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Urinary Bladder Schistosomiasis

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Abstract

Schistosomiasis is a parasitic disease caused by flukes (Trematodes) of the genus Schistosoma. Urinary tract disease is caused by Schistosomahematobium species. Urinary schistosomiasis (Bilharziasis) is often chronic and can cause pain, secondary infection and even bladder cancer. In this review, the histopathological manifestations of urinary bladder schistosomiasis are displayed with emphasis on impact of Schistosomal cystitis on development of urinary bladder cancer.

Keywords: Urinary bladder, Schistosoma haematobium, Bladder Cancer

Introduction

Schistosomiasis is the third most devastating tropical disease in the world after malaria and intestinal helminthiasis; being a major source of morbidity and mortality for developing countries. It is estimated that at least 92% of those requiring treatment for Schistosomiasis live in Africa. Schistosomiasis mostly affects poor communities without access to safe drinking water and adequate sanitation and in rural communities, particularly agricultural and fishing populations. Women doing domestic chores in infested water, such as washing clothes, are also at risk. Inadequate hygiene and contact with infected water make children especially vulnerable to infection [1].

In Egypt, Schistosomes are well-preserved parasites that have been documented to cause urinary disease in humans since ancient times, being mostly documented in Egyptian papyri, notably the Eber's and Edwin Smith's [2].

There are six Schistosomal species affecting human: S. haematobium, S. guineensis, S. intercalatum, S. japonicum, S. mansoni and S. mekongi.

Urinary tract disease is caused by Schistosoma haematobium (S. hematobium) species. Adult worm pairs live in the venous plexus surrounding the bladder and ureters. Schistosomal bladder lesions usually start in the trigone and base [3].

Pathological Features of the Schistosomal Bladder

The histopathological lesions in the bladder due to Schistosomiasis are classified into four stages according to Von Lichtenberg et al. [4].

- Active Schistosomal granulomatous stage, characterized by granulation tissue with numerous plasma cells and eosinophils around viable bilharzia eggs.
- Chronic active stage; the Schistosomal granulomata are still present,the lymphoid cells and eosinophils are the main cellular elements and 50% of the eggs are calcified.
- Late residual stage; 80% of the eggs are calcified and there is an evidence of healing granulomata with few eosinophils.
- Inactive stage; characterized by dense fibrous scar, sparse lymphocytic infiltrate, and absent eosinophils. All the eggs are particularly calcified.

Schistosomal bladder lesions are most common conveniently described on a topographical basis. Thus mucosal, submucosal and mural lesions are recognized.

Mucosal Lesions

Congestion of the mucosa

This is due to the inflammatory reaction associated with extrusion of the ova. The resulting trauma from rupture of vessels and penetration of ova through the mucosa cause transient edema, inflammatory changes, hyperemia of the mucosa, submucosal hemorrhage and minute epithelial erosions [5].

Schistosomal ulcers

Ulceration occurs mainly during the active stage of ova deposition. With proper treatment they heal, unless they develop

into chronic stage due to supervention of secondary infection or because of their location in a relatively a vascular posterior wall [6]. Ulcers in chronic active, late residual or chronic inactive stages are superficial, irregular in outline, with sloping edges and granular yellow floor [7].

The surface of the ulcer is usually devoid of urothelium. The ulcer base shows either sloughing tissue; calcified eggs or viable eggs; inflammatory tissue; or most often a narrow band of fibrous tissue with numerous minute blood vessels. The lamina propria under the ulcer is always thickened by dense fibrous tissue, by granulomatous reaction around viable eggs or by calcified eggs in dense fibrous tissue [8].

Von Brunn's nests (Islands) (Figure 1A)

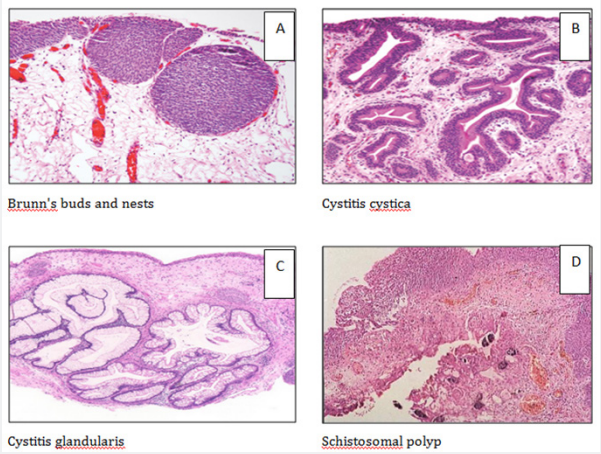

Figure 1

They are pathognomonic of Schistosomiasis. These are late lesions in which the mucosa is roughened, raised and grayish-golden-brown in color. They are proliferative invaginations of urothelium either retaining continuity with the surface (von Brunn's buds) or separate from the mucosa forming well-defined solid nests of urothelial cells within the superficial lamina propria (von Brunn's nests) [9]. The overlying urothelium may be irregularly thickened or atrophic and areas of squamous metaplasia have been described [8].

They are most commonly found in the trigone and bladder neck. It is considered as an early stage of manifestation of a basic metaplastic condition. When very florid, these changes may mimic urothelial carcinoma [10].

Cystitis cystic (Figure 1B)

Cystitis cystic is a common chronic reactive inflammatory disorder, which occur in the setting of chronic irritation. The trigone is the area most commonly affected. Grossly, they usually present as irregular mamillated lesions that may be confused cystoscopically with carcinoma. Microscopically, cystitis cystica is similar to Von Brunn's nests except that the centers of the nests have undergone eosinophilic liquefaction, when the central lumen of a nest exceeds several millimeters, the remaining urothelial cell in the periphery will be flattened and attenuated liquefaction [11].

Cystitis glandularis (Glandular Metaplasia) (Figure 1C)

It is similar to cystitis cystica except that the urothelial cells which line the cystic lesion have undergone glandular metaplasia with goblet cells identical to those of the large bowel. Gross cystoscopic picture may show it as a papillary lesion. It appears histologically as submucosal nests of columnar epithelial cells surrounding a central liquefied region of cellular degeneration. Patients in whom the intestinal metaplasia is very extensive are at high risk for the development of adenocarcinoma of the urinary bladder [12]. If that epithelium acquires intestinal-type goblet cells, then the term cystitis glandularis with intestinal metaplasia is used [13].

Submucosal Lesions

Schistosomal tubercles

Tubercles are the earliest specific lesions of Schistosomiasis. Grossly, they are seen as multiple shiny yellowish elevated nodules and by time they become brownish and surrounded by a zone of hyperemia. They are most often found on the trigone or posterior wall of the bladder. Histologically, these are small lesions formed of living ova surrounded by neutrophils and eosinophils. They may leave a pit on the surface of the mucosa [14].

Schistosomal polyps (Figure 1D)

Schistosomal polyps develop in 13% of Schistosomal cystitis [15]. Polypoid lesions result from irritation of the mucosa by Schistosomal products, so that the epithelium is pushed in the direction towards the bladder cavity [6]. They may be single or multiple but are few in number and mostly located in the trigone and near by the ureteric orifices [8]. They increase the frequency of developing carcinoma [16].

Schistosomal granulomata

The basic tissue reaction to Schistosoma eggs is the formation of granulomata around them [17]. The granulomatous reaction can be divided into three stages according to histological criteria:

i. Early active granuloma characterized by a marked eosinophilic response followed by diffuse infiltration with numerous macrophages and multinucleated giant cells surrounding the ova, with a peripheral mantle of eosinophils, plasma cells and lymphocytes;

ii. Intermediate lesions showing macrophages and giant cells in the center surrounded by spindle cells and thin layers of fibrous tissue;

iii. Late lesions showing few or no macrophages and giant cells, increased number of spindle cells and prominent layers of fibrous tissue of variable thickness [18].

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Mural Lesions

Weakening of the muscle layer occurs due to trapping of Schistosoma ova associated with fibrosis and endarteritis obliterans leading to ischemia of the muscle layer [19].

The Impact of Schistosomiasis on the Pathology of Bladder Carcinoma

The mechanism by which Schistosomiasis produces bladder cancer remains unknown, but may be related to:

i. The prolonged chronic mechanical irritation of the bladder epithelium caused by Schistosomal ova deposition provoke an intense inflammatory reaction, associated with the production of oxygen-derived free radicals, which may induce genetic mutations or promote the production of carcinogenic compounds such as N-nitrosamines and polycyclic aromatic hydrocarbons) leading to malignant transformation [20].

ii. Schistosomiasis is often accompanied by chronic bacterial super-infectionoftenly gram-negative bacteria that can:

o change urinary nitrites and nitrates into nitrosamines which have carcinogenic effects;

o secrete beta-glucouronidase enzyme that may cleave conjugated carcinogens yielding free carcinogenic products; and

o produce hyperplasia, metaplasia, and dysplastic changes in the urothelium that play an important role in initiating bladder cancer [21-22].

iii. The tryptophan metabolites released from the worms in the blood and excreted in urine may be carcinogenic, as high levels have been reported to correlate with tumor recurrence rates [23].

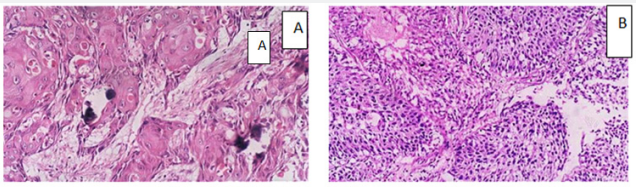
Schistosoma-associated urinary bladder cancer has some distinctive features regarding

Age: Schistosoma-associated bladder cancer (SA-BC) with positive Schistosomal eggs tends to occur at a relatively young age with a high tendency towards bladder muscle invasion, compared to non-Schistosomal associated cancers in western countries [24-25].

In Egypt, SA-BC was reported in younger age group than non-Schistosomal carcinoma (median age is 46 years) [26]. However, more recent studies showed changing trends of the urinary bladder tumor incidence as a result of the control of Schistosomal infection with increase of median age of diagnosis [27-28].

Sex: In Egypt, El-Bolkainy [26] reported a male predominance in SA-BC. Male to female ratio was 5.6: I. However a recent study by Salem and Mahfouz [28] found the male/female ratio changed to be 4.2:1.

Histological type: A 54–81% incidence of squamous cell carcinoma was found in all cases of bladder cancers in endemic areas, opposed to 3-10% in Western countries [21]. In Egypt, cancers of the urinary bladder accounts for 30.3% of all cancers, of which the majority are squamous cell carcinoma related to Schistosomal infection (Figure 2A). This is similar to other African countries, such as Sudan, Kenya, Uganda, Nigeria and Senegal [29-30]; however other studies showed a changing of the urinary bladder tumor incidence as a result the control of Schistosomal infection with decrease in incidence of squamous cell carcinoma. Transitional cell carcinoma was the commonest form of cancer with low eggs positivity (Figure 2B) [27,31]. Furthermore, Salem and Mahfouz [28] reported a decrease in incidence of SA-BC from 80% to 50%, a significant increase in transitional cell carcinoma from 20% to 66%, with a significant decrease in squamous cell carcinoma from 73% to 25%.



Squamous cell carcinoma, grade II, associated with Schistosomal infestation

Transitional cell carcinoma, grade III

Figure 2

Genetic changes in Schistosomal associated bladder cancer (SA-BC)

Among the most common genetic changes in bladder cancer is the loss of heterozygosity (LOH) on chromosomes 9p and 9q, which is found regardless of tumor grade and stage [32].

The over expression of the Bcl-2 gene in SA-BC patients was found to be up-regulated in squamous but not transitional cell cancers. Mutations of TP53 were detected in 73% of tumors, Bcl-2 expression in 32% and abnormalities of both TP53 and Bcl-2 in 13% [33].

The cyclooxygenase-2 role in the complex multi-stage process of SA-BC carcinogenesis was proposed: pro-inflammatory cytokines such as interleukin-1, tumor growth factor-B and tumor necrosis factor-alpha. H-RAS, deletion of p16 and p15, increased epidermal growth factor receptor, c-erb-2 and tumor necrosis factor-alpha are additional mutation reported. These changes increase tumorigenicity by decreasing cell apoptosis and/or creating immunosuppression [34].

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