Case Report

CANDIDA ALBICANS CYSTITIS CURED BY NYSTATIN BLADDER INSTILLATIONS

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Bladder infections with *Candida albicans* have been reported frequently in the medical literature, but their successful treatment has proved uncommon.[1-11] A variety of drugs have been used in previous cases but no report has yet been noted of the use of nystatin locally in their treatment. The purpose of this communication is to draw attention to a case of cystitis caused by *C. albicans* in which nystatin bladder washouts effected a rapid cure.

CASE REPORT

History

M.D., 63-year-old Coloured female, admitted to Somerset Hospital on 12 August 1964: The patient sustained a left-sided hemiplegia from which she made a good recovery a year before admission. Six weeks before her present illness she had another left-sided cerebrovascular accident associated with dysarthria, difficulty in swallowing and faecal and urinary incontinence. A week before admission her condition deteriorated owing to the onset of weakness involving the previously

unaffected right side with mental confusion and stupor, which eventually led to her admission. She had been a diabetic under treatment with tolbutamide since 1963 and was known to have had hypertension which did not require therapy.

Examination

On admission she was an obese woman with a temperature of 101·6°F. There was a small superficial abscess on her left upper arm and an early pressure sore on her right heel. Her heart rate was regular at 120/minute; all pulses were present and equal and her blood pressure was 190/105 mm.Hg. There was no evidence of cardiac failure and her heart was normal. Chest and abdomen were also normal. She was conscious but aphasic, with no evidence of neck stiffness. She had difficulty with swallowing. She had a spastic left-sided hemiplegia and a flaccid right-sided hemiplegia. Both plantar responses were extensor. There was no sensory abnormality. Gynaecological examination showed a reddened vulva and vagina with a profuse yellow discharge. She also had an acute cervicitis with an erosion; uterus and adnexae appeared normal.

Investigations. Routine urinalysis showed a heavy glycosuria and an occasional pus cell in the urinary sediment. Haemoglobin was 14·5 G/100 ml., blood sedimentation rate 37 mm./1st hour (Westergren); WBC 20,850 (polymorphs 77%, lymphocytes 20%, monocytes 2%, eosinophils 1%); and the blood smear was normal.

Lumbar puncture. The cerebrospinal fluid was under normal pressure with free dynamics and normal chemistry, except for a glucose of 158 mg./100 ml. in keeping with her diabetic state, and 7 lymphocytes/cu.mm.; Gram stain was normal and the culture sterile; blood and CSF Wassermann and Berger reactions were normal. X-ray examination of skull was normal and radiographs of the chest showed left ventricular cardiomegaly, which was confirmed on electrocardiogram. A pus swab from the small abscess which ruptured on her left arm gave a scant growth of *Staph. aureus* sensitive to all antibiotics tested. A vaginal swab grew similar *Staph. aureus* in heavy growth. A catheter specimen of urine was sterile on culture. Her serum electrolytes were as follows: sodium 150 mEq./l., chloride 109 mEq./l., potassium 4·4 mEq./l., and bicarbonate 24·1 mEq./l.; blood urea was 70 mg./100 ml.

Course and Management

In view of her dysphagia, a nasogastric tube was passed and she was tube-fed with a liquid diet. With adequate hydration her elevated blood urea fell to 18 mg./100 ml. within a few days. Because her urinary incontinence provided a considerable nursing problem and enhanced the ever-present risk of further pressure sores developing, an indwelling Foley's bladder catheter was passed. Her diabetes was stabilized on 40 units lente insulin daily and a low-calorie liquid diet. While in hospital her diastolic blood pressure ranged between 100 - 110 mm.Hg and no therapy was given in the circumstances. Physiotherapy was given daily with prevention of contractures but without return of any useful muscle function. Her mental state remained unchanged throughout her stay in hospital.

Because of the *Staph. aureus* cultured from her abscess and vagina, treatment was commenced with 250 mg. of ampicillin 6-hourly for 11 days plus P.S.S. pessaries for 20 days for the vaginal discharge. On this treatment her pyrexia settled within a week, the vaginal discharge cleared, and her abscess healed. Twelve days after admission a catheter urine specimen was cultured as a precaution in the early detection of urinary infection in a diabetic patient with an indwelling catheter. A heavy growth of *Klebsiella aerogenes* was obtained sensitive to nitrofurantoin which was therefore commenced in doses of 100 mg. every 6 hours.

Five days later she again became pyrexial and a further 3 catheter specimens of urine all showed numerous pus cells, masses of yeasts on staining, and a heavy growth of *C. albicans.* A vaginal swab at this time gave a heavy growth of coliforms but no candida.

An intravenous pyelogram performed the day before commencing nystatin was completely normal. Nitrofurantoin was continued and nystatin bladder instillations were instituted. 200,000 units of nystatin suspension were dissolved in sterile water to a volume of 30 ml. and were introduced 6-hourly via the indwelling catheter. The catheter was clamped for 1 hour after each instillation to allow retention of the nystatin suspension.

Within 2 days of commencing nystatin therapy a urine specimen obtained by catheter showed only scanty candida on staining and there was no growth on culture. On the third day no candida were seen or cultured. Thereafter urine specimens were checked on alternate days without evidence of fungal infection being found. Nystatin therapy was continued for 16 days on the empirical basis that therapy be stopped after 3 consecutive urine specimen results received failed to show candida infection.

The patient's further course in hospital was complicated by the development of a staphylococcal infection of a pressure sore on the scalp which required incision and drainage and courses of penicillin, streptomycin and novobiocin. The use of these antibiotics and the continued presence of the bladder catheter did not lead to reinfection with candida although subsequent urine cultures grew several other organisms including enterococci, coliforms, paracolon and *K. aerogenes.* She was eventually transferred to another hospital which cares for the chronically sick.

DISCUSSION

Diagnosis

C. albicans has been isolated from the faeces, skin, mouth and vagina in a varying proportion of apparently healthy individuals;[12-14] Skinner[15] reported its presence as a commensal in 10 - 20% of the population and it has been cultured from the lungs in 15% of routine autopsies.[16] Infection of the vagina by candida with or without symptoms is extremely common.[17] With such an ubiquitous organism, when, therefore, does the presence of *C. albicans* in urine cultures signify whether it is in fact a pathogen? Where fungi are isolated in pure culture from the urine, as happened in the patient described on 3 consecutive specimens, the diagnosis presents no problem. However, as pointed out by Guze and Haley,[7] where there is mixed or secondary infection, frequent quantitative urine cultures become necessary to establish the diagnosis. Clinically, no help is forthcoming, for the symptoms and signs of fungal and bacterial infections of the kidney and bladder are indistinguishable, and since they often occur together the onus for diagnosis rests on the bacteriologist. Apart from cases such as the patient described, where candida is cultured in pure, heavy growth, Guze and Haley[7] suggest that fungus counts of more than 1,000 organisms/ml. of urine can be regarded as significant.

Frequency. Some idea of the frequency of candida infection of the urinary tract, can be gained from the ever-increasing number of cases described in the medical literature. Goldman *et al.*[9] microscopically examined centrifuged urinary sediments in an estimated 200 cases of cystitis over a 1-year period and found only 1 positive specimen in which 5,000 colonies per ml. urine were grown on subsequent culture. Guze and Haley[7] examined 1,500 unselected urine specimens submitted for bacteriology in hospital. Fifteen of these showed significant fungal infections of which 6 were candida.

Predisposing factors. Of interest are the factors which predispose to fungal infections of the urinary tract. Females are more commonly affected as they are by any urinary tract pathogen; of the cases of fungal infection so far reported in the literature, women have outnumbered men by approximately 4:1. In the 15 cases found on routine urine culture by Guze and Haley,[7] 13 were women. Sauer and Metzner[3] assumed that the organisms invaded

the bladder along the urethra from the vagina since the vagina is such a common site of candida infection. Gibberd and Williams[11] made the same assumption in their case of bladder infection but no mention was made of vaginitis or vaginal cultures. In the patient described in this paper a vaginal swab grew no candida, at the time when the catheter specimen of urine showed a heavy growth. In searching for undetected cases of candida bladder infection, Goldman *et al.*[9] acted on the assumption that they would most readily be found in women with candida vaginal infections with associated urological symptoms. Urines from an unspecified number of such patients were checked and all were found to be negative for candida.

Diabetes mellitus undoubtedly favours candida infections. Of the 15 patients described by Guze and Haley,[7] 9 were diabetic, as was the patient described above. Johnson[18] showed that the rate of growth of *C. albicans* rose in proportion to the concentration of glucose present where the level was above 150 mg./100 ml.

It is widely believed that antibiotic therapy favours fungal infection, but Winner and Hurley[17] in a recent authoritative work on *C. albicans* regard the question as largely unresolved. If, then, antibiotics do encourage candida infections, yet another predisposing factor existed in the patient described who had received antibiotics before the development of her fungal infection. Other factors said to predispose to candida invasion are steroid therapy,[17] debilitating diseases,[17] and instrumentation.[5] Hypothyroidism, hypoparathyroidism, blood dyscrasias and Addison's disease, which are known to encourage fungal overgrowth, have not yet been particularly implicated in urinary tract candidosis.[17] Although instrumentation in the form of an indwelling catheter was employed in the patient described, there seems no special reason that fungal infection should follow any more readily than bacterial infection, which is known to be introduced frequently by this means.

Form of infection. Candida infection of the urinary tract commonly takes the form of a cystitis only. The upper urinary tract appears normal on intravenous pyelography and ureteral urine specimens are sterile. The first case diagnosed during life was described by Rafin[1] in 1920. Since then, numerous case reports have appeared in the literature.[2-11] The symptoms do not differ from those of a bacterial cystitis with dysuria, frequency, urgency, nocturia and sometimes haematuria.[7] Cystoscopy may be helpful in making a diagnosis in an otherwise unsuspected case since the appearances are typical. There is a thrush-like membrane consisting of soft, pearly-white, slightly-elevated patches resembling deposits of coagulated milk, which adhere firmly, so that the mucosa bleeds when they are removed.[2,3,9,10] Occasionally a fungus ball forms in the bladder which may be mistaken for a neoplasm or calculus.[19] Similar aggregations may occur in the ureters or pelvi-calyceal systems showing as filling defects on intravenous pyelography[8,20,21] in those cases not confined to the bladder.

Those with candida in the upper urinary tract comprise another large group of cases of urinary tract candidosis, which may be examples of isolated renal involvement[7,8,20-26] from which secondary bloodstream dissemination may occur,[27,28] or more commonly the kidney may be one of many organs affected by candida septicaemia.[20,25,27-35] The pattern of renal involvement following intravenous injection of candida in experimental animals has been well described by Hurley and Winner[36] and parallels most of the clinical presentations in man.

Results of treatment. Despite the abundance of literature on the subject of urinary tract infection by candida there has been a singular lack of success in treatment until very recently.[37] Moulder[2] claimed a cure in a patient treated with sulphathiazole, penicillin, silver nitrate and gentian violet instillations, mapharsen and alkalinization of the urine with benefit only after a 2 months' drug-free period, making assessment of success in relation to therapy difficult.[24] In 1958, Gillam and Wadelton[21] successfully treated a case of renal candidosis with oral nystatin, pyelotomy and irrigation of the renal pelvis with solution G and 1 - 1,000 merthiolate for an unspecified time. Antibiotics have been freely used, but sulphonamides or broad-spectrum antibiotics have understandably frequently caused a marked increase in the severity of the symptoms.

Gibberd and Williams[11] in 1962, employing alkalinization of the urine, continuous bladder drainage and dequalinium solution as a bladder washout, rapidly cured a case of candida cystitis. A more difficult case of renal candidosis described by Cowan *et al.*[10] in 1962 responded to nephrostomy with irrigations of clorpactin WSC 90 solution through the nephrostomy tube and into the bladder, but therapy had to be continued for 4 months and clorpactin is known to be an irritative substance. They also used oral nystatin concurrently but pointed out in their discussion that it is not absorbed in sufficient quantity from the gastro-intestinal tract to produce therapeutic blood levels. In their paper they suggested the use of amphotericin B, which was not available at the time of treating their patient.

Perhaps the most convincing treatment of candida cystitis was that of Goldman *et al.*,[9] who cured 2 patients quickly and without untoward side-effects using daily bladder irrigations of a solution of amphotericin B plus concurrent alkalinization of the urine. The latter manoeuvre is a rational one, since alkalinization alone appears to decrease the symptoms markedly and reduces the number of fungi recoverable from the urine, while both recur on cessation of alkali therapy.[9] Benham[38] has shown that *C. albicans* grows most profusely at pH 5·1 - 6·4, which provides a rational basis for artificially increasing the urinary pH in treatment.

Because of the uniform success of local application of nystatin in the treatment of oral thrush, it seemed the obvious choice in the treatment of the bladder infection in the patient described, and it was astonishing in retrospect to find that it had not been used in similar circumstances before. Alkalinization of the urine was not employed, but it appears to be a rational adjunct to therapy. The dose of nystatin, the frequency of instillation and the duration of therapy were chosen empirically. Since the urine contained no candida on the third day after commencing therapy it seems likely that the 16-day course of therapy might have been unnecessarily long and it is also conceivable that a smaller dose could have been used.

Unfortunately the patient was aphasic, and any possible subjective irritative side-effects could not be assessed. A thorough search of the literature has failed to produce any previously reported case of candida cystitis treated with nystatin instillations and it would seem that this offers an effective and simple means of therapy.

SUMMARY

The first documented case of bladder infection with *C. albicans* cured by instillations of nystatin solution is described.

The literature of candida urinary tract infections and their treatment is discussed.

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