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Case Report

Potential beneficial effect of tamoxifen in retroperitoneal fibrosis

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Introduction

Retroperitoneal fibrosis is a rare disorder that entraps the ureter [1]. Retroperitoneal fibrosis occurs twice as frequently in males as in females and is most often seen between the ages of 30 and 60 years [2]. About two-thirds of all cases of retroperitoneal fibrosis are idiopathic and are thought to be immunological in origin [3]. The remaining one-third of cases are associated with the use of various medications, malignant disease, or with other conditions affecting the retroperitoneum, including infection, haemorrhage, trauma, or abdominal aortic aneurysms [2,4]. In the early stages of the disease histological examination reveals a loose network of collagen containing many fibroblasts and inflammatory cells with capillary proliferation [4]. The mature plaque is composed of collagen which has become densely hyalinized and in which few cellular elements can be recognized [4].

In 1985 Kinzbrunner *et al.* [5] first reported the successful use of the anti-oestrogen tamoxifen in the treatment of desmoid, another type of benign fibrotic tumour. Following this report Clark *et al.* [6] were prompted to treat retroperitoneal fibrosis with tamoxifen, with good results in two patients. We report a case of retroperitoneal fibrosis treated with surgery and tamoxifen.

Case report

The patient, a 64-year-old male presented with a history of low back pain of 7 months duration. The pain was continuous, blunt in character, worsening, and radiated to the loins bilaterally. The pain was unaffected by physical activity, but eased slightly on bending forwards. In the last month he reported nausea and vomiting. He had no history of medication. The history was otherwise unremarkable.

Physical examination showed the patient to be hypertensive with a blood pressure of 170/110 mmHg. Examination of the cardiovascular and respiratory systems was unremarkable. On abdominal examination a systolic murmur was heard in the right para-umbilical region and bilateral costovertebral angle tenderness was noted.

Laboratory examination revealed the patient to be anaemic with a Hb of 10.7 g/dl and a Hct of 32.8%. The WBC count was 9800/mm^3 and the ESR 66 mm/h. Abnormal biochemical parameters were BUN 69 mg/dl, serum creatinine 5.9 mg/dl, serum P 8.1 mg/dl and serum calcium 7.8 mg/dl. Urine analysis and microscopy were unremarkable. The creatinine clearance was estimated to be 12 ml/min. Serology revealed C reactive protein (CRP)+++.

In view of the raised serum creatinine levels IVU was not performed but ultrasonography showed bilateral hydronephrosis and ureteric obstruction and a tentative diagnosis of retroperitoneal fibrosis was made. The diagnosis was confirmed by abdominal CT, which revealed bilateral decrease of renal parenchymal thickness, more prominent on the right side, increased soft-tissue density between the third and fifth lumbar vertebrae in the para-aortic region, and bilateral hydronephrosis, the dilated ureters being visualized to the level of L_4, beyond which they could no longer be distinguished from the para-aortic soft tissues (Figure 1).

Bilateral ureteral catheterization was performed with rapid improvement of renal function, the BUN dropping to 37 mg/dl and the creatinine to 3 mg/dl 1 week following the procedure. Following relief of the obstruction the patient's blood pressure also returned to normal. Bilateral renal ureterolysis with biopsy of the plaque was performed and tamoxifen 10 mg/b.i.d. prescribed. Pathology confirmed the diagnosis of idiopathic retroperitoneal fibrosis. One month after ureterolysis the BUN was 21 mg/dl and serum creatinine 1.9 mg/dl.

The patient has now been followed up for 5 years since surgery. Serial CAT has demonstrated no recurrence of fibrosis in this time, and tomogrpahy 4 years later revealed no sign of the original plaque although

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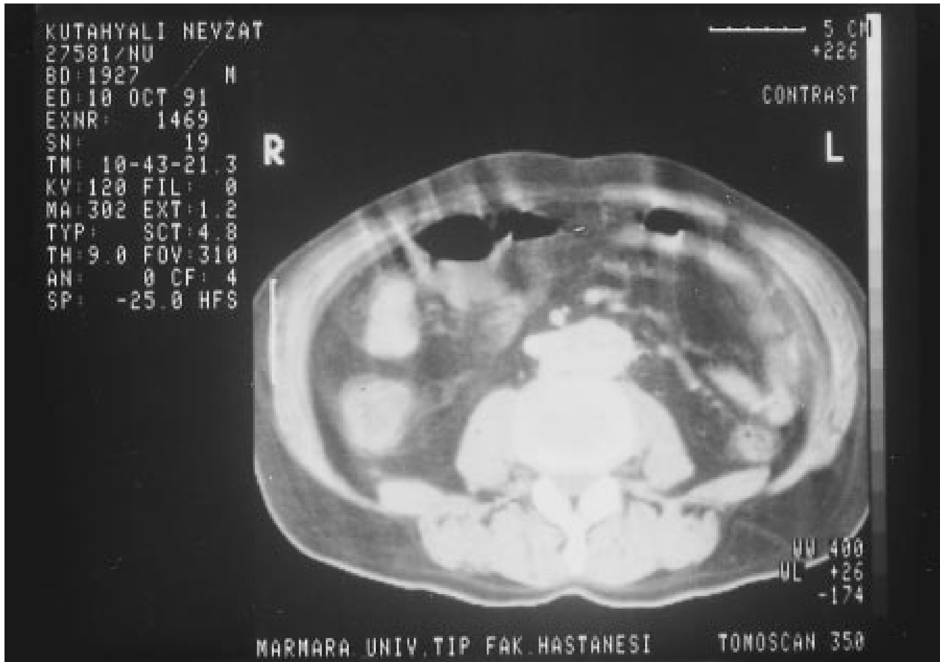

Fig. 1. Increased soft-tissue density in the para-aortic region between the 3rd and 4th lumbar vertebrae.

the right kidney was reported to be non-functioning and atrophic (Figure 2). The left kidney had not undergone compensatory hypertrophy. The patient remains normotensive with a BUN of 29 mg/dl, a serum creatinine of 1.7 mg/dl, and a creatinine clearance of 52 ml/min. He continues to take tamoxifen 10 mg b.i.d.

Discussion

Diagnosis of retroperitoneal fibrosis is possible only if there is a high index of clinical suspicion and should be considered in patients with unexplained abdominal pain and retroperitoneal lesions. Signs and symptoms may be related to compression and entrapment of

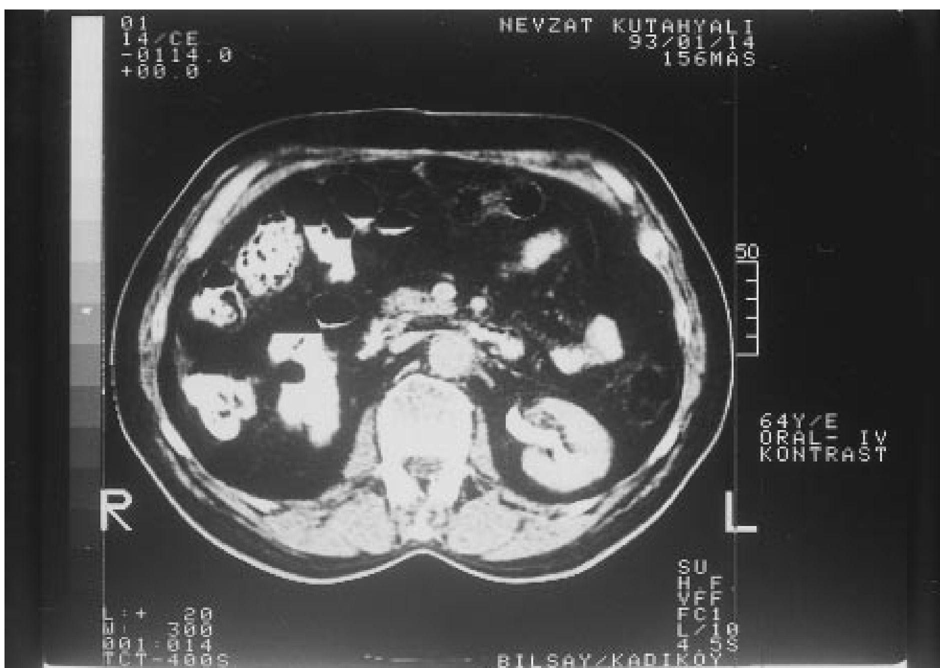

Fig. 2. Original plaque has disappeared, relieving ureters; atrophic right kidney, but no compensatory hypertrophy of the left.

retroperitoneal structures, including the inferior vena cava, aorta, and most commonly the ureters. Radiologically the lesion may be demonstrated by IVU or retrograde pyelography [7] but is best imaged using CT or MRI, although neither of these techniques can be used to differentiate benign from malignant plaques [4].

Retroperitoneal fibrosis secondary to drug therapy may regress when therapy is withdrawn [4,7] and rarely other non-malignant forms of retroperitoneal fibrosis resolve spontaneously without treatment [8]. The therapy of retroperitoneal fibrosis is dependent upon the stage of the disease at diagnosis. If ureteric obstruction is present ureteral catheterization and/or decompression by ureterolysis is indicated. Following surgery adjunctive immunosuppressive therapy with steroids has been used as primary therapy in a small number of patients [9], and there are also reports of the use of azathioprine [2] and chlorambucil [2,10]. In 1990 Clark *et al.* [6] described the successful treatment of two patients with retroperitoneal fibrosis using tamoxifen.

Tamoxifen is an anti-oestrogenic agent used in the treatment of oestrogen-receptor-positive breast cancers. However, it is also effective in 10% of oestrogen-receptor-negative breast cancers, implying another mechanism by which it exerts its tumorostatic effect. Clark *et al.* report that one of their cases of retroperitoneal fibrosis responding to tamoxifen was oestrogen-receptor negative. This, and the fact that the majority of patients with retroperitoneal fibrosis are males, suggests that oestrogens do not play a role in the pathogenesis or treatment. Exactly how tamoxifen exerts its effect remains unclear although it is an inhibitor of protein kinase C [11], an enzyme which through its role as a protein phosphorylator is essential for cell proliferation in mouse lymphoma cells [12].

Tamoxifen was chosen for adjunctive therapy in our patient because of its lower incidence of complications as opposed to immunosuppressives. We have chosen to continue long-term therapy in the light of tamoxifen's tumorostatic rather than tumorocidal action [11] and because any recurrence of the fibrosis might be potentially harmful to the patient's single functioning kidney.

It is noteworthy that the plaque, which was not removed at surgery, had resolved 1 year after the initiation of tamoxifen therapy and has not recurred at 2.5 years. Although we cannot predict the outcome if therapy had not been given we feel that this case supports the finding of Clark *et al.* that tamoxifen is an effective agent in the treatment of retroperitoneal fibrosis.

Tamoxifen would appear to be a safer drug to use in primary treatment since it is unlikely to promote tumour growth and is associated with a lower incidence of side-effects.

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