

Bilharziasis of the genitourinary tract

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Introduction

The larvae of *Schistosoma haematobium* continue to develop in the veins of the infected human host and on reaching maturity, the coupled worms migrate to the veins of the vesical and pelvic plexuses, where they mate and the female begins to lay eggs. Involvement of the various urogenital organs varies markedly and appears to correlate with the extent of their venous circulation. Thus the urinary bladder, lower ends of the ureters and seminal vesicles are most commonly affected by the disease, because they have a rich venous supply. Mohamed [1] reported the percentage distribution of the eggs of *S. haematobium* among the endopelvic organs as 90% in the urinary bladder, 80% in the seminal vesicles and 19% in the prostate. Furthermore, the intensity of egg deposition in the tissues bears a similar correlation. In a quantitative postmortem study, Smith *et al.* [2] noted a mean egg count of 4313/g of tissue in the urinary bladder, 19 929 in the seminal vesicles and 8058 in the prostate. There was a significant correlation between egg burden and the histological severity of tissue reaction.

Pathology and development of lesions

The initial response

The primary pathology represents a reaction of the host directed against the deposition of schistosomal eggs. Initially, a granulomatous lesion forms in the lamina propria (Fig. 1). The extent of this lesion and its subsequent development by healing, progression or complication depends on several factors, the relative importance of which are not yet clearly defined. These factors include the tissue egg load, the frequency of re-infestation, the efficiency of treatment and the onset of secondary infection.

The subsequent pathology

The secondary responses represent an epithelial reaction resulting from events which started originally in the submucosa. The deposited eggs secrete a histolytic antigen which is tissue-fixed and evokes a cell-mediated

immune response in surrounding host tissue. The cellular infiltrate is characterized by the presence of eosinophils and the overlying mucosa is raised into polypoid patches surrounded by hyperaemia. The pattern of the subsequent changes may be atrophic, proliferative or metaplastic.

Atrophic changes result from heavy submucous ova deposition with a subsequent reduction of the blood supply to the overlying epithelium. The development of secondary bacterial infection may also play an aggravating role. Eventually, erosion of surface epithelium results in the formation of bilharzial ulcers.

In hyperplasia, the number of epithelial strata is increased beyond the normal value of six layers. In simple hyperplasia there is no cellular atypia, whereas in dysplastic forms of hyperplasia, nuclear atypia is present but limited to the basal layers. The hyperplastic mucosa may be thrown into papillary surface projections, producing the lesion known as polypoid cystitis.

The transitional epithelium overlying and surrounding the lesion may undergo squamous or columnar metaplastic changes. Columnar metaplasia may be typified by predominant glandularis changes or cystica changes of epithelial enclosures. These are causally related and represent columnar metaplasia of the urothelium rather than inflammatory epithelial inclusion. It is not unusual to find the concomitant association of cystitis cystica and glandularis in the same lesion (Fig. 2).

Secondary bacterial infection

The frequency of bacterial superinfection in urinary schistosomiasis appears to be related to the age of the patient and to the severity of infestation. In a survey of rural Egyptian children, *Escherichia coli* and *Salmonella* bacteriuria were detected in 5% of those assessed, but in patients with bilharzial cystitis bacterial infection was invariably present, and half of these were caused by *E. coli* [3].

In addition to aggravating the symptoms of bilharzial cystitis, secondary bacterial infection contributes greatly to the morbidity of urinary bilharziasis by leading to ascending infection of the upper tract and serious deterioration of renal function. Furthermore, bacterial infection may play a significant role in the development

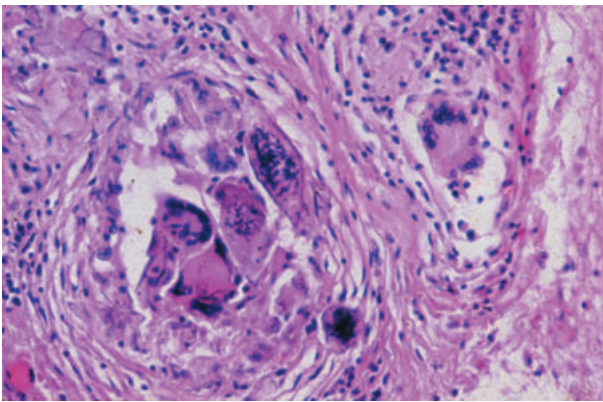


Fig. 1. The initial lesion is a bilharzial granuloma. The bilharzial eggs are surrounded by inflammatory cells. Haematoxylin and eosin $\times 100$.

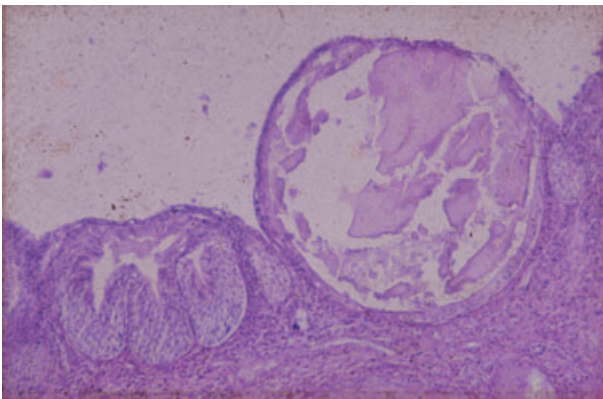


Fig. 2. Columnar metaplasia: cystitis cystica and glandularis. Haematoxylin and eosin $\times 100$.

of other urinary complications, e.g. strictures, fistulae, calculi and malignancy.

Healing

The natural history of urinary schistosomiasis depends upon three main factors: the severity of infestation, frequency of re-infestation and the adequacy of therapy. Thus, with occasional infestation and adequate treatment, favourable healing is the usual outcome. Active granulomatous lesions encountered in children and young adults are particularly reversible [4]. Favourable healing encompasses a reasonable amount of mural fibrosis and dystrophic calcification.

Chronicity and complications

Frequent re-infestation and inadequate treatment are usual among farmers living in endemic areas. The development of fixed and irreversible pathological states is not unlikely. These include the development of ureteric strictures, chronic cicatricial ulcers, bladder contraction,

BOO, leukoplakia, carcinoma *in situ* and overt bladder malignancy.

Bilharziasis of the ureters

The main site of involvement is the endopelvic part of the ureters. Less commonly, the lumbar portion of the ureter may also be affected [5]. Zahran *et al.* [6] suggested that ovideposition is mainly peri-ureteric but other studies have shown that the eggs are found in all layers, particularly suburothelially and between the muscle layers. The end result is healing with a variable degree of mural fibrosis, with loss of muscle and peri-ureteric adhesions. The sum of these changes is an obstructive uropathy caused by stricture formation and/or atony and dilatation of the involved segment. VUR has also been reported in $\approx 15\%$ of cases [7]. Eventually, urinary stasis invites secondary bacterial infection and stone formation.

Clinical features and evaluation

Loin pain and renal colic with or with no symptoms of pyelonephritis are the main presenting features. Patients may also present with a silent clinical hydronephrosis. Less commonly, the first presenting symptom is anuria [8]. The diagnosis is based on findings from urography, retrograde or antegrade studies (Fig. 3). Radioisotope renography has a definite place in evaluating renal function, determining the degree of obstruction and in the follow-up after surgery [9].

Management

Anti-schistosomal therapy should be given for the early lesions. Some authors advise the administration of adjuvant corticosteroid therapy to reduce the intensity of the inflammatory and fibrotic reactions [10]. Endourological procedures may be also useful for early short-segment strictures. Endoscopic dilatation and visual internal ureterotomy with stenting were successful in 40–60% of such cases [11].

Open surgery is usually indicated for the more established lesions. Resection and re-anastomosis is very suitable for the well localized short-segment stricture. Reimplantation of the ureter into the bladder is the procedure of choice for strictures of the lower ureter. Concomitant involvement of the bladder, and dilatation and thickening of the ureter above the strictured area may render adopting an antireflux procedure extremely difficult. Under such circumstances anastomosis of the ureter to a sufficiently long Boari bladder tube flap provides an excellent alternative. For long segment or multiple strictures of the ureter, replacing the pathological segment by an isoperistaltic segment of ileum may

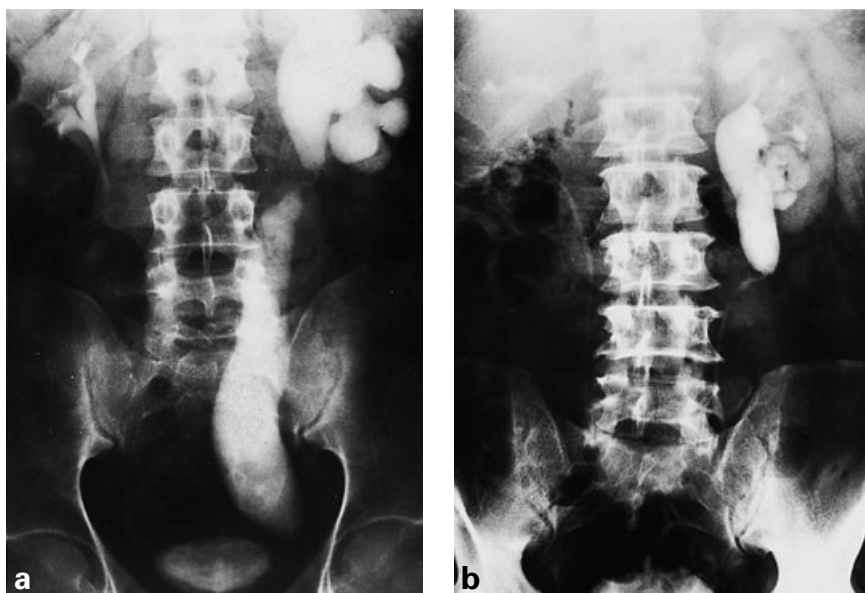


Fig. 3. IVU showing a, a stricture of the lower end of the left ureter, and b, a stricture of the lumbar part of the left ureter.

be the only solution. There is evidence that tailoring the ileal ureter to reduce its cross-sectional diameter and creating an intussuscepted nipple valve at its distal end to prevent reflux are followed by better functional results [12]. Nephrectomy is indicated in advanced cases with loss of renal function.

Bilharziasis of the bladder

Clinical features and evaluation

Patients with bilharzial lesions of the lower tract present essentially with a common symptom complex, i.e. painful micturition, frequency, pyuria and haematuria. Pain is usually intense, with bladder ulceration, and may be referred to the tip of the penis and to the perineum. In the active phase, there is invariably heavy excretion of viable eggs in the urine and there may also be bacteriuria. Anaemia and eosinophilia are common.

The diagnosis is usually evident in patients from endemic areas and with the finding of schistosomal eggs in the urine. A plain X-ray may show bilharzial calcification and cystography sometimes reveals filling defects of proliferative bladder lesions or may suggest the more chronic manifestation of contracted bladder or outlet obstruction. However, the critical evaluation of bladder lesions requires endoscopic examination and this remains the most important tool in managing this group of patients.

Endoscopic features of the bilharzial bladder

Cystoscopy allows the morphological identification of the gross bladder lesion and permits a histopathological verification of obtained biopsy material.

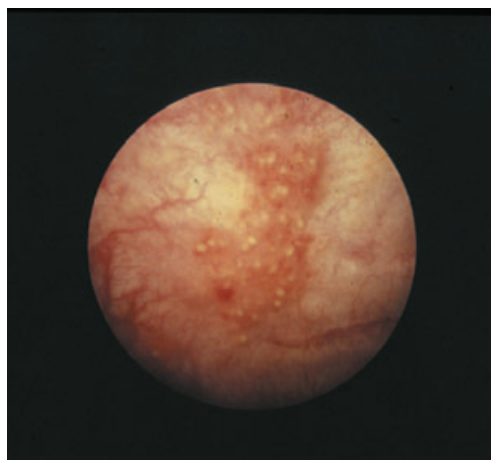


Fig. 4. An endoscopic view of active bilharzial 'tubercles'.

Bilharzial tubercles (Fig. 4) are characteristic of early and active infestation, and appear as seed-like, yellowish specks, slightly prominent above the mucous membrane. Initially, each tubercle is surrounded by a circle of hyperaemia, but later these may fade or disappear. Lesions which are distinctly larger and more prominent are sometimes described as bilharzial nodules.

Bilharzial polyps. El Badawi [13] observed these lesions in 7.2% of bilharzial patients who underwent endoscopic examination, and described three types: (i) granulomatous polyps, which were the commonest finding (60.5%), and represented an active and dense granuloma in the submucosa. The preferred site is the bladder trigone, usually in the para-ureteric region, and lesions may be pedunculated, red and occasionally, multiple or clustered (Fig. 5); (ii) fibrocalcific polyps, usually encountered in older patients (> 20 years); these lesions are commonly

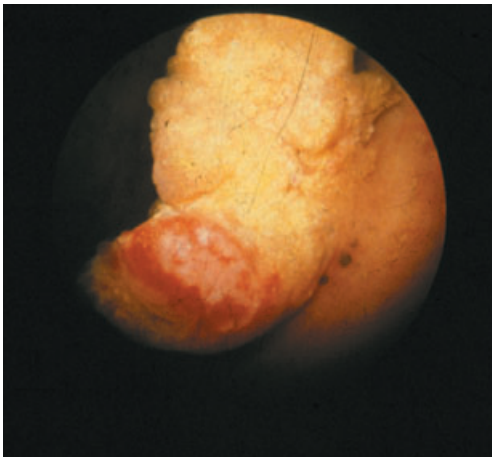


Fig. 5. A giant bilharzial granuloma 'polyp'.

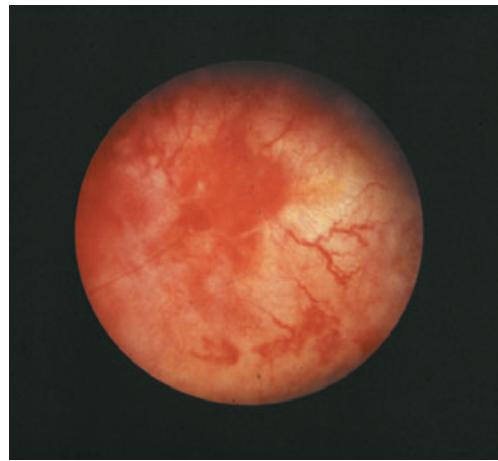


Fig. 6. An active ulcer.

single, pedunculated and of a dull yellowish hue. Histological features are those of a healed granuloma covered by atrophic epithelium and there may be varying degrees of calcification; (iii) villous polyps are indistinguishable from vesical papillomata by cystoscopy. However, biopsy examination will reveal the characteristic bilharzial granulations at the pedicle of the polyp.

Sandy patches. As described, atrophy of the surface epithelium over bilharzial lesions results in a thinned covering, so that the old calcified bilharzial eggs buried immediately beneath the mucosa appear visually like sand seen through shallow water. With repeated infestation, the bladder lining loses its healthy pink appearance and becomes a pale, dull translucent lustre. The normal subepithelial branching of blood vessels is no longer visible. This picture is usually described as the 'ground-glass' mucosa. Less commonly, the heavy deposition of eggs is localized and the calcific submucosal granuloma appears as a raised white plateau usually known as a calcific plaque.

Bilharzial ulcers. Ulceration of the surface epithelium is generally attributed to local ischaemia, caused by the bilharzial obliteration of deeper vessels and/or onset of secondary bacterial infection. Shokeir *et al.* [14] reported the presence of bladder ulcers in 8% of 350 bilharzial patients assessed by cystoscopy. According to their appearance during endoscopy they may be classified into: (i) active ulcers, seen in children and young adults. These are overtly active granulomata located superficially in the bladder submucosa, with loss of surface epithelium. The surface bleeds readily on vesical distension during diagnostic cystoscopy (Fig. 6); (ii) cicatricial ulcers, characterized by dense fibrosis. Three morphological types were described, i.e. stellate ulcers (Fig. 7), which are shallow with thin margins and surrounded by radial puckering; punctate ulcers, appearing as tiny bleeding spots with extensive circumferential fibrosis;

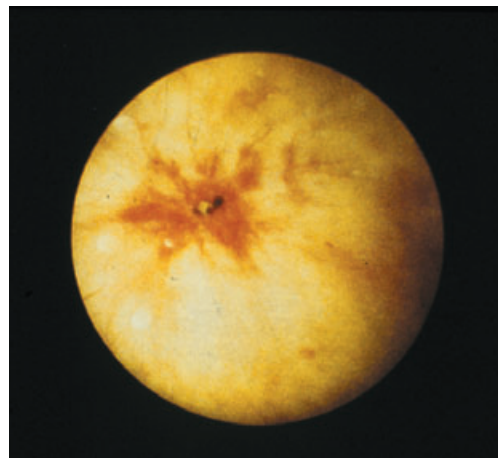


Fig. 7. A chronic stellate ulcer.

and linear ulcers, which are flat with thick and raised indurated margins.

Cystitis cystica and glandularis

At cystoscopy, cystitis cystica appears either as tiny rounded, transparent vesicles or as dark-brown, well-defined structures (Fig. 8). The benign course of this lesion is undisputed but cystitis glandularis has a natural history that is thought to lead to the subsequent development of adenocarcinoma. Nevertheless, firm evidence supporting this contention is lacking. The lesions of glandular cystitis appear at cystoscopy as a velvety-red elevation of the mucous membrane. Biopsy and histopathological examination are essential for the definitive diagnosis.

Leukoplakia

Chronic urosepsis, chronic epithelial irritation from the presence or passage of schistosomal eggs, and vitamin A

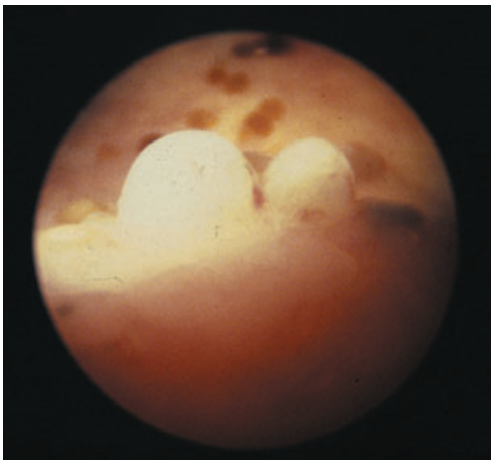


Fig. 8. Cystitis cystica.

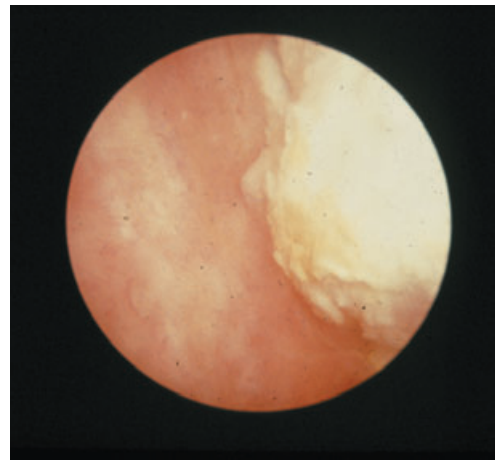


Fig. 9. Leukoplakia of the bladder.

deficiency are all possible causes for the development of squamous metaplastic changes. The endoscopic appearance is of well-defined, thick and raised white patches. The surface of these lesions may be covered with phosphatic encrustation, and the surrounding mucosa is red and inflamed. These can be differentiated from other types of metaplasia and calcific plaques only after biopsy resection and histological examination (Fig. 9).

Carcinoma in situ

The incidence of this change in the bilharzial bladder is not yet known. There are no characteristic endoscopic findings and the bladder is generally noted to be inflamed, red and bleeds easily with over-distension. There may be areas of ulceration and phosphate encrustation. Biopsy is essential for a definitive diagnosis.

The management of benign superficial bilharzial lesions

Active bilharzial bladder tubercles and polyps respond readily to specific antibilharzial therapy. Currently, the agent of choice is praziquantel; a single oral dose of 40 mg/kg is recommended and this can be repeated with minimal side-effects. Antimicrobial agents will also be required for treating secondary bacterial infection. Resection and biopsy may be indicated for residual lesions, as many of these may be difficult to diagnose from a morphological examination alone.

Active bilharzial ulcers may also respond satisfactorily to chemotherapy, but the classical treatment of chronic ulcers is total excision by partial cystectomy. The recurrence rate after this procedure is $\approx 5\%$. Excellent results have also been reported more recently after the endoscopic resection of such lesions. The management

of the contracted bladder, BOO and of carcinoma of the bilharzial bladder require special consideration and will be described in further detail.

The contracted bilharzial bladder

The bilharzial contracted bladder is the outcome of severe and prolonged infection. Sayegh and Dimmette [15] reported that this serious complication occurred in 0.6% of their urological admissions.

Affected patients are usually men in their third or fourth decade of life. The presenting symptoms are intractable frequency, painful micturition and urge incontinence. The severity of these symptoms is directly related to the volume of the bladder. Urographic studies show a small bladder in the cystographic phase (Fig. 10). There is upper tract dilatation in a third of cases and VUR in two-thirds. Cystoscopy under a general anaesthetic will readily show the reduced bladder capacity.

Surgery is indicated in cases where the bladder capacity is reduced to < 100 mL. The procedure of choice is augmentation cystoplasty, using either ileum or colon [16,17].

BOO

Shokeir *et al.* [14] reported that bladder neck obstruction was a significant feature in 7.5% of patients with complicated bilharzial cystitis. Koraitim [18] stressed that three factors are largely responsible for the pathogenesis of BOO in the bilharzial bladder: muscle destruction, fibrosis of the trigone and bilharzial infestation of the first part of the urethra.

The patients, usually men aged 20–40 years, present with symptoms of cystitis and difficulty on micturition. Calculus disease and secondary bacterial infection are

sometimes coexisting findings. The diagnosis is based on urodynamic evaluation with simultaneous recording of the voiding pressure and flow rate. Endoscopic incision of the bladder neck provides the best functional results [19].

Carcinoma in the bilharzial bladder

Carcinoma of the urinary bladder is the commonest solid tumour among adult males in Egypt [20]. A causal relationship between urinary bilharziasis and cancer of the bladder was first reported by Fergusson [5] and has since been supported by other studies. Bilharzial bladder cancer may be initiated by exposure to an environmental or locally produced chemical carcinogen. Nitrates are present in human urine, particularly among individuals living in agricultural areas where nitrate fertilizers are used liberally. These compounds are readily reduced to carcinogenic nitrosamines as a result of secondary bacterial infection.

The association of bladder cancer with urinary bilharziasis determines a distinct clinicopathological behaviour [21]. The peak age of incidence is between the third and fifth decades; the male : female ratio is 4 : 1.

Patients present with symptoms of cystitis, painful micturition, frequency and haematuria. Urography may reveal an irregular filling defect in its cystographic phase. The diagnosis depends upon cystoscopy, biopsy and careful bimanual examination under anaesthesia.

Grossly, the tumours are generally of the nodular fungating type and occupy the vault, posterior or lateral walls of the bladder (Fig. 11). Histologically, two-thirds of cases show squamous cell features, most being of low-grade malignancy (Fig. 12).

There are several treatments:

Endoscopic resection. In view of the bulk and advanced stage of these tumours, transurethral resection appears unfeasible for definitive treatment. Endoscopic resection is currently limited to obtaining biopsy material for histopathological diagnosis and evaluation.

Segmental resection. Local resection is only feasible in certain conditions: (i) if the tumour is solitary, does not involve the trigone, and its size allows excision with adequate safety margin; and (ii) the rest of the bladder is free of any associated precancerous lesion. Very few patients with carcinoma of the bilharzial bladder satisfy these criteria.



Fig. 10. IVU showing a contracted bilharzial bladder.



Fig. 11. A sagittal section of a cystectomy specimen, showing a nodular fungating tumour.

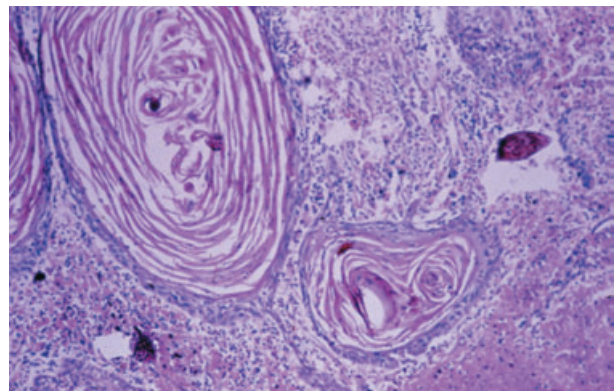


Fig. 12. Low grade squamous cell carcinoma.

Radical cystectomy. Because of the pathology and natural history of the disease, radical cystectomy and some form of urinary diversion provide the logical surgical approach to most cases with resectable tumours [20,21]. The extent of excision includes the bladder with its perivesical fat, peritoneal covering, prostate, the seminal vesicles, together with the distal common iliac, internal iliac and external iliac lymph nodes. In the female bladder resection includes the urethra, uterus and upper two-thirds of the vagina, with pelvic cellular tissue and the aforementioned lymph nodes.

The reported 5-year disease-free survival after radical cystectomy is $\approx 48\%$ [22]. In that study, survival data were correlated with several patient and tumour characteristics. The multivariate analysis indicated that only three factors had an independent effect on survival, i.e. tumour stage, grade and lymph node involvement. This is of interest as evidence was provided that the tumour histology and/or the presence of bilharzial pathology did not influence the outcome. Furthermore, the radical operation can provide a disease-free survival for 23% of patients with endopelvic nodal disease.

Radiation therapy. Early experience with EBRT for definitive control of these tumours showed disappointing results, particularly as many of these cases were already far advanced [23]. A randomized prospective trial was carried at the Mansoura University Hospital comparing the results in 92 patients with carcinoma of the bilharzial bladder who underwent either radical cystectomy alone or with preoperative radiation [24]. The postoperative mortality and morbidity were similar in both groups. Patients were followed for a minimum of 60 months. Overall, there was a marginal statistically insignificant improvement in survival among patients receiving preoperative radiotherapy.

Chemotherapy. Several chemotherapeutic agents have been evaluated in patients with bladder cancer at the cancer Institute of Cairo University. All patients had unresectable T4 lesions. The most promising results were obtained with epidoxorubicin. Clinical trials with this agent as a neoadjuvant chemotherapy have also been started in patients with T3 lesions [25].

Bilharziasis of the urethra

Adult *S. haematobium* worms may gain access to the urethra via connections between the vesicoprostatic venous plexus, the urethral veins and the dorsal vein of the penis. Because of its rich venous network, the commonest site of involvement is the roof of the bulbous urethra. Less commonly, the pathology involves the floor of the penile urethra [26].

Lesions usually develop in three successive phases. The initial phase of infiltration is characterized by the

formation of bilharzial granulations in the submucosa. This is followed by atrophic changes in the overlying mucosa and the development of superficial ulcers. Mild ulcers may heal with a variable degree of scarring. If the disease is more extensive, and especially if there is additional bacterial infection, the inflammatory process may invade the periurethral tissues and lead to the development of periurethral abscess and fistulae (the 'watering can' perineum).

Any recent uncomplicated perineal fistula may completely resolve with adequate antibilharzial and antibiotic drug therapy. In chronic cases, and where a large indurated mass is evident, temporary urinary diversion by suprapubic cystostomy is also necessary, and is maintained for an average of 2 weeks. Intermittent urethral dilatation may be indicated during convalescence, to prevent the development of a urethral stricture. In advanced or recurrent cases, complicated by stricture formation, a two-stage skin-inlay urethroplasty may be necessary.

Bilharziasis of the male genital tract

Bilharzial seminal vesiculitis

Involvement of the seminal vesicles is usually bilateral. The pathological lesion develops in three phases, i.e. congestive, hyperplastic and fibrotic [27]. Microscopy invariably shows bilharzial ova randomly deposited in all layers of tissue. There may be complete replacement of glandular tissue by calcified sheets of bilharzial infiltration.

Symptoms of seminal vesiculitis are often masked by those of concomitant bilharzial cystitis. Haemospermia is a characteristic feature and has been reported in 8% of cases with clinical evidence of bilharzial seminal vesiculitis [28]. Painful ejaculation, burning micturition and low backache may also be encountered [29]. A rectal examination reveals bilaterally enlarged, firm and nodular or cystic seminal vesicles. The vesicular masses are characteristically 'date-shaped'.

Examination of the seminal fluid shows bilharzial ova in 34% of cases [28]. Radiological examination may show calcification in the involved seminal vesicles and, characteristically, this shows a honeycomb appearance.

Studies by Aboul-Azm *et al.* [29], using the fructose test and seminal vesiculography in patients with bilharzial seminal vesiculitis, showed that the vesicular and ampullary canals, together with the ejaculatory ducts, remained patent. Therefore it seems unlikely that bilharziasis plays a direct role in the development of obstructive infertility in the male patient.

Anti-bilharzial treatment, supported by antibiotic therapy, is the main management. In troublesome

cases, with marked enlargement of the glands, seminal vesiculectomy may be indicated [29], and is undertaken through an extraperitoneal, retrovesical approach.

Bilharzial prostatitis

In a series of postmortem and surgical studies, bilharziasis was shown to involve the prostate in 18–47.3% of cases [1,28,30]. Grossly, the involved prostate is enlarged and granulomatous in the early stages, and small and fibrous in the late stages. Bilharzial ova are distributed mainly in the stroma between acini. The latter are dilated and contain large, well-formed corpora amylacea. In the late stages, the acini are compressed by stromal fibrosis and corpora amylacea are no longer evident within their lumen. Secondary infection may cause a chronic bacterial prostatitis.

The early features are perineal heaviness, low backache and painful micturition. With late fibrosis, the patient often complains of diminished sexual libido, weak erection or rapid ejaculation. Fibrous involvement of the bladder neck may result in frequency or difficulty in micturition and a poor urinary stream.

These features are generally not specific and are similar to those of chronic bacterial prostatitis. The diagnosis is based on the finding of bilharzia ova in tissue specimens obtained by needle biopsy or transurethral prostatic resection.

Concluding remarks

Bilharzial pathology of the genitourinary tract presents several interesting clinical models, e.g. obstruction, infection, stones and malignancy. Undoubtedly the severity of infestation and the relative incidence of complications will change significantly with mass treatment using the new and safe orally administered antibilharzial agents. Hopefully, all the conditions described here will be soon be consigned to history.

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