Brief original

Ormond's disease: Experience with five cases

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Ormond's disease (OD) is an uncommon process with an annual incidence nearing 1 per million inhabitants. The etiology in most of the cases is unknown and several pathogenic mechanisms are implicated in secondary OD. Ormond disease is characterized by a fibrotic and inflammatory mass with three different clinical features: 1) retroperitoneal fibrosis, 2) periaurysmatic retroperitoneal fibrosis and 3) inflammatory abdominal aortic aneurysms. Classic management is based on surgical treatment associated or not with steroids. Immunosuppressive agents have been used in the last years with unclear results. We report five cases from the University Hospital of Salamanca occurring during 2000-2008. We highlight the lack of trials designed to establish clinical guidelines for the treatment of the disease and improvement of outcome.

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ABSTRACT

Ormond's disease (OD) is an uncommon process with an annual incidence nearing 1 per million inhabitants. The etiology in most of the cases is unknown and several pathogenic mechanisms are implicated in secondary OD. Ormond disease is characterized by a fibrotic and inflammatory mass with three different clinical features: 1) retroperitoneal fibrosis, 2) periaurysmatic retroperitoneal fibrosis and 3) inflammatory abdominal aortic aneurysms. Classic management is based on surgical treatment associated or not with steroids. Immunosuppressive agents have been used in the last years with unclear results. We report five cases from the University Hospital of Salamanca occurring during 2000-2008. We highlight the lack of trials designed to establish clinical guidelines for the treatment of the disease and improvement of outcome.

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Enfermedad de Ormond: experiencia de cinco casos

RESUMEN

La enfermedad de Ormond (EO) es una enfermedad infrecuente con una incidencia aproximada de 1/1.000.000 personas-año. La etiología en la mayoría de los casos es desconocida, y en la EO secundaria se han implicado múltiples procesos patogénicos. La EO se caracteriza por la presencia de un masas fibroinflamatoria retroperitoneal con tres formas clínicas diferentes: 1) fibrosis retroperitoneal; 2) fibrosis periaurysmático retroperitoneal, y 3) inflamación de los aneurismas de la aorta abdominal. El manejo clásico se basa en el tratamiento quirúrgico y puede asociarse a esteroides. En estos últimos años se han empleado otros inmunosupresores sin resultados bien establecidos. Presentamos cinco casos acontecidos en el Hospital Clínico Universitario de Salamanca durante el período 2000-2008. Destacamos la falta de estudios para establecer guías de práctica clínica que faciliten el manejo y mejoren el pronóstico.

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Introduction

The first description of retroperitoneal fibrosis, chronic disease, periaortitis or Ormond's disease (OD) was made by Albarran in 1905. OD is a rare disease with an incidence of approximately 1/1,000,000 persons-years. Usually OD clinical data is nonspecific, and focal details will depend on the organs involved. OD can damage the bladder, ureters, thoracic aorta, the celiac, mesenteric vein, duodenum, small intestine, colon and reproductive organs, although it has a predilection for the urological system. Currently there are well-established diagnostic criteria, so histology is necessary for a definite diagnosis. However, the need for biopsy is discussed in all suspected cases of OD given the current cost-effectiveness of imaging tests. Regarding treatment, we need more studies to clarify the different stratification and therapeutic possibilities.

Material and methods

We conducted a retrospective study of cases diagnosed during the period from January 1, 2000 to December 31, 2008 at the Hospital Universitario de Salamanca, a tertiary center serving a population of 350,000 patients and with 1,000 beds (Table). The case search was conducted in the computerized database of the medical records...
erythorcyte sedimentation rate; HTA, hypertension; MR, magnetic resonance.

ANA indicates antinuclear antibodies; AS, ankylosing spondylitis; CRF, chronic renal failure; CRP, C reactive protein; CT, computerized tomography; DM, diabetes mellitus; ESR, erythrocyte sedimentation rate; HTA, hypertension; MR, magnetic resonance.

unit. The cases included fulfilled 1) suggestive clinical and analytical data; 2) supported by X-ray, computed tomography (CT) or nuclear magnetic resonance imaging (MRI), and 3) the consideration of possible secondary causes. The most representative variables were characterized.

Case 1

Fifty year old female. She had a history of hypothyroidism treated with levothyroxine and smoking of 25 packs-years. She came due to left lumbar pain radiating to the groin. Laboratory analysis highlighted hemoglobin 11 g/dl, C reactive protein (CRP) 7 mg/dl and erythrocyte sedimentation rate (ESR) of 80 mm/1h. Renal ultrasonography showed minimal ectasia of the left kidney with a normal intravenous urography. The CT showed evident thickening of the distal aortic wall and both iliac arteries, with increased density in the surrounding fat planes and thickening of the celiac trunk that extends to the thoracic aorta. The MRI image showed soft tissue surrounding the aorta, particularly at the infrarenal level, isodense with muscle and enhancing with contrast, compatible with retroperitoneal fibrosis. She was treated with prednisone (1 mg/kg/day) for 8 weeks and then with a maintenance doses (7.5 mg/day). The MRI scan at three months did not show significant thickening of the aorta. Treatment was withdrawn after 24 months, with the patient remaining asymptomatic.

Case 2

Fifty-five year-old male. He had a history of hypertension and untreated dyslipidemia and smoked 25 pack-years. He began presenting fever, pain in the umbilicus and a short clinical dysuria. Laboratory analysis highlighted a creatinine of 9.63 mg/dl and a CRP of 4 mg/dl. The abdominal ultrasound showed marked bilateral ureteric ectasia with normal sized kidneys and an irregular solid mass in the retroperitoneum, anterior to the aortic bifurcation, along with mild dilatation of the latter. MRI showed a thickened retroperitoneum, which includes the aorta and both ureters with extension to aortoiliac bifurcation. He was treated with prednisone (0.75 mg/kg/day) for 8 weeks followed by a maintenance dose of prednisone (15 mg/day) and azathioprine (0.5 mg/kg/day) were prescribed. The patient improved on MRI at 6 months, with removal of the catheters after a year. After 24 months the patient is asymptomatic with creatinine of 1.50 mg/dl and resolution of lesions on the control MRI.

Case 3

Forty-eight year-old male. Personal history of hypertension and diabetes mellitus treated with enalapril, doxazosin, insulin glargine and glimepiride. He presented referred pain from the left flank to the testis. Laboratory showed hemoglobin 11 g/dl, CRP 6 mg/dl and ESR 70 mm/1h. Intravenous urography was normal. Abdominal MR image showed unaffected aortic soft tissue and mild left renal ectasia suggestive of retroperitoneal fibrosis. The Ga-67 scintigraphy showed retroperitoneal uptake. He was treated with tamoxifen (40 mg/day) with improvement at 16 weeks, suspended afterward. At the 6 month control there was progressive deterioration of renal function and the abdominal MRI showed bilateral pyelocalyceal dilatation, which required a the double-J stent insertion in both kidneys and was treated with prednisone (1 mg/kg/day) for 8 weeks with a posterior maintenance dose (15 mg/day) and azathioprine (1 mg/kg/day). He presented clinical and radiological improvement on MRI at six months and maintained treatment for 20 months.

Case 4

Forty-four year-old male. He had a personal history of ankylosing spondylarthritis treated occasionally with nonsteroidal antiinflammatory drugs. He started with pain in left renal fossa of over a month of duration. Laboratory showed creatinine 2.4 mg/dl. Abdominal ultrasonography showed minimal ectasia of the right

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, years</th>
<th>Gender</th>
<th>Risk factor</th>
<th>Clinical</th>
<th>Diagnosis</th>
<th>ANA</th>
<th>ESR/CRP</th>
<th>Complication of ectasia</th>
<th>Treatment</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>Female</td>
<td>Smoking</td>
<td>Lumbar pain</td>
<td>MR</td>
<td>Negative</td>
<td>80/7</td>
<td>No</td>
<td>Prednisone: 24 months</td>
<td>Clinical and radiological resolution at 3 months</td>
</tr>
<tr>
<td>3</td>
<td>48</td>
<td>Male</td>
<td>HTA and DM</td>
<td>Lumbar pain</td>
<td>MR</td>
<td>Negative</td>
<td>70/6</td>
<td>Yes</td>
<td>Urologic. Double J bilateral: 8 months-</td>
<td>Clinical and radiological response at 1 year. Asymptomatic after 5 years of follow up</td>
</tr>
<tr>
<td>4</td>
<td>44</td>
<td>Male</td>
<td>AS</td>
<td>Lumbar pain</td>
<td>MR</td>
<td>Negative</td>
<td>Normal/normal</td>
<td>Yes</td>
<td>Urologic. Double J bilateral: 8 months-</td>
<td>Clinical and radiological response at 6 months</td>
</tr>
<tr>
<td>5</td>
<td>44</td>
<td>Male</td>
<td>Smoking, HTA and dislipidemia</td>
<td>Lumbar pain</td>
<td>CT and MR</td>
<td>Negative</td>
<td>20/2.44</td>
<td>Yes</td>
<td>Urologic. Double J unilateral. Prednisone and azathioprine</td>
<td>Asymptomatic after 2 years of follow up</td>
</tr>
</tbody>
</table>

Table. Main characteristics of the 5 patients

ANA indicates antinuclear antibodies; AS, ankylosing spondylitis; CRF, chronic renal failure; CRP, C reactive protein; CT, computerized tomography; DM, diabetes mellitus; ESR, erythrocyte sedimentation rate; HTA, hypertension; MR, magnetic resonance.
urine and left ureterocalicial ectasia. CT and MRI were performed, with an evident plaque that included large retroperitoneal vessels and ureters. With the diagnosis of retroperitoneal fibrosis, he was treated with prednisone (1 mg/kg/day) for 6 weeks and azathioprine (1.25 mg/kg/day). After six months the patient presented normalization of creatinine levels, improvement of abdominal symptoms and resolution of lesions on control MRI, remaining with treatment until reaching 18 months.

Case 5

Forty-four-year-old male. As a personal history he was a current smoker of 30 packs-year, had hypertension and dyslipidemia treated with valsartan, and pravastatin. His case began with colicky pain in the right lumbar area lasting three months. Laboratory analysis showed creatinine of 1.7 mg/dl, CRP of 2.44 mg/dl and ESR 20 mm/1st h. Abdominal CT showed dilation of the excretory system with dilation of the right ureter and the ascending aorta cava to the iliac bifurcation. MRI revealed the existence of a retroperitoneal soft tissue mass covering the aorta and the cava from the duodenum to the iliac artery bifurcation, which incorporated the right ureter and led to pyelocalyceal ectasia. Before the diagnosis of OD, a double J stent was placed in the right ureter and he was treated with prednisone (1 mg/kg/day) and azathioprine (0.75 mg/kg/day), Progression at 3 months is pending.

Discussion

Although no exact data on the incidence of OD exists, it is estimated that idiopathic OD (which constitutes 60-70% of OD) has an incidence between 1/1,000,000 and 1:10,000 person-years.6 The prevalence is 1.38 cases per 100,000.7 The male/female ratio is 2.1:3.1 with a peak presentation at 40-60 years.8 It has been shown that environmental factors, such as asbestos exposure and smoking increase the risk of developing this condition and certain genetic factors, such as HLA-DRB1-03, may influence its appearance. However, ethnic factors were found to predispose to OD.3 Pathogenesis of idiopathic OD is unknown, although various mechanisms have been postulated.4 The first postulates that OD is the result of a local reaction against specific antigens of plaque in the abdominal aorta, such as low-density lipoproteins.7 Another scenario involves vasculitic phenomena present in up to 80% of patients.8 The autoimmune theory is supported by the frequent association of this entity with other autoimmune diseases such as Wegener’s granulomatosis, lupus erythematosus, ankylosing spondylitis, vasculitis, periarteritis nodosa, Hashimoto’s thyroiditis or Riedel’s disease.4,8 The pathogenesis of secondary cases varies according to the triggering process: drugs (coca-blockers, methylsergide, methyl dopa, hydralazine, etc.), tumors (lymphomas, sarcomas, carcinoid tumors, etc.), infectious diseases, radiation and trauma.1

The gross appearance of retroperitoneal fibrosis is a nonspecific chronic inflammatory mass. Through the microscope one can see a conglomerate formed by bands of collagen with abundant capillary proliferation and inflammatory cells, particularly lymphocytes, plasma cells and fibroblasts in the early stages of the disease. In advanced stages it appears as an acellular and avascular mass consisting almost entirely of dense connective tissue. There are histological differences between primary and secondary forms or with other diseases such as Riedel’s thyroiditis, orbital pseudotumor, sclerosing cholangitis and mediastinal fibrosis.9 Immunohistochemistry observed in perivascular aggregates is composed of B cells and other elements.

The clinical data consists often of nonspecific systemic and local symptoms, as in our five patients. The characteristic triad consists of abdominal pain, an ill-defined dull, throbbing mass and an elevated ESR. Local involvement is caused by entrapment of retroperitoneal structures, notably the ureters (80-100% of cases), as in four of our five patients, and less frequently of the vessels, digestive and reproductive organs.1 Among local symptoms, abdominal pain/lower back pain, edema, varicocele, dysuria, oligoanuria, deep vein thrombosis, etc. stand out. General symptoms of malaise, anorexia, fever, myalgia and arthralgia are also present. The laboratory results are of little help and can occur in many inflammatory processes, with positive rheumatoid factor, antineutrophil cytoplasmic antibodies, anti smooth muscle and antinuclear antibodies with their real impact or a clear clinical significance not well established.1,8

The diagnosis presents several difficulties in clinical practice. The first is the absence of established diagnostic criteria, so the diagnosis is made with a suggestive clinical signs and blood test and a compatible imaging technique. The role of radiology is becoming increasingly important, both for initial diagnosis and monitoring. Among the diagnostic tools, ultrasound, CT and MRI have replaced intravenous urography. At present, MRI is the method of choice to give a more complete diagnosis of location and extension and improved anatomical definition, without using radiation or iodinated contrast (which is potentially nephrotoxic).19,20 The major disadvantages of MRI are a lack of correlation between disease activity and radiographic changes and sometimes difficult to differentiate between OD from other processes. The real usefulness of Ga-67 scintigraphy is yet to be elucidated, but it appears effective in monitoring therapeutic response in the early stages of OD or in cases with poor clinical and/or inflammatory response or recurrences.21 Positron emission tomography scans with fluoride-18 has indications similar to Ga-67 scintigraphy, although experience is still limited.22 The demand for biopsy for a definitive diagnosis is another issue pending clarification. Currently, due to the advancement of Radiology, biopsy is considered necessary only in unusual location OD or when an infectious process or tumor is suspected.23-24 For this reason, only one patient in five is biopsied. General treatment aims to preserve renal function, reduce inflammation and treat the etiology, if it is known. The current lack of information causes difficulties in distinguishing between the different therapeutic possibilities and makes the inclusion of new drugs difficult.

The classic management techniques are based on urethral decompression (intrapерitonealization, lateralization, etc.). Open urological surgery has now been replaced by laparoscopic techniques and double-J catheter placement, especially in cases of severe urethral obstruction with impaired renal function.2

Immunosuppressive therapy is based on the use of steroids. The initial regimen of steroids ranges between 30-75 mg/day with a later maintenance dose (5-10 mg/day) and duration of treatment varies widely, from 4 weeks to 19 months.2

A recent review comparing different treatment options showed that the success rate of urological surgery by isolated ureterolysis technique is 73%, corticosteroids 86% and the combination of both 73%. The combination of corticosteroids and other immunosuppressive agents improves 97% of cases of OD. In this review, the authors point out that the low success rate of combined therapy of corticosteroids and surgery is related to the use of the latter in refractory cases, and that we need a higher level of scientific evidence for the management of these patients, since treatment with data supporting the use of other immunosuppressants such as azathioprine, cyclophosphamide, methotrexate, mycophenolate, and so on are weak.20 Another new possibility that has good results and minimal side effects is tamoxifen, which demonstrated response in 15 of 19 patients.15 Its mechanism of action is not fully elucidated: it appears that the effect on retroperitoneal tissues is based on the inhibition of protein kinase C, binding mediators of cell proliferation, and increasing apoptosis.26 In our series, patients treated with tamoxifen only failed treatment, while treatment with corticosteroids or the association of corticosteroids with other immunosuppressive drugs and/
or tamoxifen were effective. As noted above, corticosteroid and/or tamoxifen for at least a year is recommended as the mainstay of treatment over other immunosuppressive agents. OD’s prognosis is good, despite relapses, with a cumulative mortality of 9%, except in cases secondary to tumors. Long-term follow-up with clinical assessment, laboratory (ESR, CRP and creatinine) and radiological tests is needed, to be performed every three months during the first year, since most recurrences occur early in the disease. Recurrences reach up to 70%, but usually have a good response after the reintroduction of treatment.  

**Disclosures**

The authors have no disclosures to make.

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