Eosinophilic cystitis mimicking invasive bladder tumour: discussion paper

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Eosinophilic cystitis is a rare condition originally described in 1960 by Brown[1] in a 50-year-old woman and associated with severe atopy. In the same year Palubinskas[2] described a case occurring in a 31-year-old woman which was associated with eosinophilic gastroenteritis. Over the next 19 years, 20 more cases were reported in the English literature and a predominance of young women and children was noted. In 1979 Hellstrom *et al.*[3] reviewed 16 cases over a 5-year period, occurring in adult men and usually associated with other conditions of the bladder or prostate.

In the 1960s and 1970s many aetiological factors were proposed. In children a parasitic association was found in two cases, one to *Toxacara canis*[4] and the other to *Echinococcus granulosus*[5]. Some cases were associated with eosinophilic gastroenteritis[6] but in the majority no clear aetiological factor could be determined. The association with allergy has generally been well accepted and on review of the literature this has occurred in 14 out of 26 women but only nine out of 36 men (including our own cases) and one out of 12 children.

It is known that eosinophilic cystitis may affect the bladder diffusely or in a localized form; in either case it may be mistaken for a tumour. On review of the literature we found that out of a total of 62 adult cases described, 38 were said to have had diffuse disease. Of those with diffuse disease there was a history of allergy in some form in 12 out of 19 women, but only in eight out of 19 men. It seems therefore that a history of allergy is found more often in women than in men and that in women it is usually associated with diffuse disease. Chantepie *et al.*[7], however, described a series in older women with diffuse disease in whom allergy was not found, but even in these drug hypersensitivity was considered to be a possible aetiological factor. Similarly, Nakada *et al.*[11] reported eight patients with asthma treated with an antiallergic compound (Tranilast) who developed diffuse disease. Peripheral eosinophilia was present in 50% of adults with a history of allergy.

By contrast, peripheral eosinophilia was found in nine out of 12 children with eosinophilic cystitis but in only one case was there clinical evidence of allergy, and only three of the 12 cases had diffuse disease. In children, therefore, peripheral eosinophilia appears to be a frequent finding, whereas a history of allergy and the diffuse form of the disease are uncommon.

Of the other postulated aetiological factors previous bladder injury is the most frequently mentioned. In one woman a tenuous link with radiotherapy treatment for carcinoma of the cervix was proposed[8] whereas in 19 men there was a history of previous surgery to the bladder or prostate[3,7,11-13] and 12 of these cases had localized disease. In all, seven women and 17 men had localized disease; of these only two women and one man gave a documented history of allergy. It appears therefore that a previous bladder condition or surgery is strongly associated with localized disease, and that in this group allergy is not a significant factor.

The incidence of urinary tract infection is poorly documented and has not usually been considered an aetiological factor. In five out of 12 children hydronephroureterosis was described[16,18,19], but this abnormality was thought to be secondary to the disease process. Four cases of hydronephroureterosis[9,20-22] and three cases of ureteric stenosis[3,7,10] have been described out of 62 adults, and in these, also, the disorder appeared to be associated with the disease rather than having a causative role.

Most patients, including our first case, have responded to medical treatment. Withdrawal of treatment with a drug which may have initiated the allergic reaction has sometimes been followed by resolution of the inflammation, as in Nakada's series[11], where Tranilast was the offending agent. In many patients the combination of antibiotics, antihistamines and corticosteroids has been used with success. Recently the use of azathioprine with intravesical dimethyl-sulphoxide has been found effective in adults[7]. Medical treatment in children has proved less successful; cyclophosphamide was used in three cases, 250-400 mg intravenously daily for one week for a clinical diagnosis of rhabdosarcoma of bladder, but fatal depression of the bone marrow ensued in one of these[15]. Although in six of the 12 children the disease tended to chronicity with relapses, there have been no reports of adults with eosinophilic cystitis since childhood, and so it may be that the disease in children is self-limiting.

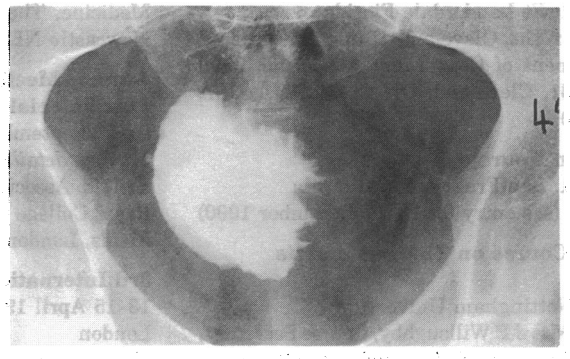

Figure 1. Intravenous urogram in case 1 showing large filling defect on left side of bladder

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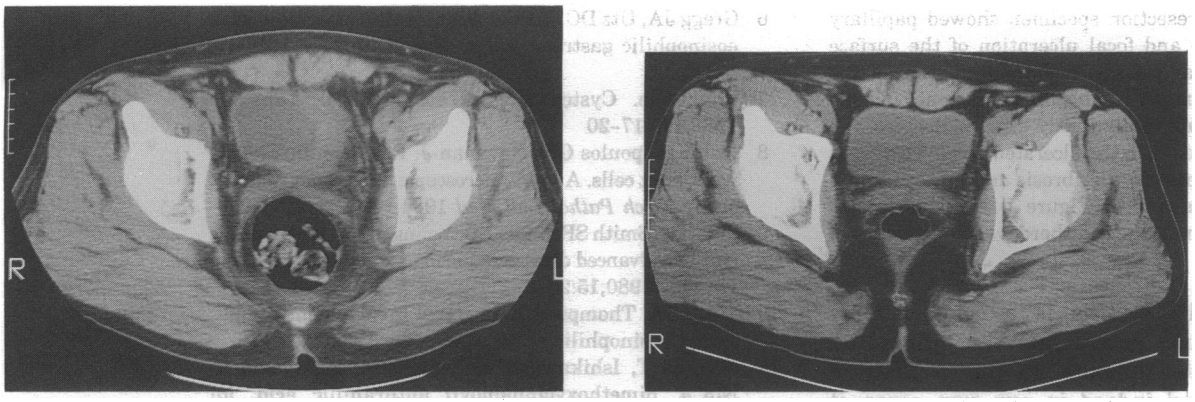

Figure 2. Case 1: CT Scans of bladder (a) before and (b) 8 weeks after cystoscopy

The disease sometimes proves refractory to medical treatment and in 14 cases some form of surgery has been undertaken[4,7,9,10,12,13,16,17,20,22]. Transurethral resection of the bladder lesion, partial cystectomy, ureteric implantation and occasionally urinary diversion has been necessary. In a few cases where benign prostatic hyperplasia was demonstrated resection of prostatic tissue was followed by resolution. In general the results of surgical treatment have been good.

Case reports

Case 1

A 58-year-old man presented with a 10-day history of dysuria and haematuria with clots. There was a previous history of two episodes of non-specific urethritis, in 1969 and 1982, and a single episode of genital herpes. He was otherwise in good health. He had lived in East Africa for a 2-year period, during which time he admitted to paddling on the shores of Lake Victoria, but had had a negative test for bilharzia since that time. His father had a bladder 'papilloma', which cleared after 3 years' treatment.

General examination was unremarkable except for suprapubic tenderness. A mid-stream specimen of urine showed gross haematuria but was sterile on culture. Urine cytology showed squamous cells and pus cells with some atypical transitional cells; malignancy could not be excluded. A full blood count and biochemical profile were normal; there was no peripheral eosinophilia.

Intravenous urogram showed normal upper tracts with a large filling defect on the left side of the bladder (Figure 1). At cystoscopy a large papillary and solid area was seen occupying the left side of the bladder. Three deep biopsies were taken. A 5-cm mobile mass was felt bimanually. Ultrasound guided fine needle biopsy produced an aspirate which showed blood only.

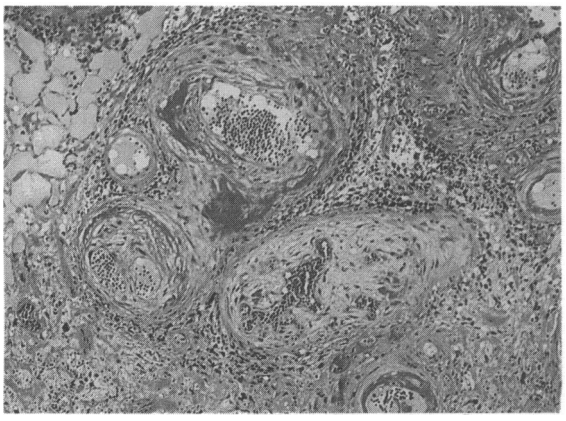

Figure 3. Case 1: Angiomatous malformation composed of muscular walled large vessels with evidence of thrombosis (H&E ×69)

CAT scan showed a bladder tumour mainly on the left but extending to the mid-line anteriorly and beyond the mid-line posteriorly (Figure 2). There was evidence of diffuse extravesical extension and enlarged left-sided lymph nodes were noted in the mid-pelvis. Barium enema was normal.

Microscopy showed polypoid oedema and focal epithelial hyperplasia, but no carcinoma. There was focal ulceration, with subjacent necrosis, oedema and fibrosis of muscle. There were congeries of thick walled vessels, some with thrombus and perivascular fibrinoid deposits, and there was an infiltrate of neutrophils and eosinophils which were focally prominent (Figure 3). This was considered to be eosinophilic cystitis secondary to necrosis, possibly following thrombosis within an angiomatous malformation.

Following cystoscopy he was started on co-trimoxazole one tablet twice a day. Within 24 h his symptoms had resolved and at cystoscopy 8 weeks later the bladder appeared normal with minimal scarring and no palpable mass. The CT changes had completely resolved (Figure 2).

Case 2

A 35-year-old man presented with retention of urine. He gave a 2-week history of increasing urinary frequency, dysuria and haematuria. There was no relevant previous history, though he had had a single episode of diarrhoea and vomiting 3 months earlier. There was no history of allergy, or previous genitourinary disorder. On clinical examination he was found to be in acute urinary retention. General examination was normal. On catheterization 900 ml of bloody urine was drained. Examination of the urine confirmed gross haematuria, but no organisms were seen; urine cytology showed no malignant cells. Biochemical profile and full blood count were normal and there was no peripheral eosinophilia.

Intravenous urogram was normal. At cystoscopy a papillary solid area was seen at the dome of the bladder, adjacent to what appeared to be a urachal remnant. Biopsies were taken which showed mucosal oedema with numerous eosinophils and fewer lymphocytes in the lamina propria, but no evidence of malignancy. In view of the macroscopic appearance partial cystectomy was done from which he made an uneventful recovery.

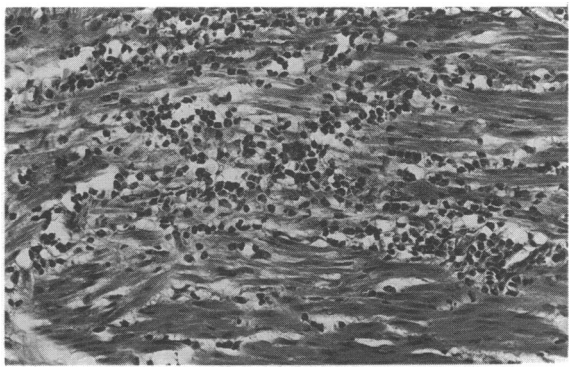

Figure 4. Case 2: Eosinophils infiltrating bladder wall muscle with focal necrosis of fibres. (H&E ×141)

Microscopy of the resection specimen showed papillary mucosal architecture and focal ulceration of the surface epithelium. There was oedema and inflammation of the lamina propria with many eosinophils, occasional plasma cells and multinucleate foreign body type histiocytes, the latter mainly associated with the ulcerated areas. There was focal eosinophilic myositis with fibrosis and necrosis of the superficial muscularis propria (Figure 4). No schistosomes or other parasites were seen and there was no evidence of carcinoma.

Thus, eosinophilic cystitis is a comparatively rare condition which enters into the differential diagnosis of bladder tumours. In the majority of cases described, and indeed in our own cases, it did not enter the clinical differential diagnosis. It is also possible for the diagnosis to be missed even by pathologists unaware of the condition who may describe only a non-specific lesion associated with an eosinophil infiltrate. It is worth enquiring about a history of allergy or considering drug sensitivity, especially in the diffuse form of the disease. The localized form of disease is more commonly associated with bladder injury. The treatment in children is by no means straightforward and relapse is common, though the natural history is not clear. The recent use of azathiaprine and intravesical dimethylsulphoxide in adults appears to be promising. This has not been used in children but may prove beneficial in some cases.

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