Review

Prostatic adenocarcinoma coexisting with schistosomiasis: A case report and review of literature

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Adenocarcinoma of the prostate is the commonest form of cancer in men and the second leading cause of cancer death. Not much is known about the aetiology of prostatic cancer. We report a rare case of prostatic adenocarcinoma coexisting with schistosomiasis of the prostate, and review of literature. The association between schistosomiasis and cancer has been well documented in bladder cancer, implicating the genotoxic effect of chronic inflammatory process from the generation of reactive oxygen species (ROS) and the nitrosating action of bacterial infection. There are no data yet proving the association of this disease with prostate neoplasia. The theory of the genotoxic effect of chronic inflammatory process may explain a "cause and effect" association between prostate cancer and schistosomiasis. A pertinent question therefore is, does schistosomiasis cause tumorigenesis in all tissues affected? This is the first record of prostatic schistosomiasis in association with prostatic cancer in our centre.

Key words: Tropical disease, parasite, carcinoma, prostate.

INTRODUCTION

Adenocarcinoma of the prostate is the commonest form of cancer in men and the second leading cause of cancer death according to American Cancer Society (2004). His-tologically, most lesions are adenocarcinomas that pro-duce well defined, readily demonstrable gland pattern (Epstein, 1995, 2002; Young et al., 2000). Prostatic can-cer may show squamous differentiation resulting in either adenosquamous or pure squamous carcinoma (Little et al., 1993). Not much is known about the aetiology of pro-static cancer. However, several risk factors such as age, race, family history, hormone levels and environmental influences are suspected of playing roles (Gronberg, 2003; Nelson et al., 2003; Yip et al., 1999; Boyle et al., 2003). Of the environmental factors, no direct link to inf-ectious agents has been documented.

Several studies have reported schistosomiasis of the prostate gland. Gelfand et al. (1970) documented the fin-ding of schistosome eggs in 20% of 200 cadavers in their study. In another study by Vilana et al. (1997), schisto-somal eggs were found in 50% of postmortem studies of prostate and seminal vesicles in endemic areas.

The association between schistosomiasis and cancer has been well documented in bladder cancer, however, there are no data yet proving the association of this dis-ease with prostate neoplasia (Bacelar et al., 2007). Basilio-De-Oliveira et al. (2002) reported a case of coexi-stence of prostatic adenocarcinoma and schistosomiasis which they said was the fifth reported in literature, while Bacelar et al. (2007) reported a similar case which they said was the third reported in literature. In all the reported cases, no cause and effect association was known. This is the first time we are seeing prostatic schistosomiasis in association with prostatic cancer in our centre.

Case presentation

AM is a 70-year-old man who presented in the surgical outpatient clinic of our teaching hospital in June 2008 with a 3-month history of features of prostatism. There was no history of diabetes, sexually transmitted infection or trauma. On examination, his vital signs were essen-tially normal. Direct rectal examination showed a modera-tely enlarged prostate with smooth surface and mild ten-derness. His serum prostatic specific antigen (PSA) was

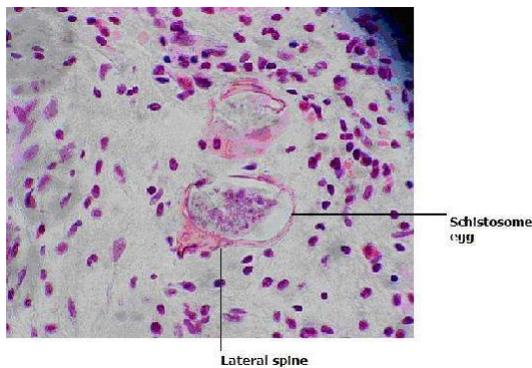---
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Figure 1. Shows two viable ova of *S. mansoni* with lateral spine in the lower ovum. Epitheliod cells, eosinophils, lymphocytes and plasma cells are seen surrounding the ova. Haematoxylin and eosin (H and E) stains. 40X objective.
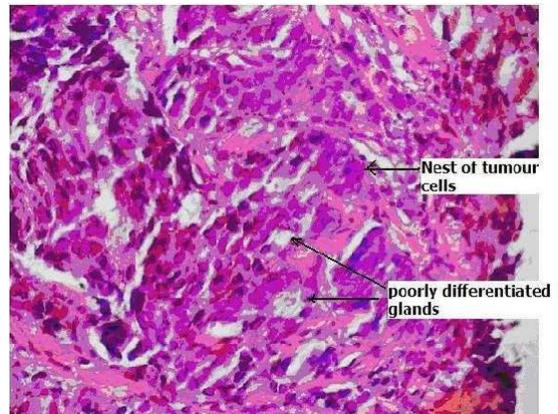

Figure 2. Showing some degenerating ova (arrows) with aggregates of mixed inflammatory cells. Several benign acini lined by columnar epithelium are present in this field. (H and E) stains. 20X objective.

17.11 ng/mL, which is high for age/assumed prostatic volume. A working diagnosis of nodular hyperplasia was made to rule out malignancy. After some preliminary laboratory tests were done to establish the patient's haematological and renal function status which were essentially normal, a tru cut biopsy of the prostate was done using the trans- rectal approach. Three cores of grayish white specimen were obtained and sent to the histopathology laboratory.

Gross and microscopic findings

At the cut-up bench of the histopathology laboratory, we found 3 cores of grayish white tissue preserved in 10% formal saline. These were subjected to routine tissue processing procedures. Five micron (5) thick sections were obtained from the paraffin wax embedded tissue and then stained with haematoxylin and eosin (H and E) stains.

Figure 3. This field Shows nests of hperchromatic neoplastic cells with some forming poorly differentiated glands. (H and E) stains. 20X objective.

Histology showed several ova of *Schistosoma mansoni* having lateral spine surrounded by aggregates of epithelioid cells, eosinophils, lymphocytes, and some plasma cells. Some poorly differentiated neoplastic glands in addition to nests of pleomorphic and hyperchromatic epithelial cells were also seen in the fibromuscular stroma (Figures 1, 2, and 3).

DISCUSSION AND REVIEW OF LITERATURE

In endemic geographical areas schistosomiasis has been implicated as an aetiological agent in the pathogenesis of bladder, colorectal and renal carcinoma (Ronald et al., 1995). In particular bladder carcinoma commonly occurs in such geographical location almost two decades earlier than in non-endemic areas (Ronald et al., 1995). Schistosome-related tumours are largely squamous cell carcinomas, but transitional cell carcinomas and adenocarcinomas of the bladder have also been reported (El-Bolkainy et al., 1972, 1981). Most studies of the pathology of schistosomiasis especially in association with tumours have been mainly on bladder lesions.

Schistosomes express numerous glycoconjugates with terminal LacNAc or LacdiNAc, (both soluble egg antigens) that provoke humoral and cellular immune responses in the infected human host. The main pathology is due to the formation of granulomas around tissue-trapped eggs and the resulting organ damage (Koen et al., 2006). One of the hallmark activities of tumour promotion in animals is their ability to recruit inflammatory cells to an application site and stimulate a respiratory burst in these cells. The cells release reactive oxygen species (ROS) such as superoxide anion and hydrogen peroxide, as well as lipid oxidation products (Harris et al., 1992; Gordon et al., 1988). This activity may be critical to tumour promotion. There is a strong concordance between the capacity of tumour promoters to stimulate inflammatory cells to release ROS and their capacity to promote tumours

(Frenkel, 1992). Further more, blocking the respiratory burst in animal models with agents such as retinoids, steroids, or antioxidants leads to the inhibition of tumour promotion. There is accumulating evidence that stimulated inflammatory cells are capable of inducing genotoxic effects, such as DNA strand breaks (Bimboim, 1982; Shacter et al., 1988) sister chromatid exchanges (Weitberg, 1989), and mutation (Weitzman et al., 1984; Yamashina et al., 1986) and of promoting neoplastic transformation (Zimmerman et al., 1986; Weitzman et al., 1985) in nearby cells. Inflammatory cells have been shown to participate in the metabolic activation of procarcinogens to DNA-damaging species (Kensler et al.,1992; O'Brien, 1988; Trush et al., 1990). Neutrophils activate aromatic amines, aflatoxins, oestrogens, phenols and polycyclic aromatic hydrocarbons by oxidant dependent mechanisms (Kensler et al., 1992). Inflammatory cells are also implicated in the formation of carcinogenic nitrosamines (Marietta, 1988). Since the aromatic amines are an important group of bladder carcinogens, an increased number of inflammatory cells in the urinary bladder of schistosomal patients may enhance the carcinogenic potential of these agents by increasing their rate of activation. Various strains of bacteria have been identified in the livers of animals (Ottens et al., 1972), in human gastric juice (Massoud et al., 1990), and urine (El-Hawey et al., 1989; Mostafa et al., 1994) in association with schistosome infection. Some of these organisms are thought to play a significant role in the endogenous formation of *N*-nitrosamines. Nitrate-reducing bacteria, including *Staphylococcus aureus*, hemolytic *Staphylococcus albus*, *Proteus mirabilis*, *Klebsiella* spp., and *E. coli* (Hicks et al., 1982) were isolated from the urine of *S. haematobium*-infected patients. Several of these organisms can mediate nitrosation reactions *in vitro* between secondary amines and nitrate under the conditions of physiological pH normally encountered in the urinary bladder (Calmels et al., 1986). A correlation between schistosomiasis and bacterial infection of the urinary tract thus provides supporting evidence for the endogenous formation of *N*-nitroso compounds and the possible consequent induction of preneoplastic initiating events in schistosome-infected subjects. Bacterial infection of the urinary tract per se has been reported to increase the risk of bladder cancer in patients with associated with advanced disease and tumor recurrence (Coombs et al., 1991). and c-*myc*, leading to more aggressive and invasive tumor properties (Kroft et al., 1994). Overexpression of c-chronic or repeated cystitis (Kantor et al., 1984; Radomski et al., 1978), paraplegia (Melzak, 1966), or *S.haematobium* infection (Hicks et al. 1976), as well as to increase the risk of all cancers (Nordenstam et al., 1986). The mechanisms of initiation of these and many different types of cancer could be due to the nitrosation of secondary amines with ingested or metabolically derived nitrite that leads to *N*-nitrosamine formation (Hill, 1988).

Miriam et al. (1994) in their study using the exfoliated cell micronucleus test reported that individuals with urinary bladder schistosomiasis have elevated levels of genomic damage in their bladders, and that treatment that kills the parasite also reduces the micronucleus frequencies (Miriam et al., 1994) . Micronuclei are formed by damage to chromosomes or to the spindle apparatus in the basal cells of the tissue epithelium. When these cells divide, chromosomal fragments (or entire chromosomes lacking an attachment to the spindle apparatus) lag behind and are excluded from the main nuclei in the daughter cells. These fragments form their own membranes and appear as Feulgen-positive bodies in the cytoplasm of the daughter cells which mature and are exfoliated into urine (Miriam et al., 1994).

Several studies have shown the possible loci on some chromosomes affected in schistosome-related tumours. Miriam et al. (1994) suspected involvement of certain loci on chromosome 11 responsible for DNA repair process as reported in earlier study by Parshad et al. (1992). Miriam et al. (1994) then found out that insertion of a normal chromosome 11 by microcell-mediated transfer led to lowering of micronucleus frequencies in the exfoliated cells from schistosome infected individuals (Miriam et al., 1994).

Recent other studies have attempted to identify molecular events associated with specific genes that underlie neoplastic progression in the development of schistosomal bladder cancer. These include the activation of H-*ras* (Knowles et al., 1993), inactivation of *p53* located on chromosome 17 (Sidransky et al., 1991), and inactivation of the retinoblastoma gene (Ishikawa et al., 1991). For Egyptian schistosomiasis-associated bladder cancers (Habuchi et al., 1993), it was reported that about 86% (six of seven) of these had *p53* mutations in exons 5, 6, 8, and 10 and that in a Japanese group (61 patients) the mutation frequency increased with the tumor grade. These findings are in agreement with a literature based observation that the frequency of *p53* mutations varies with the different grades of schistosomiasis-associated bladder cancer (Badawi, 1996). Thus, *p53* inactivation ranged from 0 to 38% at the early stage of the disease, as opposed to 33 to 86% in the advanced tumor stage (Badawi, 1996). Experimental studies on *ras* mutations *in vitro* have also shown a cumulative effect with other genetic alterations, including those of c-*erbB-2 erb-B-2* in transitional cell carcinoma (TCC) has been Allelic loss of chromosome 9 was also observed in both superficial and invasive bladder cancers (Miyao et al., 1993). Recently, Warren et al. (1995) found that 30 of 90 Egyptian patients with a history of schistosomiasis had tumors with mutations in exons 5 through 8 of the *p53* gene: 17 of 53 of these mutations were in squamous cell carcinoma (SCC), 8 of 23 were in TCC, 4 of 13 were in adenocarcinoma and 1 of 3 was in other tumors.

Changes in cell cycle control are thought to be critically associated with cancer development (Nurse, 1997). In fact, cyclin D1 is over-expressed in some cancers, includ-

ing bladder cancer (Tamimi et al., 1996). Seven CDK inhibitors, including p57, p21, p27, p19, p18, p16*INK4*, and p15, have been characterized. Tamini et al. (1996) found that a p16*INK4* deletion was present in 23 of 47 samples from schistosomiasis associated bladder cancer patients and that mutations were present in another 2 patients (in all, 53% of tumors exhibited *p16INK4* gene alterations). They concluded that *p16INK4* alterations are more frequent in schistosomiasis- associated bladder can-cer than in other bladder tumors and may thus be asso-ciated with a specific etiology (Tamimi et al., 1996).

Conclusion

These elaborate studies of the association between blad-der tumours and schistosomiasis have not been done in schistosome associated prostate cancer probably becau-se of its rarity. However, the genotoxic effect of chronic inflammatory process from the generation of ROS and the nitrosating action of associated bacterial infection may be a genuine explanation to "cause and effect" asso-ciation between prostate cancer and schistosomiasis. A pertinent question therefore is, does schistosomiasis cause tumorigenesis in all organs or tissues affected, and does this follow a metaplastic change or outright transfor-mation of native parenchymal/epithelial cells? This can only be found out by such dedicated fact finding studies as have been done in the case of schistosome asso-ciated bladder cancer.

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