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## RETROPERITONEAL FIBROSIS (ORMOND'S DISEASE): CLINICAL PATHOLOGIC STUDY OF EIGHT CASES

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### Introduction

Retroperitoneal fibrosis (RF) was first described by Albarran, a French urologist, in 1905.<sup>1</sup> Ormond in 1948 first reported this entity in the English literature.<sup>2,3</sup> RF is a relatively unusual condition characterized by a widespread fibrosis, usually occurring in the retroperitoneum.<sup>1,3</sup> Also known as Ormond's disease, sclerosing fibrosis, or sclerosing retroperitonitis, RF is composed of proliferating fibrous tissue dissecting through adipose tissue and ensheathing the abdominal aorta and the branches of the common iliac vessels. This fibrotic tissue usually involves the ureters causing their compression with secondary hydronephrosis, pyelonephritis, uremia, abdominal and back pain.<sup>1-6</sup> Initially believed to represent an idiopathic, nonmalignant, inflammatory process of unknown etiology,<sup>7-11</sup> it later was proven that about one third of all cases are related to specific predisposing factors (secondary RF) including previous surgery, radiation therapy, pelvic tumors, or the use of certain drugs.<sup>12,13</sup> The etiology, clinical presentation, and radiologic features of this condition are variable, and RF is often misdiagnosed at presentation, mostly as a malignancy.

In this report of 8 cases, we discuss the differential diagnosis and the difficulty in recognizing this condition from the clinical and pathologic point of view, and we describe histochemical and immunohistochemical properties of this lesion, which may help in formulating the correct diagnosis.

### Materials and Methods

We retrieved eight cases of RF over the last 10 years from the pathology files. The patients' clinical histories, laboratory data, and radiologic and pathologic findings were retrieved (Table).

Slides that were stained with hematoxylin-eosin were reviewed. Special stains for fibrous tissue (trichrome) and plasma cells (methyl pyronine), as well as immunohistochemical stains for kappa and lambda light chains, were performed. The three idiopathic RFs were additionally stained for Leu-M1 (1:35), Ki-1 (1:15), and LCA (1:30), (all from Dako Corp, Santa Barbara, Calif). The immunostains were performed on deparaffinized sections (4  $\mu$ m in thickness) using the avidin-biotin-peroxidase complex method (Vectastain Elite ABC Kit, Vector Laboratories, Burlingame, Calif) and following the manufacturer's instructions. All the immunohistochemical stains were performed manually at room temperature. Endogenous peroxidase and nonspecific background staining were blocked by incubating slides with 3% aqueous hydrogen peroxide for 10 minutes. After washing with phosphate-buffered saline (PBS) for 5 minutes, slides were blocked with normal serum for 20 minutes, followed by incubation with the primary antibody for 60 minutes at the dilution given. After rinsing with PBS for 5 minutes, sections were incubated with a biotinylated secondary antibody for 20 minutes. Following washing with PBS for 5 minutes, slides were incubated with avidin-

Characteristics of Patients With Retroperitoneal Fibrosis

Case	Age	Sex	Race	Presentation	Predisposing Factors	Macroscopy	Radiologic and Laboratory Findings
1	49	F	B	Right lower-extremity deep vein thrombosis	None	Right common iliac vein and right ureter encased by firm, white to tan tissue	Ultrasound and scan of abdomen: mass along right wall of pelvis Right leg venogram: external compression of right common iliac and deep vein thrombosis
2	39	M	B	Bilateral hydronephrosis, chronic back pain	None	Medially displaced ureters encased by firm, white to tan tissue	Ultrasound of abdomen: bilateral hydronephrosis and medial displacement of ureters Blood urea nitrogen = 33 mg/dL Plasma creatinine = 3.9 mg/dL
3	48	F	B	Right hydronephrosis	S/P hysterectomy (1951), hypertension, drugs (methyldopa and hydrochlorothiazide)	Irregular areas of fibroconnective tissue with soft, tan areas of adipose tissue	Ultrasound of kidney: right hydronephrosis and obstructive uropathy Ultrasound of para-aortic areas and laparotomy: irregular masses of firm tissue encasing the right ureter and overlying the abdominal aorta
4	54	F	B	Bilateral hydronephrosis	S/P cholecystectomy, S/P total abdominal hysterectomy (1970)	Irregular mass of firm, white to tan tissue surrounding ureters and aorta	Ultrasound of kidney: bilateral hydronephrosis Computed tomography scan of abdomen and pelvis: soft-tissue mass in pre- and para-aortic region from the level of origin of superior mesenteric artery to the level of aortic bifurcation
5	54	F	B	Rectosigmoid adenocarcinoma, infiltrating full thickness of intestinal wall and involving pericolic soft tissue	Colonic adenocarcinoma	Large pelvic mass impinging on left ureter with obstruction and encasing sigmoid, ileum, and appendix	Laparotomy: large rectosigmoid mass with extension to pelvis, involving the bladder wall and pararectal soft tissue Encasement of left ureter with dilation Mass extends to small bowel at the level of ileocecal junction
6	55	M	W	Leg edema	S/P right orchidectomy (1975): seminoma S/P radiation therapy S/P appendectomy H/O pancreatitis, hypertension	Large retroperitoneal mass compressing inferior vena cava	Laparotomy: mass compressing the inferior vena cava
7	63	F	N/A	Abdominal pain	Hypertension, drugs (propranolol)	Large mass of firm tan tissue compressing deep pelvic veins	Computed tomography scan abdomen: pelvic mass
8	33	M	N/A	Abdominal mass R/O lymphoma	None	Irregular mass of soft tissue encasing both ureters with medial displacement	Ultrasound of kidney: no ureteral compression
<p>S/P = status post H/O = history of R/O = rule out N/A = not available</p>							



Fig 1. — Polarized view of suture material incidentally found during the microscopic examination of the specimen from patient 3. This patient had a past history of hysterectomy.

biotin complex for 30 minutes and washed again. Chromogen was developed with 10 mg of 3,3'-diaminobenzidine tetrahydrochloride (Sigma Chemical Co, St. Louis, Mo) diluted in 12 mL of Tris buffer, pH 7.6 for 2 minutes. All samples were lightly counterstained with Mayer's hematoxylin for 30 seconds before dehydration and mounting. Positive controls and nonimmune protein-negative controls were used for each section. No antigen retrieval was performed.

## Results

Of the 8 cases of RF, 5 were proven to be secondary and 3 were classified as idiopathic RF. In the former group, previous surgery (2 cases), radiation therapy (1), use of beta blockers (1), and carcinoma of the colon (1) were identified as predisposing factors. In the idiopathic group, all the known etiologic factors, including injury, inflammation, drugs, radiation, and neoplasms, were excluded.

The age at presentation ranged between 33 and 63 years (mean 49 years). Five patients were women

and three were men. In 4 cases the clinical symptoms were produced by compression of the ureters, and in 4 cases vascular compression was present. Two cases were clinically diagnosed as retroperitoneal tumor masses. Interestingly, case 1 presented with a pelvic mass on ultrasound and computed tomography scan, suggesting an initial clinical diagnosis of ovarian carcinoma. In case 3, initially thought to be idiopathic, suture material was identified from a prior hysterectomy (Fig 1). The ratio of idiopathic to secondary RF is 3:5 in our small series as in the cases previously reported in the literature. Interestingly, case 1 presented with a pelvic mass on ultrasound and CT

scan, suggesting a clinical diagnosis of probable ovarian carcinoma.

Intraoperative examination of both forms revealed bundles of firm, gray-white, fibrous-like tissue encircling the aorta, its major branches, and the vena cava. The ureters were usually compressed and drawn toward the aorta. In case 5 a rectosigmoid adenocarcinoma elicited extensive fibrosis involving bowel, bladder, and left ureter and extending to the pelvis (Fig 2A).

Microscopic examination revealed in all the cases two types of fibrosis. One was the "immature" cellular type, rich in plasma cells,

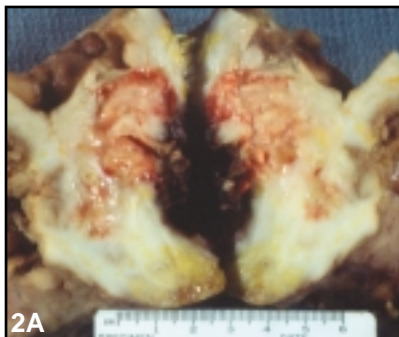


Fig 2A. — Gross appearance of the resected specimen from patient 5. Rectal adenocarcinoma elicited extensive fibrosis encasing ileum, sigmoid, appendix, bladder, and left ureter.

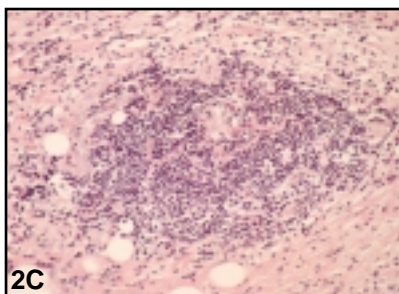


Fig 2C. — High-power view of the "immature" type of fibrosis (hematoxylin-eosin,  $\times 100$ ).

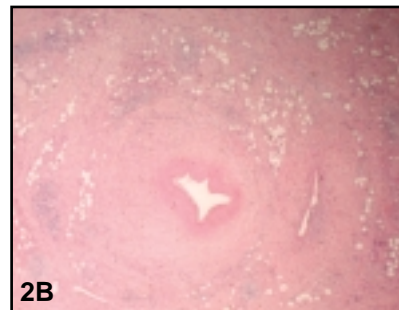


Fig 2B. — Ureter constricted by a dense connective tissue containing aggregates of lymphocytes, plasma cells, and eosinophils. The fibrosis also partially replaces the surrounding adipose tissue (hematoxylin-eosin,  $\times 25$ ).

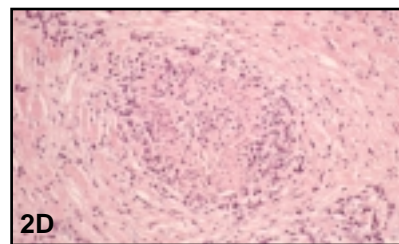


Fig 2D. — "Mature-type" fibrosis in the granulomatous phase showing lymphocytes and plasma cells surrounding blood vessels (hematoxylin-eosin,  $\times 100$ ).

lymphocytes, and eosinophils (Fig 2B). A trichrome stain and a methyl-pyronine stain were useful in detecting this type of fibrosis by highlighting the presence of numerous plasma cells (Fig 3A-B). The second type of fibrosis, the so-called “mature” type, was mainly composed of a dense, homogeneous, and hyalinized connective tissue containing only occasional fibroblasts, mast cells, or lymphoplasmacytic infiltrates. Microscopically, we could also identify three stages during the progression of RF. Stage I is characterized by infiltration of the retroperitoneal adipose tissue with round mononuclear cells, composed mostly of lymphocytes and plasma cells (Fig 2B-C). Stage II includes a granulomatous phase in which capillary proliferation and an eosinophilic inflammatory infiltrate are the most prominent features. During this phase, the inflammatory cells, including lymphocytes and plasma cells, have propensity to accumulate around blood vessels (Fig 2D). In stage III (scarring stage), the mature type of fibrosis is prevalent, mainly composed of a dense, homogeneous, and hyalinized connective tissue containing only occasional fibroblasts and inflammatory cells. During this stage, the amount of elastic fibers usually surpasses that of the reticulum fibers and the ground substance. In all of the cases, we could identify considerable overlapping of these stages. However, a prevalence of stage II lesion was evident in case 7 and case 8, and a prevalence of stage III lesion was seen in cases 2, 3, and 6. The idiopathic RF cases (1, 2, and 8) stained negative for

Leu-M1, Ki-1, and LCA, thereby excluding the possible diagnosis of Hodgkin’s disease and sclerosing retroperitoneal lymphomas. In addition, the nature of the lymphoplasmacytic infiltrate was polyclonal in all the cases as demonstrated by the diffuse positivity for kappa and lambda light chain immunohistochemistry (Fig 3C-D).

## Discussion

RF is an uncommon condition, occurring in 1 of every 200,000 subjects.<sup>14</sup> This disease can be primary or secondary. Secondary RF can have unusual and challenging clinical presentations, depending on the wide variety of conditions that in turn have been associated with this entity. Malignancies,<sup>12,15</sup> inflammation injury,<sup>16</sup> infections,<sup>17</sup>

drugs,<sup>13,18</sup> and foreign bodies have all been indicated as possible causes of secondary RF. Moreover, RF has been reported in association with connective tissue disorders such as Takayasu arteritis,<sup>19</sup> primary biliary cirrhosis,<sup>20</sup> and sclerosing pancreatitis,<sup>21</sup> as well as Riedel’s struma,<sup>22</sup> sarcoidosis, Dupuytren’s contracture, and Peyronie’s disease.<sup>3</sup> Therefore, it has been suggested that RF may represent a manifestation of autoimmune diseases.<sup>7</sup> The idiopathic form of the disease is a diagnosis of exclusion and a condition of unknown etiology.<sup>4,6,8</sup>

In our review of the largest series of patients with RF reported in the English literature, we have found that the mean age at presentation is between 50 and 60 years with a male predominance of 3:1.

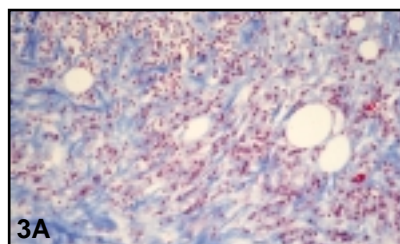


Fig 3A. — A trichrome stain highlighting the collagenous component of the fibrosis (colored in blue). The plasma cells are prominently colored in purple-red (trichrome,  $\times 250$ ).

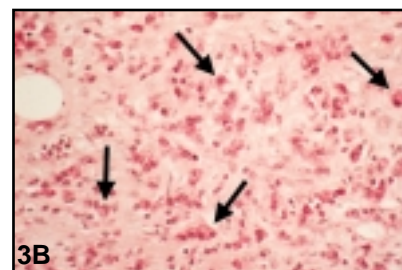


Fig 3B. — Methyl-pyronine stain decorating the plasmacellular component of the lesion (arrows) (ethyl-pyronine,  $\times 250$ ).

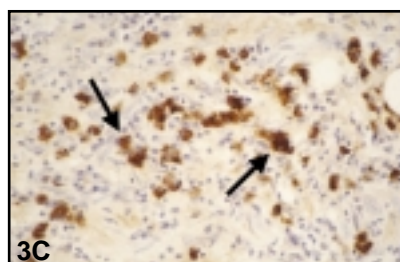
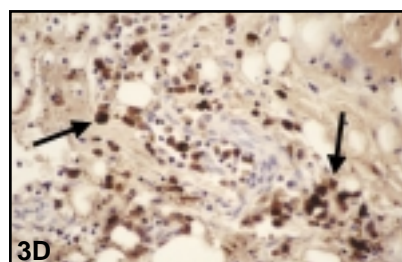


Fig 3C-D. — Immunohistochemical stain showing the polyclonal composition of the lymphoplasmacytic infiltrate (arrows): (C) lambda light chain and (D) kappa light chain (immunostains,  $\times 400$ ).



The most common presenting symptoms are flank and abdominal pain, weight loss, and polyuria.<sup>5,11</sup>

The common denominator in all of the cases reported is the exuberant formation of fibrous tissue, which compresses nearby hollow organs and vessels. Typically, the vessels outside the fibrotic mass are uninvolved. The ureters are frequently compressed with edema and lymphocytic infiltration, causing hydronephrosis, eventual loss of renal function, and possible secondary hypertension.<sup>1,4,10</sup> Four of our patients (2, 3, 4, and 5) presented with this condition. Approximately one third of the patients reported in the literature have a nonfunctioning kidney damaged by a long-standing obstruction.<sup>6,11,23</sup> Lymph nodes and nerves are encircled but not invaded. This was the case in all of our patients. The most suggestive diagnostic finding was unilateral or bilateral dilatation of the upper ureters on intravenous pyelography or computed tomography scan. The ureters are characteristically deviated medially. This feature is of diagnostic significance since most retroperitoneal neoplasms displace the ureters laterally.<sup>24</sup>

Approximately 8% to 10% of all cases of RF have an associated neoplasm.<sup>25</sup> The most common type of tumor found in association with secondary RF is a colorectal adenocarcinoma, as it was in case 5. However, carcinomas of the breast, stomach, prostate, lung, kidney, and uterine cervix have also been described as causes of secondary RF.<sup>15</sup> The fibrosis in these cases is

the result of the intense desmoplasia following the tumor infiltration of the retroperitoneum.

Microscopically we defined three stages in the progression of the disease, from the early immature cellular lesion to the mature, scarring stage. The common denominator in all the cases studied is the exuberant formation of fibrous tissue, which compresses nearby hollow organs and vessels, thus presenting a wide variety of clinical presentations.

Perhaps the most challenging differential diagnosis for the pathologist is to distinguish between RF and a sclerosing lymphoma. RF characteristically discloses areas of dense, homogeneous, eosinophilic, and hypocellular connective tissue interlaced with areas where the fibrous tissue is of the immature type containing numerous lymphocytes, plasma cells, and fewer eosinophils, with normal widely spaced germinal centers. Sclerosing lymphomas involving the retroperitoneum are usually B-cell lymphomas of follicular center cell origin, disclosing a monotonous population of small cleaved cells or large cleaved and noncleaved cells. These lymphomas may have a follicular or diffuse pattern.<sup>26</sup> In all the cases reported here, the immunostains for kappa and lambda light chains clearly revealed the polyclonality of the lymphoplasmacytic infiltrate, thus making the diagnosis easily interpretable. We advocate the use of immunostains including c-Kit, Leu-M1, Ki-1, LCA, and kappa and lambda light chains in cases of

RF to exclude the possibility of Hodgkin's disease and sclerosing retroperitoneal lymphomas.

From the therapeutic point of view, idiopathic RF may be successfully treated by stent placement to relieve the ureteral obstruction and restore renal function and by treating and/or preventing infections. In secondary RF, the associated condition also needs to be treated. At least a subset of RF is successfully responding to the administration of corticosteroids, antiestrogen, immunosuppressives, and/or tamoxifen.<sup>27-30</sup>

## Conclusions

The diagnosis of RF is challenging for both the clinician and the pathologist. A systematic and meticulous study to rule out secondary causes of RF should be undertaken before the idiopathic nature of the disease is confirmed.

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