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Case Report

Schistosomiasis-induced squamous cell bladder carcinoma in an HIV-infected patient

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S U M M A R Y

The burden of Schistosoma haematobium-associated bladder cancer is very high in Africa; nevertheless the disease can pose considerable diagnostic challenges in low prevalence countries. We present the case of a 40-year-old HIV co-infected woman, originally from Mozambique, who had persisting haematuria for more than a year. Investigations revealed invasive S. haematobium-associated squamous cell bladder cancer. If her origin had been taken into account, the diagnosis might have been made earlier. Awareness of the disease prevalence among HIV co-infected patients from endemic areas and timely screening of such patients is important for the early diagnosis of schistosomiasis and related complications, such as S. haematobium-associated squamous cell bladder cancer.

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1. Introduction

Schistosomiasis, or bilharzia, is an acute and chronic disease caused by the trematodes of the genus Schistosoma. Schistosomiasis is one of the World Health Organization’s (WHO) 17 neglected tropical diseases. Furthermore, the WHO has estimated that 249 million people required preventive treatment for schistosomiasis in 2012 and that at least 90% of these people live in Africa.1

There are five main species of Schistosoma: S. mansoni, S. haematobium, S. japonicum, S. intercalatum, and S. mekongi. These species vary in geographic distribution and importance.1 S. haematobium is responsible for the urogenital manifestations of the disease and causes more than half of worldwide Schistosoma infections.2 The adult S. haematobium inhabit the venules surrounding organs of the pelvis where they lay between 20 and 200 eggs daily. The secreted eggs cause inflammatory and granulomatous reactions in the vesical and urethral walls, resulting in symptoms such as pelvic pain, post-coital bleeding, and haematuria.1,2 Squamous cell bladder carcinoma, together with chronic renal failure, is considered a long-term consequence of chronic urogenital schistosomiasis; these serious complications can be prevented by early anti-schistosomal treatment with praziquantel.3

The control of schistosomiasis is based on large-scale treatment of persons at risk, together with improved sanitation, hygiene education, snail control, and access to safe water. Unfortunately, only 14.4% of people requiring treatment aimed at reducing the disease and morbidities were reached in 2012.1

The case patient presented below originates from Mozambique, where the overall prevalence of S. haematobium is 47% and the prevalence of HIV infection in adults aged 15–49 years was 10.8% in 2013 according to the WHO.

2. Case report

A 40-year-old woman was evaluated for haematuria. The patient originally came from Mozambique and had immigrated to Denmark in 2002. She was diagnosed with an HIV infection in 2001 in Mozambique. At that time her CD4 cell count was 126 cells/μl and antiretroviral treatment was initiated. The first laboratory results in Denmark showed a CD4 cell count of 380 cells/μl and HIV RNA of <40 copies/ml. The patient had no AIDS-defining diagnosis and was a non-smoker. She was newly transferred to our outpatient clinic for HIV care.

At a routine consultation for HIV, the patient complained of small amounts of bleeding after voiding for about a year. She also had intermittent dysuria. Her general practitioner had investigated
the urine several times for infection, but urine cultures were without growth. Her haemoglobin was 7.2 mmol/l (normal range 7.3–9.5 mmol/l), leucocyte count was $3.4 \times 10^9$/l (normal range $3.5–8.8 \times 10^9$/l) without eosinophilia, and C-reactive protein was 6.0 mg/l (normal range <6 mg/l). Kidney and liver function were normal. A routine gynaecological examination, ultrasound, and cervical smear 5 months earlier had found a normal cervix and uterus. In addition, cervical cytology was normal. She was referred to the Department of Urology for further examination of persisting haematuria.

Computed tomography (CT)-urography revealed thickening of the posterior wall of the bladder (Figure 1A). Subsequently a transurethral resection of the bladder (TURB) showed a solid broad-based tumour on the posterior wall of the bladder spreading to the left. Furthermore, there were papillary lesions bilaterally. The histopathological result was poorly differentiated squamous cell carcinoma. In several of the tissue samples there were partially calcified Schistosoma eggs. In some places the carcinoma was muscle-invasive (Figure 1B). On staging, the tumour was evaluated to be T2b.

Following the TURB, an integrated CT and positron emission tomography (PET) was done. This showed pathological activity in several places in the wall of the bladder and in a few of the iliac lymph nodes. A biopsy of one of the iliac lymph nodes was then performed. Fortunately, histopathological examination of the lymph node did not show signs of malignancy. The patient then underwent robotic-assisted radical cystectomy and hysterectomy. An orthotopic neobladder was constructed and 13 lymph nodes were removed.

The final histopathological examination revealed that none of the removed lymph nodes showed signs of malignancy. Neither the uterus nor the cervix was affected. The final stage was recorded as pT2aN0M0. Because the disease was not disseminated, the patient did not undergo chemotherapy. The patient was clinically well postoperatively and she had no major complaints with respect to her orthotopic neobladder. Her CD4 count has since been >500 cells/μl and HIV RNA undetectable.

### 3. Discussion

Epidemiological studies of HIV and *S. haematobium* in Africa show a substantial overlap between regions where *S. haematobium* is endemic and regions with a high prevalence of HIV infection. A study from Zimbabwe found that women with *S. haematobium* ova in the genital tract had a three-fold increased risk of having HIV, and in Tanzania women with *S. haematobium* infection were found to have a four-fold risk of having HIV. *Schistosoma* usually precedes infection with HIV and it appears likely that urogenital *schistosomiasis* increases the risk of HIV infection. Women with *S. haematobium* may have lesions in the genital tract, referred to as female genital *schistosomiasis* (FGS), which may facilitate HIV entry. Moreover it has been hypothesized that sustained systemic chronic stimulation of the immune system caused by *S. haematobium* increases susceptibility to HIV. Monocytes and T-cells expressing the CD4 receptor and the chemokine receptor CCR5 can be infected with HIV. A study from South Africa showed that women with FGS had a higher frequency of CD4+ T-cells expressing CCR5 in blood samples than FGS-negative women. It was also found that this proportion decreased significantly after treatment with praziquantel. In cervical cytobrush-derived cells, a higher CCR5 expression on CD4+ cells in women with FGS compared to women without FGS was found.

Furthermore, evidence suggests that *S. haematobium* may accelerate HIV disease progression, by raising plasma HIV RNA. Does HIV infection accelerate the long-term complications of chronic *schistosomiasis*? This needs to be elucidated.

The 5-year disease-free survival rate after radical cystectomy due to squamous cell carcinoma is 57.7%. Factors with significant and independent influence on survival are tumour pathological stage, histological grade, and lymph node status. Early diagnosis is of pivotal importance for the disease-free survival rate.

In low-prevalence settings, routine *schistosomiasis* screening and treatment of the population at risk appear to comprise an important public health tool. In an HIV clinic in Glasgow, all patients of African origin were screened for *schistosomiasis* using antibody tests to determine the prevalence. In total, 17% of all HIV cases were positive and offered treatment. A positive antibody test among patients at known risk would lead to the early diagnosis and treatment of *schistosomiasis* in low-prevalence countries. However, due to low sensitivity and specificity of the antibody test, the diagnostic work-up should be combined with direct tests.

This patient was fortunate that the disease had not metastasized and no lymph nodes were involved at the time of diagnosis. If the patient’s symptoms had been considered in relation to her origin, the diagnosis might have been made earlier. It is important to remember that persistent haematuria is a warning sign and needs to be taken seriously.

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