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Editorial Comments

XI Congresses of the Balkan Cities Association of Nephrology, Transplantation and Artificial Organs-Bantao, Timisoara, 26-29 September 2013

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Now when approaching the XI BANTAO Congress in Timisoara, we should remind ourselves about the beginnings of our Association, which was established 20 years ago in Ohrid. The Balkan Cities Association of Nephrology, Dialysis, Transplantation and Artificial Organs (BANTAO) was born on October 9, 1993 during the I Congress of the Macedonian Society of Nephrology, Dialysis, Transplantation and Artificial Organs (MSNDTAO) held in Ohrid [1]. At that time there was a bloody and devastating war in former Yugoslavia, but the nephrologists from the Balkans showed willingness to continue the mutual cooperation. The idea was to create an association between nephrologists from the cities of the Balkans (who are friends and) who would support the mutual cooperation without borders or any negative ideology. Hence, the main goals of BANTAO were set: to promote scientific and technical cooperation in the field of renal disease and artificial organs between the cities of the Balkan Peninsula and the world, giving an opportunity for exchange of experience and knowledge among the experts in the area and to engage them in collaborative projects in order to demonstrate the cooperation is possible even on the turbulent Balkans. A task force was formed from representatives of different cities from the Balkan Peninsula to make this project a reality including the following members: S. Kodra (Tirana), D. Nenov (Varna), Z. Kirjakov (Sofia), Gj. Masin (Skopje), M. Polenakovic (Skopje), F. Akcicek (Izmir), E. J. Dorhout Mess (Izmir), Lj. Djukanovic (Belgrade), A. Radmilovic (Belgrade) and S. Strahinjic (Nis). Momir H. Polenakovic, the President of the MSNDTAO, was elected as chairman of the task force. Besides nephrologists from Balkan cities, our international colleagues H. Klinkman, J. Vienken, E. J. Dorhout Mees, D. Falkenhagen and P. Ivanovich helped us in the creation of platform for the Association. The I BANTAO Congress was held in Varna from September 22nd to 24th, 1995. The President of the congress was D. Nenov (Varna). The congress in Varna was very successful, with more than 80 papers presented by nephrologists from the Balkans as well as from other European cities. The I Congress of BANTAO was accepted very positively among the nephrology community in Europe as well. Our well known colleague from Spain, F. Valderrabano has published a congress report [2]: "Nephrologists of the Balkan countries meet across political frontiers and war fronts-an example to politicians! BANTAO: a new European medical association overcomes political obstacles". This is an extraordinary initiative of nephrologists working in cities throughout the Balkan countries who have been able to create a scientific association and to organize its first congress, despite the boundaries of war, the rupture of internationnal relations and other serious political problems which emerged in the Balkan countries after the disappearance of the former Republic of Yugoslavia.

The main goal of BANTAO is to promote scientific and technical cooperation in the field of renal diseases and artificial organs between the Balkan cities. This goal will be achieved not only through a periodical congress, but also through lecturers exchange, fellowship exchange, scientific research methods exchange, joint meetings and courses, publications and cooperation in the field of renal transplant. BANTAO wants to work closely with other international societies, especially with EDTA-ERA. BANTAO represents an extraordinary initiative and should receive both scientific and economic support from the EDTA-ERA. The exceptional effort of collaboration shown by our Balkan colleagues, who have been able to carry out scientific activities in extremely adverse human conditions, is an example to the European nephrological community, which should not hesitate to offer all possible help to this new association. The II Congress of BANTAO was held in Struga, Republic of Macedonia from September 6th to 10th, 1997 [3]. The II Congress of BANTAO was sponsored by the European Society for Artificial Organs (ESAO), the International Society for Artificial Organs (ISAO), the International Faculty for Artificial Organs (INFA) and the ERA-EDTA. It was held in conjunction with the Second Congress of the Macedonian Society of Nephrology, Dialysis, Transplantation and Artificial Organs. The President of the Congress was M. Polenakovic [4]. The III BANTAO Congress was held in conjunction with the Sixth Yugoslav Congress of Nephrology in Belgrade from September

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18th to 20th, 1998. The President of the Congress was Lj. Djukanovic (Belgrade). The main topics were: renal replacement therapy in the BANTAO region, the role of auxiliary therapy in chronic renal failure and tubulointerstitial disorders and diseases. A post-congress symposium was devoted to Balkan endemic nephrology. The IV Congress of BANTAO in conjunction with the 16th Congress of the Turkish National Nephrology, Dialysis, Transplantation and Hypertension Society was held in Izmir, Turkey from 14th to 16th November, 1999. F. Akcicek (Izmir) was the President of the Congress. The V Congress of BANTAO was held in Thessaloniki from September 30th to October 3rd, 2001. Ch. P. Stathakis (Athens) was the President of the Congress. The Congress was a great success. Seventy-two lectures were presented, 59 of which were published in a special supplement to Nephrology Dialysis Transplantation: Official Publication of the ERA-EDTA. In total 250 abstracts were submitted and approximately 600 participants attended the Congress [5]. The VI Congress of BANTAO was held for the second time in Varna from 6th to 9th October 2003 under the Presidency of D. Nenov (Varna). More than 400 medical doctors from 72 Balkan cities participated in the work of the Congress presenting the highest ever number of abstracts-343. A very important event for the Association was the First issue of the BANTAO journal [6]. The VII Congress of BANTAO was held in Ohrid from 8th to11th September, 2005. A total of 270 abstracts were accepted, 43 for oral presentation (free communications) and the remaining 227 for poster presentations. The President of the Congress was M. Polenakovic (Skopje). Here, at the VII BANTAO Congress for the first time a CME Course was organized by ERA-EDTA and ISN-COMGAN entitled *Frontiers in Nephrology* organized by G. Spasovski [7]. The VIII BANTAO Congress was held in Belgrade, from 16th to 19th September, 2007. The President of the Congress was V. Nesic. There were 184 abstracts submitted to the Congress, 47 as oral presentations and 137 posters, as well as 60 guest lecturers. The IX BANTAO Congress was held in Antalya, from 18th to 22nd November, 2009. The President of the Congress was A. Basci (Izmir). The Congress was held together with the 26th National Congress of nephrology, hypertension, dialysis and transplanttation-Turkey and the 19th National congress of renal diseases, dialysis and transplantation nursing-Turkey. A total of 220 abstracts were submitted; there were 50 guest lecturers, 52 oral and 168 poster presentations. The X BANTAO Congress was held in Chalkidiki from 13th to 15th October, 2011. It was jointly organized with the 82nd Scientific meeting of the Hellenic Society of Nephrology. Also, an ERA-EDTA CME Course entitled *Vasculitides* was held. The President of the Congress was D. Tsakiris. Overall 245 abstracts were submitted; there were 56 guest lecturers and 41 oral and 204 poster presentations.

An extremely important event in the existence of BANTAO was the appearance of the BANTAO journal in 2003, which is published biannually. In the past 10 years, 20 regular issues and 2 supplements (Antalia and Chalkidiki congresses) have been published. Editors of the journal were as follows: Dimitar Nenov (2003-2005); Ali Basci (2005-2009); Goce Spasovski (2009). Until now, 332 papers have been published. The BANTAO journal is included in the following databases: EBSCO, DOAJ and SCOPUS. Hence, it may be said that the journal is a "glue" between the nephrologists from the Balkan cities.

Despite the difficulties imposed by major events, such as devastating wars and catastrophic earthquakes in many countries of the Balkan Peninsula BANTAO has made a considerable progress. The BANTAO Congress was established as the major scientific and institutional forum for Balkan nephrologists, with its own journal, indicating our will to communicate, to collaborate, to get to know each other and to share our difficulties. We do expect our further successful work of BANTAO.

What should be our aims for the future?

- To improve further cooperation between the nephrologists and doctors from other related medical specialties from the Balkan cities as well as with colleagues from Europe and the world.
- To improve basic and clinical education and research in nephrology as well as research equipment and facilities.
- To discover, treat and register patients with CKD as well as accomplish registers for renal biopsy, rare renal diseases, etc.
- To perform an early diagnosis of diabetes mellitus and hypertension, to stop or postpone renal tissue damage and/or progression and prevent the end-stage renal disease development.
- To improve renal transplantation, to establish Balkan transplant network and to join the other renal transplant networks in Europe.
- To improve fight against infections (especially against hepatitis C).
- To organize mutual clinical trial.

Finally, we need further improvement of our BANTAO journal as the most important bond between the nephrologists of the Balkan cities. At the same time, we should make efforts to include the journal in Medline/PubMed and to receive an impact factor as a respected journal in the field of nephrology.

We expect further successful work of the XI BANTAO Congress and the ERA-EDTA supported CME Course "*Improving the patient and graft survival in kidney transplantation-an update"*.

Conflict of interest statement. None declared.

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Editorial comment

Editors' Observation: Scientific Research and Publication Opus of the Balkans' Nephrologists is Worth Mentioning

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The research and science rely on human potential, availability of facilities and resources, and seems to be a privilege of the developed world. What is the current situation in the developing countries from Balkans and central and east Europe has never been analyzed. The aim of this observation was to show the potential of nephrologists in our region, i.e. their current status of publication throughout publicly available database search. A Medline search of literature was conducted by various filters on display settings as well as using additional filters showing reviews and case reports. Google scholar tool and published JIF for 2012 was used for citations. Thus, the nephrologists from various Balkan countries retrieved with more than 50 publications were analyzed for a number and type of articles, type of journal (international/national) and its journal impact factor (JIF), the number of citation per publication, Hirsch index (HI), collaborative international authorship, and number of papers being first (including single authorship), last or single author.

The contribution of other nephrologists with lower registered number of articles in Medline database is also well appreciated, but we have arbitrarily decided upon the limit of papers included in order to adapt data at the limited journal pages. Additionally, one should be aware of our scientific predecessors and teachers, who have previously published articles in their native language medical journals that were available to physicians in their respective countries. After all, the main purpose of these articles was rising of the health problems awareness and education of younger colleagues. In fact, the socio-political situation on the Balkans was significantly different 20 years ago. In the majority of countries it was difficult to access medical journals from Western Europe and USA, and Balkan authors had somewhat limited ability to publish scientific articles in those journals. Later on, after the changes in socio-political system and improvement of the economy in Balkan countries there was an expansion in the field of nephrology. It resulted with an improved care of kidney patients, participation in many clinical trials and numerous articles published in prestigious European and other international medical journals which reflect the current reality.

All together, there were 23 authors from Croatia, Macedonia, Romania, Serbia and Slovenia, who published 2375 papers included in the Medline database (Table 1). Three authors published more than 200 papers, one author published 167 papers, three authors published between 100-150 papers and others published between 50-100 papers. Croatian authors published substantial proportion of their articles as reviews and case reports, while the lowest proportion of such articles was published by Slovenian authors. Majority of papers (71,3%) were published in international and only 28,7% in national journals, with an extreme of only 2 papers in national journals published by Slovenian authors. The highest JIF rate varied between 3,4 and 53,3, but the majority of authors have published in journals with JIF up to 10. Overall maximum citation rate per author's paper varied from 37 to 914, but generally, with a very few papers cited more than 50 times. The HI of the authors varied between 6 and 41. Finally, the international composition of the authors in published papers was very low-17,8%, showing a low rate of collaboration of Balkan nephrologists in international studies.

In Turkey and Greece more than 50 and 30 authors were retrieved, so only global data and explanation are presented. Namely, Turkey as the largest country for both, population and territory on the Balkan region, is also the 17th largest economy of the World. Reasonably, the high number of universities leads to an improved standings in the global scientific league and Turkey is ranked 9th in the "Neph-

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rology" subject category. Furthermore, the close collaboration of Turkish nephrologists with the major academic centers in US and Europe, have great impact on the progress of Turkish nephrology. Thus, the present number of nephrologists in Turkey with more than 50 publications is more than 50 and could not be included individually in this analysis. Greece is another big country on the Balkans, and there are at least 30 Greek nephrologists with more than 50 publications in Medline. The Hirsh index fluctuates between 13 and 27 and the highest number of citation of one author is 1338.

These data clearly show that the potential from nephrologists that originate from developing countries is worth mentioning and we should be aware of. Despite the restricted resources and insufficient registry data, an emerging collaboration in single and multicenter national studies on clinical and epidemiological rather than basic research is favored. Nevertheless, the potential of scientific collaboration in international clinical studies seems to be yet underused and should be improved in the future. Hence, we tried to analyze the factors influencing scientific contributions from Balkans. According to our previously published data [1], there is a growing interest for mutual participation in clinical trials from the side of sponsors as well as the Balkan researchers. This breakthrough was done in the last decade of the previous century, but the real expansion happened over the last decade. The motivation for the clinical studies in the Balkan coun tries was best explained by the sponsors of clinical trials who described their positive experience

Table 1. Data on scientific publications by nephrologists from Balkan region

	N	Type of paper		Type of J.		JIF			N of paper cited			HI	Coll	Author		
	Paper	Rev.	CR	Int.	Nat.	1-3	>3	Max	51-100	>100	Max		Int.	First	Last	Single
CRO																
Kes P	202	43	28	60	142	34	13	7,9	1	0	54	12	6	104	41	24
Basic-Jukic N[#]	122	34	25	62	60	37	7	13,1	1	1	275	11	4	41	22	5
Ljutic D	62	7	8	44	18	17	5	5,2	0	0	49	8	5	15	3	6
Jelakovic B	52	11	3	24	28	19	5	6,1	3	0	237	10	10	19	17	1
Galesic K	51	9	19	28	23	15	3	3,4	2	0	39	7	1	24	13	1
MK																
Polenakovic M	168	6	29	103	65	44	22	38,3	6	1	109	17	19	40	73	10
Spasovski G	83	19	7	70	13	27	26	9,7	4	3	346	20	40	27	23	10
Grcevska L	59	1	21	47	12	26	11	5,4	0	0	49	8	1	35	8	0
Sikole A	58	2	1	37	21	20	9	9,7	4	1	245	11	13	11	16	1
Ivanovski N	53	3	5	47	6	17	7	9,7	1	0	92	8	9	20	7	1
RO																
Covic A	276	82	10	229	47	107	111	53,3	21	9	196	41	184	76	83	2
Voiculescu M	70	15	8	25	45	15	10	53,3	1	2	914	14	28	43	21	9
SER																
Stefanovic V	258	38	6	209	49	53	10	14,1	6	0	78	23	29	93	122	1
Djukanovic L	146	4	4	100	46	49	18	6,6	2	2	245	18	7	21	63	2
Dimkovic N	85	10	14	60	25	26	17	35,5	5	1	245	15	31	22	14	4
Stojimirovic B	80	13	4	24	56	14	3	5,4	1	0	61	11	3	11	48	1
Lezaic V	65	0	0	51	14	26	7	6,4	0	0	37	11	2	28	11	0
Djordjevic V	53	0	2	44	9	19	4	6,6	1	0	52	6	4	10	5	2
SLO																
Buturovic-Ponikvar J*	110*	7	4	109	1	91	11	5,3	1	0	70	17	9	28	23	5
Ponikvar R	88	3	3	88	0	76	4	3,4	1	0	70	17	4	9	34	5
Kandus A	86	0	3	85	1	74	5	4	1	0	70	10	5	15	16	0
Bren A	85	1	4	85	0	70	8	4	1	0	58	11	5	8	34	1
Hojs R	60	2	5	60	0	42	8	53,3	1	2	747	12	2	15	19	6

[#] Basic-Jukic or Basic N or Jukic NB or Jukic BN

* Buturovic-Ponikvar J + Buturovic J + Ponikvar JB

Abbreviations: Rev - review; CR - case report; Int/Nat - international/national; type of J – journal; Coll – collaboration.

with the countries already involved. In addition, these already performed clinical trials have generated a higher scientific impact by a few nephrologists from the region who have become well known by their publications in Medline cited journals.

Another possible explanation for this enthusiastic work of the Balkan nephrologists could be explained by the continuous effort of International organizations (ERA-EDTA, ISN), which in collaboration with national societies, put a lot of effort to organize multidisciplinary meetings, continuous medical education (CME) courses and workshops aiming to update us with the latest scientific data. In addition, there were plenty of possibilities for grants and collaborations between developed and developing nephrology centers and their doctors in the form of sister centers or twining projects. As a consequence of such collaboration, joint projects were established and some important scientific results were published in well recognized nephrology journals.

Finally, the Universities in Balkan countries have established rules for evaluation of candidates in their applications for an academic position and their further promotions. These rules were shown as demanding and in return mobilized the efforts for a scientific progress done by our nephrologists despite poorly allocated national budgets for science and research. Most often, this effort has been sponsored by

authors themselves providing required reagents for laboratory analyses, statistical evaluation, writing and eventually, the cost of publishing. Therefore, it is not surprising that the majority of publications have been published by nephrologists with university carrier who are also opinion leaders and mentors.

In conclusion, Balkan nephrologists seem to get and keep the pace with the nephrologists from the developed countries, and their effort is really worth mentioning considering long-lasting impediments in the region concerning the scientific work in general.

Conflict of interest statement. None declared.

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Disclosure: *Authors would like to apology for eventual errors in the presented data in this editorial, especially when two or more authors were retrieved under the same surname or different letters used into their surnames!*

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Viewpoint Article

ABO-Incompatible Kidney Transplantation: Past, Present and Future

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Key words: ABO-incompatible kidney transplantation, paired kidney donation

Introduction

Kidney transplantation (KTx) is the treatment of choice for end-stage renal disease [1]. Compared with dialysis it confers a survival advantage, enhances quality of life and is more cost-effective. There are two types of potential donors in renal transplants: deceased and living donors. Transplantation from living donors provides better survival rates in comparison to those from deceased ones [2]. Furthermore, transplantation from living donors could be the solution for the shortage of cadaveric donated organs. Unfortunately, for many years a significant number of potential living donors were rejected due to blood group incompatibility with the recipient. ABO-incompatibility was considered to be an absolute contraindication to transplantation. However, during the last 15years the implementation of new transplant protocols has significantly diminished this barrier and has lead the way for the induction of ABO-incompatible (ABOi) transplantation worldwide.

History of ABO-incompatible kidney transplantation

The first successful ABOi transplantations were reported by Alexandre, *et al*. in 1987 [3]. These transplantations were performed using living donors, splenectomy, plasmapheresis and an immunosuppressive regimen with cyclosporine, steroids, azathioprine and antilymphocyte globulin. Further development in the field of ABOi KTx came from centers in Japan. With the use of plasmapheresis or double filtration plasmapheresis for removing anti-ABO antibodies, splenectomy for physically removing the source of the antibody-producing cells and new pharmacological immunosuppressants, the Japanese group presented significantly improved graft survival [4]. Based on these promising results, in the first decade of this millennium ABOi KTx began to expand slowly and in other centers of USA and Europe. However, many institutions approached the need for splenectomy with a degree of skepticism, considering the related long-term infections and the increased surgical risk. The concept of a "medical splenectomy" with the introduction in clinical practice of Rituximab-a monoclonal antibody against CD-20 on B cells- made ABOi KTx more feasible [5]. Also, the introduction of new immunoadsorption techniques with the use of specific anti-A or anti-B immunoadsorption columns (Glycosorb®), which effectively and specifically depletes anti-A or anti-B antibodies without any apparent side effect, made transplantation preconditioning easier. Nowadays, ABOi KTxs are worldwide performed with remarkable outcomes.

Current desensitization protocols and long - term outcomes

Although there are some differences in the desensitization protocols among different transplant centers, most include a combination of plasmapheresis or immunoadsorption, intravenous immunoglobulin and a triple-drug immunosupression consisting of tacrolimus, mycophenolate and prednisolone. In addition, monoclonal or polyclonal antibody agents are used during the induction period. Splenectomy is still in use selectively, while rituximab administration is in use. After transplantation, close monitorring of the ABO antibody titer is necessary and usually some more plasmapheresis sessions are needed to eliminate the antibodies rebound. The major determinant of successful graft outcome is the prevention of hyperacute rejection and the establishment of accommodation as early as possible. Accommodation is defined as the absence of antigen-antibody reaction, despite the presence of "foreign" antigen on the vascular endothelial cells of the graft and the presence of antibody in recipient's blood [6]. Independently of the different protocols that are used in various centers, the short-and long-term outcomes of ABOi transplantations are now comparable with those of ABO-compatible KTxs. In Japan during the past two decades, about 2000 ABOi KTxs were performed. The patient and graft survival rates for the 1427 procedures performed after 2001 were 98% and 96% for the first year and 91% and 83% for 9 years respectively [7]. In the USA, the outcomes were also excellent with patient and graft survival of 89,4% and 89%, respectively reported by the Johns Hopkins University after 5 years follow-up. [8]. From Europe, the results of a Swedish Group for 3 years follow-up were 100% for patient survival and 86,7% for graft survival [9]. Also, the Melbourne Group reported 100% patient and graft survival after 2,2 years of follow-up [10].

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At our center, we have performed 30 ABOi kidney transplantations since 2005. Pre-transplant desensitization was made according to an amendment of the Swedish protocol. More specifically we have used repeated immunoadsorptions mostly with the Glycosorb ABO-collumns or in combination with the Immusorba-collumns to achieve an isoagglutinin titer of ≤ 1:16 at the day of transplantation, intravenous immunoglobulin 0.5g/kg of body weight at the end of immunoadsorptions course, rituximab 375mg/m^2 body surface area on day 20 pre-transplantation, and oral immunosupression instituted a week prior to KTx. As induction therapy monoclonal antibodies against interleukin-2 were used, while at least three immunoadsorption sessions were performed postoperatively depending on anti-A/B titers thereafter. The main difference from the Swedish protocol was the use of everolimus or mycophenolate acid in the triple-drug combination with tacrolimus and corticosteroids. One-year patient and graft survival rates were 100%, while the 5-year patient and graft survival rates were 91,7%. In comparison with the ABO-compatible KTxs we did not observe differences in the incidence of viral or bacterial infections.

Futures expectations

Since many centers report results comparable with conventional ABO-compatible transplants, it is obvious that ABOi transplantation is an acceptable alternative. It is an option that patients must have as it decreases the waitlist and the associated morbidity and mortality.

New techniques for antibody removal in combination with novel pharmacological agents for B-cell depletion could facilitate the preconditioning for ABOi transplantation in the future. The better understanding of incompatible kidney transplant histology and graft accommodation could also improve graft survival results and reduce the risk for rejection.

One of the remaining obstacles for ABOi KTx is the cost. The need for preconditioning prior to transplantation, post-transplant immunoadsorptions and monitoring significantly increase the cost related to ABOi KTx. However, in terms of cost-effectiveness, studies from the USA and Europe showed that, despite the increased initial mean cost of ABOi transplantation, on a long-term financial plan this turned out to be a cost saving therapy, considering the expenses associated with maintenance dialysis [11].

On the other hand paired exchange kidney donation (PKD) could be an option for some patients, especially in low-income countries. PKD allows an exchange of kidneys between two or more donor/recipient pairs that are ABOi or HLA incompatible, with the aim of achieving compatible pairs. The main problem of PKD programs is the size of donors' pool. With the creation of international networks of PKD programs, this goal could be attained. Furthermore, with the current established PKD programs in Europe, such as in the Netherlands [12] and United Kingdom [13], the implementation of this strategy seems to be more feasible.

Conclusions

Over the last two decades advances in technology and pharmacotherapy made ABOi transplantations to be a reality. ABOi KTx can now be part of daily practice in most of the transplants centers with the support of an appropriate organized laboratory, clinical and renal pathology teams. This offers a new option for end-stage renal disease patients to improve the length and quality of their life.

Conflict of interest statement. None declared.

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Viewpoint Article

AV Fistulae and Catheters for Hemodialysis: How Much Should Nephrologists be Involved in Vascular Access for Hemodialysis

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Key words: AV Fistulae, central venous catheters, vascular access

Cimino-Brescia AV fistula

Native arteriovenous (AV) fistula which was introduced into clinical practice in 1966 by Brescia, Cimino, Appel and Hurowich [1] is still a vascular access of choice for chronic hemodialysis patients. The main advantages were longevity and fewer, especially infectious, complications. For the patients with exhausted vasculature, AV grafts made of expanded polytetrafluoroethylene (ePTFE), introduced in 1976, were the second best choice to native AV fistula. They had shorter life span, with outflow stenosis of the vein as the most common complication. Infection usually necessitated complete removal of the graft in spite of antibiotic therapy.

Ultrasound/ Doppler examination

Preoperative Duplex sonography of arteries and veins became the golden standard for preoperative examination before AV fistula or graft creation. It prevents unsuccessful and unnecessary surgery and pain to the patient in circumstances when arteries are too narrow (<1,8-2,0 mm) or veins are absent or flebitic. In our Dialysis center for acute and chronic dialysis at the University Medical Center in Ljubljana more than 400 vascular mapings are being performed by nephrologists every year.Ultrasound/ doppler examination is being performed both before AV fistula or graft creation and before salvage surgeries.

Native AVF and grafts

Data from registries published in NDT 2009 revealed that percentage above 80 of native AV fistula is achieved only in few countries in the world [2]. Slovenian ESRD registry revealed that in 2005 85,1% of chronic hemodialysis (HD) patients had native AV fistula, 4,7% had grafts and 10,5 % catheters. In 2010, still 82% of our patients had native AV fistula. However, in 2011 the percentage dropped to 79% and the percentage of hemodialysis catheters increased to 15%, while the percentage of grafts remained stable, 6% [3]. One of the reasons for the reduced number of AV fistulas in our hemodialysis population might also be the shift of dialysis patients (having been in excellent health condition with predomonantly AV fistula as vascular access) to transplantation (with functioning fistulas) and their loss from hemodialysis registry. In the remaining hemodialysis population the mean age rose, number of comorbidities increased, possibilities for native AV fistula placement declined and more AV grafts have been created. Interestingly, mortality rate of old hemodialysis patients (>80 years) between those with native AV fistula and those with AV graft, was the same [4].

At the beginnings of hemodialysis, nephrologists like Cimino and Brescia gave the idea of AV fistula creation, and others like Stanley Sheldon, were access surgeons themselves. In our Dialysis center vascular access has been performed by nephrologists since 1974 and since then more than 6,500 vascular access surgeries have been performed in chronic hemodialysis patients. The autor of this paper, a nephrologist, has performed more than 3,000 surgeries, of which about 1,500 in the last 10 years. Majority of access interventions (85%) were performed by nephrologists in Italy while other countries rely mainly on vascular surgeons [5]. Nevertheless, the opinion that nephrologists should be closely involved in AV fistula creation is getting an increased support [6,7]. Preferable surgical technique is "end to side" anastomosis as distal as possible. AV grafts could be placed in the forearm as loop or in the upper arm or in the thigh. Surprisingly, thigh AV grafts have longer lifespan in comparison with native AV fistulae [8,9]. A new challenge has arosen recently with functioning vascular access in transplant partients: there is an additional hemodynamic burden for the heart, increasing dilation of AV fistula aneurysm, cosmetic effects and painful thrombosis with usually seen systemic signs of inflammation [10].

Salvage of thrombosed AV fistulas and grafts is at least as important as creation of new ones. Successful salvage means immediate function, no need for a catheter, no need for a new AV fistula/graft creation, thus sparing vasculature and at last but not least it increases the patients' sense of safety and wellbeing. Salvage could be perfor-

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med by interventional radiologists or interventional nephrologists. The latter could act endovascularly or by surgery. Surgical thrombectomies and revisions of AV fistulas and grafts had better results compared to endovascular procedures. This is true especially for thromboses due to perianastomotic stenosis. In our group of 111 thrombosed native AV fistulae, 128 surgical salvage procedures were performed, immediate success rate was 93.8% and 1-year postinterventional patency rate was 68% (for both thrombectomies alone and thrombectomies with creation of a new anastomsis) and 73% for thrombectomies with reanastomosis [11]. Analysis of our group of 59 AV grafts thrombosis revealed that 129 thrombectomies were needed, immediate success rate was 78% and 1-year postinterventional rate was 76%. In all grafts fistulography was performed after thrombectomy and percutaneous transluminal angioplaty was performed if necessary [12].

Hemodialysis catheters as acute or permanent vascular access

For acute hemodialysis and apheresis patients as well as for chronic hemodialysis patients without possibility of creating either native AV fistula or AV graft, central vein catheters were vascular access of choice or, for few of them, the last resort for hemodialysis. Femoral catheters were introduced by Stanley Sheldon in 1961, jugular in 1971 and subclavian in 1978. Broviac introduced silastic catheters for cancer patients and they were modified by Hickman and used for hemodialysis vascular access in 1977. According to the European and American guidelines tunneled, cuffed catheters have been suggested as the best permanent vascular access for certain chronic HD patients with exhausted vasculature for creating AV fistulas or grafts. The main reasons for this suggestion were lower incidence of catheter-related infections, at exit site, and bacteremias or septicemias compared to nontunneled ones. Our experience with 103 tunneled, cuffed catheters, placed by nephrologists, can be compared with the experience of other experts. The median time free of complications was 3 months, incidence of exit site infection was 0,09/1000 and septicemias 0,1/1000 catheter days [13]. An important issue in the catheters is locking solution, the most promissing is 3-sodium citrate [14]. Surprisingly, design of temporary jugular catheters might also have an important impact on catheter-related infections: in precurved catheters, compared to straight ones, the incidence of bacteremia was 0 vs. 5,6/1000 catheter days [15]. Our experience with 30 temporary, precurved jugular cathters, locked with 4% and 30% citrate, with antibiotic ointment at the exit site, was similar to tunneled catheters: incidence of exit site infections and bacteremias was 0,2/1000 and 0,2/1000 catheter days, respectively. However, these results should be confirmed by controlled randomized clinical analysis. The advantage of our precurved jugular temporary catheters as permanent vascular access was in the easier way to insert or to replace by guidewire or to remove it. All these maneuvers could be done by the majority of the nephrologists at any time, even at night, whilst insertion, replacing or removal of tunneled catheters require surgical skills [16].

Conclusions

Since the introduction in 1966, native AV fistula is still a vascular access of choice for the majority of chronic hemodialysis patients. The second best access choice is AV graft and the worst but many times the last resort, tunneled catheters. Recent publications have revealed surprising data that thigh AV grafts are of high quality, comparable to native AV fistula. Salvage of AV fistula or graft, mainly by thrombectomy, is as important as creation of a new fistula. It should be performed at any time after thrombosis, it is optimal to do it as soon as possible and is quite successful. Although the European and American quidelines recommend exclusive use of tunneled catheters as permanent vascular access when vasculature is exhausted, there arre data revealing that temporary jugular catheters, especially designed (precurved), locked with citrate have as low incidence of catheter-related infection as tunneled catheters. However, randomized controlled trials should be performed to confirm these observations. Growing amount of evidence has indicated that locking solution of choice for hemodialysis catheters is citrate.
Nephrologists, at least those who are treating hemodialysis patients, should be involved in the process of vascular access: they should be capable of performing ultrasound/doppler sonography along with vascular mapping before access surgery and before salvage procedures. They should also be capable to insert (at least temporary) hemodialysis catheters at any time. Nephrologists are also very much interested in creating and maintaing vascular access for hemodialysis. Although they can create technically excellent AV fistula or AV graft, their perfect understanding of the problems of vascular access for hemodialysis together with their knowledge of hemodialysis therapy, give them the advantage over vascular surgeons.

Conflict of interest statement. None declared.

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Original Article

BMP-2 Protein Expression in Clear Cell Renal Carcinoma

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Abstract

Introduction. Bone morphogenetic protein-2 (BMP-2) is a member of BMP family of proteins. In human, it has role in skeletal repair and regeneration, as well as in heart formation. Kidneys of BMP-2 heterozygous null mutant mice have normal gross anatomy, but exhibit increased ureteric bud branching. Dysregulation of BMP-2 signaling has been suggested in carcinogenesis.
Methods. We determined BMP-2 protein expression in CCRC and in healthy renal tissue, and evaluated its prognostic significance after five years of follow-up. Twenty patients with localized clear cell carcinomas at the time of diagnosis were included in the investigation. Immunohistochemical staining for BMP-2 was evaluated semiquantitatively and the specimens were scored according to the distribution of positive cells.
Results. In normal tissue, the expression of BMP-2 was localized predominantly in tubular cells, with less intensive staining in glomerular mesangial cells. Other glomerular cells were BMP-2 negative. The cellular staining pattern for BMP-2 was both cytoplasmic and membranous. In 14 of 20 patients, loss of BMP-2 staining was observed in the malignant tissue. However, three out of six patients with positive BMP-2 staining died from disseminated malignant disease, one of them had concomitant acute myeloid leukemia.
Conclusions. According to our results, BMP-2 expression in CCRC may be associated with an adverse outcome with development of bone metastatic disease.

Key words: BMP-2, clear cell renal carcinoma, outcome, bone metastases, immunohistochemistry

Introduction

Bone morphogenetic protein-2 (BMP-2) is a member of BMP family of proteins. BMP-2 heterozygous null mutant mice die at embryonic day 7,5-9 with failure of proamnionic canal to close and abnormal development of the heart. In human, it has role in skeletal repair and regeneration, as well as in heart formation [1]. During kidney development, BMP-2 transcripts are expressed in condensed metanephric mesenchyme close to the tips of the ureteric bud [2]. Kidneys of BMP-2 heterozygous null mutant mice have normal gross anatomy, but exhibit increased ureteric bud branching. It is believed that BMP-2 inhibits branching morphogenesis at the tips of the branching ureteric bud [3]. Dysregulation of BMP-2 signaling has been suggested in carcinogenesis [4-10]. Clear cell renal carcinoma (CCRC) at the localized stage is considered as curable surgical disease. Still, almost 30% of patients who present with limited disease at the time of surgery develop metastasis within the next 3 years [11]. Numerous molecular markers have been investigated in terms of predicting disease progression, as well as potential therapeutic targets for CCRC. The clinicopathological significance of BMP-2 expression in human CCRC has not been investigated.
In the present study, we determined BMP-2 protein expression in CCRC and in healthy renal tissue, and evaluated its prognostic significance after five years of follow-up.

Materials and methods

Tissue samples were obtained at the Department of Urology, University Hospital Zagreb, Zagreb, Croatia, from 25 consecutive patients who underwent nephrectomy for renal cancer. Out of 25 tumor samples, there were 20 clear cell carcinomas that were further processed and these patients were included in the investigation. The study was approved by the investigators' Institutional Review Board.
The study included 12 male and 8 female patients ranged in age from 39 to 83 years (mean 63 years), 6 of them being smokers for more than 10 years. Tumor size ranged from 2 to 4,8 cm (average 2,5 cm). Renal cancer was incidentally found on routine examination in 6 patients. Presenting symptoms included haematuria in 6 patients, flank pain in 6 patients, while one patient presented with a palpable mass. Laboratory investigations at diagnosis demonstrated elevated sedimentation rate in 12 patients. Thrombocytopenia, anemia and erythrocytosis were found in 1 patient each. Elevated liver chemistries were found in two patients. Sixteen patients had one or more concomitant diseases including urolithiasis, diabetes mellitus, valvular heart disease and angina pectoris. One patient had

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previously been treated for acute myeloid leukemia with allogenic bone marrow transplantation.
Besides the abdominal multi-slice computed tomography, all patients underwent bone scan and chest X-ray to exclude disease dissemination before surgery. Tumor samples and corresponding healthy parts taken from the normal tissue located as far as possible from the tumor site were collected.

Immunohistochemistry

Formalin-fixed, paraffin-embedded tissues (3-4 μm) were deparaffinised in xylene and then rehydrated through graded alcohol. Endogenous peroxidase activity was blocked with 0,3 % hydrogen peroxide for 10 min. The sections were blocked with 20% normal rabbit serum for 30 min prior to 1 h of incubation with primary antibody (mouse monoclonal BMP-2 antibody, Abcam, UK). The slides were washed twice in Tris-buffered saline and incubated with biotinylated rabbit-antimouse antibody (DAKO, Glostrup, Denmark) diluted 1:500 in blocking serum. The detection of antibody reaction was carried out with a standard streptavidin-biotin complex (Dako, Glostrup, Denmark). Negative control sections were processed in an identical manner after omitting the primary antibody and showed no staining.

Evaluation of immunohistochemistry

Immunohistochemical staining for BMP-2 was evaluated semiquantitatively and the specimens were scored according to the distribution of positive cells. Immunostaining results were graded according to the following protocol: 3+, more than 50 % of cells positive; 2+, 50-75% of cells positive; 1+, 10-49 % of cells positive; and 0, if < 10 % of cells demonstrated positive staining.
The cellular localization and pattern of immunoreactivity were examined in a blinded fashion independently by two investigators.

Statistical analysis

SAS for Windows, version 9.1 (SAS Institute, Cary, USA) was used to perform statistical calculations. The chi-square test was used to evaluate the association between BMP-2 expression and the clinicopathologic parameters. P values <0.05 were considered statistically significant.

Results

Expression of BMP-2 in normal kidney tissue

Expression of BMP-2 was investigated in specimens of normal kidney by using immunohistochemistry (Figure 1). Tissue samples were collected from the site most distant from the tumor. In normal tissue, the expression of BMP-2 was localized predominantly in tubular cells, with less intensive staining in glomerular mesangial cells. Other glomerular cells were BMP-2 negative (Figure 1). The cellular staining pattern for BMP-2 was both cytoplasmic and membranous. All healthy samples exhibited positive BMP-2 staining with average score 2.77 (range 2-3).

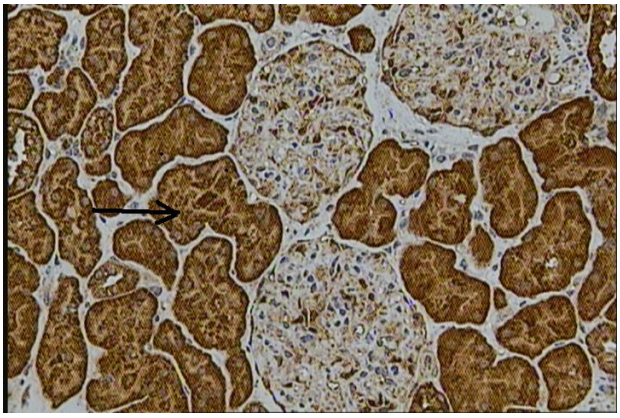

Fig. 1. Essentially all tubular cells show strong and uniform cytoplasmic positivity for BMP2 (arrow)

Expression of BMP-2 in clear cell renal carcinoma

Next, we examined BMP-2 expression in a series of clear cell renal carcinoma specimens. In 14 of 20 patients, loss of BMP-2 staining was observed (Figure 2).

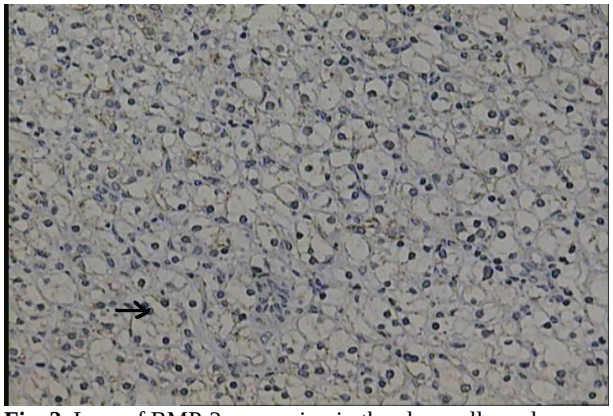

Fig. 2. Loss of BMP-2 expression in the clear cell renal carcinoma (arrow)

Six samples exhibited positive BMP-2 staining. It is interesting that 5 out of 6 patients with positive BMP-2 staining in malignant tissue presented with macrohaematuria, compared with occurrence of macrohaematuria in only 1 out of 14 patients with negative BMP-2 staining in the malignant tissue ($p<0.05$). BMP-2 expression did not correlate with other presenting symptoms.

BMP-2 protein expression and survival

During the mean follow-up of five years 12 patients died. Average age of deceased patients was 78 years. Four of them had positive BMP-2 staining in malignant tissue. Three of the patients with positive BMP-2 staining died from disseminated malignant disease, one of them had concomitant acute myeloid leukemia. Two patients died from acute myocardial infarction. Cause of death of other patients is unknown, but they had no signs of disease dissemination.

Discussion

In addition to their roles in tissue morphogenesis, recent literature suggests that different members of the BMP family of proteins may be involved in human cancers. Thus, in recent years, BMP-2 has generated considerably attention in cancer biology. It was found in various human cancers including pancreatic cancer [9], fibrosarcoma, serous adenocarcinoma, prostate carcinoma [12], mucinous adenocarcinoma, fibrosarcoma, mesothelioma [7], glioma [13], ovarian cancer [8], oral carcinoma [14] and osteosarcoma [15]. It was found to be 8,9 fold upregulated in invasive human bladder cancer [16].

Besides the aberrant expression of BMP genes in tumorous tissues, an important factor of their action is expression of BMP receptors located on plasma membrane of the cell. Overexpression of BMP receptors may allow more ligand molecules to bind with receptors inducing abnormal cellular function. For example, BMP-2 is expressed in both osteosarcoma and malignant fibrous histiocytoma. However, BMP receptor could not be demonstrated by immunohistochemistry in malignant fibrous histiocytoma that may help to differentiate these two types of tumour, as well as explain why malignant fibrous histiocytoma does not ossify [17]. Enrichments of BMP2 in non-small cell lung cancer tumor cell enhance tumor growth in vivo [18,19], due to activation of second messengers SMAD 1 and 5 [20].

Bone morphogenetic proteins may demonstrate both stimulative and anti-proliferative action on tumor growth based on expression of their promoters or inhibitors, recaptors and second messengers.

BMP-2 is involved in heterotopic ossification in metastatic lesions from different types of malignant cells including urothelial bladder carcinoma [21], malignant melanoma [22] and gastric cancer [23,24]. It was found to enhance motility and invasiveness of prostate cancer cell lines [25] as well as migration and invasion of gastric cancer cells by activating the phosphatidylinositol 3-kinase pathway [6]. It may differently affect mesenchymal to epithelial and epithelial to mesenchymal transformation depending on the dosage in colon cancer cells [6].

Besides the role in cell proliferation, BMP-2 has generally being proposed to be an angiogenic factor [26,27], promoting neoangiogenesis when associated with VEGF (vascular endothelial growth factor) in lung cancer [4].

Increased expression of BMP-2 has recently been found by two independent investigators in cases of bone metastasis and muscle invasion of bladder urothelial carcinoma [28,29]. They conclude that BMP-2 correlates with bone metastases in bladder urothelial cancer.

Our data demonstrated that BMP-2 expression in malignant tissue was associated with development of metastatic disease and with mortality. Results are in line with published data dealing with BMP-2 expression in other malignancies [4-10, 21-30]. Over the last years, nephron sparing surgery has been used to treat majority of patients with small kidney cancers. However, even small cancers may spread throughout the body as demonstrated by our study. Further investigations with more patients with tumors of different stages and grades are necessary to define the role for BMP-2 in renal clear cell carcinoma.

Conclusions

BMP-2 may have different functions in tumor biology depending on the type of tissue or even on the type of cell, as well as conditions in the microenvironment. Current data suggest that BMP-2 may be involved mostly in metastasis, epithelial to mesenchymal transformation and invasion of cancers.

Conflict of interest statement. None declared.

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Original Article

Attainment of Clinical Guideline Targets is Associated with Improved Survival in Prevalent Hemodialysis Patients

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Abstract

Introduction. The development and implementation of clinical guidelines aims at delivering better healthcare by means of quality improvement. In a single-centre, retrospective cohort study we examined the association between achievement of guideline targets and clinical outcomes of prevalent hemodialysis patients..

Methods. Forty-seven stable, prevalent, end-stage renal disease patients treated with thrice weekly, in-centre hemodialysis were included in the analysis. The guideline targets examined at the initiation of the study were: 1) use of an arteriovenous (AV) fistula as vascular access or not, 2) haemoglobin ≥ 11 g/dl, and 3) serum albumin ≥ 3,8 g/dl. Mean follow-up time was 11,2±2,0 months.

Results. At baseline, 78,7% of patients had an AV fistula as vascular access, 72,3% of patients had haemoglobin ≥11 g/dl, 76,6% of patients had serum albumin ≥3,8 g/dl, whereas 17,0%,31,9%,48,9% of patients met any one, two or all three guideline targets, respectively. The largest survival benefit was found for the use of an AV fistula (unadjusted mortality hazard ratio: 0,11, p=0,002). The simultaneous attainment of more than one guideline target was also associated, in a graded manner, with lower mortality over the study period (unadjusted mortality hazard ratio: 0,10 and 0,07 for any two or all three guideline targets met, respectively, p<0,05).

Conclusions. The attainment of clinical guideline targets, especially the use of an AV fistula as vascular access, is related to improved mid-term survival in prevalent hemodialysis patients in a single centre and possibly contributes to the so-called centre effect.

Keywords: guidelines, hemodialysis, arteriovenous fistula, haemoglobin, albumin

Introduction

The evolution of modern medical practice over the last decades has relied heavily upon evidence-based data from clinical trials. Alongside this trend, large professional societies have developed and published clinical guidelines based on hard evidence whenever possible and alternatively on expert opinion. These clinical guidelines aim at defining the standard of care and at reducing discrepancies in practice patterns without compromising the role of physician judgement and individualization of patient care. KDIGO (Kidney Disease Improving Global Outcomes) and KDOQI (Kidney Disease Outcomes Quality Initiative) are premier examples of guideline developing organizations of interest to the nephrology community.

In an era of global financial restraints and stringent control over health expenditures, the notion of 'pay for performance' has gained special attention and has incurporated the use of clinical guidelines targets. These act as performance measures and their attainment by the healthcare provider serves as a financial incentive. For example, KDOQI clinical guidelines for vascular access [1], anemia [2] and dialysis adequacy [1] in end-stage renal disease (ESRD) patients are officially endorsed in the United States by a quality improvement program [3] and attaining the specified targets leads to compensation of in-centre dialysis facilities [4].

Several studies have examined the association between achievement of KDOQI parameters, either separately or grouped, and clinical outcomes [5-7]. Decreased mortality and morbidity, lower rates of hospitalizations and lower health costs have been reported for patients satisfying the target values. Among KDOQI parameters, serum albumin, a marker of nutrition and inflammatory status, is considered a strong predictor of mortality in ESRD and, thus, it has been extensively studied [8,9]. Data from Southeastern Europe on the issue of guideline targets attainment in hemodialysis are sparse. We evaluated the relation between achievement of guideline targets and clinical outcomes of prevalent hemodialysis patients in a single-centre study from Greece.

Subjects and methods

Study design and participants

This study is designed as a retrospective cohort analysis. Forty-seven Caucasian prevalent end-stage renal disease patients who underwent thrice weekly chronic hemodia-

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lysis (HD) in a single centre were enrolled. The eligibility criteria were: age more than 18 years and receiving chronic HD for more than 3 months. Exclusion criteria were: scheduled living donor renal transplantation and severe comorbidities (active malignancy, active infection, end-stage organ disease namely cardiac, pulmonary or hepatic failure). Residual renal function was negligible in all patients.

Hemodialysis prescription

All patients were dialyzed for a minimum of 4 hours per session. Extended HD duration was applied whenever clinically indicated. Blood flow rate ranged between 250-300 ml/min and dialysate flow rate was fixed at 500 ml/min as per centre`s protocols. Dialysate composition was individualized according to each patient`s clinical needs. Dialysate sodium ranged from 138 to 142 mmol/l, dialysate calcium ranged from 1,5 to 1,75 mmol/l and dialysate potassium ranged from 2 to 3 mmol/l; rest of the dialysate ingredients were the same among all patients. Sodium or ultrafiltration modeling was not applied. The dialysis monitors in use were the same for all patients (AK 200™ S, Gambro AB, Lund, Sweden). Two types of dialyzers were used during the study period: a high-flux membrane dialyzer (Toraysulfone® TS 2.1, Toray Industries, Inc., Tokyo, Japan) and a low-flux membrane one (Filtryzer® B3 2,0, Polymethylmethacrylate-PMMA membrane, Toray Industries, Inc., Tokyo, Japan).

Study variables

At study initiation the following parameters were categorized as to whether they satisfied the respective KDOQI guideline targets or not: 1) use of an AV fistula as vascular access, 2) haemoglobin ≥11 g/dl, and 3) serum albumin ≥3,8 g/dl (lower normal limit for the reference range of our laboratory). Follow-up clinical assessment was performed monthly during the study period. In addition, biochemical tests were also performed on a monthly basis and the time-averaged values of the latter two independent variables were calculated. All blood samples were analyzed at the same, central, certified laboratory (Medisyn SA). Primary outcome variable was all-cause mortality. Follow-up time was continued until death, kidney transplantation, switch to peritoneal dialysis or loss to follow-up.

Statistical analysis

Descriptive data were expressed as mean ± standard deviation (SD) and percentages of the total. The comparison between baseline and time-averaged values was done using the paired Student's t-test, where appropriate; chi-square test was used for categorical data. We used the Cox proportional hazards model for estimating the association between guideline targets attained and mortality. Model results were summarized by the use of hazard ratio (HR) and 95% confidence intervals (CI). The level of statistical significance was set at $p<0,05$. All analyses were performed using SPSS software, version 17.0 (SPSS Inc, Chicago, IL).

Results

Baseline patient data are displayed in Table 1. Mean patient age was 69,4±15.4 years. Mean time on dialysis was 1,8±1,1 years. 25,5% of the patients were diabetics whereas 50% had cardiovascular disease. Mean follow-up time was 11,2±2,0 months. No patients were switched to peritoneal dialysis, transferred to another HD unit or underwent kidney transplantation during the study period; as such, no losses to follow-up were recorded.

Table 1. Baseline demographic, clinical, laboratory data. URR, urea reduction ratio

Age (years)	69,7	±15,4
Sex: Males (%)	74,5	
Females (%)	25,5	
Diabetes (%)	23,4	
HD burden (years)	1,8	±1,1
AV access: AV fistula (%)	78,7	
AV graft (%)	6,4	
Catheter (%)	14,9	
Causes of ESRD:		
Diabetic nephropathy (%)	18,2	
Glomerulonephritis (%)	13,6	
Hypertension (%)	18,2	
Other/unknown (%)	50,0	
Cardiovascular disease (%)	50,0	
URR (%)	72,5	±5,7
Haemoglobin (g/dl)	11,3	±1,2
Albumin (mg/dl)	3,9	±0,3

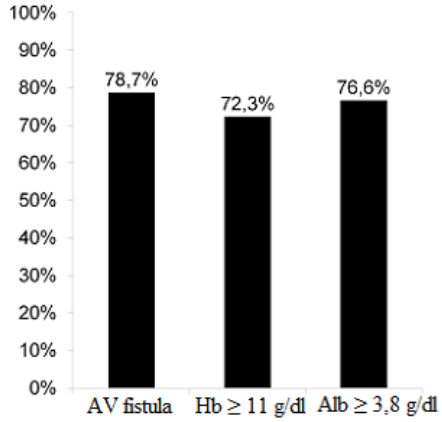

Fig. 1. Percentage of patients with functioning AV fistula, haemoglobin ≥ 11 g/dl and serum albumin ≥ 3,8 g/dl

The percentage of patients with a functioning AV fistula at baseline was 78,7% (Figure 1). Likewise, 72,3% of patients had haemoglobin ≥11 g/dl and 76,6% of patients had serum albumin ≥3,8 g/dl. Time-averaged values of haemoglobin and serum albumin were kept constant over the course of the study and did not differ significantly from baseline. The percentage of patients who simultaneously attained any one, two or three guideline targets was 17,0%, 31,9% and 48,9%, respectively (Figure 2). Of the patient subset who achieved only one target, the majority (62,5%) had achieved the target of haemoglobin ≥ 11 g/dl.

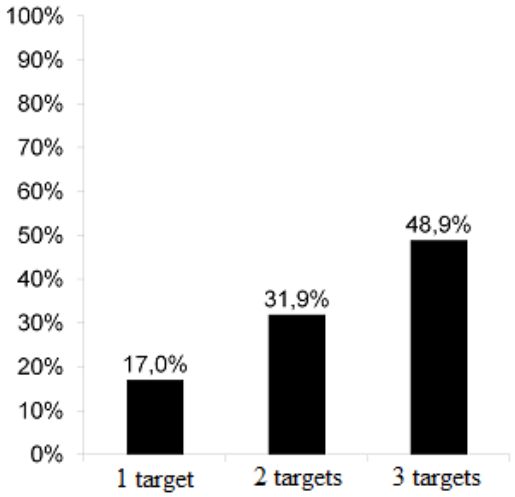

Fig. 2. Percentage of simultaneously attained guideline targets

Seven patients (14,9%) deceased during the follow-up period. Three patients died from cardiovascular causes (abdominal aortic aneurysm rupture, thoracic aortic dissection and ischemic cerebrovascular accident) and three patients from infectious complications. One of them had satisfied one guideline target, four had satisfied two guideline targets simultaneously and the remaining one had satisfied all three guideline targets simultaneously. The unadjusted all-cause mortality hazard ratio for use of a functioning AV fistula was 0,11 (95% CI: 0,02-0,59) (Table 2). Satisfying each individual guideline for haemoglobin ≥11 g/dl and serum albumin ≥3,8 g/dl was also correlated with decreased mortality, albeit it did not reach statistical significance. The simultaneous attainment of more than one guideline targets was also associated with a robust survival benefit. Unadjusted mortality hazard ratio for satisfying any two guideline targets simultaneously was 0,10 and unadjusted mortality hazard ratio for satisfying all three guideline targets was 0,07 ($p<0,05$).

Table 2. Hazard ratio (HR) for mortality associated with guideline targets attained

Guideline target	Frequency (%)	HR (95% CI)
None	2,1	1
AV fistula	78,7	0,11 (0,02-0,59)
Haemoglobin ≥ 11 g/dl	72,3	0,81 (0,15-4,43)
Albumin ≥ 3,8 g/dl	76,6	0,25 (0,05-1,25)

Discussion

The results of this study confirm previous trials that achievement of guideline targets in ESRD patients is associated with reductions in mortality [6,7]. Although patient characteristics of this specific case mix, such as mean age of 69,7 years, mean HD burden of 1,8 years and 50% prevalence of cardiovascular disease, a high risk cohort in terms of morbidity and a potential survivor bias, the proportion of achieved targets may as well reflect the time and efforts consumed by the medical and nursing staff to reach and preserve a survival benefit. An overall 80,8% of the patients had achieved simultaneously two or more of the targets studied, whereas over 70% of them had achieved each of the targets separately. Moreover, the consistency of time-averaged values over follow-up time secures a stable effect during the study period and adds to the strength of the observed outcome. The selection of clinical guideline targets to be studied requires further attention. According to the U.S. ESRD Clinical Performance Measures Project [3] the parameters used for the 'pay per performance' schema of in-centre dialysis facilities are urea reduction ratio (URR) ≥65%, haemoglobin ≥11 g/dl and the use of AV fistula as vascular access. However, differences in clinical practice between U.S. and the rest of the world limit the comparison of URR as a guideline target across different populations. Even in large, multicenter trials [10], mean dialysis session duration in U.S. hardly reaches four hours, which is the minimum accepted norm in Europe and Japan. Consequently, U.S. dialysis units strive to achieve the URR target within these time limitations. By contrast, almost all our patients had URR ≥ 65% and we chose not to use this guideline target because of the obvious bias. Instead, we selected the use of serum albumin, a KDOQI guideline target [11] and a powerful risk marker in ESRD [12], which is influenced by poor nutrition and persistent inflammation. Malnutrition, inflammation and atherosclerosis (MIA) syndrome is rather common in ESRD and, hence, renders the normalization of serum albumin levels a difficult task for the attending nephrologist. The correlation of serum albumin ≥ 3,8 g/dl with mortality failed to reach statistical significance in our study but the simultaneous attainment of this target alongside the other two targets did relate to reduced mortality. The importance of AV fistula as the vascular access of choice in ESRD patients is indispensable. Its use has demonstrated longer access survival half-life and has been associated with fewer complications. Furthermore, timely creation of an AV fistula and avoidance of a central venous catheter has been argued recently to be the principal determinant of superior survival in incident hemodialysis patients, which equals that of incident peritoneal dialysis patient and thus ceasing effectively the controversy over dialysis modality choice for this population [13,14]. Fistula First initiative [15] in the U.S. has been developed solely for the purpose of increasing the rates of native AV fistula use. The utility of haemoglobin as a clinical guideline target is even more plausible partly because it is easily modifiable by the use of erythropoiesis stimula-

ting agents (ESAs). However, caution should be exercised regarding the targeted upper limit of haemoglobin in fear of severe cardiovascular complications [16,17]. In our study, mean haemoglobin was 11,3±1,2 g/dl, whereas in seven patients on ESAs it was over the cutoff of 12 g/dl, ranging from 12,1 to 12,7 g/dl.

The financial implications of guideline targeting reveal a large cost benefit [18]. According to Plantinga, *et al*. [6], attainment of each target resulted in a decrease in annual Medicare hospital payments of approximately $762 per patient-year. Vice versa, every 0,1 decrease in Kt/V was independently associated with an additional $940 of Medicare inpatient expenditures in another study [19]. Moreover, the benefits of reduced hospitalizations on overstressed healthcare systems and on health related quality of life of patients must also be taken into account. Although our study did not address specifically the issue of expenditures and hospitalizations, there is ample evidence that guideline targeting is cost effective.

We feel that certain possible limitations to this study deserve to be mentioned. First of all, the small sample size of a single centre study may attenuate the robustness of our results. On the other hand, there exists a homogeneous approach by the healthcare providers in the same clinical setting that reduces variability in practice and prevents suboptimal performance. Secondly, the retrospecttive, observational nature of this study demonstrates associations among the study variables and outcomes but it cannot prove causality. Residual confounding due to unknown variables cannot be excluded with certainty.

In conclusion, the attainment of clinical guideline targets represents a therapeutic challenge requiring strenuous efforts and vigilance by the healthcare team. Nevertheless, the potential benefits are becoming more and more tangible. Our study adds to the existing literature that improved survival is a feasible outcome together with reduced morbidity and expenditure costs.

Conflict of interest statement. None declared.

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Original Article

Short-Term Complications in Kidney Transplantation - Single Center Experience

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Abstract

Introduction. Kidney transplantation in a small developing country faced with political and economical burden, such as Bosnia and Herzegovina, represents a great problem for dedicated medical staff. The aim of this paper was to show results of kidney transplantation with special focus on frequency and causes of poor outcomes in the first year after transplantation.

Methods. For this retrospective review we have used the medical database of the University Clinical Center Tuzla, Department for Nephrology, Dialysis and Transplantation, for the period from September of 1999 through July of 2013. During that period, 117 renal transplantations were done, out of which 99 (84,62%) from living related donor, five (4,27%) from living unrelated donor (spouse) and 14 cadaveric (11,11%) transplantations. We have analyzed patient and graft survival as well as development of medical and surgical complications. Poor outcome in the first post-transplantation year was defined as death and graft loss.

Results. Gender structure of 117 transplanted patients was 76 males (64,96%) and 41 females (35,04%) with an average age of 33,68 (±10,47), including six children younger than 16. During the first post-transplantation year, five recipients died (4,27%), with cardiovascular incidents as a direct cause in three and sepsis in two cases. Nine patients (7,69%) had lost graft function during the first year post-transplantation. Causes of graft loss were acute humoral rejection in two and sepsis in two recipients, with venous and arterial thrombosis, rupture of renal artery and multiorgan insufficiency after hemorrhagic shock. Acute rejection was diagnosed in ten (8,55%) and new onset diabetes mellitus in five (4,27%) recipients.

Conclusions. We can conclude that survival of kidney graft and recipients after first post-transplantation year was 92,31% and 95,73%, respectively which is in accordance with modern recommendation, especially when we talk about small transplantation center in the developing country with political and financial problems.

Keywords: kidney, transplantation, short-term survival

Introduction

Kidney transplantation in Bosnia and Herzegovina (BH) dates back to the 70-ies of the last century in Sarajevo, and after the break during the war, it was started again during 1997 in Sarajevo and in 1999 in Tuzla. However, despite such an early start, transplantation in BH is still limited to mainly living related transplantation, while deceased donor transplantation is still waiting for better days. During the period from 2006 to 2011, there were seven deceased donors, so 14 kidney transplantations were done. Current situation can be explained by our geopolitical circumstances, divided health system within the state, lack of motivation among doctors and poor financial support. Kidney transplantation in a small developing country faced with political and economical burden, such as BH, represents a great problem for dedicated medical staff. The aim of this paper was to show the results of kidney transplantation in the University Clinical Center Tuzla, with special focus on frequency and causes of poor outcomes in the first post-transplantation year.

Materials and Methods

For this retrospective review we have used the medical database of the University Clinical Center Tuzla, Department for Nephrology, Dialysis and Transplantation, for the period from September of 1999 through July of 2013. During that period, 117 kidney transplantations were done, out of which 99 (84,62%) from living related donor, five (4,27%) from living unrelated donor (spouse) and 14 transplantations from deceased donors (11,11%). All transplanted patients were preoperatively prepared in the Department for Nephrology, Dialysis and Transplantation from where they were directly sent to the operating theatre. After they spent 4 to 7 postoperative days in the Intensive care

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unit (with daily nephrologists visits), they were sent back to the Department for Nephrology, Dialysis and Transplantation for additional 15-30 days. After that period, they have had continuous follow-up in the Nephrology outpatient clinic for transplanted patients. During the period from 1999 until 2002 we used ATG and triple immunosuppressive therapy consisting of corticosteroids, azathioprine and cyclosporine. Since 2002 we have switched to basiliximab and replaced azathioprine by mycophenolate mofetil, and from 2006 on, half of our patients use tacrolimus. More than 80% of transplanted patients have got urethral stent for 2 to 3 weeks. Poor outcome in the first post-transplantation year represent death and graft loss.

Results

Gender structure of 117 transplanted patients was 76 males (64,96%) and 41 females (35,04%). The average age of kidney graft recipients was 33.68 (±10,47), ranging from 12 to 60. There were six children younger than 16. Primary renal disease was glomerulonephritis in 54,7% of recipients (mainly without pathohistological confirmation); undefined in 17,1%, reflux in 10,25%, interstitial nephritis or pyelonephritis in 7,69%, lupus nephritis in 2,56% and diabetes in 2,56% of recipients. Living related donor was mother in 31,31%, father in 31,31%, sister in 12,12%, and brother in 13,13% of cases. In 10,10% of cases donors were distant relatives. In all five cases of living unrelated donations, donors were spouses. Out of seven deceased donors, three had head trauma as a cause of brain death, and four had acute neurologic incident. The overall average living donor age was 49,66±11,19 (25-72), while the average deceased donor age was 48,71±16,99 (25-62).

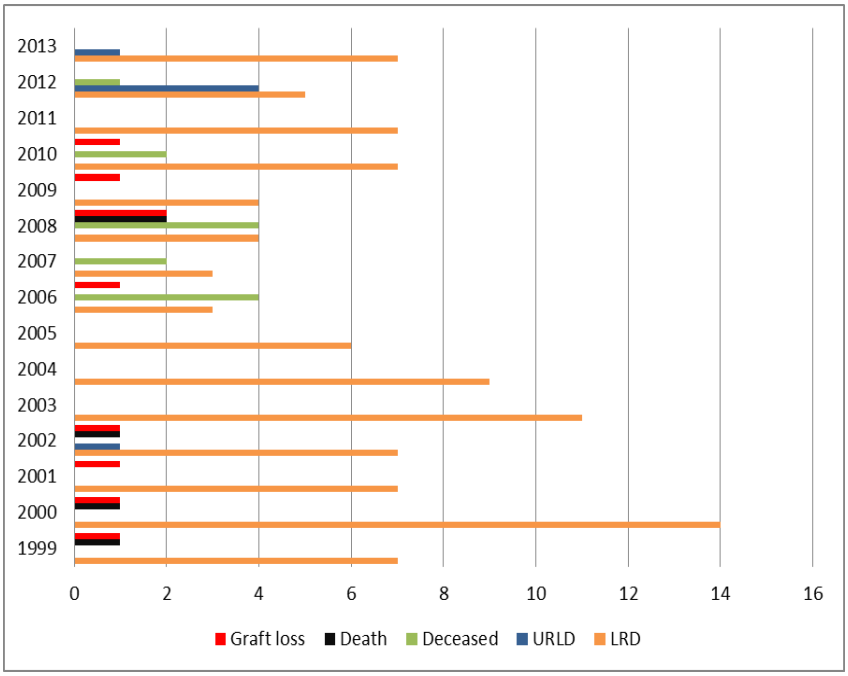

Fig. 1. Frequency of death and graft losses during the first post-transplantation year
Legend: Deceased - transplanatation from deceased donor, URLD-unrelated living donor transplantation, LRD - living related donor transplantation

During the first post-transplantation year, five recipients died (Figure 1), out of whom four with non-functional graft and one with functional graft. Causes were cardiovascular incidents in three and sepsis in two cases. Three of those five got a kidney from living related donor and two from deceased donors. Overall nine patients lost graft function during the first year post-transplantation (Figure 1), out of whom three with kidney from deceased donors. Causes of graft loss were acute humoral rejection in two and sepsis in two recipients, with venous and arterial thrombosis, rupture of renal artery and multiorgan insufficiency after hemorrhagic shock being the cause of the remaining graft losses. The average age of patients who died or lost the graft was 40(26-60), and the average number of months spent on dialysis for those was 71(8-264).

Among other complications emerging during the first year after transplantation the most frequent ones were: acute rejection in ten, diabetes mellitus in five, lymphocella in four, urinome in three, urinary tract infection in three and intramuscular hematoma in two patients. Besides that, one patient had stent obstruction with consequential hydronephrosis, the other one profound hypokaliemia and the third one reactive stress disorder. One child had posterior reversible encephalopathy syndrome (PRES), and one patient with delayed graft function had pathohistologically confirmed acute tubular necrosis.

Discussion

According to the data from BH Renal register, in year 2011, 2362 patients were treated by one of renal replacement

therapies; therefore prevalence was 665,2 per million population. Unfortunately, only 7% were those subjected to transplantation and with functioning renal graft. The Society for nephrology, dialysis and kidney transplantation in BH, with the help of international nephrology and transplantation societies, puts great effort in realization of the kidney transplantation project. However, support from official health institutions in BH is not sufficient at the moment, so the transplantation medicine in BH is dependent on isolated efforts of medical personnel in three university clinical centers. Despite the fact that the legislative regulation for transplantation exists and that it is in concordance with the European regulations, lack of, mainly political, will to commence with necessary activities on implementing those regulations has resulted in scarce number of realized transplantations in previous 15 years.

However, under such circumstances, 117 kidney transplantations done solely in Tuzla represent result worthy of respect, with great chance of growing number of transplanted patients in the near future. Small transplantation centers in developing countries encounter numerous obstacles such as providing political and public support, financial support, education programs and technological environment, and BH is not an exception. Starting the program of kidney transplantation in Tuzla, in 1999, only four years after the devastating war (1992-1995), was not at all an easy task.

Analysis of the results of transplantation in Tuzla in the past 15 years shows that patient and graft survival is in accordance with the widely accepted recommendations and guidelines [1]. 85% is assumed to be an acceptable minimum of graft survival in the first post-transplantation year, and 90% for patient survival [2].

The results obtained from seven years of living donor kidney transplantation in Great Britain showed that graft survival during that first post-transplantation year was 95%, while patient survival was 99% [1]. In our series of 104 (related and un-related) living donor kidney transplantations, three patients died in the first year following the procedure, which means that patient survival was 97%. In the same time period, four patients lost graft function, which means that graft survival was 96%.

Introducing basiliximab in immunosuppressive protocols in year 2002 significantly influenced transplantation results by lowering a number of acute rejection episodes in the first year after transplantation, as shown in large patient series [3]. In the available literature there are scarce reports on transplantation results in non-experienced transplantation centers, but in the report from Great Britain graft survival was 93%after the first post-transplantation year, while incidence of early acute rejection was 11% [4]. The result from our center show lower incidence of acute rejection episodes (8,55%), most probably due to the fact that living related donor transplantations prevailed.

New onset diabetes mellitus is one of the important complications of transplantation. It is estimated that incidence of developing diabetes mellitus after transplantation is 4-20% [5]. Five of our patients developed this complication (4,27%), with four of them taking tacrolimus as calcineurin inhibitor. Three of those five patients had graft from deceased donors. Graft infection, frequently complicated with sepsis, is also a significant complication and one of the leading causes of graft failure and loss, and death as well [6]. We had two patients, both with graft from deceased donors, who died as a result of sepsis developed on the basis of graft infection with primary delayed graft function.

The frequency of postoperative complications such as lymphocellae, urinomes and urinary tract infections in our patients was 8,6%. Surgical interventions were necessary in those with urinomes, while lymphocellaes were spontaneously resolved. Urinary complications may produce great problems in early postoperative period and jeopardize graft function and patient's health; therefore, a good surgical explantation technique is of great importance, especially in deceased donor transplantation [7], as well as transplantation surgeon skills, since it has been proved that urinary complications are significantly more frequent in non-experienced surgeons [8].

5,27% of vascular complications in our patients do not represent high frequency, but it was significant since these complications resulted in death in four patients, and one emergency graftectomy in one patient with arterial thrombosis. Vascular complications in the earliest postoperative time, together with sepsis, are leading cause of graft loss in transplanted patients [9]. Thromboses in renal graft in adults are responsible for 2-7% of early graft loss, while in children those are much more frequent, reaching up to 35% [10]. Our six transplanted children, all getting graft from living related donor, fortunately did not have such complications. Cardiovascular complications with consequential death are very frequent in transplanted patients, and their frequency is in correlation with the number of pretransplantation dialysis months [11]. This was also valid for our rather little series of transplanted patients.

Only one girl out of our six transplanted children had early neurological complication (PRES) that resolved without further consequences. In a paper dealing with these complications, it is stated that frequency of neurological complications in children was 9%, PRES being the most frequent one [12].

Our results, together with those from the literature, show that incidence of early complications in kidney transplantation is reduced, according to the opinion of the majority of researchersdue to the usage of modern immunosuppressive drugs [13]. In one Irish study, frequency of early complications was lowered from around 7% in the nineties to a less than 1% at present time [14].

Conclusions

We can conclude that survival of kidney graft and recipients after first post-transplantation year was 92,31% and 95,73%, respectively and is in accordance with modern recommendations, especially when we talk about small transplantation center in the developing country with political and financial problems.

Conflict of interest statement. None declared.

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Original Article

Kidney Transplantation from Living-Unrelated and Elderly Living-Related Donors: Analysis of 5 Years Graft Survival and Outcome

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Abstract

Introduction. The shortage of kidney availability has increased utilization of other donor categories. The aim of our study was to compare the graft survival and outcome between living-unrelated donors (LURD) and elderly living related donors (LRD).

Methods. Fifteen LURD kidney transplanted patients in the period between 2000 and 2006, and 18 randomly selected recipients from elderly LRD (>60 years) kidneys were retrospectively evaluated from their patients' charts. The regular immunosuppressive protocol consisted of induction therapy with steroids and IL-2 receptor antibodies (Daclizumab in five doses), and maintenance therapy with mofetil mycophenolate, cyclosporine A and steroids. The analyzed variables were recipient and donor age and sex, glomerular filtration rate of donated kidney (evaluated by DTPA scan of the donor), HLA matching, cold ischemic time (CIT), delayed graft function (DGF), acute rejection episodes (AR), urinary infections (UTI), present status of the graft (determined by estimated GFR), and graft survival data.

Results. The two groups were similar with regard to age, gender and body weight of the recipients, CIT and cyclosporine targeted C_0/C_2 levels. The LURD group donors were younger, and GFR of the donated kidney signifycantly higher when compared to the elderly LRD group, (47,6±11.4 vs. 65,9±3,6 years, p<0,05; 53,3±14,2 vs. 44,1 ±10,1 ml/min; p<0,05). LURD group of patients was characterized by significantly higher percentage of AR and UTI, as well as longer hemodialysis duration when compared to the elderly LRD group (34,5% vs. 18,6%, p<0,05; and 36,4% vs. 20,2%, p<0,05; 34,7±12,2 vs. 8,0±6,9 months, p<0,01). No difference in graft survival rates was found between the groups at 5 years follow up, with graft survival rate of 100% in both groups. In addition, the graft function at 5 years after transplantation did not differ significantly between the groups, although the LURD group maintained slightly higher GFR compared to the elderly LRD group (55,7±15,6 vs. 46,3±16,8 ml/min, p>0.05).

Conclusions. Kidney transplant recipients from LURD have shown to yield 5 years graft survival rates and outcome similar to that of LRD older than 60 years. A possible partial explanation may be the higher GFR of donated kidney in LURD group, compared to the lower number of HLA mismatches in the group of kidney transplants from older LRD and their lower percentage of UTI and episodes of AR. Although these results are obtained in a pilot study, they confirm that in the presence of organ shortage from cadavers, LURD and older LRD may become a valuable source of potential organ for patients on the kidney waiting list.

Key words: kidney transplantation, living kidney donation, elderly related donors, unrelated donors

Introduction

Kidney transplantation with organs from living related donation (LRD) has been performed for many years with good results [1]. Namely, since its introduction over 50 years ago, live-donor kidney transplantation has been associated with better graft and patient outcomes compared to the deceased donor kidney transplantation [2,3].

However, organ shortage and a steadily increasing waiting time for cadaver kidney transplant have made it necessary to search for alternatives. Kidney transplantation from living unrelated donors (LURD), i.e. between persons who have close emotional bonds only, has been proposed as another possibility. Thus, the evidence of unexpectedly high rates of survival of kidney grafts from spouses and other living unrelated donors in patients with end-stage renal disease has been mounting in recent years [4-7]. Moreover, donors aged >60 years are now frequently accepted as another alternative for living kidney transplantation [8-10].

The aim of our study was to identify and evaluate the risk factors for graft outcome and survival and their comparison between the LURD and elderly LRD (>60years) groups of patients.

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Materials and methods

In our study 15 kidney transplant patients from LURD performed in the period 2000-2006, and 18 randomly selected recipients from elderly LRD (>60 years) were retrospectively evaluated from their patients' charts. All kidney transplant recipients included in the study received their first allograft. As an induction therapy we used methylprednisolone (500mg) and IL-2 receptor antibodies-Daclizumab (Zenapax®; 1mg/kg/BW at implantation and thereafter every 2 weeks in five doses). The maintenance immunosuppression consisted of cyclosporine A (Neoral®; 4-6mg/kg/day) initiated at least 36hrs after transplantation to reach target C2 levels of 800-1200 ng/ml, prednisolone (1 mg/kg/day tapered to 0,1 mg/kg/day after 4 weeks) and mycophenolate mofetil (Cellcept®; 1 g bid.).

Patients with DGF during the first postoperative month, manifested as post-transplant acute tubular necrosis (ATN), were treated with hemodialysis, and those who experienced an episode of acute rejection AR (increase in serum creatinine >20% or a decrease in urine output for 2 consecutive days), were treated with pulse corticosteroids. Biopsies were done by ultrasound-guided automated gun. Biopsy specimens were considered as adequate if they contained more than 7 glomeruli and at least one artery that were further histologically processed according to the Banff 97 scoring scheme [11].

The analyzed variables were as follows: recipient and donor age and sex, glomerular filtration rate of donated kidney (evaluated by DTPA scan of the donor), HLA matching, cold ischemic time (CIT), delayed graft function (DGF), acute rejection episodes (AR), number of urinary tract infections (UTI), present status of the graft (determined by estimated GFR e.g. calculated creatinine clearance-cClCr), and graft survival data. There were two groups of patients: Group 1: LURD group (n=15), including 10 kidneys donated from female and 5 from male spouses, and Group 2: LRD (>60 yr) group (n=18) consisted of 4 siblings, 13 parents and one cousin.

The clinical and biochemical data were recorded at the time of transplantation, at 1th, 6 months, and at 1th and 5 years posttransplant.

Data are expressed as mean values ± SD for continuous variables and as percentage for categorical data. For numeric data, ANOVA and Student's *t* test to compare the differences between 2 groups and Kruskal-Wallis and Mann-Whitney *U* test as nonparametric analysis were used when appropriate. Chi square (Fisher's exact test) was used to compare the categorical data. A difference was considered significant at a *P* value of <0.05.

Results

The groups did not differ regarding the cause of ESRD (Table 1).

Table 1. Demographic characteristics of recipients (cause of ESRD)

	LURD (nº=15)	LRD>60 yr (nº=18)
Glomerulonephritis	7	9
Diabetes	2	3
Hypertensive renal disease	2	2
Polycystic renal disease	1	1
Reflux nephropathy	0	1
Lupus nephropathy	0	1
Other	3 pts	2 pts

Table 2. Comparison of demographic characteristics, biochemical and clinical data between the groups

Parameters	LURD (nº=15) Mean±SD	LRD>60yr (nº=18) Mean±SD	p-value
Donor age (yr)	47,6±10,4	65,9±3,6	<0,05
Recipient age (yr)	35,1±9,8	30,3±10,0	ns
Recipient BMI	22,4±4,0	22,8±3,8	ns
GFR don. kidney	53,3±14,2	44,1±10,1	<0,05
Time on HD (mo)	34,7±12,2	8,0±6,9	<0,01
HLA mismatch	4,4±1,8	2,1±1,1	<0,01
CIT (hours)	2,5±1,4	3,1±1,8	ns
DGF	15,3%	17,6%	ns
AR post-transplant	34,5%	18,6%	<0,05
UTI post-transplant	36,4%	20,2%	<0,05
CyA (C2 level)	867,4±28,8	748.6±36,6	ns
CAN evidence	21,4%	39,5%	<0,05
Graft survival 5yrs rate	100%	100%	ns

Baseline patients' characteristics are shown in Table 2.

The groups were similar with regard to recipient's age, gender and body weight and cyclosporine targeted C_2 levels. LURD recipients tended to be older (35.1±9.8 vs. 30,3±10,0 years), and had significantly higher HLA mismatching (4,4±1,8 vs. 2,1±1,1, p<0.01). On the other hand, CIT in the group of LRD recipients seemed to be longer (3,1±1,8 vs. 2,6±1,4 hours), and the percentage of DGF in this group higher 17,6% vs. 15,3%, but none of these variables have reached the level of significance, when compared to the LURD group.

Nevertheless, donors in the LURD group were younger, and GFR of donated kidney was significantly higher than those in the elderly LRD group (47,6±11,4 vs. 65,9±3,6 years, p<0,05; 53,3±14,2 vs. 44,1±10,1 ml/min; p<0,05). In addition, LURD group of patients was characterized by significantly hig-

her percentage of AR and UTI, as well as longer hemodialysis duration when compared to the elderly LRD group (34,5% vs. 18,6%, p<0,05; and 36,4% vs. 20,2%, p<0,05; 34,7±12,2 vs. 8,0±6,9 months, p<0,01) (Table 2).
Importantly, chronic allograft nephropathy (CAN) histological evidence was present in a significantly higher percentage in biopsy specimens of the elderly LRD group of patients when compared to those of LURD group (39,5% vs. 21,4%, p<0,05). No difference in graft survival rates was found between the groups at 5 years follow up, with graft survival rate of 100% in both groups.
Serum creatinine levels (sCr) were slightly higher while estimated GFR (calculated creatinine clearance-cClCr) tended to be lower during the whole period of follow-up in the elderly LRD group, not reaching statistical difference between the groups (Table 3).

Table 3. Graft function at 1 and 6 months, and 1 and 5 years after kidney transplantation in both groups

Parameters	LURD (n°=15) Mean±SD	LRD>60yr (n°=18) Mean±SD	p-value
sCr 1 month	121,3±33,2	133,8±35,4	ns
sCr 6 months	144,6±46,2	154,9±42,0	ns
sCr 1 year	147,0±53,4	155,6±60,4	ns
sCr 5 years	135,7±48,6	157,9±42,8	ns
cClCr 1 month	67,3±17,7	57,7±13,6	ns
cClCr 6 month	60,7±19,0	58,5±20,1	ns
cClCr 1 year	61,4±22,0	52,5±20,4	ns
cClCr 5 years	55,7±15,6	46,3±16,8	ns

Finally, the graft function 5 years after transplantation did not differ significantly between the groups, although the LURD group maintained slightly higher GFR compared to the elderly LRD group (55,7±15,6 vs. 46,3±16,8 ml/min, p>0,05).

Discussion

Despite the improvement in immunosuppression and better graft and patient survival in cadaver transplantation, the use of living donors for kidney transplantation still results in a slightly superior graft and patient survival, and less morbidity due to fewer rejection episodes, less immunosuppression and better immediate graft function [1,2].
Furthermore, the shortage of cadaveric donor organs and the increasing number of uremic patients on waiting lists prompts transplant centers to examine all possible alternatives in addition to living-related transplantation. Amongst currently avaible options, living donors (related and unrelated) constitute a very useful source of the best quality organs with excellent outcome. Because of the superior outcome of the living compared to the cadaveric donor transplants [3], a greater shift towards living donor transplants is already evident word-wide [12]. Similarly, the same trend has been observed in our unit over the past decades. Furthermore, it has been reported that the majority of living related kidney transplantations are performed from kidneys of siblings and parents, although spousal donation is becoming increasingly more common [13,14].
Tang, *et al.* [13] reported that spousal kidney transplantation shared comparable results with LRD transplantation and should be encouraged in places where cadaveric organs remain scarce. Gjertson and Cecka [15] compared spouse and other genetically unrelated transplants and found no difference in graft survival. In our case study, we could not make such comparison due to the small number of patients in the LURD group.
A number of large single centre studies and registry analyses (United Network of Organ Sharing-UNOS and Australia and New Zeeland Data-ANZDATA) have demonstrated similar graft and patient outcomes between LRD and LURD transplants, even though LURD were more likely to be older donors and often had poorer HLA-matching [12,15,16].
HLA mismatches are known to have an impact on the transplant outcome as shown by the registry data analysis [12,17]. However, many recent single-centre studies have reported similar graft survival rates with LRD and LURD in spite of greater HLA mismatches in LURD transplants [18,19].
On the other hand, Xianming Su, *et al.* (20) examining deceased donor kidney transplants in US, reported that including the provision of safer and more potent immunosuppressive therapy, the significance of HLA matching has diminished, while non-immunological factors continue to impede more marked improvements in long-term graft survival.
In our study, although LURD group had significantly higher HLA mismatches (p<0,01) that might have contributed to the greater number of AR`s observed in this compared to LRD group (p<0,05), they did not have any impact on the graft outcome at 1 and 5 years. However, while HLA mismatches have been reported to have an impact on the long-term graft survival, our study with a mean follow-up of 5 years presents only our short/middle-term results.
Several studies have investigated the prevalence of AR episodes of LURD and LRD recipients. Matas, *et al.* [3] studied ARs occurring after the first 6 months post-transplant and reported rejection rates of 8.6% in LURD an 2,6% in LRD. Fuller, *et al.* [21] reported 1-year AR rates of 30% in LURD an 18,5% in LRD, while in the study of Voiculescu, *et al.* [7] these proportions were found to be even higher-54,2% versus 52,2%, respectively. These finding are in line with the results in our study. Namely, we found significantly higher AR rates of 34,5% in LURD when compared to those of 18,6% in elderly LRD group. Although the AR rates in our study were summarized for the whole follow-up period, AR episodes in both groups occurred predominantly during the first 6 months post-transplant, and only a few of them till the end of the first year post transplantation. In this regard, we could hypo-

thesize that it would be rather strange to have any negative impact on the long-term graft outcome if we had comparable short and mid-term results.

On the other side, it has been well established that the type (live or deceased donor kidneys) and quality (donor age and presence of donor comorbidities) of donor kidneys have a significant impact on renal allograft outcomes. The influence of donor age and recipient age on renal allograft survival has been investigated in numerous studies [16,22,23]. In some of those studies, it has been shown that graft survival of kidneys from old donors (>50-60 years) was significantly reduced as compared to kidneys from younger donors [16,22]. In addition, it has been reported from the same group of authors [16] that the functional graft survival of kidneys from old donors (>60 years) was better in old recipients (>60 years), as compared to all other age groups. Furthermore, in the study of Morales, *et al.* [23] no difference was found in 2-years graft survival between donors more than 5 years younger or older, or in those with age disparity of 10 or 15 years.

In our study, elderly LRD group has been shown to have almost equal graft outcome compared to the LURD group. Hence, although LRD group had lower age matching between the donors and recipients, in contrast and as partial explanation for the similar graft function and outcome between the groups we could consider its higher HLA matching, and lower percentage of AR and UTI.

With regard to the therapy, it has been recently shown that the use of newly proliferation signal inhibitors (PSIs, also known as mTOR inhibitors) which facilitates calcineurin inhibitor (CNI) minimization or withdrawal may be proven as particularly beneficial for "old-for-old" renal transplant recipients [24]. Furthermore, the impact of donor age on development and progression of CAN has been considered as a consequence of several potential risk factors: decreased nephritic mass, increased risk for AR, increased susceptibility for CNI-induced nephrotoxicity and a higher incidence of DGF and hypertension [25-30]. In this regard, the incidence of histological signs of CAN in biopsies performed in the elderly LRD group from our study has been found to be significantly higher when compared to the LURD group.

Fewer studies have analyzed the influence of donor kidney function and subsequent graft function but this influence has been reported as significant [31], modest [32], or even no significant [33]. Lezaic, *et al.* [34] has reported that in recipients without evidence of DGF or AR, the glomerular filtration rate of the donated kidney has no influence on the graft function and survival in LRD recipients. In our study, although the elderly LRD group had a significantly lower estimated GFR of the donated kidney, higher sCr levels and lower cClCr, during the whole period of follow-up, the difference between the groups was not statistically significant. These results might be explained by the fact that while kidney transplantation from unrelated donors was performed with a higher GFR of donated kidney, but in a setting of significantly higher HLA mismatching, the shorter hemodialysis duration and lower incidence of AR and UTI in the group of kidney transplant recipients from older related donors implied almost equal graft outcome and survival. Nevertheless, our outcome and survival rates are valid only in short-term due to the limited period of follow-up, which is the major shortcoming of our study.

Conclusions

The lack of deceased donor organs coupled with the increased utilization of elderly and unrelated live donors have gained a considerable interest in examining the outcome of such grafts. In our study, kidney transplant recipients from LURD have shown comparable 5 years graft survival and outcome to that of LRD older than 60 years. Although these results are obtained in a pilot study, they confirm that in the presence of deceased organ shortage, LURD and older LRD may become a valuable source of potential organ for waitlisted patients for kidney transplantation.

Conflict of interest statement. None declared.

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Short communication

Transplant Activity May Influence Number and Characteristics of Dialysis Patients – Slovenian Data

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Abstract

Maintenance hemodialysis (HD) and kidney transplantation were introduced in Slovenia in 1970. For decades the number of renal replacement therapy (RRT) patients has been increasing. In 2011, for the first time after 40 years, a slight decrease was observed (from 2020 RRT patients in 2010 to 2011 RRT patients in 2011; 980 p.m.p.). The number and percentage of patients with functioning kidney graft was continuously increasing, reaching 31,4% of all RRT patients at the end of 2012. The number of incident RRT patients in 2011 was stable and relatively low; 115 p.m.p., median age 68 years, 29% diabetics. Median age of prevalent RRT patients was 60 years, for HD patients 67 years, for peritoneal dialysis patients 56,5 years and for transplanted patients51 years. Hemodiafiltration was prescribed in 59,3% of HD patients. The number of dialysis patients is decreasing, however their age and comorbidity are increasing, including more demanding conditions for arteriovenous fistula construction than in the past. With stable transplant activity, senior program in Eurotransplant, possible increase in preemptive transplantation and improved chronic kidney disease care we may expect further decrease in number of dialysis patients and increase in complexity of their care in the next years, including care for patients after kidney graft failure.

Key words: hemodialysis, kidney transplantation, registry, renal replacement therapy

Introduction

Dialysis has been the cornerstone of renal replacement therapy (RRT) for end-stage renal disease for decades, with a growing number of patients in many countries and regions since the introduction of maintenace dialysis in the early sixties of the 20th century. In 2012 annual growth rate in the number of dialysis patients was estimated to be ≈ 2% for Europe and Japan, 3-4% for USA, ≈ 12% for other regions and 7-8% for the whole world [1]. However, the trend of continuous increase in the number of dialysis patients is reversed in some countries, in parallel with high and stable transplant activity. In Slovenia, 40 years after introducing maintenance hemodialysis in 1970, the decrease in the number of dialysis patients has been observed since 2010 [2]. This trend, which is expected to continue in the next years, may be a consequence of various factors: relatively low number of incident dialysis patients as compared to other European countries [3], increasing age and comorbidity, increased access to transplantation, increased awareness of chronic kidney disease (CKD) detection and treatment, introduction of preemptive kidney transplantation etc. A trend of slightly increasing mortality of dialysis patients in the last years without detectable decrease in dialysis quality or prescription may be a consequence of greater comorbidity of dialysis patients [2]. Patients with failed kidney graft represent a special, complex group of dialysis patients. The number of such patients may increase in the future (in parallel with the increasing number of transplant patients), with high comorbidity burden and high mortality, especially in the first year after graft failure [4].

Slovenian data

In 1970 maintenance hemodialysis was introduced in Slovenia. In the same year the first kidney transplantation was performed at the University Medical Center Ljubljana. Slovenian RRT Registry, collecting data on individual RRT patients, was founded in 2004. The number of RRT patients has increased until 2010. In 2011 for the first time after 40 years the number of RRT patients has sligthtly decreased compared to 2010 (Figure 1, Figure 2). In parallel with that, structure of RRT patients is continuously changing-number and proportion of the patients with functioning kidney graft is increasing and number of dialysis patients is decreasing. At the end of 2012, it was estimated that 31,4% of all RRT patients had functioning kidney graft (643 patients) (Figure 3). The number of incident RRT patients was relatively low compared to many European countries, with 115 per million of popullation at the end of 2011; median age 68 years, 29% being diabetics.

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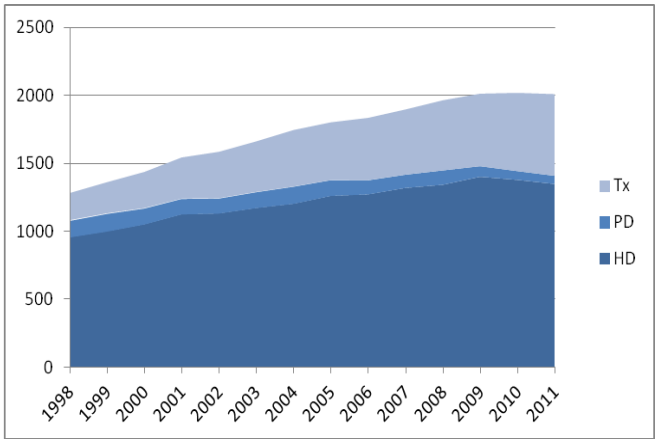

Fig. 1. Number of prevalent RRT patients in Slovenia from 1998-2011 (RRT: renal replacement therapy; Tx: transplantation; PD: peritoneal dialysis; HD: hemodialysis)

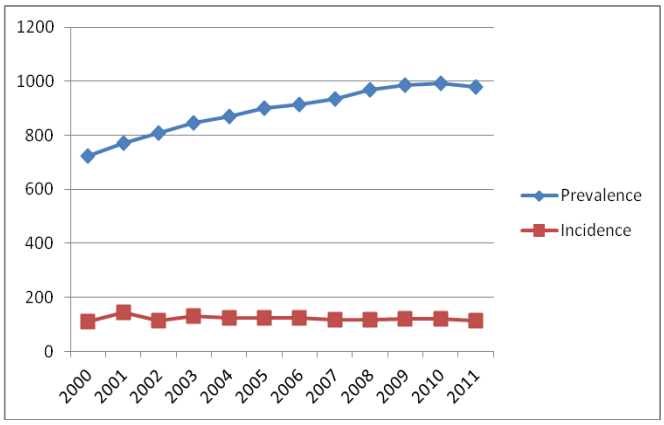

Fig. 2. Prevalent and incident RRT patients per million of popullation in Slovenia from 2000-2011 (incident patients at day 1 included; RRT: renal replacement therapy)

Fig. 3. Percentage of patients treated by different forms of RRT among all RRT patients in Slovenia from 1998-2011 (RRT: renal replacement therapy; Tx: transplantation; PD: peritoneal dialysis; HD: hemodialysis)

Prevalent HD patients are significantly older than patients treated by PD or transplantation. In 2011 median age of hemodialysis patients was 67 years, compared to 51 years for transplant patients and 56,5 years for patients on peritoneal dialysis (60 years for all RRT patients) (Figure 4). Percentage of HD patients with arteriovenous fistula decreased from 85% in 2005 to 79% in 2011, despite the active policy of timely preoperative ultrasonography mapping and vascular access surgery performed by nephrologists in many cases. Increase in the number and percentage of patients with HD catheters may be at least in part a consequence of transplant activity (many patients with arteriovenous fistula are transplanted) [5], and patients remaining on hemodialysis are older and with more comorbid conditions. Trying to balance this factor potentially

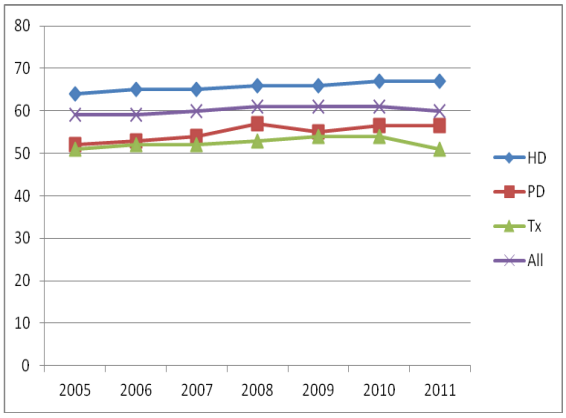

Fig. 4. Median age of prevalent RRT patients in Slovenia by RRT modality from 2005-2011 (RRT: renal replacement therapy; HD: hemodialysis; PD: peritoneal dialysis; Tx: transplanted patients; All: all RRT patients)

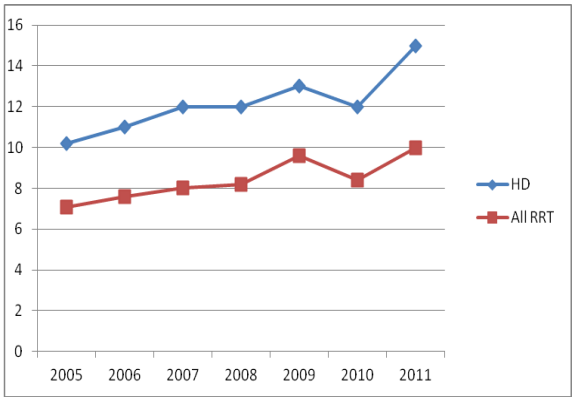

Fig. 5. Percentage of patients with hemodialysis catheters among HD and among RRT patients in Slovenia (RRT: renal replacement therapy; HD: hemodialysis)

influencing vascular access structure in HD patients, we have calculated the percentage of patients with HD catheters not only from all HD patients but also from all RRT patients (including transplant patients) (Figure 5). RRT patients having hemodialysis catheters represented 10% from all RRT patients and 15% from all HD patients in 2011. Hemodiafiltration is increasingly being used in Slovenia, with 59.3% of HD patients treated by hemodiafiltration in 2011 (Figure 6). Mortality of hemodialysis patients is slowly increasing, accompanied by increasing mortality of all RRT patients (Figure 7). As a total RRT population is relatively small and few cases may influence percentages for particular year, we have to wait for some years to see if these trends are constant and convincing.

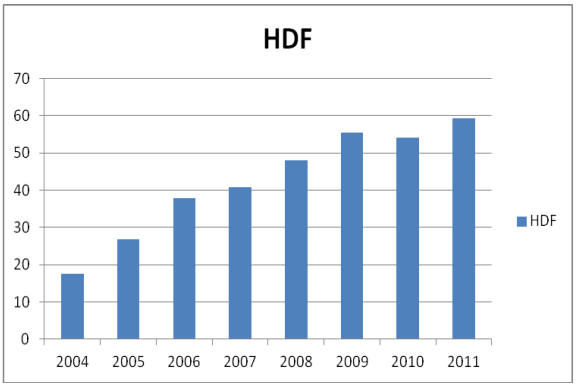

Fig 6. Percentage of hemodialysis patients treated by hemodiafiltration in Slovenia from 2004-2011

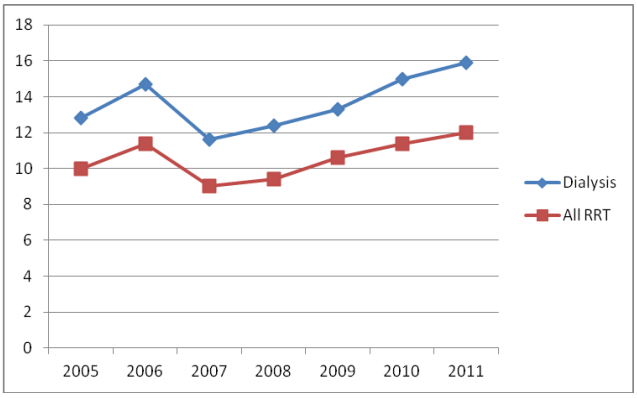

Fig. 7. Mortality of dialysis and all RRT patients in Slovenia from 2005-2011, with incident patients at day 1 included (RRT: renal replacement therapy)

Conclusions

In Slovenia, the number of prevalent RRT patients has started to stagnate or slightly decrease since 2010. Among all RRT patients, the number and percentage of patients with functioning graft are continuously increasing. Expectedly, the number of dialysis patients is decreasing, but they are increasing in age, comorbidity and have more demanding conditions for arteriovenous fistula construction than in the past. Characteristics of dialysis patients are expected to be further complicated by patients after kidney graft failure that require complex medical care and may be more numerous in the future. With stable transplant activity, senior program in Eurotransplant, possible increase in preemptive transplantation and good CKD care we may expect further decrease in number of dialysis patients and increase in complexity of their care in the next years, including care for patients after kidney graft failure.

Conflict of interest statement. None declared.

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Case report

Treatment of Resistant Hypertension with Renal Denervation in a Diabetic Patient

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Abstract

Introduction. High risk patients, such as diabetic patients, with treatment-resistant hypertension benefit greatly from the procedure of renal denervation by lowering blood pressure and preserving renal function.

Case report. A 62-year-old female came to our clinic for uncontrolled hypertension. She was obese (BMI 32) diabetic patient with neuropathy and retinopathy and renal insufficiency stage II (MDRD/CKD-EPI formula for eGFR: 66/ 72ml/min/1,73m2), but without diabetic nephropathy. All of the antihypertensive drugs were given at best tolerated dosage. Despite the therapy with 6 antihypertensive drugs (aldosterone was added to the treatment) the patient was not able to control her blood pressure and ambulatory blood pressure monitoring showed a resistant hypertension (RH): non-dipper pattern, with day average systole/diastole: 149/78mmHg, maximum values of 208/130 mmHg, pulse pressure 68mmHg and frequency 80 per minute. The patient was admitted to the hospital for testing the compliance, and the result was excellent. Thus, a device related therapeutic procedure remained as a treatment alternative, and renal artery denervation is the only possible option in Croatia.

Results. Renal sympathetic denervation was done at seven sites on both arteries without any procedure-related complications. After the procedure, the patient was stable, without worsening of the renal function and good control of blood pressure. BP measurements at 1 and 3 months follow-up visits were compared to baseline values.

Conclusions. Renal denervation is a safe and effective procedure to cure RH in patients with diabetes.

Key words: resistant hypertension, renal denervation, cost-benefit analysis

Introduction

Resistant hypertension is defined as high blood pressure that remains uncontrolled despite treatment with at least three antihypertensive agents (one of which is a diuretic) at best tolerated doses [1]. Before a resistant hypertension diagnosis can be made, obvious causes of elevated blood pressure should be sought (non-compliance, under-dosing, white-coat hypertension etc.) as well as secondary arterial hypertension. Prevalence of resistant hypertension in Croatia is not known, but in USA and in Western Europe it ranges from 9 to 13% [2,3].

Despite guideline treatment strategies, many patients with hypertension fail to achieve blood pressure control and remain at risk for cardiovascular disease [1]. Sympathetic nervous system activation has been implicated in the development and progression of hypertension, as well as associated metabolic, cardiovascular and renal disease states. Renal denervation is a successful device-based therapeutic therapy for resistant hypertension [4] and some subsequent studies reported beneficial effect on glucose tolerance, sleep apnoea, left ventricular hypertrophy, and cardiac function [5,6]. The cost of this procedure is around 65,000 HRK (8500 EUR) and it is not paid by the Croatian Institute for Health Insurance. It is considered a high cost procedure and it is not included in Diagnosis-related groups. In patients with coronary artery disease, carotid arteries disease, chronic kidney disease (CKD) uncontrolled hypertension undeniably leads to possible stroke, myocardial infarction and end-stage renal disease with a need of haemodialysis. Prices of treatment for one stroke granted by the Croatian Institute for Health Insurance are 24508,89 HRK; treatment of one myocardial infarction 24635,23 HRK and one haemodyalisis treatment is around 900 HRK; all prices are given as Diagnosis-related groups.

Patients with resistant hypertension are also at higher risk for poor cardiovascular outcomes, including death, MI, heart failure, stroke, or chronic kidney disease, meaning that "recognizing these patients and identifying means of minimizing their risk will be important to improve their overall prognosis, and there is a strong evidence for the use of spironolactone as a highly effective antihypertensive agent [7,8].

Patients with multiple comorbidities are usually refused for renal denervation, but we present a case of patient who gained benefit from this procedure with evidence of preserved renal function, improved diabetes control and lower pharmacological therapy.

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Case report

A 62-year-old female came to our clinic for resistant hypertension (RH). She was obese (body mass index 32), diabetic patient (since 1976) with complications including polineuropathy and retinopathy, history of hypertension (since 1972) and chronic kidney disease stage II (MDRD/CKD-EPI formula for eGFR: 66/72ml/min/1,73m2). Blood-pressure (BP) control was defined as <140/<90 mm Hg. So, the patient has controlled BP to <140/<90 mm Hg being on four or more blood-pressure medications and was classified as having controlled apparent treatment-resistant hypertension. Optimal therapy for this patient with uncontrolled apparent treatment-resistant hypertension was prescribing a diuretic and two or more other blood-pressure medications, with each medication at ≥50% of the maximum recommended or approved dose for hypertension. She was given losartan 200 mg/hydrochlorothiazide 25 mg, amlodipine 10 mg, nebivolole 5 mg, moxonidine 0,6 mg, spironolactone (Aldactone)100 mg, indapamide 1,5 mg, statins, aspirin and insulin therapy; all of antihypertensive drugs at best tolerated dosage. Despite the therapy ambulatory blood pressure monitoring showed a non-dipper pattern, with day average systole/-diastole: 149/78 mmHg, maximum values of 208/130 mmHg, pulse pressure 68 mmHg and frequency 80 per minute. Serum creatinine was 77 μmol/L, potassium 4,3 mmol/L, glucose 7,5-10.0 mmol/L, without albuminuria. The patient was admitted to the hospital for testing the compliance, and the result was excellent. Aldosterone antagonist was not given because of high levels of serum potassium. Thus, a device related therapeutic procedure remained as a treatment alternative, and renal artery denervation (RDN) was done at seven/sites on both arteries without any procedure-related complications. After the procedure, the patient was stable, without worsening of the renal function. Laboratory values after the procedure showed stable serum creatinine 71 μmol/L with albumin/creatinine ratio 0,5 mg/mmol. HbA1c value before RDN was 7,6% and after 3 months (with the same therapy) 7,2%.

One month after RDN the a*mbulatory blood pressure monitoring* (ABPM) showed non-dipper pattern, with day average systole/diastole: 131/68 mmHg, maximum values of 179/123 mmHg, pulse pressure 62 mmHg and frequency of 73 per minute.

Three months after RDN the ABPM showed non-dipper pattern, with day average systole/diastole: 127/62 mmHg, maximum values of 148/84 mmHg, pulse pressure 64 mmHg and frequency of 65 per minute.

One and 3 months after RDN, office systolic blood pressure values were significantly lower (P<0.001). Nevertheless, after RDN the number of antihypertensive drug classes required was 5 which was not statistically different from the baseline.

Discussion

Optimal therapy for patients with controlled apparent treatment-resistant hypertension was defined as prescription of a diuretic and three or more other blood-pressure medications, with each medication at ≥50% of the maximum recommended or approved dose for hypertension [1]. To improve treatment of uncontrolled hypertension, physicians should search for secondary causes of hypertension, rule out white-coat hypertension, expend energy to improve patient compliance, and prescribe an optimal drug regimen and adequate dosage [9]. Approximately 1 in 7 of all uncontrolled hypertensives and 1 in 2 with uncontrolled RH are prescribed ≥3 BP medications as optimal regimens. We need to answer some basic questions when treating a patient with treatment-resistant hypertension: is the patient's pressure elevated outside the office? Is the prescribed treatment adequate, and is the patient taking the medications that have been prescribed [10]. When pharmacological therapy has failed, there are new options for treating patients with resistant hypertension (RH). Renal Sympathetic Denervation (RDN), an endovascular catheter-based intervention, has been applied as a novel concomitant treatment of drug-resistant hypertension (rHT). This was the case with our patient.

Conclusions

Renal sympathetic denervation is safe and effective procedure that lowers blood pressure in patients with resistant hypertension. The most beneficial effect of the procedure has been shown in patients with multiple comorbidities such as diabetic patients, coronary arteries disease, carotid arteries disease and chronic kidney disease. These patients should not be excluded from the procedure since they will benefit greatly from it by prolonging dialysis-free time, preventing stroke and myocardial infarction and improving quality of life. For better understanding of the efficacy and safety of RDN we need clinical trials in patients with rHT and various co-morbidities.

Conflict of interest statement. None declared.

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Case report

Focal Segmental Glomerulosclerosis in a Patient with Ankylosing Spondylitis: A Rare Association

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Abstract

Ankylosing spondylitis (AS) is a chronic inflammatory disease of the sacroiliac joints and spine. Renal involvement, apart from amyloidosis, is rare in AS. Focal segmental glomerulosclerosis (FSGS) occurs extremely rarely in patients with AS. We report here a case of biopsy proven FSGS associated with AS. The exact relationship between AS and FSGS needs to be elucidated. TNF alpha may be a possible mediator involved in the development of AS-associated FSGS.

Key words: focal segmental glomerulosclerosis, ankylosing spondylitis, renal failure

Introductıon

Ankylosing spondylitis (AS) can present with back pain and morning stiffness due to inflammation of the sacroiliac joints and spine. The majority of AS patients possess the HLA-B27 antigen (> 95%). Patients with AS might suffer from anterior uveitis, enthesitis, cardiac, pulmonary and renal problems.

The incidence of renal abnormalities among patients with AS varies between 10-18%. Secondary renal amyloidosis is the most common cause of renal involvement in AS (62%), followed by IgA-nephropathy (30%), mesangioproliferative glomerulonephritis (5%), membranous nephropathy (1%), focal segmental glomerulosclerosis (1%) and focal proliferative glomerulonephritis (1%).

Primary focal segmental glomerulosclerosis (FSGS) is a glomerular disease causing proteinuria and nephrotic syndrome in children and adults. It is a common cause of end stage renal disease (ESRD), accounting for up to 20% of dialysis patients. The cardinal feature of FSGS is progressive glomerular scarring. We report here a case of focal segmental glomerulosclerosis associated with ankylosing spondylitis.

Case report

A 47-year-old man had a 20-year history of ankylosing spondylitis, with a chronic use of daily indomethacin 50-150 mg for years. On admission to the Department of physical medicine and rehabilitation, he had pain in his lumbar spine, pelvis, knees, and heels. He had been treated only with NSAIDs. His spine was stiff and painful. Mmorning stiffness lasted for about 1 hour. The patient was able to move using a couple of walking sticks. He had a history of multiple lumbar disc hernia operation. Family history of the patient was not contributory. He had typical stooped posture, with increased thoracic kyphosis and cervical forward

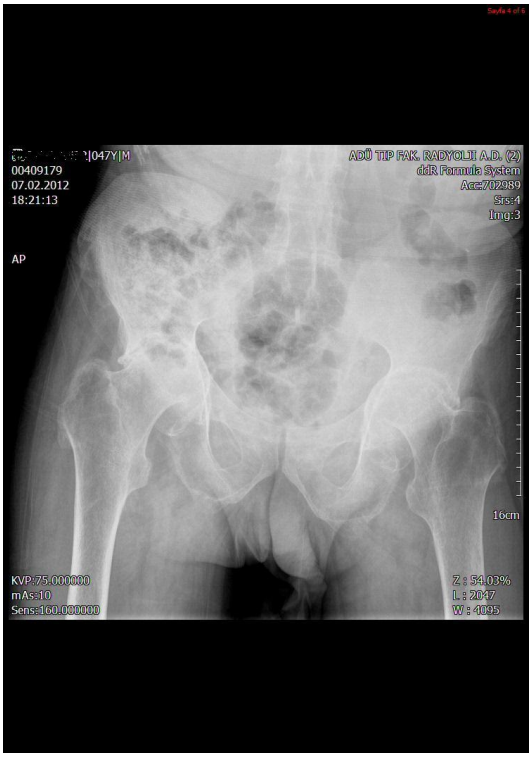

Fig. 1. Anterior-posterior pelvic X-ray film. Bilateral Grade 4 sacroiliitis and severe diffuse narrowing hip joints

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flexion. His blood pressure was 170/80 mm/Hg and heart rate 90/min and apart from kyphosis his physical examination was normal. His waist and neck movement was markedly restricted in all directions whereas his bilateral hip flexion contractures were about 60^0. The flexion of left knee was limited to 90^0. All other joints were normal.
Anterior-posterior pelvic X-ray film showed sacroiliitis and narrowing hip joints (Figure 1).
Laboratory investigations showed elevated ESR: 97 mm/ first hour, hematocrit: 30%, hemoglobin: 9.5 g/dl, WBC 7920, platelets: 295000, fasting blood sugar: 87 mg/dl, urea: 133 mg/dl, serum creatinine: 3,98 mg/dl, uric acid: 8,3 mg/dl, calcium: 8,6 mg/dl, potassium: 5,3 mmol/l, phosphorus: 4,6 mg/dl, albumin: 2,5 gr/dl, CRP: 12,37 mg/dl and PTH: 391,7 pg/ml. Urinalysis revealed density 1008, pH 6,0, protein ++, leukocytes (-), erythrocytes 6/each field. Arterial blood gas showed metabolic acidosis: pH 7,35, pCO_2 33,4, HCO_3 18,2, lac 0,78. As the patient had increased serum urea and creatinine levels, nephrology consultation was requested. Amlodipine 10 mg tb 1*1, sodium hydrogen carbonate 500 mg tb 3*1 and IV iron (ferric hydroxide sucrose complex) therapy had been added to the medication. Daily urinary protein excretion was 1595 mg/day and creatinine excretion was 805 mg/day, in the twenty-four hour urine collection. Glomerular filtration rate was calculated using the short MDRD formula and found to be 17,29 ml/min/1,73m^2. Renal ultrasonography of the right kidney was 101*47 mm and parenchymal thickness of 16 mm with a Grade 2 echogenicity. Ultrasonographic size, parenchymal thickness and echogenicity of the left kidney were 100*45 mm, 12 mm, and Grade 2, respectively. There was no sign of stone or ectasia. Serum immunoglobulins and complement components were within normal limits. Antinuclear antibodies, AMA, ANCA, ASMA and hepatitis B surface antigen were also negative. The rest of the biochemical tests revealed Fe: 27 μgr/dl, total iron binding capacity: 211 μgr/dl, transferrin saturation of Fe%: 13%, ferritin 35,94 ng/ml, vitamin B12: 540,9 pg/ml, folate: 3,2 ng/ml, RF: 0,5 U/ml; 12-lead ECG was in sinus rhythm, without pathological findings. Transthoracic echocardiogram revealed left ventricular ejection fraction 65%, LA diameter 3,9 cm, LV diastolic dysfunction grade 1, mitral regurgitation 1º and aortic regurgitation 1º. Rectal biopsy, which was performed at first step because of the high incidence of secondary amyloidosis in this group of patients, showed chronic inflammation. Histochemically samples were stained with crystal violet and Congo red. Amyloid deposition was not detected (Figure 2).
Eventually, ultrasound-guided renal biopsy was performed. Light microscopy revealed 12 glomeruli, of which 9 were globally sclerotic, and 3 with segmental glomerular sclerosis. Moderate interstitial fibrosis, tubular atrophy and medial thickening of blood vessels were apparent (Figure 3). Histochemically periodic acid-Schiff, M. Silver, Masson's Trichrome staining were used. Congo red staining was negative. No deposition of IgA, IgG, IgM, C3, C4, C1q, fibrinogen, kappa and lambda chains was identified with direct immunofluorescence method. The biopsy revealed

Fig. 2. Rectal biopsy.CONGO REDx10. Amyloid deposition was not detected

focal segmental glomerulosclerosis. Oral prednisolone therapy (0,5 mg/kg/day) was given along with prophylaxis of pneumocystis jirovecii. After nearly two months (fifty six days) from his first admission, the patient was readdmitted to the hospital with signs of pulmonary infection, temperature of 39ºC, high C-reactive protein levels

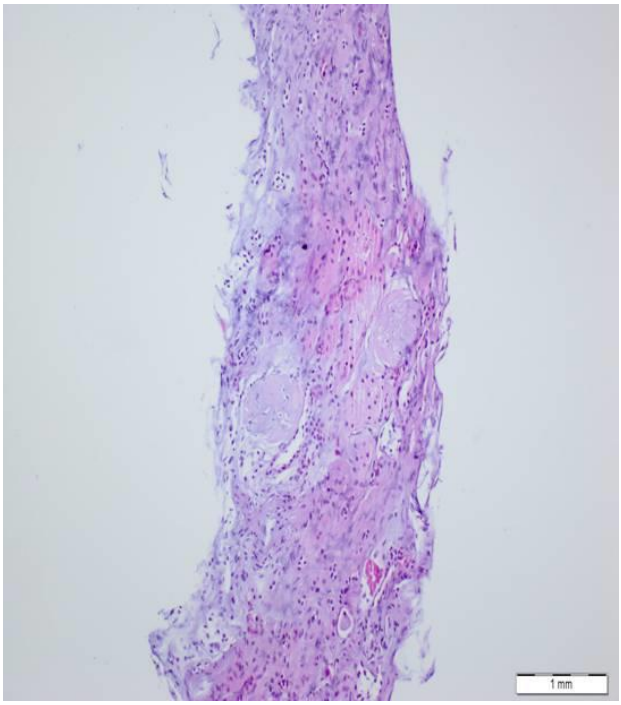

Fig. 3. Renal biopsy.H&Ex10.Glomerulosclerosis

(284,4 mg/dl), cough and a chest radiograph indicating left-side opacity consistent with bronchopneumonia. Serum creatinine and creatinine clearance were 6,43 mg/dl and 9,94 ml/min/1,73m^2, respectively. Arterial blood gas analysis showed metabolic acidosis. A central catheter was placed and he was started on intermittent hemodialysis. Steroid dose was gradually reduced and ceased eventually. Appropriate treatment with antibiotics was used and du-

ring the follow-up period pneumonia showed regression. However, chronic hemodialysis was necessary for the patient.

Discussion

Ankylosing spondylitis (AS) can present with a back pain and morning stiffness due to inflammation of the sacroiliac joints and spine [1]. It tends to be more severe in men and begins in early adulthood, the average age of onset being at 28 years [2]. It may also lead to anterior uveitis, enthesitis, cardiac, pulmonary and renal problems [3].

The incidence of renal abnormalities among patients with AS varies between 10-18%. Secondary renal amyloidosis is the most common cause of renal involvement in AS followed by IgA-nephropathy, mesangioproliferative glomerulonephritis, as well as membranous nephropathy, focal segmental glomerulosclerosis and focal proliferative glomerulonephritis.

Possible mechanisms of renal involvement in AS generally include toxic effects of nonsteroidal anti-inflammatory drugs (NSAIDs), increased incidence of glomerulonephritis and renal deposition of amyloid. Although renal amyloidosis is a considerably rare complication of AS (1-3% in European patients), it should be considered in case of proteinuria and/or renal failure in AS. In 7% of unselected AS patients, amyloid can be found in abdominal fat or rectal biopsies, but most patients do not develop clinically severe disease [4]. Proteinuria or impaired renal function can indicate IgA-nephropathy, which is interesting because of the increased serum IgA levels in AS patients during the active inflammatory phases of spondylitis [5]. In a recent study, secondary renal amyloidosis and nephrolithiasis were the most common causes of renal involvement in ankylosing spondylitis followed by IgA nephropathy [6].

Renal involvement, apart from amyloidosis, is rare in AS. FSGS occurs "extremely" rarely in association with ankylosing spondylitis [7,8]. FSGS is diagnosed when the glomerular lesion involves only a portion of some of the glomeruli with others remaining relatively uninvolved. Before a diagnosis of primary FSGS is reached, secondary forms of the disease should be carefully excluded.

We report here a case of a 47-year-old man with ankylosing spondylitis who presented with increased serum urea and creatinine values and had a percutaneous renal biopsy showing features of FSGS. No other secondary cause of FSGS was found in our investigations. The exact relationship between AS and FSGS (etiological and coincidental) still needs to elucidated [9]. The underlying immune disorder leading to FSGS is not known, but is probably multifactorial. The spectrum of FSGS includes primary forms mediated by a putative circulating or permeability factor and a few secondary forms caused by hereditable mutations in podocyte genes, drugs, viral infections and adaptive responses to reduced renal mass/other hemodynamic stress [10]. This theory of a circulating permeability factor and the reversibility of the podocyte injury before occurence of scar formation was well shown in a recently published case report [11].

Several mechanisms for TNF-alpha-induced proteinuria in FSGS have been proposed. A high level of TNF-alpha mRNA was detected in mononuclear cells from patients with FSGS [12]. Podocytes are the main cells involved in the development of FSGS. It has been shown that podocytes express TNF-alpha R2 receptors and respond to cytokine stimulation by producing TNF-alpha themselves [13]. TNF-alpha induces the production of several inflammatory mediators and enzymes by mesangial cells and glomerular epithelial cells, including reactive oxygen species (ROS), eicosanoids, and other cytokines [14]. Some of these mediators are known to alter the glomerular capillary permeability barrier. A circulating, soluble form of the urokinase receptor (suPAR) can activate podocyte β_3 integrin, leading to FSGS whereas TNF-α has been shown to be important for the expression of suPAR on platelets [15,16].

On the other hand, TNF-alpha is a proinflammatory cytokine involved in many chronic inflammatory diseases such as AS. Infliximab decreases proteinuria during secondary renal amyloidosis among patients treated for AS or other forms of inflammatory arthritis [17,18]. The effect of anti-TNF alpha therapy may be explained by a blockade of the TNF-alpha renal actions, as TNF-alpha is known to induce glomerular inflammation and to increase glomerular permeability [19]. Anti-TNF-alpha therapy has been recently tested in a child with resistant FSGS recurrence [20] and induced transient complete remission. Furthermore, anti-TNF-alpha infusion was effective in any relapse the patient showed.

Anti-TNF-alpha agents have been demonstrated to reduce renal symptoms associated with chronic inflammatory rheumatological diseases such as secondary amyloidosis, but few data are available on their efficacy in controlling IgA nephropathy associated with AS [21]. Belimumab (effective on TNF- alpha pathway) has improved activity scores in SLE patients [22]. In a recent animal study it has been shown that the kidney is protected from damage by TNF-α blockade [23].

The anti-TNF-alpha agent infliximab may be effective in treating rheumatological symptoms of AS and control associated FSGS, suggesting that the mechanisms involved in AS and the development of AS-associated FSGS might be alike. Unfortunately, we did not have the chance for our patient to analyze TNF-alpha levels and this is a limitation of our case report.

Renal side effects and possible pre-existing renal involvement should be taken into consideration while choosing an appropriate treatment for AS. The ocurrence of a rare association needs to be recognised and differentiated from other more common causes of renal dysfunction in AS. For this reason, renal biopsy may be very helpful. In conclusion, this is a rare case report of a patient with AS combined with biopsy proved FSGS.

Conflict of interest statement. None declared.

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Case report

An Unusual Site of Calciphylaxis: A Case Report and Review of the Literature

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Abstract

Calciphylaxis is a rare and potentially fatal condition usually observed in patients with long-standing history of chronic kidney disease. It's a challenging disorder with a multifactorial etiology. Calciphylaxis occurs more often in fatty tissues of the abdomen, buttocks, genital and inner thigh regions. In these areas blood flow is lower, the potential for vascular kinking is higher and subsequently the risk for occurrence of thrombosis is increased compared to other areas of the body. Lesions of calciphylaxis typically need only days to a couple of weeks before the full picture is developed and it's difficult to establish a defined prognosis. The mortality rate is very high and the leading cause of death is sepsis from infected, necrotic ulcerated skin lesions. We report a patient on hemodialysis treatment suffering from calciphylaxis located at an unusual site. Because the mortality rate of patients with calciphylaxis is very high and depends especially on the presence of necrotic ulcerated lesion and possible bacterial contamination, which can lead to sepsis, early recognition and treatment is extremely important.

Key words: calciphylaxis, vascular calcification, thrombosis, skin necrosis

Introduction

Calciphylaxis or calcific uremic arteriolopathy (CUA) is a rare and potentially fatal condition usually observed in patients with long-standing history of chronic kidney disease. However, sporadic cases in patients with normal renal function have also been reported. The prevalence of calciphylaxis is assessed between 1 to 4% of dialysis patients [1,2]. It is characterized by calcification of tunica media of skin arteries, subcutaneous fat tissues and visceral organs with or without endovascular fibrosis, extravascular calcification and vascular thrombosis, leading to tissue ischemia and hence necrosis of tissues supplied by respective vessel. These histological features are associated with a clinical picture characterized by the presence of tender red areas developing into a livedoid pattern or violaceous nodular lesions of the skin that can evolve into tissue necrosis, eschar followed by frank ulceration, gangrene, or sepsis. In advanced stage lesions may be found in internal organs such as the heart and the lungs with consequent clinical symptoms. Lesions of calciphylaxis typically develop suddenly and progress rapidly. Calciphylaxis means a massive reduction in quality of life and is associated with a high mortality rate, ranging from 60 to 80% [3,4]. The leading cause of death is sepsis from infected, necrotic ulcerated skin lesions. Early diagnosis and treatment are vital for the patient. Herein, we report a patient newly on hemodialysis treatment suffering from calciphylaxis located at an unusual site. Calciphylaxis remains a condition under recognized by nephrologists and by other physicians including dermatologists and internists.

Case report

A 73-year-old woman with ESRD due to chronic calculous pyelonephritis presented at our outpatient clinic with black leathery eschar on the right breast. The lesion was

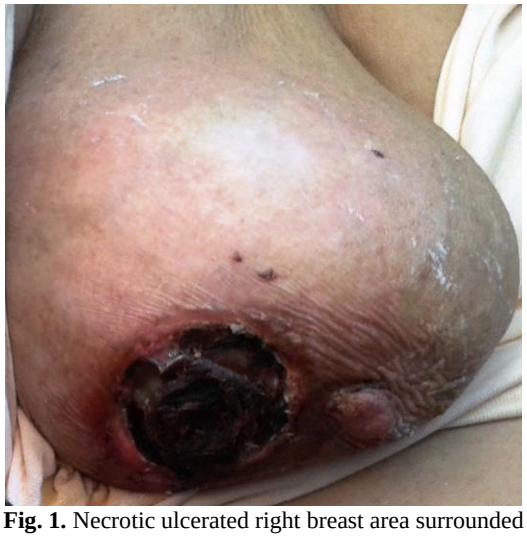

Fig. 1. Necrotic ulcerated right breast area surrounded by erythema.

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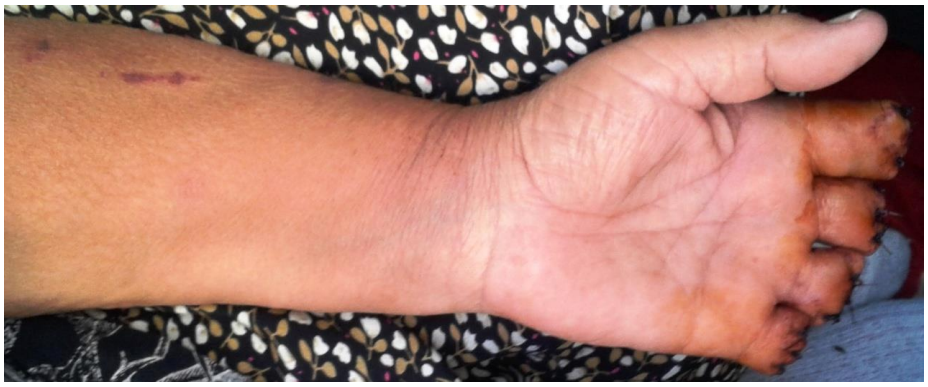

Fig. 2. Left hand with four fingers amputated.

associated with intense local pain and the patient had a low grade fever of 38,1º C. She referred the first symptoms were purpuric skin lesions that had appeared about 6 weeks earlier. Three weeks after the onset of the first symptoms, the patient noticed an ulcer, which was quickly covered by necrotic eschar. Relevant aspects of her medical history included nephrolithiasis, recurrent episodes of pyelonephritis, and arterial hypertension, but no other comorbidities and she was a non-smoker. She had been receiving hemodialysis for one month, using a central provisory catheter as vascular access. There is no information about the patient's chronic renal failure before starting hemodialysis because it was a late referral case. Physical examination revealed an obese lady (BMI 32,5).There was a painful necrotic ulcerated area surrounded by erythema on the right breast located at areola mamme near the nipple with a diameter of 4 cm (Figure 1).

The peripheral pulses were normally felt on the lower limbs. Four fingers of her left hand have been amputated several days before (Figure 2). She said that her fingers had had red to blue aspect (cyanosis) before amputation. The rest of her systemic examination was unremarkable. On presentation, her medication included: moxonidine 0,4 mg once daily, lercanidipine 10 mg once daily, calcitriol 0,25 mcg daily, calcium carbonate 3 g daily, erythropoietin ß adapted to haemoglobin levels, ferrum sucrose adapted to ferritin levels, omperazole 20 mg once daily, acetylsalicylic acid 100 mg once daily, furosemide 80 mg daily. Laboratory data showed the following abnormalities: BUN 89 mg/dl; creatinine 9,1 mg/dl; corrected plasma calcium 10.4 mg/dl; phosphorus 6,9 mg/dl; albumin 3,4 g/dl; alkaline phosphatase 428 IU/L; iPTH 869 pg/ml. Ht 29 %, Hb 9,8 g/dl, WBC 11300, platelets 255000, CRP 32 mg/l. Cryoglobulin, rheumatoid factor, antinuclear antibodies and antineutrophil cytoplasmic antibodies were all negative. Multiple blood cultures and wound swab cultures were also negative. The radiologic examination revealed an extensive vascular calcification. Lateral lumbar plan X-ray showed calcification of abdominal aorta and calcification of mesenteric artery (Figure 3a). Plain X-ray of pelvis demonstrated calcification of both femoral arteries and calcification of iliac vessels (Figure 3b). In radiography of hands calcification of an intermetacarpal artery and calcification of both radial arteries were readily visible (Figure 3c). Based on X-ray data of pelvis and hands, the vascular calcification score

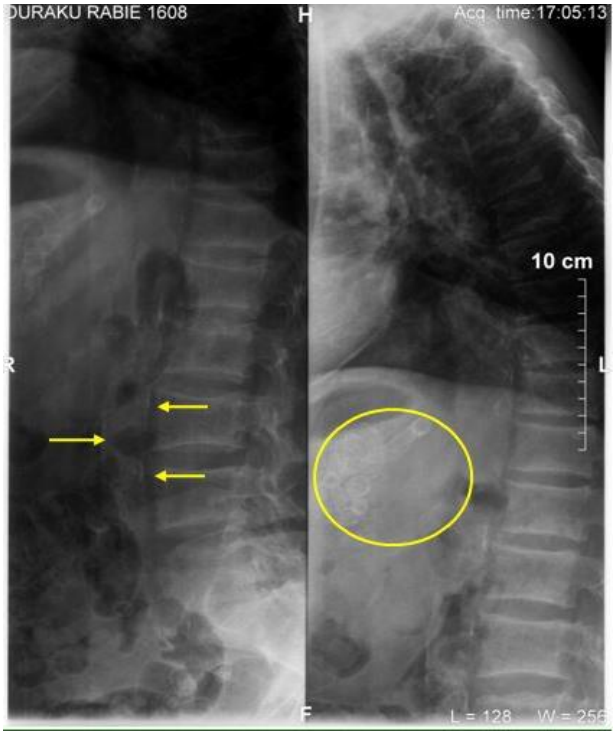

Fig. 3a. Lateral lumbar plan X-ray. Arrows indicate calcification of abdominal aort and circle shows calcification of the mesenteric artery.

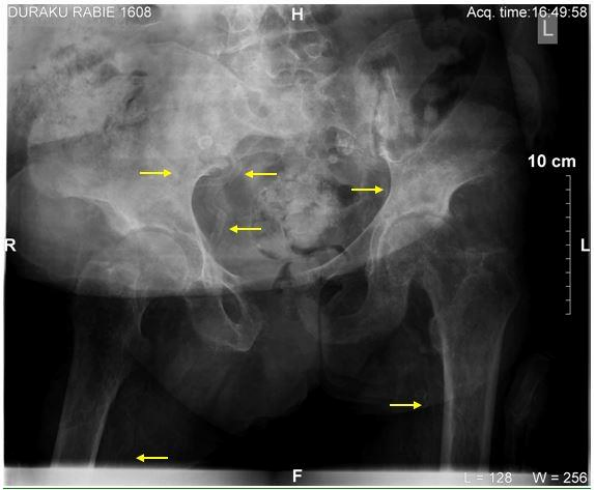

Fig. 3b. Plain X-ray of pelvis. Arrows show calcification of both femoral arteries and iliac vessels.

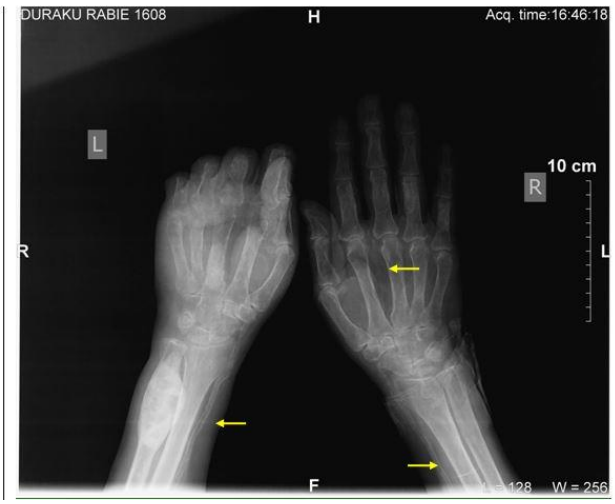

Fig. 3c. Radiography of hands. Arrows demonstrate calcification of an intermetacarpal artery and calcification of both radial arteries.

as prescribed by Adragao was seven (39). What was our dilemma? The history of chronic renal disease, presence of markedly raised PTH levels along with the clinical picture of widespread necrosis with erythema made calciphylaxis a possibility. But, the location and picture of the lesion was suggestive not only of calciphylaxis but of breast cancer also (i.e. Paget's disease of the nipple). On the other side, the prevalence of malignancy is growing up in end-stage renal disease patients. Thirteen percent of patients evaluated for a transplant and 10% of patients on waiting list carry the diagnosis of a malignancy [5].At this point the confirmation of diagnosis was a crucial issue in order not to initiate a cascade of unjustified therapeutic measures. The patient was reviewed by the oncologists and a deep incisional skin biopsy was performed. The specimens showed intimal hyperplasia and intramural calcification in an arteriole of the subcutaneous tissue which is characteristic for calciphylaxis (Figure 4).

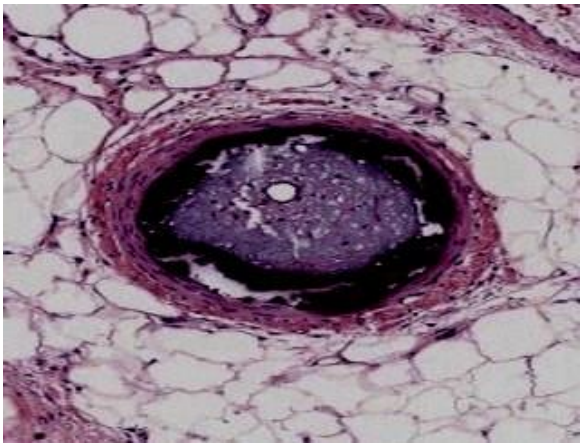

Fig. 4. Intramural calcification and intimal hyperplasia in an arteriole of the subcutaneous tissue (hematoxylin-eosin, original magnification ×400).

These typical pathological findings and characteristic skin lesions established the diagnosis of calciphylaxis. The first steps of therapy were toward lowering of serum phosphorus, calcium and PTH levels. For this reason calcitriol was discontinued, cinacalcet 30 mg daily was initiated, the dose of calcium carbonate was reduced from 3g to 1g daily (further dose was titrated), sevelamer hydrochloride was started 3200 mg daily and low calcium dialysate (calcium concentration 1,25 mEq/L) was instituted. We started to treat the patient with antibiotic, cefuroxime at a dose of 2 g daily. 25 grams of sodium thiosulphate (100mL of a solution at 25% STS) were infused three times per week. The thiosulphate was administered immediately after dialysis. The dry necrotic lesions were gently hydrated to promote a moist wound environment, encouraging autolytic debridement and cell migration. Tramadol was used for pain relief. Two weeks later the serum parathyroid hormone, calcium, and phosphorus levels improved; 623 pg/ml, 9,6 mg/dl and 6,2 mg/dl, respectively, but clinical status worsened. Multiple blood cultures and wound swab cultures were repeated and pseudomonas aeruginosa was isolated. Based on germ sensitivity imipenem-cilastatin and ciprofloxacine were instituted. After 3 days gentamicin was added. The patient died eight days later from sepsis.

Discussion

Calciphylaxis is a challenging disorder with a multifactorial etiology. The term calciphylaxis was originally coined by Hans Selye based on his early animal experiments in the 1960s [6]. He induced systemic and local inflammation and soft-tissue calcification in rodents with a combination of local trauma and an inducer (such as parathormone, active vitamin D, hypercalcemia). Thus, it was thought that this disorder involved "anaphylactic" inflammation and calcification, hence the name: calciphylaxis. But, calciphylaxis has very little to do with true anaphylaxis.
The pathogenesis of calciphylaxis is not fully understood. There are local and systemic risk factors and underlying causes that finally lead to development of calciphylaxis. Reported mineral abnormalities do not explain the process of thrombosis leading to ischemia [7]. Vascular calcification is an active process and is not sufficient to produce skin necrosis. However, calcific narrowing of small vessels provides the background for additional processes that may ultimately culminate in the development of CUA. Vascular calcification and thrombosis are both required to produce lesions of calciphylaxis [8]. Significantly low functional levels of protein C and S, which are known for their role in the anticoagulation pathway, have been reported in patients with CUA. But, low persisting levels have been shown even when lesions were healing [9]. Calciphylaxis is more common in whites and females are affected three times more frequent than males [10]. It occurs more often in fatty tissues of the abdomen, buttocks, genital and inner thigh regions. In these areas blood flow is lower, the potential for vascular kinking is higher and subsequently the risk for occurrence of thrombosis is increased in comparison with other areas of the body [11].

There is a long list of presumed risk factors. Uremia seems to be a very important pathogenetic factor besides other predisposing condition such as: use of vitamin D, use of calcium-based and aluminum-based phosphate binders, obesity, rapid weight loss, elevated calcium, phosphate and PTH levels, use of vitamin K antagonists (warfarin), hypotensive dialysis episodes, local trauma, injection of medications such as iron dextran, remote and/or recent use of corticosteroids, coagulation abnormalities, diabetes mellitus and insulin injections, concomitant vascular disease, fetuin A deficiency and liver disease [4,12-14]. Cases of calciphylaxis are also reported to be associated with primary hyperparathyroidism, cirrhosis, multiple myeloma, leukemia, rheumatoid arthritis and the milk-alkali syndrome [10,12]. But all these risk factors suffer from the inability to establish the cause-effective relationship between marker and clinical event-a condition for defining a parameter as risk factor. Although these abnormalities are frequently seen in patients with kidney failure, calciphylaxis is relatively rare. The previous factors are more trigger factors than real risk factors. Lesions of calciphylaxis typically need only days to a couple of weeks before the full picture is developed. In majority of cases it is difficult to formulate a defined prognosis. We should be carefully and highly suspicious in patients with risk factors for calciphylaxis complaining of dermal pain and associated skin changes such as subcutaneous nodules, plaques or livedo reticularis in order to prevent future events. Development of skin ulceration places the patients at high risk for sepsis and increased mortality. We should intensively treat the underlying metabolic abnormalities and not allowing the development of non-healing skin ulceration.

Because of the lack of specific laboratory tests we should carefully consider other possible diagnosis as erythema nodosum, leukocytoclastic vasculitis, pyoderma gangrenosum, cellulitis, venous ulcers, bullous pemphigoids, and vibrio vulnificus infection. Radiological examinations are helpful but do not confirm the diagnosis. Plain X-ray of involved parts of the body may reveal area of calcification representative of small vessel calcification. Calcification is common in persons with ESRD, and not specific for calciphylaxis. However, a recent study including patients with calciphylaxis have presented with more vascular calcifications, and a net-like pattern of calcifications [15]. Ultrasound is a noninvasive and less painful alternative. It can show diffuse parenchymal edema, skin thickening and more importantly echogenic foci with posterior acoustic shadow that are suggestive of calcification [16]. Bone scintigraphy may be used as a noninvasive diagnostic tool with tracer accumulation in the calcified subcutaneous areas [17]. Nuclear bone scans have been reported as promising diagnostic tool for calciphylaxis. Serial bone scanning can also possibly be used to monitor progression or regression of the disease [18]. Histologic examination is considered the gold standard in diagnosis of calciphylaxis. The role of skin biopsy in the diagnosis of calciphylaxis is controversial. A punch or deep incisional biopsy is usually performed. Punch biopsies may not be adequate because the quantity of tissue obtained may not be enough for diagnosis. A deep incisional cutaneous biopsy is usually diagnostic. But, a deep incisional biopsy may invite further infection in the presence of an active infection and performed on a non-ulcerated lesion it could result in a non-healing wound or could exacerbate the pain [19]. However, only a biopsy allows a reliable diagnosis. Formulating appropriate therapy has been limited by a lack of clear understanding of the disease pathophysiology. No drug has official approval for treatment of calciphylaxis and no randomized controlled trial is available to guide management of affected patients. Treatment approaches to CUA are widely variable and derived from case reports or case series, or from pathophysiological considerations. A multidisciplinary therapeutic approach is recommended. The potential harmful trigger factors should be eliminated, including the discontinuation of therapy with calcitriol, calcium based phosphate binders, vitamin K antagonists and parenteral iron treatment.

The basis of therapy in patients with CUA is normalization of calcium, phosphorus and parathyroid hormone metabolism. Restriction of calcium and phosphorus intake should be considered. Use of noncalcium, nonaluminum phosphate binders and low-calcium bath dialysis is advocated [20]. In calciphylaxis cases associated with hyperparathyroidism successful use of calcimimetics has been reported [21,22]. Parathyroidectomy in patients with high levels of serum PTH appears to improve clinical condition, but evidence regarding improved survival is lacking [23,24]. Beneficial effect of bisphosphonates has been reported in some cases of calciphylaxis. These drugs can increase osteoprotegerin production and inhibit vascular calcification [25,26]. Wounds that are very painful require analgesia. Non-steroidal anti-inflammatory drugs or opioid pain medications should be used instead of morphine as byproducts of morphine can cause hypotension and slow the flow in the pannicular arterioles and consequently increase the risk of thrombosis [27]. The use of hyperbaric oxygen therapy may be an option in treatment of cutaneous ulcers of calciphylaxis. The aim is to restore tissue oxygen to normal or above-normal levels and thus enhance angiogenesis, fibroblast proliferation, and collagen production [28,29]. Sodium thiosulphate (STS) is the most used and studied drug in cases of calciphylaxis. Although the mechanism of action of STS is not completely elucidated, it is proposed to increase solubility of the calcium deposits and thereby be efficacious whether in uremic or nonuremic cases [30-32]. STS is an antioxidant agent and a chelator of cations (e.g., calcium) and initially was used as an antidote for cyanide and cisplatin toxicity. The antioxidant properties may help repair endothelial cell dysfunction and promote vasodilation. The mechanism for pain relief has been hypothesized to be due to the antioxidant properties of STS. Pain relief has been prescribed as the most remarkable change in cases of use of STS. This relief has been noted in majority of patients within the first days after initiation of treatment. Furthermore, the enhanced aqueous solubility of calcium thiosulphate allows successful mobilization and clearance of the vascular and soft tissue calcium deposits [33,34]. STS can be given orally [35], intravenously [36] or intraperitoneally [37]. The most commonly reported dose has been 25 g after or during each dia-

lysis session (5-75 g). Infusion times vary from 30 to 60 minutes. Generally it is well tolerated. But, some adverse effects such as nausea with emesis and development of an anion gap metabolic acidosis have been reported.
Low-dose tissue plasminogen activator has been successfully used in some cases of calciphylaxis (38). The role of anticoagulation in all cases of calciphylaxis is controversial, because most patients with ESRD have a prolonged bleeding time due to the uremic condition.

Conclusions

To the best of our knowledge there are very few cases reported in the literature with lesion of calciphylaxis located on the breast and moreover the lesion appeared during the first month of hemodialysis treatment. On the other hand, the majority of cases of calciphylaxis due to uremic condition need a long-standing history of renal replacement therapy. Because the mortality rate of patients with calciphylaxis is very high and depends especially on the presence of necrotic ulcerated lesion and possible bacterial contamination, which can lead to sepsis, early recognition and treatment is extremely important.

Conflict of interest statement. None declared.

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Case report

Retroperitoneal fibrosis: a case report

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Abstract

Retroperitoneal fibrosis is characterized by development of extensive fibrosis, leading to entrapment and obstruction of retroperitoneal structures, notably the ureters. In most cases, the etiology is unknown. It is occasionally associated with autoimmune diseases. Response to corticosteroids and immunosuppressive therapy suggest it is probably immunologically mediated. The symptoms and signs associated with retroperitoneal fibrosis are non-specific, and diagnosis requires a high degree of suspicion. We should always have in mind retroperitoneal fibrosis in differential diagnosis of hydronephrosis.

Key words: retroperitoneal fibrosis, hydronephrosis, corticosteroid

Introduction

Idiopathic retroperitoneal fibrosis is a subgroup of chronic periaortitis. Chronic periaortitis presents usually with a fibroinflammatory mass which surrounds the abdominal aorta and iliac arteries. Sometimes this mass causes compression of adjacent organs such as ureter and inferior vena cava. There are three subtypes of chronic periaortitis (CP); these are inflammatory abdominal aortic aneurysm (IAAAS), perianeurysymal retroperitoneal fibrosis (RPF) and idiopathic retroperitoneal fibrosis. Aorta aneurysm in the idiopathic retroperitoneal fibrosis is not usual and the retroperitoneal mass can cause compression of adjacent organs. The major difference between IAAAS and RPF is that IAAAS aneurysm sac does not cause compression on adjacent organs and obstruction. Chronic periaortitis pathogenesis is not clear. According to Parums and Mitchinson's hypothesis CP is caused by an autoimmune response directed against ceroide in atherosclerotic plaques [1,2]. The other hypothesis is that CP is a systemic autoimmune disease [3]. According to the first hypothesis patients have critical atherosclerosis. Highly positive anti-nuclear antibody and acute phase reactants are the evidence supporting the second hypothesis. However, this disease is associated with autoimmune disorders affecting other organs, and the disease is associated with HLA-DRB1*03. This gene is associated with other diseases such as SLE, autoimmune thyroid disease, type 1 diabetes mellitus and myasthenia gravis [4-7]. Idiopathic retroperitoneal fibrosis is a rare disease. The knowledge about the treatment of this disease is based on case reports or studies of small groups. Thus, we think it is important to present each case of idiopathic retroperitoneal fibrosis.

Case report

A 65-year-old male patient was admitted to the hospital with complaints of bilateral lower quadrant pain which had started 15 days ago. Creatinine and urea were 5mg/dl and 100 mg/dl, respectively He also complained on change in bowel habits. There were no previously known kidney diseases, diabetes, hypertension, family history of chronic kidney disease, or previous pyelonephritis, urolithiasis which could explain the high levels of urea and creatinine at presentation. He had no decrease in urine output, or any symptoms of prostatism. He had not used any herbal medicine and had no history of trauma, arthritis, skin rash. Physical examination revealed good general condition; his blood pressure was 130/90 mmHg, pulse 88; body temperature 37°C, with no globe on his urinary bladder. Other system examinations were unremarkable. Uric acid was 9,5 mg/dl, Hb: 11,1 g/dl, CRP: 62 mg/dl; the electrolytes, liver function tests, anti-nuclear antibody tests were normal. Urine pH was 7,5, protein 3 (+), erythrocyte 2 (+), density 1015 on urine strip. Microscopy analysis showed 4-5 leukocytes and 14-15 erythrocytes in the urine. He had no pathological findings on chest radiograph. ECG findings were normal. Urinary catheter was inserted. After the hydration of 10 hours, 1000 cc urine output was recorded. On urinary tract ultrasonography, kidney sizes were (right: 117 x 51 mm, left: 120 x 62 mm) in normal range, parenchymal thicknesses (right: 15 mm, left: 17 mm) were normal, the level of the right renal parenchyma echogenity increased to grade 1 and bilateral grade 2 hydronephrosis was observed. Based on these results, non-contrast abdominal computerized tomography (CT) was planned. Kidney size and contours

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were regular, minimal dilatation of the pelvicalyceal structures was detected in abdominal CT. Irregularly shaped, and increased density of soft tissue around the abdominal aorta, starting from infrarenal level up to the proximal left common iliac artery and to the middle of right common iliac artery were detected (Figure 1).

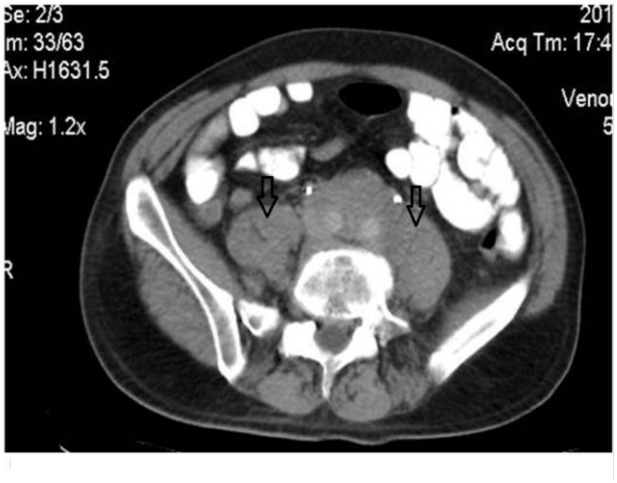

Fig. 1. Non-contrast abdominal computerized tomography of abdomen showing minimal dilatation of pelvicalyceal structures.

The patient had no previous history of trauma and surgery. Blood pressure was normal and there were no signs of peripheral circulatory disorders. The patient was referred to the Vascular Surgery Department for compression of ureters secondary to the intra-abdominal hematoma and abdominal aorta aneurysm. Lesions on the CT were not accepted as an aneurysm and contrast-enhanced abdominal CT scan was recommended. Finally, CT supported the diagnosis of retroperitoneal fibrosis (Figure 2). Bilateral double J catheters were placed in both ureters.

We started the therapy with 0,6/mg/kg of methylprednisolone. Urine output had progressively increased and urea and creatinine decreased to normal levels. Further investigations were planned for exclusion of the malignancy.

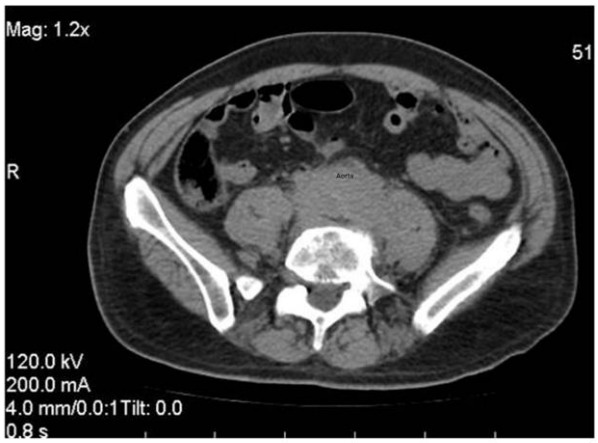

Fig. 2. Computerized tomography of abdomen excluding hematoma or aneurysm of aorta.

Chest X-ray was normal. Tumor markers were unremarkable. Fecal occult blood test was positive in two consecutive times. However, total colonoscopy revealed no pathologic findings.

Methylprednisolone of 60 mg/day (per oral) was initiated; urea and creatinine levels returned to normal in 10 days and the patient was discharged from the hospital. The dose tapering was planned during the control visits. At the end of the first month, control CT scan revealed a decrease in the lesion size to 15 mm. Three months later, the JJ catheters were removed (Figure 3). Steroid treatment stopped at the end of 6 months and monthly visits showed normal renal functions.

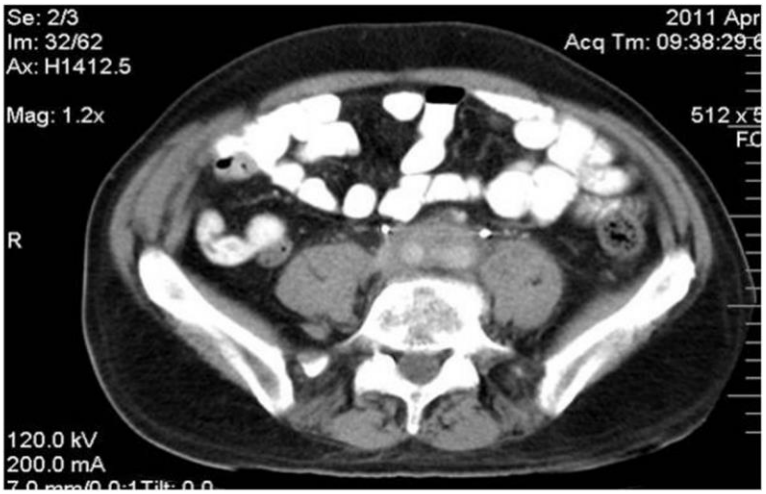

Fig. 3. Computerized tomography of abdomen (one month after treatment) showing retroperitoneal fibrosis recovery.

Discussion

Waist, abdomen, lumbar pain, constitutional symptoms, weight loss and fever may be present in idiopathic retroperitoneal fibrosis. In this case, there are complaints on abdominal pain. The most common complication of idio-

pathic RPF's is hydronephrosis and renal failure. 75% of patients with RPF are expected to loss renal function at the time of diagnosis. The treatment of idiopathic RPF includes steroid therapy, immunosuppressive agents and invasive urologic procedures (ureteral stent insertion, percutaneous nephrostomy). There is not a strict guideline for treatment. Fry, *et al*. suggested usage of corticosteroids alone [8]. Maillart, *et al.* recommended immunosuppressive treatment in addition to corticosteroids, which is superior to corticosteroid therapy alone (97%-70%) [9]. Steroids can be stopped if steroid drugs are used in combination with immunosuppressive agents (such as azathioprine, cyclophosphamide, methotrexate, cyclosporine, and micophenolate mofetil (MMF)) other than steroids alone [10,11]. Recently there has been an increasing evidence of the benefit of MMF, which made it the treatment of choice in these patients. However, a few studies have shown that azathioprine was highly effective in idiopathic retroperitoneal fibrosis [11]. Another advantage of azathioprine over MMF is its lower cost. There is no difference between side effects of these two drugs. Moroni, *et al*. showed the treatment response with azathioprine in their six patients' study [12]. In the present study, the patient responded to methylprednisolone therapy. In our opinion, steroids as the first-line therapy could be given alone in RPF patients. , If needed combination with MMF or azathioprine may be suitable. Perhaps the only common sense in the treatment of RPF that comes with urinary obstruction, with no major metabolic disorders, is the steroid therapy alone as an initial therapy. However, in more severe cases, steroid treatment with intravenous pulse cyclophosphamide therapy may be the treatment of choice [13].

Conclusions

Post-renal acute kidney injury needs careful evaluation. We wanted to emphasize that RPF has to be taken into consideration in the differential diagnosis of post-renal acute kidney injury although it is not very common. Appropriate treatment prevents progression of renal injury to further chronic kidney disease.

Conflict of interest statement. None declared.

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