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Successful treatment of idiopathic retroperitoneal fibrosis with combined immunosuppressive therapy

Uspešno lečenje idiopatske retroperitonealne fibroze kombinovanom imunosupresivnom terapijom

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Abstract

Background/Aim. Idiopathic retroperitoneal fibrosis (IRF) is characterized by the fibroinflammatory periaortic tissue that affects the ureters, causing obstructive nephropathy and variable impairment of renal function. The findings strongly suggest an autoimmune etiology. The optimal treatment has not been established. The aim of this study was to analyze a long-term efficacy of combined corticosteroid therapy with mycophenolate mofetil (MMF) in the patients with IRF. **Methods.** We retrospectively followed 13 patients (8 males and 5 females) with IRF. All patients received corticosteroids and MMF. For the patients with severe renal failure, an initial ureteral decompression was made and prednisone was started orally 0.5 mg/kg with fast tapering. In cases with a mild renal failure corticosteroids were administrated as intravenous methylprednisolone pulses for 3 days, followed by oral prednisone. The dose of MMF was 1000 mg twice a day. MMF was stopped after 18 months and prednisone after 48 months. **Results.** Systemic symptoms resolved in all patients. Erythrocyte sedimentation (SE) rate declined from the mean of 67.6 to 26.3 mm/h and C-reactive protein (CRP) from the mean of 18.5 to 6.3 mg/L. In 7 out of 8 patients, the ureteral stents were successfully removed 13 weeks on average. Seven patients had 100% of reduction in the periaortic mass, and the average percent reduction was 76.9%. The kidney function improved and remained normal in 6 treated patients. In 4 patients a mild chronic renal failure remained due to afunction of one kidney. Three patients, with a prior chronic renal failure, did not get worse renal function. The disease recurred in 3 patients. There were no treatment side effects noted. **Conclusion.** Combination of corticosteroids and MMF is a potentially effective treatment in restoring the renal function and reducing the fibrotic tissue in the patients with idiopathic retroperitoneal fibrosis. It could prevent the need for ureteral stenting and surgery. Longer treatment may reduce a possibility of recurrence.

Key words:
retroperitoneal fibrosis; renal insufficiency; autoimmune diseases; adrenal cortex hormones; mycophenolic acid; remission induction; recurrence.

Apstrakt

Uvod/Cilj. Idiopatska retroperitonealna fibroza (IRF) karakteriše se periaortnim fibroinflamatornim tkivom koje zahvata uretere dovodeći do opstruktivne nefropatije i različitog stepena bubrežne insuficijencije. Oboljenje je najverovatnije autoimune etiologije. Optimalna terapija do sada nije definisana. Cilj rada bio je analiza dugoročne efikasnosti kombinovane imunosupresivne terapije kortikosteroidima i mikofenolat mofetilom u lečenju IRF. **Metode.** Retrospektivno je praćeno 13 bolesnika (8 muškaraca i 5 žena) sa IRF. Svi bolesnici su primili kortikosteroide i mikofenolat mofetil (MMF). Kod bolesnika sa izraženom bubrežnom insuficijencijom, prvo je učinjena dekompresija urinarnog trakta i potom započeta terapija peroralnim prednizonom 0,5 mg/kg sa brzim smanjivanjem doze. Bolesnici sa umerenom bubrežnom slabošću primili su inicijalno tri pulsne doze metilprednizolona intravenski, a potom je nastavljeno sa prednizonom. Doza MMF je bila 1000 mg dva puta dnevno. MMF je obustavljen nakon 18 meseci, a prednizon nakon 48 meseci. **Rezultati.** Kod svih bolesnika došlo je do povlačenja opštih simptoma bolesti. Vrednost sedimentacije eri-

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trocita (SE) smanjena je sa prosečnih 67,6 na 26,3 mm/h, a C-reaktivnog proteina (CRP) sa prosečih 18,5 na 6,3 mg/L. Kod sedam od ukupno osam bolesnika, ureteralni stentovi su uspešno izvađeni nakon prosečno 13 nedelja. Sedam bolesnika imalo je 100% redukciju periaortnog tkiva, a prosečni stepen redukcije je bio 76,9%. Bubrežna funkcija je poboljšana, kod šest bolesnika je normalizovana, dok je kod četiri zaostala umerena hronična bubrežna slabost usled afunkcije jednog bubrega. Tri bolesnika sa prethodnom hroničnom bubrežnom insuficijencijom nisu pogoršala funkciju. Recidiv bolesti imala su tri bolesnika. Nisu registrovani neželjeni efekti terapije. **Zaključak.** Kombinovana primena kortikosteroida i MMF je potencijalno efikasna terapija u poboljšanju bubrežne funkcije i smanjenju debljine fibroznog tkiva kod bolesnika sa IRF. Ona bi mogla otkloniti potrebu za plasiranjem ureteralnih stentova i hirurškim lečenjem. Duže trajanje terapije moglo bi smanjiti mogućnost recidiva bolesti.

Ključne reči:
retroperitonealna fibroza; bubreg, insuficijencija; autoimunske bolesti; kortikosteroidni hormoni; mikofenolna kiselina; remisija, indukcija; recidiv.

Introduction

Retroperitoneal fibrosis (RF) is characterized by the development of inflammatory fibrotic tissue surrounding the infrarenal aorta, the iliac arteries and other retroperitoneal structures. The fibrotic tissues spread laterally and entrap one or both ureters causing obstructive uropathy and variable impairment of renal function. About one-third of all cases of RF are secondary to certain drugs, malignant disease, infection, radiation therapy or surgery. The remaining two-third of RF cases are considered idiopathic as no specific cause can be identified [1].

Idiopathic retroperitoneal fibrosis (IRF) is a rare disorder with an estimated annual incidence of 0.1–1.3 cases per 100,000 persons [2]. Males are affected twice to three times more frequently than females with the mean age at presentation between 50 and 60 years, but it has also been reported in children and other adults [1, 3].

The pathogenesis is not clear. Parum et al. [4] postulated that the disease could be the result of an inflammatory state triggered by an autoimmune response to some antigens in atherosclerotic plaques of the abdominal aorta. Recent findings suggest a systemic nature of the disease with the presence of constitutional symptoms, elevated acute phase reactants, often positive autoantibodies (especially antinuclear antibodies) and concomitance of the other autoimmune conditions [1, 5]. The current researches consider IRF as part of the IgG4-related disease, but this association was proved only in 30%–60% of cases [6, 7].

The clinical presentation of idiopathic retroperitoneal fibrosis (IRF) is often insidious with the localized symptoms due to the compressive effects of the retroperitoneal mass (abdominal or back pain, leg oedema, oligoanuria and uraemia), and the systemic symptoms (fatigue, fever, anorexia, weight loss) due to the inflammatory nature of the disease [1].

The diagnosis is usually made by either computed tomography (CT) or magnetic resonance imaging (MRI) of abdomen. These techniques can visualize the extent of the fibrosis and determine the possible presence of the tumour or lymphadenopathy. A confirmatory biopsy is sometimes needed (atypical localisation, therapy nonresponding cases) [8].

Considering the possible autoimmune etiology, various immunosuppressive (IS) drugs were successfully used in the nonsurgical management of IRF [1, 9–13]. However, the experiences in treatment are mainly based on the observations of case reports, or small groups of patients. So far, the optimal IS agent, the dose and the length of the treatment have not been established [1].

The aim of this retrospective study was to analyze a long-term efficacy of combined steroid therapy with mycophenolate mofetil (MMF) in the patients with IRF.

Methods

Patient population

From January 2004 to May 2016, 13 patients were referred to the Nephrology Clinic for management of IRF. All patients underwent the CT or MRI, intravenous urography and ultrasound examination (US).

The patients were asked about past or current use of methysergide, β blockers, ergotamine, methyldopa, or a history of recent infections, abdominal trauma, pelvic or abdominal surgery and external beam radiation. They, all underwent the appropriate cancer screening, according to the gender and age. The IRF diagnose was based on characteristic clinical and CT findings. Two patients had prior histological confirmation from the biopsy material taken during ureterolysis.

The baseline laboratory screening included the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complete blood count, chemistry profile with creatinine, antithyroid peroxidase antibodies (anti-TPO antibodies), thyroglobulin antibodies, thyroid stimulating hormone (TSH), testing for antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA) and rheumatoid factor (RF).

Treatment

All patients received steroids with MMF. The patients with severe acute renal failure received a double-J ureteral stent (DJS) or percutaneous nephrostomy (PNS). After that, steroids were started as oral prednisone 0.5 mg/kg/day for one month, then tapered to maintenance of 10–5 mg/day. In the patients with a mild renal failure with no placement of DJS/PNS, steroids were given as an intravenous methylprednisolone pulses: 250 mg/day each for three consecutive days, followed by oral prednisone 0.5 mg/kg/day for one month, with tapering the dose as mention above. MMF was administered orally in a dose of 1000 mg twice daily for the first 6

months, then reduced to 500–750 mg twice daily, as the maintenance dose, till the end of 18 months. Steroids were stopped after 48 months from the start of the therapy.

Follow-up

All patients were followed monthly in the first 6 months, then every 3 months till the end of the second year. After that, the patients were seen once in 4–6 months. At each control, the patients were submitted to the clinical examination, US examination and to the following laboratory tests: ESR, CRP, serum creatinine level, complete blood count and urine analysis.

Normal range for ESR according to gender was: 0–25 mm/h in males, 0–30 in the females, and for CRP 0–5 mg/L.

The CT scan, or MRI of abdomen was performed at 6, 12, 24 and 48 months after the initiation of the therapy. After that, the CT scan, or MRI was performed in the case of suspected recurrence of disease.

A decision to remove the ureteral stents, or PNS was made in collaboration with an urologist. It was based on the improvement in laboratory parameters and radiographic evidence that the fibrotic mass no longer encased the affected ureter.

Active disease was defined by the presence of a periaortic mass surrounding one of both ureters with hydronephrosis at CT/MRI associated with an increase in CRP and/or ESR.

Remission of the disease was defined by a regression of hydronephrosis and by a reduction of the fibrotic tissue at CT/MRI in comparison with the basal examination together with the normalization of CRP and/or ESR.

Recurrence of the disease was defined by the CT/MRI-proven increase of the periaortic mass with, or without entrapment of one, or both ureters associated with a new increase in CRP and/or ESR.

Radiographic review

The abdominal cross sectional imaging either by the contrast enhanced CT, or MRI was reviewed by a single radiologist. The patients were classified based on the extent of the soft-tissue mass verified on the first visit using a classification previously described by Scheel and Feeley [14]: class I: the soft-tissue density surrounding the infrarenal aorta and/or iliac vessels; class II: the soft-tissue density surrounding the infrarenal vena cava; class III: the lateral extension of inflammation/fibrosis with compression of one or both ureters; class IV: the extension of fibrosis to include the renal hilum with the compression of the renal artery and/or renal vein.

The patients could be categorized in multiple classes based on the extent of disease seen on imaging. The temporal change in the disease was determined by measuring the thickness of soft tissue relative to the aorta on the CT scan, or MRI.

Statistical analysis

The complete statistical analysis of data was done using the statistical software package, PASW Statistics 18® [SPSS (Hong Kong) Ltd., Hong Kong]. All variables were presented as frequency of certain categories. The χ^2 test was used for analysing the significance of differences of categorical variables. The continuous variables were presented as means and standard deviations, or median with a range and were compared using the Mann-Whitney *U* test, or the Kruskal-Wallis test. The distribution normality was tested by using the Shapiro-Wilk test (number of subjects was less than 50). All analyses were estimated at $p < 0.05$ level of the statistical significance.

The principles of International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice guidelines were strictly followed. Ethical approval from the Ethics Committee of the Military Medical Academy was obtained for the study protocol on January 21st, 2016.

Results

Of the 13 patients, there were 8 males and 5 females (Table 1). The mean age at the time of diagnosis was 54.0 ± 6.9 years (range 36–60 years). The patients were followed for a mean period of 99.1 ± 34.6 months (median 99.4, range 41.6–150.1 months).

Table 1

Demographic and clinical characteristics in the patients with retroperitoneal fibrosis

Patient characteristics	Values
Age (year), mean ± SD (range)	54 ± 6.9 (36–60)
Male, number (%)	8 (61.5)
Female, number (%)	5 (38.5)
First presentation/recurrence, number	10/3
Symptoms on presentation, cumulative number (%)	
weight loss	11 (84.6)
back pain	8 (61.5)
fatigue	7 (53.8)
nausea	4 (30.8)
leg edema	4 (30.8)
abdominal pain	3 (23.1)
new onset of hypertension	2 (15.4)
both (abdominal, back) pain	1 (7.7)
hydrocele	1 (7.7)

SD – standard deviation.

Table 2

Baseline and follow-up laboratory parameters

Parameters	Baseline mean ± SD	Follow-up mean ± SD	*p* value*
ESR (mm/hr)	67.6 ± 33.8	26.3 ± 30.2	$p < 0.001$
CRP (mg/L)	18.5 ± 10.4	6.3 ± 5.2	$p < 0.001$
WBC ($\times 10^9$/L)	8.3 ± 1.7	8.6 ± 1.6	$p = 0.001$
Hgb (g/L)	113.7 ± 18.1	141.1 ± 17.2	$p < 0.001$
Serum creatinine (μmol/L)	334.5 ± 326.3	124.5 ± 69	$p = 0.010$
GFR (mL/min)	33.3 ± 21.6	59.2 ± 20.8	$p = 0.014$

ESR – erythrocyte sedimentation rate; CRP – C-reactive protein; WBC – white blood cells; Hgb – hemoglobin; GFR – glomerular filtration rate; SD – standard deviation; * – Kruskal Wallis test.

The most frequent symptoms at the time of diagnosis were the weight loss, back pain, fatigue, nausea, leg oedema, abdominal pain, new onset of hypertension and simultaneously abdominal and back pain (Table 1). The other symptoms were hydrocele, headache, appetite loss and weakness. The duration of symptoms before diagnosis ranged from 3–15 months.

Only 2 of 13 patients had an identified risk factor for RF (use of β blockers). Ten patients had a history of prior comorbidities: hypertension in 10, diabetes mellitus in 3 and hypothyroidism in two patients.

At presentation, 12 of 13 patients had ureteral obstruction which was bilateral in 11 of them. In 8 out of 12 patients with hydronephrosis, the ureteral obstruction was relieved by a placement of the DJS in 7 and PNS in one patient. These procedures were done in other hospital in 7 of these patients.

As a complication of this procedure, 6 patients (75%) had a urinary tract infection which was resolved by using the appropriate antibiotics.

Figure 1 shows the radiographic classification of the patient population at presentation. All patients had active disease. Twelve patients had renal dysfunction with a mean serum creatinine of 334 μmol/L (range was from 108–1022 μmol/L). Out of these, 9 patients presented as the acute renal failure which was oligoanuric in 5 (38.5%). One was treated with hemodialysis before the admission to our hospital. Initially, three patients already had chronic renal failure. They were admitted for recurrent disease, after the previous treatment with surgical and/or IS therapy.

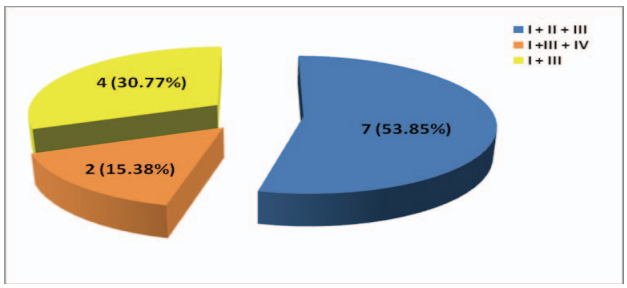

Fig. 1 – Radiographic classification at initial visit. Class I: soft-tissue density surrounding the infrarenal aorta and/or iliac vessels; Class II: soft-tissue density surrounding the infrarenal vena cava; Class III: lateral extension of the inflammation/fibrosis with compression of one or both ureters; Class IV: extension of fibrosis to include the renal hilum with compression of the renal artery and/or renal vein.

Table 2 shows the initial and follow-up laboratory data. ESR and CRP were elevated in 11 patients (range 26–140 mm/hr and 5.8–31 mg/L respectively). The mean hemoglobin level was 114 g/L (range 78–140 g/L).

Two patients with hypothyroidism had positive anti-TPO antibodies. Other autoantibodies were negative in all patients.

The remission occurred in all patients 12.7 ± 15.9 weeks (median 4 weeks) on average. The relief of pain and systemic symptoms was achieved in average 4 weeks.

The obstruction relief was observed after 4 weeks in 8 patients (61.5%), after 6 months in 10 (77%), and at the end of follow-up in 12 patients (92%). In 7 patients DJS and PNS were successfully removed, on average, 13 weeks after insertion (range from 3 to 32 weeks). In one patient, previously treated by ureterolysis, bilateral DJS were replaced by bilateral PNS due to the persistant obstruction, and was successfully removed after one year from one side. The other side required continued decompression due to the focal ureteral stricture for the total of 4 years. After that period, he stopped coming for the control examination and he was lost from the follow-up.

The ESR values declined from a mean 67.6 mm/hr to 26.3 mm/hr and the CRP values declined from the mean of 18.5 mg/L to 6.3 mg/L (Table 2, Figure 2).

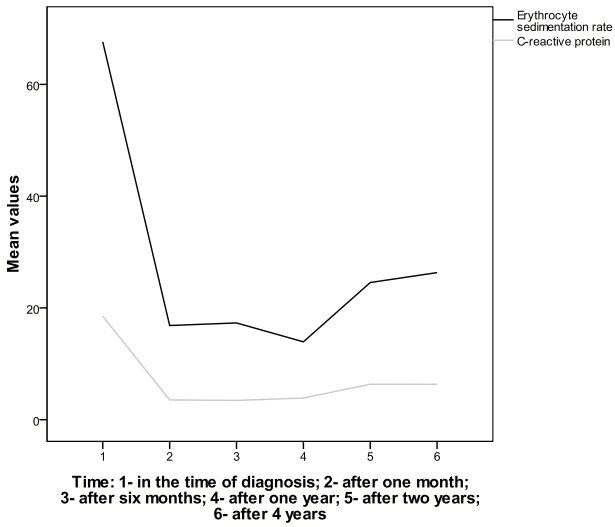

Fig. 2 – Erythrocyte sedimentation rate and C-reactive protein values during the 4-year follow-up.

The kidney function improved with increasing the GFR from the mean of 33.3 to 59.2 mL/min (Figure 3). In 4 patients, the chronic renal failure remained with GFR lower than 60 mL/min due to afunction of one kidney and in 3 patients with the chronic renal failure before treatment the renal function did not get worse.

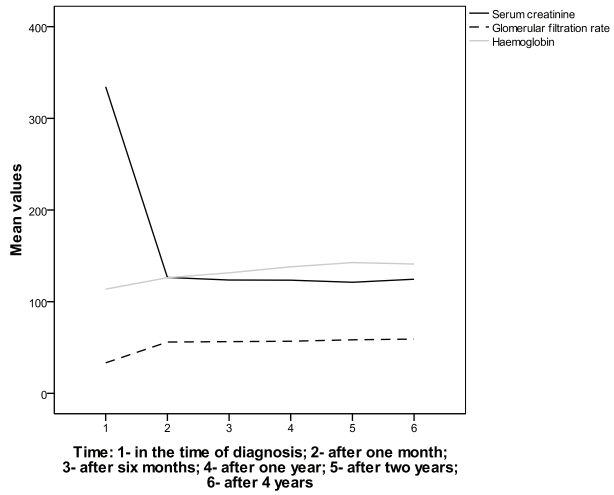

Fig. 3 – The serum creatinine, glomerular filtration rate and hemoglobin values during the 4-year follow-up.

All patients had a reduction of the fibrotic tissue on the MSCT/MR imaging. Seven patients had 100% of reduction in the periaortic mass, and the average percentage reduction was 76.9%. Figure 4 shows a representative baseline and follow-up MSCT scan of this study population.

The recurrence of disease was observed in 3 patients (23%). Two of them stopped the therapy after 6 and 31 months, respectively. The recurrence of the disease occurred 18 and 4 months after cessation, respectively. They were retreated, and one fully responded to the therapy while the second did not, and he received ureterolysis. In the third patient, the recurrence occurred after completing the protocol at the end of 48th month; she was retreated with complete remission.

There were no serious side effects of the treatment. Three patients with the previous diagnose of diabetes mellitus did not require change of the current therapy: 2 stayed on oral hypoglycaemic, and the third one was already on insulin therapy without a significant worsening of glycaemia.

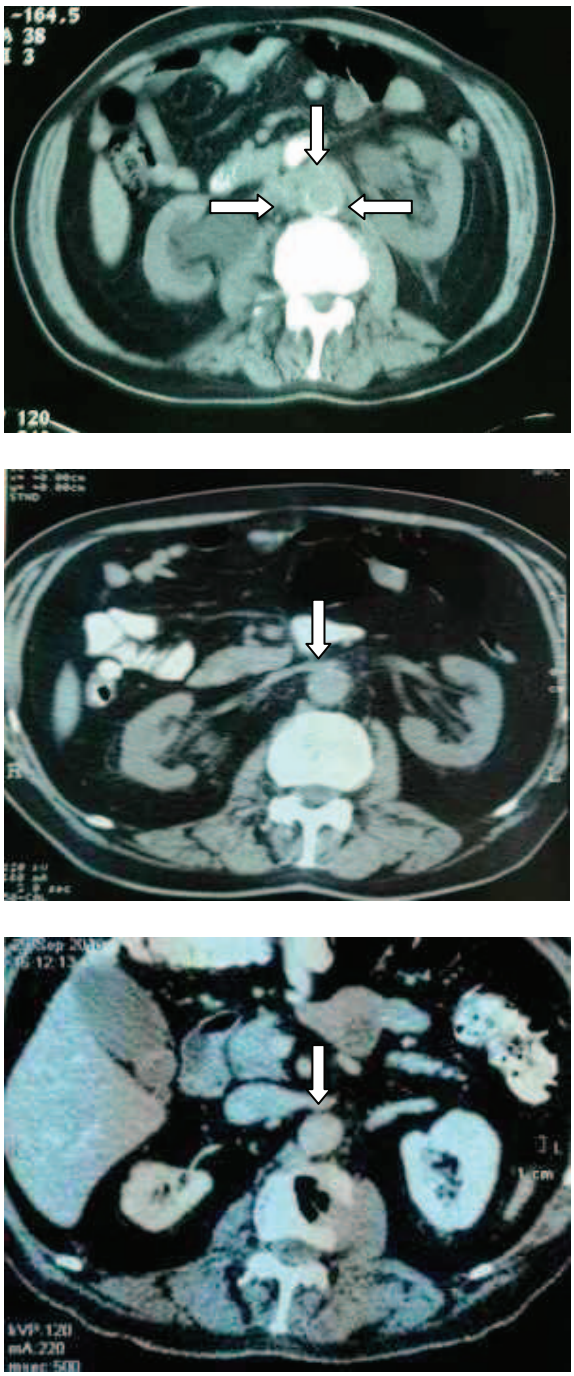

Fig. 4 – The reduction of the fibrotic tissue (Class I, II and III retroperitoneal fibrosis): A) before treatment; B) after 6 months and C) after 48 months of treatment.

Discussion

We retrospectively examined the medical outcome of 13 patients with IRF, receiving combined immunosuppressive therapy with corticosteroids and MMF.

The demographics of our patient population were similar to those of other reported series. Males were affected more often (61%) with diagnose made mostly in the fifth decade of life [14]. The most frequent constitutional symptom was the weight loss in 84.6% of the patients. The less frequent were the fatigue, nausea, appetite loss and weakness. The total of 92% of patients reported pain (back, abdominal, or both), which is consistent with other reports [9, 14, 15].

The etiology of IRF is not known, but several factors such as medications (β blockers, hydralazine, methysergide, ergotamine), surgery, radiation, infections and exposure to asbestos have been described as predisposing factors for developing retroperitoneal fibrosis, despite a scarcity of data to establish clear causal relationship [1]. In our study, two patients had a prior use of β blockers. This association was however described in the limited case reports in the relevant literature [16, 17]. Having in mind that the large number of patients take β blockers worldwide, we agree with some authors observation that this connection seems unlikely [14, 15, 18–20].

Additionally, one patient from our series decided to restart with β blockers after entering remission, and he did not experience recurrence of the disease for 74 months of follow-up.

Some studies reported frequent association of IRF with other autoimmune diseases (Hashimoto's thyroiditis, Graves' disease [21], ANCA-associated vasculitis [22], membranous nephropathy [23], rheumatoid arthritis [24], systemic lupus erythematosus [25], psoriasis [26]), or autoantibody positivity which emphasizes the autoimmune mechanisms in the pathogenesis of the disease [5]. ANA were the most frequent antibodies, detected in 60% of patients with IRF without evidence of connective tissue disease [5]. In our group, we observed two patients with Hashimoto's thyroiditis and positive anti-TPO antibodies. This is consistent with the previous observations that autoimmune thyroiditis is the most frequent autoimmune disease associated with IRF [1, 21]. Other autoantibodies (ANA, ANCA, RF) were negative in all patients.

Idiopathic retroperitoneal fibrosis is a progressive disease for which the consistent therapeutic recommendations have not been devised. Encasement of the ureters by retroperitoneal fibrous tissue leads to the obstructive nephropathy and serious complication including the end stage renal failure [1]. Because of the insidious clinical course and absent signs of impaired renal function until the late stage of the disease, about 75% of the patients had a renal failure and an irreversible shrinking of at least one kidney when diagnosis was made [27].

The treatment goals are to relieve ureteral obstruction, to stop the fibroinflammatory reaction and to prevent the recurrence of the disease.

Nowadays, a surgical treatment alone (ureterolysis with intraperitonealization and omental wrapping of the ureters) is not considered the first–line approach because of the high recurrence rate of the ureteral obstruction in up to 50% of patients [28–30]. Also, the surgical treatment has no effect on the systemic manifestation of the disease. As such, the conservative procedures – DJS, or PCN placement followed by a medical therapy is usually recommended, with surgery reserved for refractory cases [10, 31].

Considering the hypothesis that IRF represents a systemic autoimmune disease, various immunosuppressive (IS) agents were successfully used in the medical treatment of IRF. Some case studies and small series reported treatment with corticosteroids alone, or in a combination with cyclosporine, cyclophosphamide, methotrexate, azathioprine, MMF and antiestrogen drug tamoxifen [1, 9–13, 29, 32–36].

Corticosteroids are the most used IS drugs with the rapid improvement of the symptoms and obstruction relieve [28]. However, corticosteroids alone must be given in a high dose to control the inflammation, with the risk of known side effects. Additionally, there was no agreement in the literature about the dose and duration of the steroid therapy. Numerous duration of 6 weeks, 6 months and up to 2 years were proposed, but a significant number of patients have relapses after discontinuation of therapy and require additional treatment [10, 27, 29, 30, 37, 38]. To avoid relapses as well as to reduce the risk of side effects associated with a long-term intake of high doses, steroids were combined with other IS agents. The use of MMF was based on its known immunosuppressive and anti-fibrotic action [39, 40]. Combination of MMF and steroids was described in several case reports [41–44], small series [10] and a few larger series of 16 [40] and 31 patients [11]. In the study of prednisone and MMF, 89% of the patients had 25%, or a greater reduction in periaortic fibrotic mass with the average percentage reduction of 52.42%. The ureteral stents were successfully removed in 93% of obstructed ureters; only three patients (9.6%) had a recurrence of the disease. The duration of prednisone therapy in this study was 6 months, and MMF was given on average 23 months (range 6 to 63 months) [11].

In our study, the duration of steroid treatment was longer than in some published series [10, 27, 29, 37]. Our decision to use this approach was based on the observation that some patients needed a longer time (6 to 20 months) to achieve reduction of the size of the retroperitoneal mass [29], as well as on the reported high recurrence rate after discontinuation of steroids. The relapsing rate was observed in up to 72% of the patients [37], with the usual time of recurrence within 5 years after the diagnosis, although the rare case of recurrence was reported even after 9 and 10 years of follow-up [30, 45]. The recurrence of the disease appeared after a shorter time of steroid treatment (3–6 months) [10, 36] as well as after giving steroids for a year or longer [27, 29, 37]. The use of MMF, on the other hand, was limited by the fact that this drug is not registered for the treatment of IRF. Considering the significant number of relapsing patients, the usual time of the recurrence within 3–5 years, the serious complication of impaired renal function in this disease, and limitation in MMF use, we tried with steroid therapy for the total of 48 months, with faster initial tapering, in combination with MMF for 18 months.

The initial management of our patients depended on the level of renal impairment.

In cases of severe renal failure, with oligoanuria and elevated serum creatinine, DJS, or PNS are usually placed to achieve immediate upper urinary tract decompression. Although no guidelines exist, in a mild ureteral obstruction without the severe kidney function impairment, it seems advisable to start medical therapy without urinary drainage [27, 38, 46]. We treated 5 patients with the mild acute renal failure and preserved diuresis with i.v. corticosteroid pulses in 3 consecutive days with a rapid relief of the obstruction. This allowed avoidance of the complication with the DJS, or PNS placement, especially urinary tract infections which can be persistent and recurrent. In 8 of our patient with urinary drainage, 75% had urinary tract infection.

In all our patients, the combination of corticosteroids and MMF was successful in achieving the relief of the symptoms and correcting the laboratory abnormalities (ESR, CRP and haemoglobin level).

Whether the ESR and CRP levels are the reliable parameters for monitoring the disease activity is still unclear. Warnatz et al. [9] could not find a good correlation of disease activity with the CRP levels, but with the contrast enhancing lesions on CT, as well as Adler et al. [10] concerning that some patients had the normal CRP values despite radiologically detectable inflammation and a good response to the IS ther-

apy. Pelkmans et al. [47] found that the long-term decrease in ESR and CRP correlated with CT–documented mass regression. Like Scheel and Feeley [14], we observed a positive correlation of ESR as well as CRP with the disease activity.

All patients had reduction of the fibrotic tissue on MSCT/MRI, with the average 76.9% of reduction. Six patients did not achieve 100% of the mass reduction. The complete regression of the fibrotic tissue after therapy is very infrequent and a thin layer persists even in the patients who maintain complete remission. This residual mass, probably in most cases, represents metabolically inactive tissue [48].

Additionally, the kidney function improved and remained normal in 6 treated patients. In 4 patients the mild chronic renal failure remained due to afunction of one kidney. In 3 patients, with prior chronic renal failure, the renal function did not get worse. They all were previously treated for IRF with different strategies: by the first strategy – only with ureterolysis, disease was reoccurred after 4 months, by the second strategy – with ureterolysis and the IS agents (azathioprine and tamoxifen), the relapse occurred 33 months after cessation of IS therapy, and by the third one – with ureteral stenting for 12 months. None of the patients died during the follow-up.

The recurrence rate in our study was 23% (3 patients). Two patients did not finish the protocol and stopped the therapy after 6 months and 31 months, respectively. Third patient has completed the protocol and the recurrence occurred at the end of 48th month. This could indicate a need for longer duration of the treatment.

We did not observe the serious side effects of the treatment. In 3 patients with prior diagnose of diabetes mellitus the glycaemia did not worsen, and MMF was well tolerated without gastrointestinal, hematologic, or other abnormalities.

In this study, we used a radiographic classification system based on the anatomic location of the disease proposed by Scheel and Feely [14] which we found useful in making a correct diagnose and standardizing the extent of disease. Also, different classes could have different clinical outcomes, or complications. By definition, all patients should have class I disease. In our series, the majority of patients, 7 of them, had class I + II + III, 4 patients had class I + III, and 2 patients had I + III + IV class. The class IV usually had the lowest frequency, but these patients should be carefully monitored for the renal artery stenosis and had the endovascular stent placed, as it was required in one of our patients.

Study limitation

Our study, like many others, is limited by a small number of patients; the optimal management of IRF needs to be determined by prospective clinical trials in large patient cohorts.

Conclusion

Combined corticosteroid and the MMF therapy appears to be effective in restoring the renal function and reducing the fibrotic tissue in this small number of patients with IRF. It could prevent the need for the ureteral stenting and surgery. Longer treatment may reduce the possibility of recurrence. The long-term follow up is strongly recommended to estimate this regimen of treatment.

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