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RETROPERITONEAL FIBROSIS (ORMOND'S DISEASE): CLINICAL CASE

Abstract

Retroperitoneal fibrosis (Ormond's disease) is a nonspecific inflammatory process in the retroperitoneal tissue with the formation of fibrous tissue that causes compression of the ureter and other adjacent structures. The disease is rare: its incidence is about 1 per 200 thousand people. This explains little knowledge about the disease, the absence of a real standard of patient's management with the determination of drug therapy and the most effective method of surgical treatment. The prognosis is determined by the activity of the disease with the development of urinary tract obstruction and the occurrence of renal failure and other complications. The article presents a clinical case of a 40-year-old patient suffering from Ormond's disease. In this case, the initial treatment to remove retroperitoneal fibrosis was undertaken by surgeons 5 months after the onset of the disease. Drug therapy was started 10 months later, when the final diagnosis was made using immunohistochemistry, and the progression of the disease developed (the retroperitoneal fibrosis area increased). On the background of immunosuppressive therapy, a decrease of the severity of retroperitoneal fibrosis was noted, however, it was not possible to achieve the full effect, most likely due to the late start of treatment and the irreversible fibrosis formed in this connection. Treatment was also complicated by the persistently recurring urinary tract infection. The best method of treatment in this situation (with persistent obstruction of the ureter and the risk of renal damage worsening) can only be surgical treatment aimed at restoring adequate urodynamics. Based on the presented clinical case, we can make the following conclusions: Ormond's disease (retroperitoneal fibrosis) needs further study and development of standards for the management of such patients; immunosuppressive, which can prevent the development of irreversible fibrosis, therapy should be prescribed as soon as possible; and, in advanced stages of the disease, treatment should be comprehensive, including both drug and surgical treatment.

Key words: *retroperitoneal fibrosis, Ormond's disease, immunosuppressive therapy*

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CT — computed tomography; USD — urinary stone disease; MRI — magnetic resonance imaging; MSCT — multislice computed tomography; RPF — retroperitoneal fibrosis; USS — ultrasound scanning; CRF — chronic renal failure

Retroperitoneal fibrosis (posterior peritoneal fibrosis, periurethral fibrosis, retroperitoneal granuloma, Ormond's disease) is a non-specific inflammatory process in the retroperitoneal tissue with the formation of fibrous tissue, causing gradual compression of adjacent structures. Retroperitoneal fibrosis (RPF) is the most common name for this disease. For the first time, a disease, which is characterized by proliferation of dense fibrous tissue in retroperitoneal fat and causing obstruction of the ureter, was described by Ormond, the urologist from Baltimore, in 1948.

RPF is a rare disease, with an incidence about 1 in 200 thousand people. It is usually diagnosed in patients between 30 and 60 years of age [2]. Men are affected twice as often as women. Mortality

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depends on the severity of obstruction and associated complications.

There is primary (idiopathic) and secondary RPF. Autoimmune mechanisms play the leading role in the development of idiopathic RPF. Secondary RPF is a consequence of various pathological conditions and diseases (cancer, infections, chronic inflammation of the liver, intestines, pancreas and female genital organs, spinal tuberculosis, toxic effects of certain drugs, etc.) [1, 7]. The primary idiopathic form is about 60–70 %, and the secondary form ranges from 30 to 40 % of all cases in the Russian Federation [7].

Usually, RPF begins in the retroperitoneal tissue surrounding the iliac vessels, at the site of their intersection with the ureter (at the site of L4–L5). Fibrosis extends gradually to the sacral promontory and to the kidney hilum. The process is bilateral in 30 % of cases. The vessels and the ureter are involved in the process so intimately that it is impossible to determine the border between adventitia and fibrous tissue. Diffusely growing scar tissue compresses the ureters first of all, then the inferior vena cava, the aorta and its main arteries are involved in the process. The disorder of urine flow through the ureter leads to an increase in intrapelvic pressure and the development of hydronephrosis, pyelonephritis, urinary stone disease (USD), renovascular hypertension, and ultimately to chronic renal failure (CRF) and renal scarring. In rare cases, RPF causes intestinal obstruction, obstruction of venous and arterial vessels.

The clinical picture depends on the stage, activity and extent of the process. The disease develops slowly, gradually progressing. There are three periods in the course of the disease: 1 — period of onset and development of the disease; 2 — period of the disease activity when the proliferating cellular and fibrous processes surround the retroperitoneal structures. 3 — period of contraction of fibrous mass with compression of the structures involved.

The first complaint is a constant dull pain localized in the lower back, abdomen, hypochondria with radiation to the groin, genitals, lower limbs. In the early stage of the disease, moderate fever, leukocytosis, and an increase in ESR are often observed. Symptoms due to compression of tubular retroperitoneal structures: hydroureteronephrosis, pyelonephritis, hypertension, CRF can follow the initial complaints in various terms: from 1 month to 2 years. Partial or complete obstruction of the ureters is observed in 75 % — 85 % of patients, oliguria or anuria is observed in 40 % of patients.

To confirm the diagnosis of RPF, intravenous urography is traditionally used, which allows to detect a triad of symptoms indicating the presence of this disease: hydronephrosis with dilated tortuous upper segment of the ureter; medial deviation of the ureter and external compression of the ureter. Recently, ultrasound scanning (USS), computed tomography (CT) and magnetic resonance imaging (MRI) of the abdominal organs and retroperitoneal space have been used in case of RPF to clarify the diagnosis, which allow to detect a space-occupying lesion, assess its extension, and monitor time-related changes during treatment. Multislice CT (MSCT) with contrast enhancement, as well as MRI are the most informative in the diagnosis of RPF and complement each other. MSCT with contrast enhancement allows to differentiate RPF from the aortic aneurysm, reveal the involvement of the arteries (lower mesenteric, testicular and vertebral), kidneys and ureters, and rule out enlargement of lymph nodes. MRI is superior to CT in differentiating between inflammatory tissue and mature fibrosis and can help to determine malignancy [3]. However, the final diagnosis can only be made on the basis of biopsy [4]. Differential diagnosis of the malignant and benign disease is performed using multiple deep biopsies, and, in some cases, only after laparotomy and open biopsy of this mass, followed by immunohistochemistry.

At the present time, there is no real standard of treatment for RPF; there is no clear definition of the role of drug therapy and the most effective method of surgical treatment [2]. Conservative treatment depends largely on the cause of the disease. Discontinuation of medication often leads to recovery, if the use of the drugs was the cause of the RPF. Treatment of malignant diseases is carried out in accordance with their cell type. Idiopathic RPF is often treatable with glucocorticoids and adjunctive immunosuppressive and antifibrotic agents [5, 6]. If necessary, anti-inflammatory, antibacterial therapy, detoxification, and symptomatic therapy are employed. If there is no effect from conservative

therapy, a surgical intervention is often required to release the ureters and other structures from dense connective tissue in order to reduce their obstruction.

The rarity of the condition and the difficulty of diagnosing RPF are a frequent cause of late onset and prolonged ineffective treatment of patients for the manifestations of various diseases and complications: hypertension, cancer, chronic colitis, cholecystitis, pancreatitis, gastric and duodenal ulcers, urinary stone disease, acute pyelonephritis, hydronephrotic kidneys, anuria, CRF, etc. In this clinical case, physicians faced similar challenges, which determined the lack of efficacy of conservative therapy.

Clinical Case

The patient K., 43 years of age, first complained of nagging pain in the left lumbar region, mostly at rest and at night, in January 2015 (at the age of 40). Since the pain arose after the removal of the intrauterine device, the patient was examined by gynecologist and received antibacterial therapy without effect. Body temperature was 37.0 °C. Stool and urination disorders, as well as menstrual cycle disorders were not observed. In March 2015, ultrasound scanning, followed by an MRI scan, performed at the Saratov City Clinical Hospital No. 2, revealed a soft tissue lesion measuring 55×33×82 mm, located in the retroperitoneal space, surrounding the aorta and adjacent to the inferior vena cava. Its structure was heterogeneous due to areas with fluid signal characteristics, irregular contours with moderately pronounced perifocal edema of retroperitoneal tissue. The uterus had normal dimensions, was unremarkable.

In April 2015, a dense, circumscribed, mobile lesion measuring 100×60 mm was revealed during laparotomy. It was located in the projection of the inferior vena cava and aorta, from the lower edge of the pancreas to the bifurcation of the vessels and was adhered to the duodenal inferior horizontal part and the anterior wall of the inferior vena cava. On the left, the lesion was surrounding the aorta and the left iliac vessels. Histological study of the lesion suggested the presence of fibrous histiocytoma. In May 2015, CT scan of the abdominal and retroperitoneal organs was performed at the N. N. Blokhin Russian Cancer Research Center, which confirmed the presence of a retroperitoneal lesion measuring 55×40×70 mm, with indicated localization, surrounding the aorta circumferentially (the aortic lumen was narrowed to 1.2 cm) and the inferior vena cava along its anterior surface. The lesion was removed; its histological structure corresponded to the retroperitoneal neurofibroma with pronounced secondary changes: (hyalinosis of stroma, lymphoid infiltration, accumulation of xanthoma cells).

Discomfort persisted in the lower abdomen in the postoperative period. Body weight loss of 15 kg and periodic increase in BP to 145–160/100 mm Hg were observed. The patient took captopril as needed. CT on September 2015 revealed a band of infiltration measuring 3–4 mm in thickness and 60 mm in length at the site of the lesion described previously, surrounding the aorta like a cuff up to its bifurcation, and extending by up to 20 mm to the proximal segments of the iliac arteries. Hepatomegaly was discovered. No other abnormalities were revealed during CT and USS.

Given the lack of treatment, follow-up CT carried out at N. N. Blokhin RCRC in February 2016 revealed negative time-related changes: an increase of thickness (up to 13 mm) and length (up to 70 mm) of the lesion that was extending to the common iliac vein and the upper third of the left ureter, causing dilation of its proximal parts to 8 mm and pyelectasis measuring up to 23 mm. Nephrostomy was performed in the left side, an immunohistochemical study was performed, according to the results of which the diagnosis was changed to idiopathic RF (Ormond's disease). Taking into account the outflow disorder in the left ureter detected during angiography, a stent was inserted into the left ureter, and the nephrostomy tube was closed. Follow-up and treatment by the rheumatologist were recommended.

Over the next 2 years, the patient was regularly (once every 3–5 months) followed-up at the Departments of Rheumatology and Urology of the Saratov Regional Clinical Hospital where she was undergoing USS, CT of the abdominal and retroperitoneal organs, as well as duplex ultrasound of the abdominal and retroperitoneal vessels and general clinical laboratory tests. Treatment

with Metypred (24 mg with a gradual decrease to 8 mg), D-penicillamine 250 mg/day, Coronal 2.5 mg/day was prescribed. Occasionally, the patient noted the appearance of turbid urine with meat slops color. Proteinuria, with a maximum of 1.45 g per day, bacteriuria, massive leukocyturia, and hematuria were revealed. Repeated catheterization of the left ureter with stent replacement (every 3–5 months) was performed; antibacterial therapy was prescribed with a short-term effect. In May 2016, she reported that the nephrostomy tube fell out without adverse effects. From the beginning of this conservative therapy, a gradual decrease in the RPF thickness from 13 mm (February 2016) to 4 mm (July 2017) has been observed: Figure 1. During the following year, no further positive changes were observed despite continued treatment. The length of the lesion did not change significantly.

In March 2018, the patient developed a partial ptosis of the upper eyelid on the right, after that D-penicillamine was canceled, a CT scan of the head was performed taking into account the possible development of a tumor of the orbit in this disease, but this abnormality was not revealed. Since the eyelid function has fully recovered after the discontinuation of D-penicillamine, we considered ptosis as an adverse reaction to this drug with the development of myasthenia gravis. Instead of D-penicillamine, methotrexate was prescribed at low doses (10 mg per week). The lack of further positive changes regarding the RPF, persistent ureteral obstruction with the development of hydronephrosis of the left kidney, and recurrent urinary tract infection were the basis to recommend surgical treatment to the patient, aimed at restoring the patency of the left ureter.

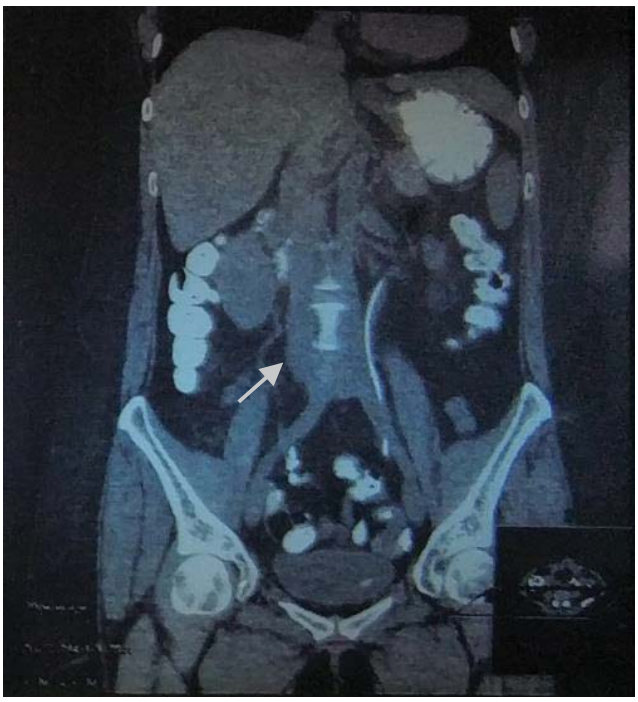

Figure 1. *Retroperitoneal Fibrosis (October, 2016)*

Discussion

The low incidence of RPF in the population and associated difficulties in obtaining statistically significant results, the lack of sufficient experience of individual clinical centers in the diagnosis and management of patients led to the lack of a unified approach to the treatment of patients with this condition. Some authors begin with glucocorticoids and other drugs and, in the lack of effect, resort to surgical treatment. Others opt for a surgical procedure immediately, and then prescribe or do not prescribe drug therapy.

In this case, the initial treatment (removal of RPF) was undertaken by surgeons. Drug therapy was started only 10 months after the surgery (one year after the first symptoms of the disease appeared), when the final diagnosis was made and the progression of the disease became apparent (an increase in the lesion thickness from 3–4 mm to 13 mm and in its length from 60 mm to 70 mm with dilation of the proximal left ureter and the development of pyelectasis).

With immunosuppressive therapy, some positive changes were observed (a decrease in RPF thickness up to 4 mm), however, late diagnosis of the disease and, accordingly, delayed start of treatment did not allow achieving the full effect, apparently due to the development of irreversible fibrosis. Recurrent urinary tract infection limiting the possibility of long-term immunosuppressive therapy in adequate doses was a factor aggravating the treatment.

Thus, the rarity and little knowledge of Ormond's disease caused delayed diagnosis and untimely medical therapy; surgical treatment without subsequent immunosuppressive therapy does not prevent the progression of the disease; although

delayed and insufficient (due to urinary tract infection) drug therapy caused a decrease in RPF, it did not result in its complete elimination, thus creating the risk of further disease progression and the need for repeated surgical intervention.

Conclusions

1. Ormond's disease (retroperitoneal fibrosis) needs further study and development of standards for the management of patients with this condition
2. Immunosuppressive therapy should be prescribed as soon as possible to prevent the development of irreversible fibrosis
3. In advanced stages of the disease, treatment should be comprehensive, including both medical therapy and surgical intervention.

Conflict of interests

The authors declare no conflict of interests.

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