Ormond's Disease – IgG4-related Disease

Miroslav Průcha[1], Ivan Kolombo[2], Petr Štádler[3]

[1]Department of Clinical Biochemistry, Haematology and Immunology,
Na Homolce Hospital, Prague, Czech Republic;
[2]Department of Urology, Third Faculty of Medicine, Charles University in Prague
and University Hospital Královské Vinohrady, Prague, Czech Republic;
[3]Department of Vascular Surgery, Na Homolce Hospital, Prague, Czech Republic

Abstract: Ormond's disease is a relatively rare disease with unclear etiology,
characterized by chronic periaortitis and retroperitoneal fibrosis. The inflammatory
process affects the infrarenal part of the abdominal aorta and the iliac arteries, and
the presence of infiltrates encasing the ureters and inferior vena cava. This disease
is currently classed as an IgG4-related disease. In our review we analyse the clinical
history, diagnostic approaches, surgical and immunosuppressive therapies.

Mailing Address: Assoc. Prof. Miroslav Průcha, MD., PhD., Department
of Clinical Biochemistry, Haematology and Immunology, Na Homolce Hospital,
Roentgenova 2, 150 30 Prague 5, Czech Republic; Phone: +420 257 273 051;
e-mail: miroslav.prucha@homolka.cz

Introduction

As early as 1905, the French urologist of Cuban origin, Joaquin Albarran, described the external compression of the ureter during an unknown illness in the retroperitoneum (Albarran, 1905), but it was the later description of two cases by John Ormond and published in English in 1948 and his later work that provided the impetus for the classification of retroperitoneal fibrosis (RF) as a new nosological condition (Ormond, 1948). RF is a relatively rare disease with unclear etiology, characterized by chronic periaortitis and retroperitoneal fibrosis. The inflammatory process affects the infrarenal part of the abdominal aorta and the iliac arteries, and the presence of infiltrates encasing the ureters and inferior vena cava is also commonly found. Its incidence is 1.3/100 000 people (van Bommel et al., 2009). This disease is currently classed as an IgG4-related disease. The course of the disease is associated with the incidence of complications, the most serious of which are renal failure, and aneurysm of the abdominal aorta or the iliac arteries. The disease is generally identified during the analysis of findings from recently diagnosed renal failure or hypertension. It is not always possible to obtain a biopsy, and therefore the principle diagnostic methods are imaging, immunological and biochemical diagnostic procedures. Thanks to further advances in medicine, diagnostic and, in particular, therapeutic strategies are gradually changing. Improved results from pharmacotherapy regimens lead to a greater emphasis on early comprehensive medication therapy with corticosteroids and new immunosuppressive or immunomodulatory drugs. Surgical interventions continue to occupy an irreplaceable position in the treatment algorithm, which reflects the current view of and medical options for the diagnosis and treatment of this disease. The therapeutic approach involves a combination of surgical and immunosuppressive treatment.

Pathogenesis

Idiopathic retroperitoneal fibrosis is a systemic disease of as yet unexplained pathogenesis. The term covers a number of common diseases – chronic periaortitis, inflammatory abdominal aortic aneurysm (IAAA) and perianeurysmal retroperitoneal fibrosis. Approximately two-thirds of retroperitoneal fibrosis cases are idiopathic, i.e. no primary specific cause has been identified. In this case the condition is known as Ormond's disease. In one-third of patients, symptoms of fibrosis are found after a primary malignancy, infection or iatrogenic effects of medication – secondary RF (Gilkeson and Allen, 1996; Vaglio et al., 2006). Interesting cases of secondary RF were described to the use of biological therapy – a monoclonal antibodies against tumour necrosis factor-α and soluble receptor of TNF (Couderc et al., 2012). In 70% of patients, the first symptoms of the disease are recorded between 30 and 60 years of age, in idiopathic retroperitoneal fibrosis, men predominate in a ratio of 2:1. Parums proposed theory, which defined idiopathic retroperitoneal fibrosis as an autoimmune disease associated with aortic

atherosclerosis (Parums, 1990). Idiopathic RF is rather a manifestation of a systemic autoimmune disease which involves primary aortitis and peri-aortic fibrosis (Vaglio et al., 2003).

Ormond's disease – IgG4-related disease

Ormond's disease is a condition currently classified as an IgG4-related disease (Zen et al., 2012; Brito-Zerón et al., 2014). It is primarily Japanese authors who have been involved in the discovery and classification of the so-called IgG4-related diseases. The number of common diseases included in this group is shown in Table 1. These disorders are characterised by increased concentrations of IgG4 in the serum and the presence of IgG4 producing plasma cells in the infiltrate. The pathognomonic significance of the antibodies produced has not yet been sufficiently determined. Published studies suggest that only a portion of patients with Ormond's disease meet this criterion (Zen et al., 2009; Takahashi et al., 2010; Laco et al., 2013). Findings of elevated levels of IgG4 in the serum have no effect on the success of the immunosuppressive therapy. In the context other studies (Zen et al., 2012; Khosroshahi et al., 2013; Koo et al., 2014) it would appear that not all patients with retroperitoneal fibrosis fall into the category of IgG4-related diseases. One of the complex and very important issues to be addressed in the diagnosis of RF involves distinguishing between the infectious and non-infectious etiology of the inflammation. The emergence of retroperitoneal or paraaortal infiltrate may also be induced by an infectious etiology. Given the use of immunosuppressive therapy, the failure to recognise this difference may have fatal consequences for the patient. Potential causative agents may include viruses-hepatitis, mycobacteria, bacteria – *Staphylococcus aureus*, *Salmonella* (Seth et al., 2001; Cartery et al., 2011).

Diagnostics

Initial assessment

In typical cases where RF manifests, confirmation of the diagnosis is based on the medical history, clinical findings and imaging results. Obstruction of the ureters is generally indicated by dilatation of the calico-pelvic system in the kidneys, detected

Table 1 – IgG4 associated diseases

IgG4 associated diseases
Autoimmune pancreatitis
Sclerosing sialoadenitis
Sclerosing cholangitis
IgG4 related sclerosing inflammatory pseudotumours involving meadistinum, lung, gastrointestinal tract and soft tissue

under ultrasound (USG), which is routinely available. However, USG itself does not allow for an exact assessment of the nature and extent of the obstruction. The results of laboratory tests for renal function values are supplemented by other imaging methods. At present the most common method is spiral computed tomography (CT) – an examination of the abdomen and pelvis, which can be performed without the administration of contrast agents in cases of severe renal insufficiency. Provided the patient's renal function parameters are favourable, the basic method is a radiographic examination using a contrast medium. In this case we advocate intravenous, excretory urography – IVU or simply CT excretory urography. The standard finding is usually bilateral hydronephrosis with a medial deviation of the proximal and middle ureter with the ureter gently tapering at the level of the obstruction (Figure 1). If the patient has advanced renal insufficiency, an ascending urography is performed, or, when the invasion is advanced, a native spiral CT can again be performed (Figure 2) or an MRI (magnetic resonance imaging) examination (Restrepo et al., 2011; Schmidt, 2013). MRI is increasingly commonly used because it does not expose the patient to radiation and does not burden the kidneys through the application of a contrast medium. It is noteworthy that

Figure 1 – Bilateral obstructive hydronephrosis identified by intravenous urography in a 58-year-old patient, where both ureters are encased in retroperitoneal fibrosis.
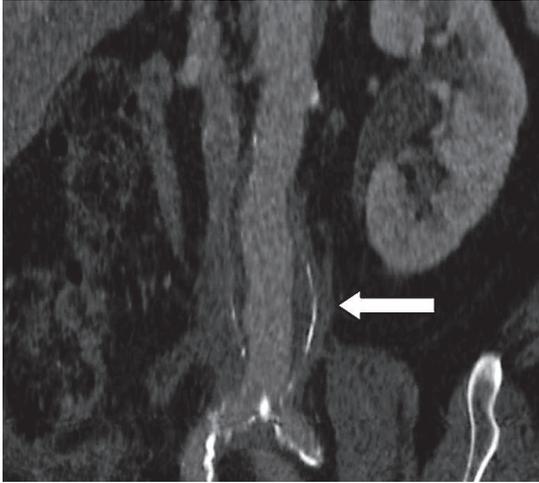
Figure 2 – Maximum fibrotic changes seen in the sub-renally located abdominal aortic aneurysm in this CT reconstruction.

not all patients demonstrate disease activity using standard inflammatory markers (erythrocyte sedimentation rate, C-reactive protein, acute phase reactants). The most valuable indication of disease activity is the PET (positron emission tomography)/CT examination, which would be use for each patient before deploying immunosuppressive treatment, as well as when deciding to terminate it. Depending on clinical question and/or history of dedicated CT investigation, the CT part of PET/CT investigation was performed after intravenous administration of a contrast media in a standard-dose mode or without i.v. contrast media administration, in a low-dose mode. In this respect it would be advantageous to find new biomarkers, which could indicate the activity of the disease and whose cost and the burden placed on the patient would be lower in comparison with PET/CT. An example of this type of marker could be pentraxin 3 (Pelkmans et al., 2012).

Differential diagnosis and biopsy
The gold standard of diagnosis is histopathological examination of the biopsy specimen. Differential diagnostics are required to exclude tumorous processes in the retroperitoneum (sarcomas, haemoblastosis, neuroblastomas, germ cell tumours, metastatic processes from other solid or carcinoid tumours). Similarly, secondary fibrosis from inflammatory processes (sarcoidosis, specific spondylitis or vasculitis, connective tissue disease) must also be excluded. Results from the biopsy may contribute to assessing the severity of the RF itself. Serial biopsies confirmed 2 basic phases of the disease, where in the early stages of RF we observe active chronic inflammation, which at a later stage progresses to chronic fibrosis. The infiltrating edge of this pathological tissue exhibits a higher degree of inflammation than its central portion. Therefore, depending on the stage of the

disease, or the location of the biopsy, lymphocytes in particular can be detected in the active inflammatory infiltrate (with a predomination of B lymphocytes and a lower proportion of T lymphocytes (CD 4+) (Corradi et al., 2007), as well as plasma cells and histiocytes, while in the central area the tissue can be very fine, unaffected, with bundles of collagen and low cellularity. Microscopically, but on a smaller scale, parietal fibrinoid necrosis of the adventitia is also common, leading to the formation of aneurysms, the development of chronic periartitis and advancing into the retroperitoneum. Depending on the patient's constitution and the extent of the disease, a biopsy may be performed percutaneously using a biopsy needle under USG navigation, or under CT navigation for better and more accurate results. The advantage of the percutaneous technique is that it is minimally invasive and the intervention can be performed under local anaesthetic. However, this may be limited by the insufficient volume of tissue obtained by needle biopsy, which may not be sufficient for a valid histological examination.

Surgical removal of tissue for histology
As was mentioned above, a needle biopsy may not provide sufficient tissue, as is the case for biopsies of lymphomas and the like. Sometimes a needle biopsy is not possible due to anatomical causes. In these individual cases, patients are indicated for surgical removal of tissue for histological examination. In certain situations where findings are not entirely clear, it may be appropriate to consider performing multiple biopsies to exclude any malignity (Kava et al., 1996). The intervention is generally performed under general anaesthetic using laparoscopic methods (retroperitoneoscopy) or under robotic assisted surgery (Kolombo et al., 2008), or through open surgery, depending on an individual assessment of the situation. Laparoscopic techniques are used on patients where there is no contraindication for the induction of capnoperitoneum and there are no adhesions or scars preventing the introduction of laparoscopic instruments. When using open surgery, the approach taken depends on the most accessible focus of the fibrosis or on whether an additional pathology is to be treated surgically. For direct access to the retroperitoneum we can use a lumbotomy or pararectal incision, depending on the site most affected or with regard to the specific anatomy. Our current practice for interventions to intra-abdominal organs is to use laparotomy. In the case of a transperitoneal approach, the rear wall of the peritoneum is opened above the palpable fibrotic mass and a sufficiently large volume of the pathologically affected tissue is excised to enable a valid histological examination.

Treatment
Initial surgical intervention and treatment for urogenital conditions
Given the vagueness of the initial symptomatology (some soreness in the lower back, lower abdomen or groin, occasionally dyspeptic syndrome accompanied

by loss of appetite and weight loss, etc.) a number of patients, even given the present standard use of imaging methods (USG, CT, MRI, etc.) are still diagnosed at a stage where significant obstructive hydronephrosis has already occurred. Although the process is bilateral, the fibrosis in the retroperitoneum may not automatically affect both ureters and there may therefore be only a unilateral manifestation of the conditions. The treatment choice depends on the level of kidney function at any given time. The initial intervention is to ensure free drainage of urine flow from the upper urinary tracts. Where there are signs of renal insufficiency, or in cases of significant engorgement, a drainage catheter must be introduced, bilaterally where required. Currently (with advances in endoscopic techniques, better hydrophilic wires, higher quality stents, etc.) there tends to be a preference for the cystoscopic insertion of urethral stents (stents in the ureter improve orientation when diagnostic or therapeutic interventions are required). Patients also tend to prefer the insertion of stents to percutaneous nephrostomy. When stenting is performed, stronger urethral stents are preferred, which provide better drainage when the ureters are compressed by the fibrotic tissue. Generally, this procedure, with subsequent immunosuppressive medication, is fully sufficient. In individual cases, where a standard stent has not provided adequate drainage from the kidney, the option of inserting two stents in a single ureter may be considered, where the urine remains congested, or a specially strengthened type of stent, the so-called self-reinforced stent, can be used (these are also used in other cases of extreme compression of the ureter by malignant expansions or for radiation-induced fibrosis, etc.). In the event a stent cannot be inserted, or where this procedure does not produce the required effect, a percutaneous nephrostomy is performed. At present, where the effectiveness of drug treatments has significantly improved, particularly over recent years, drainage interventions are the most common method of invasive treatment. Standard stents are changed at 6-month intervals. In certain cases, after medication, the regression of the condition found after this period is significant, allowing the removal of the stents. If the regression of the fibrosis is more gradual, the stent is replaced. Should a situation occur (and this is far rarer nowadays), where the patient does not tolerate the medication, or drug therapy is contraindicated or does not produce the desired effect, surgery is indicated to release the ureter from the fibrotic tissue (referred to as "ureterolysis"), followed by the exposure and permanent separation of the ureter from the fibrotic tissue (i.e. the transposition of the ureter and its protection by interposing it between other healthy tissue where required, generally the peritoneum or omentum, which is known as omentoplasty). In cases where extensive surgery is not possible due to the polymorbidity of the patient or where the patient him/herself refuses a major intervention, stents can be inserted and replaced on a regular basis or a nephrostomy performed as a permanent solution to obstruction of the ureters.

Surgical treatment of inflammatory abdominal aortic aneurysm
Surgical intervention is the treatment of choice for periaortitis and its complication – the formation of an aortic aneurysm. In surgical terms, abdominal aortic aneurysm (AAA) is a serious condition, and can place the patient at risk of life-threatening bleeding. The growing ability to detect this disease over recent decades is partly due to the ageing of the population and also to the wide availability of new imaging methods. From an epidemiological point of view, there is a 5% incidence of AAA on men over the age of 60. Besides standard AAA, which arises on the basis of structural, genetic, biochemical and microbial influences, around 10% of all AAA also occurs as an inflammatory aneurysm, again predominating in males. This type of AAA is characterised by a thickening of the AAA sac with microscopic evidence of inflammatory infiltrate. From a surgical perspective, this may represent a certain technical problem, consisting of the complicated preparation of the aorta, with the occurrence of surface bleeding at the site of surgical intervention or with possible compression of the ureters.

In terms of treatment tactics, it is advantageous to work in cooperation with an immunologist and it is crucial to differentiate between infection and non-infection based inflammation. In cases of asymptomatic AAA with non-infectious etiology, the patient first undergoes immunosuppressive treatment and, after its completion, is indicated for surgical intervention where necessary. In our experience, even after completion of immunosuppressive treatment, standard surgery is technically challenging and, where possible, we prefer to opt for endovascular treatment (Sedivy et al., 2012).

From a surgical point of view, stent graph implantation is therefore the method of choice in this situation. The principle of endovascular treatment is to exclude the AAA from the circulation through an endovascularly implanted stent graph (SG), which is actually a vascular prosthesis reinforced with nitinol fixation. The SG is usually introduced from the femoral artery via the pelvic basin into the aorta, where it is fixed in the undilated part of the artery, known as the neck of the AAA and ideally peripherally in the case of a bifurcated SG, at the branch of the pelvic arteries. In cases where it was not possible to use a bifurcated SG, we have to adopt an endovascular solution for the AAA using an aorto-uni-iliac SG, with occlusion of the contralateral common pelvic artery and subsequent femoro-femoral cross over vascular reconstruction. Where an endovascular intervention is technically impracticable, standard surgery is generally indicated. Although standard surgical treatment of AAA can employ mini-laparotomy, laparoscopic or robotic methods, in cases of post-inflammatory AAA we most frequently opt for a full laparotomy. This strategy is important given the generally laborious process of preparation, post-inflammatory changes to the tissue and the need for a perfect view of the surgical field. In terms of the surgical method, depending on the pathological findings, we perform aorto-aortal, aorto-iliac or aorto-femoral repair. To prevent injury to the ureters, we implant pigtail

catheters in both ureters prior to surgery, which significantly helps to verify their functioning.

Immunosuppressive therapy
Given that we consider RF to be a systemic autoimmune disease, the administration of immunosuppressive agents is an integral part of the therapy (Vaglio and Buzio, 2005; Warnatz et al., 2005). The original theory that it is an autoimmune response to ceroid leaked from atherosclerotic plaques has now been abandoned and RF is currently perceived to be a systemic condition with autoimmune characteristics. Important factors supporting this view include the presence of other autoimmune diseases in these patients and the histopathological nature of the inflammatory infiltrate (Dahlgren et al., 2010). Standard drug therapy involves the administration of corticosteroids. RF is usually treated with initial high-dose corticosteroids (1 mg/kg) followed by tapering to maintenance therapy. Success rates are usually high (80–95%) but also relapse rates is relatively high (van Bommel et al., 2007; Fry et al., 2008). Corticosteroids therapy may be hazardous in patients with manifest atherosclerotic vascular disease because can accelerate the atherosclerotic process. Tamoxifen therapy may be the safe alternative therapy. The exact pathophysiological effect of tamoxifen is unknown but probably hormonal-independent (Kuhn et al., 2002; Garvin and Dabrosin, 2003). Tamoxifen is an antiestrogen drug; therefore it may act as immunosuppressive and anti-inflammatory therapy (McMurray, 2001; Cutolo et al., 2004). Long-term safety and efficacy of a tamoxifen – based treatment presented van Bommel et al. in a recent study (van Bommel et al., 2013) and Brandt et al. (2014). In addition to the treatment methods referred to above, treatment regimens combining corticosteroids with other immunosuppressive agents – cyclophosphamide, azathioprine, cyclosporin A were also use to treat patients with RF (Marzano et al., 2001; Moroni et al., 2006; Binder et al., 2012). Mycophenolate mofetil (MMF) appears very promising drug in the treatment of RF. Treatment with prednisone and MMF was used with very high remission rates and low relapse (Adler et al., 2008; Swartz et al., 2008; Scheel et al., 2011). An alternative treatment for patients who do not respond adequately to treatment with corticosteroids, or for whom this therapy is associated with a higher risk, uses biological disease modifiers. These include tocilizumab – an antibody against the IL-6 receptor (IL-6R), or rituximab – a monoclonal antibody against CD20 (Catanoso et al., 2012; Maritati et al., 2012; Vaglio et al., 2013).

Personal experience
Between 1997 and 2013 our Department of Clinical Biochemistry, Haematology and Immunology, Na Homolce Hospital, in collaboration with Department of Urology, Third Faculty of Medicine, Charles University in Prague and University Hospital Královské Vinohrady, and Department of Vascular Surgery, Na Homolce

Hospital, diagnosed and subsequently treated 33 patients with idiopathic retroperitoneal fibrosis. Detailed description exceeds the scope of this text.

Conclusion

Idiopathic retroperitoneal fibrosis – Ormond's disease – is a systemic autoimmune disease with serious complications – renal insufficiency or failure, aneurysm of the abdominal aorta or iliac arteries. Its diagnosis is based on an exact diagnosis from a biopsy, or a combination of imaging methods and immunological, biochemical and microbiological tests. Standard treatment involves a combination of surgery and immunosuppressive treatment and, provided it is applied in a timely manner, patients can expect a favourable clinical outcome.

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