Can Adequate Treatment Influence the Postembolization Syndrome and Cytokine Release in Patients Undergoing Iatrogenic Renal Artery Embolization?

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Abstract: The complete renal artery embolization is an alternative to surgical nephrectomy in seriously ill patients. Iatrogenic embolization can be used in many different conditions. Refractory nephrotic syndrome represents a very rare indication for embolization. Complete renal artery embolization has usually been complicated by postembolization syndrome (PES) which is characterized by flank pain and fever. Possible immunologic contribution to the PES leads some authors to the administration of corticosteroids to the patients undergoing embolization.

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We report here a cohort of 13 patients undergoing complete embolization of total 21 kidneys due to refractory nephrotic syndrome non-responding to the various specific treatment regimes. We treated our patients undergoing renal artery embolization according to special protocol containing combination of antibiotic drugs and corticosteroids (CS) to diminish PES and evaluated its influence to the cytokine production. The incidence of PES was less frequent and milder in comparison with the historical group of patients. Significant decrease in plasma levels of tumor necrosis factor α during first post-embolization day (8.37 pre- vs. 5.74 pg/ml post-embolization, P=0.0002) could partially explain the reduction of PES symptoms. The procedure was not complicated by severe complications and represents an elegant alternative to surgical procedure. The accurate timing of the embolization remains a controversial point in this intervention.

Introduction

Spontaneous thromboembolism into the branches of renal arteries is frequently associated with hypercoagulation status, which can be caused by various diseases (nephrotic syndrome, antiphospholipid syndrome and by many inherited disorders resulting from the mutations of genes encoding some clotting factors).

Iatrogenic embolization of renal artery or arteries represents a palliative or adjuvant treatment method applied for different reasons. The more frequent indications for complete renal embolization are the following: advanced or unresectable renal cell carcinoma with bleeding and pain, a reduction of operative blood loss during renal cell carcinoma operation, treatment or prevention of bleeding from angiomyolipomas in patients with tuberous sclerosis and bleeding from the cysts in patients with polycystic kidney disease. It has been also used in patients with end stage renal disease and severe hypertension, with non-functioning hydronephrotic kidneys or non-functioning native kidneys in transplant recipients (Hom et al., 1999; Capozza et al., 2007; Hansch et al., 2011). Refractory nephrotic syndrome that threatens the life of patients by thromboembolic or infectious complications shapes a special reason for complete renal embolization (Olivero et al., 1993; Tikkakoski et al., 2001). The last group of indications for renal artery embolization derives from complications of medical interventions. Bleeding complications associated with renal biopsy or urological interventions (nephrostomy and ureteral stenting) have been frequently resolved by selective embolization of smaller renal (or ureteral) artery branches.

The complete renal artery embolization has been kept for a treatment of patients in poor general medical condition, where operative procedure could aggravate their morbidity or mortality. This method serves as a viable alternative to surgical nephrectomy in seriously ill patients, where "medical nephrectomy" (application of some drugs with goal to reduce the renal perfusion and proteinuria) has failed. The technique of complete renal embolization was firstly described by Lalli et al. (1969) as an experimental procedure for treatment of neoplasm in dogs.

In human medicine this procedure was firstly used in 1973 for the treatment of renal cell carcinoma (Almgard et al., 1973) and many observations have come from the treatment of patients with tuberous sclerosis (Moorhead et al., 1977; Koike et al., 1994; Soulen et al., 1994).

Complete renal artery embolization has usually led to complete anuria of embolized kidney and to symptoms designated as postembolization syndrome (PES) that develop depending on the extent of affected tissue. PES is characterized by pain in the flank region and fever that can be severe. In men pain sometimes irradiates to the scrotum and paralytic ileus can be observed (due to coincidental embolization into the testicular artery or into the truncus coeliacus). Leukocytosis accompanied by an increase number of eosinophils has usually been detected in the blood count. PES is probably caused by an inflammatory response to the presence of necrotic tissue after embolization (Bissler et al., 2002) and could be mediated by interleukin (IL) 1 and 6 and by tumor necrosis factor alpha (TNF-α). Possible immunologic contribution to the PES leads some authors to the administration of corticosteroids (CS) to the patients undergoing embolization (Biegler et al., 1996; Diego et al., 1997).

We report here a cohort of patients undergoing complete embolization of renal artery for reason of refractory nephrotic syndrome non-responding to the various treatment regimes. As only few data concerning minimization of PES symptoms are available in the literature we decided to treat our patients undergoing renal artery embolization according to a special protocol containing combination of antibiotic drugs and CS and to evaluate its influence on cytokine production.

Patients and Methods

Patients

13 patients were included into our cohort of patients undergoing complete embolization of one our both renal arteries. Basic characteristic data are given in Table 1. Median of age at the time of embolization was 41 year. 8 patients were men. Amyloidosis (AA in 5 cases, AL in 2 cases) was the leading diagnosis. Several different treatment regimens were administered in all patients without achieving a favourable effect (Table 2). Despite treatment severe nephrotic syndrome with excessive urinary protein losses (median of proteinuria/24 h was 10 g) persisted in all patients, accompanied by very low plasma levels of albumin (median 13 g/l). Four patients were regularly hemodialyzed at the time of renal embolization, 2 patients underwent acute dialysis with ultrafiltration or slow continuous ultrafiltration because of extreme overhydration and incapacity to keep their dry weight within the normal ranges. Renal function in the rest of patients was normal (or near the normal ranges). One patient had mono-functional kidney. Bilateral embolization was performed in 8 patients, in four of them being subsequently followed by a repeat embolization within one or two month interval. The median time from the assessment of diagnosis to the embolization was 11 months (range from

Table 1 – Demographic and laboratory data in the set of patients before embolization of the kidney/kidneys

	Gender	Age	Diagnosis	S-creatinine (μmol/l)	S-albumin (g/l)	Protein excretion (g/24 h)
1	M	39	FSG	350 (HD/UF)	20	8
2	M	41	AA amyloid	70	13	8
3	F	58	AA amyloid	110	13	10
4	M	30	FSG	830 (HD)	16	21
5	M	33	AA amyloid	370 (HD/UF)	14	38
6	F	47	FSG	80	10	10
7	F	64	AA amyloid	675 (HD)	<10	18
8	F	36	IgM GN	250	12	12
9	F	22	MCD/FSG	100	13	8
10	M	58	AL amyloid	300	<10	8
11	M	59	MCD/FSG	660 (HD)	19	17
12	M	74	AL amyloid	712 (HD)	<10	14
13	M	37	AA amyloid	45	<10	10

FSG – focal segmental glomerulosclerosis; MCD – minimal change nephropathy; AA amyloid – secondary (reactive) amyloidosis; AL amyloid – amyloidosis with light chains; IgM GN – glomerulonephritis with IgM deposits; HD – hemodialysis; UF – ultrafiltration

Table 2 – Specific treatment before embolization of the kidney/kidneys

Subjects	Diagnosis in renal biopsy	Treatment	Time between renal biopsy and renal artery embolization
1	FSG	CS, CPA,CYC, NSAID, ACEI+ARB, PE, HD/UF	2 years
2	AA amyloid	CS, Methotrexate, Sulfasalazine, CPA, Infliximab, Colchicine	8 months
3	AA amyloid	CS, CYC, Colchicine, ACEI, NSAID	12 months
4	FSG	CS, CPA, CYC, ACEI+ARB, HD	2 years
5	AA amyloid	Antibiotics, NSAID, HD/UF	2 years
6	FSG	CS, CPA,CYC, ACEI+ARB, PE	2 years
7	AA amyloid	CS, CPA,CYC, Azathioprine, Methotrexate, Mycophenolate Mofetil, ACEI+ARB, HD	4 years
8	IgM GN	CS, CPA,CYC, Mycophenolate Mofetil, ACEI+ARB	7 years
9	MCD/FSG	CS, CPA, Chlorambucil, ACEI+ARB	12 years
10	AL amyloid	Melphalan + High Dose Dexamethazone	3 months
11	MCD/FSG	CS, HD/UF	3 months
12	AL amyloid	High Dose Dexamethazone, NSAID, HD	4 months
13	AA amyloid	CS, NSAID, Colchicine	14 months

FSG – focal segmental glomerulosclerosis; MCD – minimal change nephropathy; AA amyloid – secondary (reactive) amyloidosis; AL amyloid – amyloidosis with light chains; IgM GN – glomerulonephritis with IgM deposits; HD – hemodialysis; UF – ultrafiltration; CS – corticosteroids; CPA – cyclophosphamide; CYC – cyclosporine A; NSAID – nonsteroidal anti-inflammatory drugs; PE – plasma exchange; ACEI/ARB – angiotensin converting enzyme/angiotensin receptor blocker

1–144 months). Severe infectious complications (pulmonary bacterial or fungal infections, sepsis or skin infections) or thromboembolic complications (deep venous thrombosis complicated by pulmonary embolization in three cases; low plasma levels of antithrombin III were presented in all cases) were the leading reasons for intervention.

Technique of renal artery embolization

For the embolization of the kidneys the access through the right (in minority of patients through the left) common femoral artery was used and a special sheath was inserted inside the artery and fixed. Aortogram and selective renal artery arteriograms were performed (visualization by Optiray 300 or Iomeron 400). Embolic agent (Contour SE, polymeric microspheres 500–700 or 900–1,200 μm depending on the vessels diameter) was slowly injected inside the renal artery branches until the blood flow cessation. Immediate postembolization arteriograms were obtained within a few minutes and if any perfusion of kidney could be detected an additional embolic agent was injected. Failure of the embolization procedure was demonstrably detected in three cases (normalization of diuresis after an anuric period) and re-embolization was realized. In addition to the embolic agents, the special metallic coils were placed inside the main branches of renal artery during the re-embolization procedure with an achievement of a satisfactory result.

Cytokine measurement

Cytokine profile before and after embolization was assessed through the plasma measurement of following cytokines: IL-1β, IL-6, IL-8, IL-10, TNF-α, INF-γ (interferon γ), MCP-1 (monocyte chemoattractant protein), VEGF (vascular endothelial growth factor) and NT pro-BNP (N-terminal pro-brain natriuretic peptide). Blood samples were collected from each patient in the morning at the day of embolization and at the first and third day after embolization. Human cardiovascular multiplex kit (LINCO) was used for the detection of cytokines and measurement was performed at the LUMINEX IS 100 (fluorescent intensity detection of fluorescent labelled antibodies against investigated cytokines). Concentrations of cytokines were expressed in pg/ml.

Treatment protocol for PES

Patients were treated by one intravenous pulse of methylprednisolone at a dose 250 mg/m^2 early morning at the day of embolization. Per oral treatment of prednisolone at a dose 60 mg/day was administered for two consecutive days after embolization and doses were subsequently tapered down within 10 days. Treatment with H_2-blockers or blockers of proton pump was initiated at the same time as CS treatment. The first dose of cefazoline (1 g iv.) was given 2 hours before embolization and the administration of 3 g/day was prolonged for the period

of the five consecutive days (dose reduction depending on the renal function). Paracetamol was administered regularly at a dose 500 mg three times daily during the first two days, the subsequent administration was facultative and dependent on the patient requests (as well as tramadol or opiate). This protocol represents a modification of the protocol published by Bissler et al. (2002).

Statistics

All results are expressed as median or mean ± SD. The statistical significance was evaluated using unpaired and paired Student's *t*-test and correlation coefficient r. Results were considered statistically significant at $P<0.05$.

Results

Median survival in the group was 16 months (range from 1–96), 6 patients have still survived from 16–96 months after the procedure (Figure 1). Four of them have been regularly dialyzed. Two patients, that underwent embolization of only one kidney, are independent of dialysis treatment, but their renal function remained chronically decreased (serum creatinine levels between 198 and 624 μmol/l, resp.). Their proteinuria stood stabilized or slightly decreased. In the majority of patients an increase of serum albumin of about 40–50% in comparison with the initial levels was observed. 7 patients died during the follow-up period of 8 years. Leading reason for death was sepsis (4 cases). Malignant arrhythmia with severe hypotension was the cause of death in 1 patient with AL amyloidosis, fatal acute myocardial infarction occurred in 1 patient (38 years old!) and fatal pulmonary oedema occurred in 1 patient who discontinued chronic dialysis treatment.

10 patients experienced mild or moderate pain during the post-embolization period, fever was detected only in 3 cases; paralytic ileus, nausea and vomiting were observed also three times. Singultus was observed in two cases. Subcapsular or retroperitoneal hematoma appeared in one patient and once the procedure was complicated by pancolitis, due probably to the embolization of embolic agent into the branches of arteria mesenterica superior.

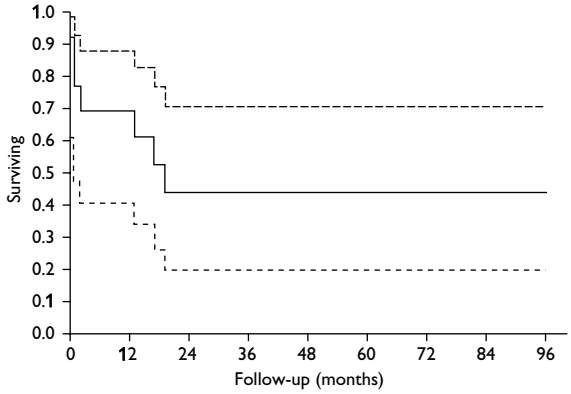

Figure 1 – Kaplan-Meier curve of survival after renal artery embolization.

Table 3 – Plasma levels of selective cytokines in 13 patients before and after embolization of the kidney/kidneys

	Time of blood taking in relation to embolization	Mean	SD	P
TNF-α (pg/ml)	morning before	8.37	11.9	0.0002
	1 day after	5.74	5.8	
	3 days after	4.48	1.9	
IL-10 (pg/ml)	morning before	130.83	159.9	0.0027
	1 day after	81.73	103.8	
	3 days after	124.13	136.6	
IL-6 (pg/ml)	morning before	51.94	117.1	<0.0001
	1 day after	98.89	184.4	
	3 days after	116.38	103.1	
IL-8 (pg/ml)	morning before	57.93	95.9	0.0007
	1 day after	96.88	163.8	
	3 days after	83.58	55.8	
MCP-1 (pg/ml)	morning before	166.49	95.9	0.1770
	1 day after	150.07	74.0	
	3 days after	157.24	85.6	
NT-proBNP (pg/ml)	morning before	1221.26	1550.3	0.3140
	1 day after	3141.04	3782.3	
	3 days after	4431.82	4610.4	

SD – standard deviation; TNF – tumor necrosis factor; IL – interleukin; MCP – monocyte chemoattractant protein; NT-proBNP – N-terminal pro-brain natriuretic peptide; P – significance of paired *t*-test between levels before and 1 day after embolization

Significant changes in plasma levels of investigated cytokines were observed within the first three post-embolization days however the trends of changes were somehow inconsistent (Table 3). Plasma levels of TNF-α significantly decreased during first day (8.37 vs. 5.74 pg/ml, P=0.0002) and such trend could be observed until the third day. Decrease in plasma levels during the first day was observed also in IL-10 and MCP-1, but in the day three a trend to their repeat elevation could be noticed. An opposite trend was appeared in IL-6 and IL-8 plasma levels. During the first post-embolization day their plasma levels significantly increased (51.94 vs. 98.89 pg/ml, P<0.0001 and 57.93 vs. 96.88 pg/ml, P=0.0007 resp.). Trend to increase of plasma levels of NT-proBNP was registered in post-embolization period, where acute anuria or oliguria were accompanied with water and sodium retention. The plasma levels of IL-1β, INF-γ and VEGF were under the limit of detection (or error was signalized during the measurement) in majority of cases, thus the results from these assessments are not given here.

Discussion

Complete renal artery embolization is a reasonable curative method accepted for the treatment of refractory nephrotic syndrome in patients with poor health condition where operative nephrectomy represents too high risk.

Many authors have currently considered that PES is a normal sequel rather than complication of complete renal embolization (Millard et al., 1989; Bissler et al., 2002). Lower extremity gangrene, bowel infarction and spinal cord infarction have been reported (Woodside et al., 1976; Gang et al., 1977; Cox et al., 1982) as potential complication of renal embolization. We observed this complication in one patient, manifesting as pancolitis. Hypertension can develop after an incomplete embolization of kidney due to an increased renin production in the ischemic renal parenchyma (Keller et al., 1986). Infection is another potential complication of renal embolization, although the reported incidence is low. We did not observe an increased frequency of acute infections in our cohort of patients, probably due to the administration of antibiotic drugs as part of a complex treatment of PES. Treatment failure (re-canalization of embolized kidneys) was detected in some cases, urging to a re-embolization (in 3 patients).

Death within one month after embolization occurred in 4 cases, from 7 deaths overall. Sepsis was the leading cause of death and the reasons may be seeking in low plasma levels of immunoglobulins, profound malnutrition and intumescence of many organs during nephrotic syndrome that support the embedding of different infectious agents. The sudden death 12 months after embolization in 38-year-old dialyzed woman deserves particular attention. Myocardial infarction was detected as the reason of death and severe atherosclerotic lesions were discovered despite the treatment of statin and aspirin. Long-term duration of nephrotic syndrome, eventually potentiated by CS administration, could possibly accelerate the atherosclerotic process in this patient and negatively influence her prognosis.

The changes and trends in the plasma levels of investigated cytokines during the whole embolization period cannot be interpreted easily. TNF-α has been found as an endogenous pyrogen and pain stimulator, so we anticipated its leading role in PES. As dexamethazone (as well as other CS) reduces effectively plasma levels of TNF-α (Aggarwal, 1992) the administration of methylprednisolone (and prednisone in following days) was associated with significant reduction in TNF-α plasma levels during the embolization period. This observation was confirmed by diminished incidence of fever and severe pain episodes in treated patients when compared them to the untreated group of patients from our historical group (unpublished data). Concentrations of TNF-α in embolized group after administration of CS got near the plasma levels in normal population.

The levels of IL-6 progressively increased despite the treatment of CS and also antibiotic drugs. Abnormally high levels of IL-6 were detected in our cohort of patients in comparison with healthy controls and also patients with AA amyloidosis and active rheumatoid arthritis (51.94 vs. 2.85 and 6.76 pg/ml, resp.; data from our different study) (Ryšavá et al., 2007). The possible role of infection in this set of patients can be probably excluded because of lack of correlation between IL-6 and C-reactive protein (data are not given). If the failure of immuno-surveillance in seriously ill patients with nephrotic syndrome remains the only reason for very

high levels of IL-6 cannot be answered on basis of our study and deserves further research. We can anticipate on the other hand, that IL-6 levels would have been higher than we detected, if the patients had not been treated by CS.

It has been shown that NT-proBNP is a sensitive indicator of left ventricle function/damage and its plasma levels are closely associated this hydration and body sodium storage. NT-proBNP and troponins I and T have been identified as important prognostic factors of survival in patients with amyloidosis so the very high initial NT-proBNP levels could be caused by myocardium involvement in patients with amyloidosis (Dispenzieri et al., 2005). We assume, on the other hand, that the increase of NT-proBNP could be also caused by heart failure in the condition of chronic over hydration accelerated by acute anuria/oliguria after embolization rather than by further myocardium impairment.

We are aware of different shortcomings of our study. First it is the low number of observed and investigated patients, which can also influence the statistical analysis. In this context it is necessary to mention that our set of patients suffering from intractable nephrotic syndrome and thus undergoing renal embolization is the largest series published until now (in other studies the embolization was performed in patients with tumours or angiomyolipomas) (Olivero et al., 1993). The second shortcoming comes from inaccuracy during the measurement of plasma levels, which could be caused by long storage of some plasma samples (more than 3 years). The last one is the absence of control group of patients. This shortcoming seems to be the most important, but the arrangement of control group has not appeared to be ethical from our point of view in this special life threatening condition.

Conclusion

Complete renal embolization is an alternative to surgical nephrectomy for patients with refractory nephrotic syndrome who are at poor health condition and at increased risk for operative complications. PES associated with complete renal embolization can be substantially diminished by administration of CS and antibiotics drugs, but the effect of administered treatment on the cytokine production remains controversial.

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