decline of symptoms and suspension on the tenth day. Subject reports immediate improvement with prednisone, but when it is discontinued, minor lower limbs myalgia and retro-orbital pain reappear. Patient decides to self-medicate with non-steroidal anti-inflammatory drugs (NSAID) 3 days prior to control with dramatic improvement in eyes' pain. Blood and urine test present hematocrit 36.2% (versus prior 39.7%), ERS 66 mm, CRP 2.9 mg/dl, hemoglobin 11.2 g/dl (versus prior 12.9 g/dl), creatinine 1.34 mg/dl (glomerular filtration rate-GFR 58 ml/min/1.73m^2) and hematuria 5-10 red blood cells/high power of field. Complementary tests were performed with the following results: platelets 312 x 10^3 µl (150-450); tests with negative results included: schistocytes or other red blood cells fragments on peripheral blood smear or elevated reticulocyte count; lactate dehydrogenase 413 UI/L (230-460); Anti-Neutrophil Cytoplasmic Antibodies (ANCA) and proteinuria. Blood pressure in normal range. Non-steroidal anti-inflammatory drugs were discontinued. A renal abdominal ultrasound was performed showing liver homogeneous echogenicity, without focal lesions; gallbladder contained millimetric images suggesting polyps; bile duct and the visible portion of the pancreas showed no apparent alterations; a mild splenomegaly of about 142 mm was observed; both kidneys presented normal size and echogenicity, with cortical cysts; abdominal aorta was of normal caliber in its visible portion.

Conclusion

Probable gallbladder polyps. Splenomegaly performed without relevant findings. Fifteen days later, a new blood analysis control was performed, presenting hematocrit 35.4%, hemoglobin 11.4 g/dl, platelets 213 × 10^3 µl (150-450), reticulocyte count 1.60% (0.5-1.5), ERS 94 mm, CRP 5.85 mg/dl, creatinine 1.37 mg/dl (GFR 56 ml/min/1.73m^2), hematuria 5-10 red blood cells/high power of field. Urine cytology evidenced an increase of moderate urothelial desquamation with nonspecific degenerative changes. Cells with cytopathic change suggestive of Polyomavirus infection were identified. With the SV40 immunohistochemistry technique, minimal positive cellularity was observed, confirming the infection. Molecular biology in urine Polyomavirus (PCR) is required. The result is Positive for BKV 15 copies/ml, confirming the diagnosis.

In subsequent controls in cooperation with Nephrology, patient was in good health condition. Eye pain had disappeared, and poor lower limbs muscle discomfort was experienced. In control analysis 21 days later, previous values had improved: creatinine 1.29 mg/dl (GFR 60 ml/min/1.73m^2), CRP 2.23 mg/dl, ERS 32 mm, hematuria and proteinuria absent in urine, and control of molecular biology in urine for BK Polyomavirus was negative. It is assumed that patient's general compromise was related to such, with acute nephritis in process of resolution without specific treatment.

Discussion

Systemic sclerosis is a connective tissue disease which affects skin, blood vessels, heart, lungs, kidneys, gastrointestinal tract and musculoskeletal system. Involvement of internal organs results in significant morbidity and mortality of SSc patients [26]. The type of autoantibody found in patients with SSc might influence which organs are affected. SSc can be classified into two types: limited cutaneous SSc (LcSSc) with skin thickening in elbows and knees; and diffuse cutaneous SSc (DcSSc) with variable skin involvement [27,28]. Less than 5% of patients are diagnosed with Systemic Sclerosis Sine Scleroderma and present most commonly Raynaud's phenomenon, digital ulcers, pulmonary arterial hypertension, and autoantibodies specific to systemic sclerosis, but there is no skin involvement [29]. Systemic sclerosis overlap syndrome can be present in any of the three subsets, although it is most commonly found in patients with LcSSc [30].

Renal involvement in patients diagnosed of SSc is of about 50%. Involvement includes Scleroderma Renal Crisis (SRC), glomerulonephritis associated with myeloperoxidase-specific anti-neutrophil cytoplasmic antibodies (MPO-ANCA), glomerular filtration rate reduction, and proteinuria [31].

Scleroderma Renal Crisis: Studies from the EULAR Scleroderma Trials and Research (EUSTAR) database suggest a lower prevalence, 5% to 9%, of DsSSc and 0.5% to 2% of LsSSc [32,33]. Clinical features include: systolic blood pressure ≥ 140 mmHg or rise in ≥ 30 mmHg from baseline, diastolic blood pressure ≥ 90 mmHg or rise in ≥ 20 mmHg from baseline; increase in serum creatinine by ≥ 50% over baseline or serum creatinine >120% of upper limits of normal for local laboratory; proteinuria ≥ 2 + by dipstick and confirmed by spot urine protein/creatinine ratio ≥ upper limit of normal; hematuria ≥ 2 + on dipstick or ≥10 red blood cells/high power of field (in the absence of menstruation); platelet count <100,000/mm^3, and hemolysis (evidenced by schistocytes or other red blood cells fragments on peripheral blood smear or elevated reticulocyte count) [34,35]. International Scleroderma Renal Crisis Survey (ISRCS) included in SRC diagnostic criteria the presence of hypertensive encephalopathy [36]. However, around 10% of these patients may present normal blood pressure or it can be elevated as compared to their baseline. Scleroderma renal crisis is more likely to occur in patients with DcSSc, especially in patients with rapidly progressive illness within the first 3-5 years of SSc onset. Predictive factors for SRC include the presence of anti-RNA polymerase III antibodies, tendon friction, synovitis and use of glucocorticoid treatment >7.5 mg daily in the last 6 months [34,35].

Initially, a diagnosis of normotensive scleroderma renal crisis was considered, due to the persistence in normal range of blood pressure in all controls. As we previously informed, he received losartan as prior treatment because of his hypertension. Scleroderma renal crisis could be the reason of renal involvement due to the presence of anti-ARN polymerase III antibody history of tendon friction and arthritis, the use of glucocorticoids as immunosuppressant as well as anti-inflammatory drugs doses for more than one year and the impairment of renal function with hematuria. However, this diagnosis was less probable because of limited SSc (over 7 years) but fundamentally due to the lack of signs of hypertensive encephalopathy, as well as microangiopathic hemolytic anemia and platelet decline. The creatinine value was no greater than 50%

from baseline and proteinuria was negative, thus, SRC diagnosis was less likely.

Glomerulonephritis associated with myeloperoxidase-specific anti-neutrophil cytoplasmic antibodies (MPO-ANCA) has been reported in scleroderma patients and it develops in those with longstanding LcSSc, presenting crescentic glomerulonephritis, progressive renal failure, mild hypertension, and proteinuria. Some cases have reported associated pulmonary hemorrhage [37]. This condition was also considered, since it is more frequent in longstanding LsSSc, being less likely in the absence of MPO-ANCA antibodies and negative proteinuria, normal blood pressure range and absence of worsening of glomerular filtration. Scheja et al. found a decreased GFR (defined as GFR less than 70% of the age-adjusted values) in 11% of patients with LcSSc and in 8.6% of those with DcSSc after the latest follow-up (median duration of 7.7 years). Among them, hypertension, cardiac involvement, and other nephropathies diagnosed by renal biopsy, were found, suggesting that these comorbidities have a role in the decrease in GFR [38]. We may consider that hypertension has a role in creatinine value, but as it was previously expressed, hypertension was controlled at all times. Non-steroidal anti-inflammatory drugs were used 3 days prior to control, but quickly discontinued. Proteinuria or albuminuria is reported in up to 25% of scleroderma patients, with intermediate-weight proteinuria in 31.3%. Although asymptomatic, renal changes are typically non-progressive in scleroderma. Systemic sclerosis patients can also present hypertension. Whether this is comorbidity or a manifestation of renal vasculopathy remains unclear [34]. Nevertheless, our reported case did not present proteinuria. In this context, the role of the anatomopathological exam of urine sample was crucial in observing the presence of cytopathic cells change suggestive of BKV infection, which was later confirmed by SV40 immunohistochemistry and molecular biology in urine Polyomavirus (PCR) for BKV. It is important to emphasize that the patient received low doses of Methotrexate (10 mg weekly), while in transplanted patients the use of a combination of immunosuppressant is more frequent.

Conclusion

The relevance of the case is that patients with autoimmune diseases may be prone to opportunistic infections or conditions that immunocompetent patients would not develop. To date, there are no other publications on renal involvement in patients with systemic sclerosis and BK polyomavirus infection. may be prone to opportunistic infections or conditions that immunocompetent patients would not develop. To date, there are no other publications on renal involvement in patients with systemic sclerosis and BK polyomavirus infection.

Competing Interests

The authors declare that there are no competing interests regarding this paper's publication.

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