Ormond`s Disease - a Review

D. Spinu[1,2], R. Anghel[2], L. Iorga[2], D. Marcu[1,2], O. Bratu[1,2], C. Pricop[3,4], D. Mischianu[1,2]

[1] *University of Medicine and Pharmacy „Carol Davila", Bucharest*
[2] *Department of Urology, University Emergency Central Military Hospital, Bucharest*
[3] *University of Medicine and Pharmacy „Grigore T. Popa", Iasi*
[4] *Department of Urology, Clinic Hospital „Dr. C I. Parhon", Iasi*

Abstract

Introduction and Objectives. Ormond's disease or the so called retroperitoneal fibrosis involves proliferation of fibrous tissue in the retroperitoneum. All retroperitoneal organs can and will be affected in time by this disease: kidneys, great vessels, ureters and so on. Symptoms vary from hypertension to hypotension, renal failure, chronic or acute back pain, deep vein thrombosis and many more. It is a rare disease with un unclear pathology owing its name to John Kelso Ormond who discovered it in 1984.

PubMed and Scopus databases were used. "Ormond disease" and "retroperitoneal fibrosis" were the key words used, special care was given to new articles.

Although in the past surgery was the mainstay treatment, nowadays glucocorticoid and immunosuppresing therapy seem to gain more and more ground. It is a serious disease which left untreated can lead to major health problems including dyalisis and/or renal transplantation.

Key-words: retroperitoneal fibrosis, Ormond disease, surgery.**Introduction**First time, retroperitoneal fibrosis was sus-

Introduction

First time, retroperitoneal fibrosis was suspected in 1905, by an urologist of cuban origin, named Joaquin Albarran, who described the an external compression on the ureter due to an unknown illness in the retroperitoneum. Almost 50 years later, John Ormond described two cases and then published them in England in 1948 and his later work that provided the knowledge for the classification of retroperitoneal fibrosis known as a self-standing disease - the Ormond disease. The incidence of this disease is 1.38 cases per 100 000 people and most of them are idiopathic.[1] Chronic inflammation and fibroblast proliferation are usually involved with this disease, with excessive extracellular matrix deposition. There are no specific serologic markers, but the C-reactive protein and the erythrocyte sedimentation rate are high. On CT scan Ormond disease appears as a density of the soft tissue around the abdominal

Correspondence to: Dr. Arsenie Dan Spinu, M.D.
University Emergency Central Military Hospital, Department of Urology
134 Plevnei Str., sector 1, code 010825, Bucharest, Romania
Tel: +40213193051; Fax: +40213193030
e-mail: dan.spinu@yahoo.co.uk

aorta or iliac vessels, which can lead to hydronephrosis of one or even both kidneys.[2]

Retroperitoneal fibrosis can be idiopathic or caused by various agents like drug exposure, infection or cancer. Almost two-thirds of retroperitoneal fibrosis cases are idiopathic, with no primary specific cause identified. Like other diseases the diagnosis is established on histopathological exam, after biopsy. Storiform fibrosis, tissue eosinophilia and obliterative phlebitis are the most common findings. As clinical manifestations, the first symptoms of the disease usually appear between 30 and 60 years of age, usually linked to the urinary tract. Ormond disease is predominant in male patients with a ratio of 2:1.

Recent studies associated the retroperitoneal fibrosis with IgG4, with unique histopathologic features in all the organs affected. On histopathologic exam lymphoplasmacytic infiltrate, obliterative phlebitis and even storiform fibrosis are displayed.[3] Also patients may present tissue eosinophilia, usually with a history of allergies that accompanies the IgG4-RD.[4] There are many contradictory studies regarding any potential relationship of IgG4-RD to "idiopathic" retroperitoneal fibrosis. Findings of high levels of IgG4 in the serum of patients have usually no effect on the effectiveness of the immunosuppressive therapy. The diagnosis of the retroperitoneal disease is important to be put clear and the difference between the infectious and noninfectious etiology of the inflammation must be made because given the use of immunosuppressive therapy, in the noninfectious etiology, the failure to recognize this difference can have unwanted even fatal consequences, for the patient.

Results

The diagnosis of the Ormond disease is based on the medical history, clinical aspects and imaging results. One of the most frequent clinical manifestation is represented by the dilatation of the pielo-caliceal system caused by the obstruction of the ureters which causes acute lumbar pain with anterior irradiation. These manifestations are usually detected on ultrasound which is routinely available. Despite its usefulness, ultrasound sonography itself does not allow for an exact assessment of the nature and extent of the obstruction, so other types of radiologic investigations are needed. The best is spiral CT, but other investigations are useful like urography or normal CT.

It is very difficult to diagnose this pathology firstly because it's easy to confuse the first manifestations with a simple kidney colic. That is why the gold standard of diagnosis is histopathological examination when there is a doubt. Differential diagnosis must be made to exclude other neoplastic retropenitoneal formations, like germ cell tumors, sarcomas, metastatic processes from other solid or carcinoid tumors, haemoblastosis or neuroblastomas. Among infections, tuberculosis must be taken under consideration because it can spread into the retroperitoneum from neighboring foci.[5]

According to a study performed by Corradi et al, lymphocytes in particular, depending on the stage of the disease and the location from where the biopsy was made, can be detected in the inflammatory infiltrate (with a majority of B lymphocytes and a proportion of T lymphocytes).[6]

There are some cases when simple needle biopsy is not sufficient to put the diagnosis, or it's not possible to be made due to anatomical causes, so in this uncertain situation surgical removal of tissue for histology exam may be necessary. There are several ways to remove the tissue for hystological exam: open surgery laparoscopic or robotic assisted surgery. In open surgery a lumbotomy can be used or from trasperitoneal approach a classic pararectal incision, depending on the affected zone. If the trans peritoneal approach is preferred, the rear wall of the peritoneum is open and the biopsy is taken from the fibrotic palpable mass. There must be a sufficiently large piece of excision for a valid histological examination.[7]

The histopathological classification of the IgG4 related retroperitoneal fibrosis is made using hematoxylin and eosin-stained slides. On a microscopic examination lymphoplasmacytic infiltration, tissue eosinophilia, obliterative phlebitis, and storiform fibrosis can be observed. Immunohistochemistry is performed with the help of specific antibodies to IgG4 and IgG. The degree of IgG4+ plasma cells within the tissue of biopsy sample is determined. For every case, the number of plasma cells stained for IgG4 is assessed in 3 nonoverlapping HPFs using a 400x magnification, and only the highest degree of IgG4 reactivity is chosen for counting. Then, to determine the IgG4/IgG ratio, the number of IgG4+ plasmatic cells is divided by the total number of IgG plasma cells. Patients with a ratio of IgG4/IgG above 40% are predisposed to have the histopathologic features of storiform fibrosis, eosinophilia and lymphoplasmacytic infiltrates, than were those with IgG4/IgG ratios under 40%. Many recent studies demonstrated that where the presence of IgG4 is noted, in the retroperitoneal fibrosis, storiform pattern of

fibrosis is significantly more often than the non IgG4 related Ormond disease, like the study performed by Yamashita et al on a batch of 29 patients with Ormond disease showed that this disease associated with IgG4+ plasma cells present a multifocal fibrosclerosis and lymphoplasmacytic infiltrations, compare with those cases where the retroperitoneal fibrosis was linked to other pathologies.[8]

Treatment

The main goal of treatment is the relief of the ureteral obstruction if it's present. In the past, the gold standard was surgical ureterolysis with intraperitonealization and even omental wrapping of the ureters. Now conservative procedures like the insertion of a double-J stent or nephrostomy which is used to drain the kidney and release the pressure, followed by medical therapy are preferred.[9] Because of the much better tolerance, patients generally prefer the use of a JJ stent rather than a percutaneos nephrostomy. In this case, and because the intense fibrotic process it is preferred to use stronger ureteral stents bigger in diameter, reinforced stents, or even metal stents, to assure a good drainage.

Given the fact that there is no specific symptom for this pathology and a lot of time is lost on various scans, significant obstructive hydronephrosis can occur. Usually the process unfolds in all the retroperitoneum and the fibrosis affects both kidneys, but in most cases only one ureter is worse affected. After the double J stent is inserted the drug treatments whose effect has significantly improved over the recent years is started.

Treatment of retroperitoneal fibrosis is usually performed using corticosteroids with or without some other immunomodulating medications or tamoxifen. New studies on a drug named rituximab, which is a monoclonal antibody that specifically targets the CD20 on the surface of B cells, showed that it's effective in achieving complete remission of proteinuria in patients with idiopathic membranous nephropathy and retroperitoneal fibrosis. This medication is used where on a histological exam a large number of CD20 cells is detected. Rituximab has been studied in in a lot of small pilot studies, and the response to this medication correlates with a significant reduction in antibodies to the M-type phospholipase A2 receptor.[10]

Because the Ormond disease affects not only the renal system but also the large vessels - surgical intervention is the treatment of choice for one of the unwanted complications – aortic aneurysm. Aortic aneurysm is a serious condition, that, if left untreated can be life-threatening because of its hemorrhagic risk. Sedivy et al in a study published in 2012, stated that in a patient with retroperitoneal fibrosis complicated with aortic aneurysm, after the immunosuppressive treatment, endovascular treatment is preferred to standard surgery due to the technical challenge.[11]

Arezou Khosroshahi et al, performed a study on a lot of 23 patients with idiopathic retroperitoneal fibrosis and identified IgG4-related fibrosis based on the presence of IgG4+ plasma cells in the tissue. The mean age of the patients was 58 years old, 73% of them were men. The most frequent presenting symptoms were back and flank pain, associated with lower extremity swelling. The first-line of treatment was glucocorticoid therapy with initial doses of 0.75–1 mg/kg per day of prednisone. Almost half of the patients, 10 of 22 developed uretherohidronephrosis and needed the placement of ureteral stents. Seven patients underwent ureterolysis procedures, and 7 patients, despite the early treatment developed chronic kidney disease. [12]

Is still debated if the use of immunosuppressants combined with glucocorticoids; have better potency or function as steroid-sparing agents. Vaglio and Buzio considered that the retroperitoneal fibrosis is a systemic autoimmune disease, and the administration of immunosuppressive agents is an important part of the therapy.[13] The use of corticosteroid therapy may be hazardous in patients with vascular complications as aneurysm because it usually accelerates the atherosclerotic process. One alternative therapy can be the use of tamoxifen. Kuhn et al stated that exact pathophysiological effect of this drug is yet to be known but there is a high chance that it's hormonal-independent.[14] Because tamoxifen is an antiestrogen drug it may act both as immunosuppressive and anti-inflammatory therapy. The exact mechanism of action of tamoxifen on fibrosis is still unknown. It is mainly use in the treatment of breast cancer, and because of its antifibroblastic effect it is also used in pelvic fibromatosis and Peyronie's disease. The single use of tamoxifen as monotherapy in retroperitoneal fibrosis, has been describe in several studies and case reports, with good results. Alexander Sascha Brandt et al used tamoxifen in monotherapy on a lot of 31 patients with idiopathic Ormond disease. The dose was 20 mg twice a day, and the mean duration of the treatment was 5 months. The result of the treatment showed 3 cases of disease progression, retroperitoneal fibrosis remained stable without any regression in 6 cases. The disease regressed mildly in 7, significantly in 11 and completely in 4 patients.[15]

Discussions

The retroperithoneal disease or Ormond disease associated with IgG4 is a newly defined group of diseases, some of which have been known previously. This disease can affect all the structures in the retroperithoneum, mostly the renal system but also the large vessels. There is no typical symptom for this disease, it usually presents itself as low back pain mimicking a simple kidney colic. It has been clinically demonstrated that this disease responds well to systemic corticosteroid therapy. Immunosuppressive therapy associated with corticosteroid therapy has showed good results. Many case reports and small series done in the last years have documented successful nonsurgical treatment with a large variety of immunosuppressive agents. In the past years elevated serum concentrations of IgG4 was discovered in patients with Ormond disease.

Patients with IgG4-related disease usually have lesions in several organs situated in the retroperitoneum, that can be either synchronous or metachronous. Because the pathological features of each organ differ, a consensus was created with 2 diagnostic criteria for the IgG4-related disease to be confirmed: Firstly, the serum IgG4 concentration must be greater than 135 mg/dL, and the second criteria is that more than 40 % of IgG+ plasma cells are IgG4+ and more than 10 cells per high-power field of biopsy sample.[16]

Conclusions

Ormond disease is a serios systemic and autoimmune disease which can present severe complications like renal insufficiency or failure, and aneurysm of the abdominal aorta or iliac arteries. Its exact diagnostic is put on a biopsy or a combination of test that includes biochemical, microbiological and immunological tests with imaging methods. The treatment is a combination of corticoid and immunosuppressive treatment with surgical treatment when the most frequent complication appears. Its baseline consists of relieving ureteral obstruction and inducing disease regression.

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