IJKD
INDIAN JOURNAL OF KIDNEY DISEASES
An official scientific publication of Women In Nephrology-India

Editor-in-Chief: Dr Anupama Y J

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Indian Journal of Kidney Diseases (IJKD) is an official scientific publication of the ‘Women in Nephrology-India’. WIN-India is a young group formed by the women Nephrologists in India with the focus on showcasing the exemplary contribution of women Nephrologists to the growth of Nephrology specialty in India. It aims to provide an array of activities extending from academics to mentorship activities and to patient advocacy. The overall objective of the group is to nurture the young nephrologists in the country and to provide a support system promoting the growth of Nephrology specialty as well as the nephrologists. It is still in its infancy but has made remarkable advances in pursuing its goal.

IJKD is an example of one of its activities marked with tremendous forethought. The journal aims to present high quality information in the field of Nephrology and allied subjects with focus being on clinical medicine and research. It is a peer-reviewed, quarterly e-journal and covers all the aspects of Nephrology, dialysis and kidney transplantation.

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From the
EDITOR’S DESK

As we begin the year 2022, we, in the young group ‘Women in Nephrology, India’, are filled with a new hope. Hope of a new dawn in the academic horizon, hope of making a new beginning and a new mark in the Nephrology world. We take a new step in this direction by presenting the first issue of our official scientific publication ‘Indian Journal of Kidney Diseases’(IJKD).

Although the women nephrologists in India, had the dream of coming together as a group for many years, it attained fruition just about six months back. But it is remarkable that over a short span of six months, the group has made a commendable impact in the academic world. The dynamism of its leaders has taken the shape of a quarterly, open access, journal covering all aspects of Nephrology -General Nephrology, dialysis and transplantation. We aim to provide a platform for the young nephrologists of India and elsewhere to publish their scientific work and shape their academic career.

It is my privilege and honor to present the first issue of Indian Journal of Kidney Diseases to the readership. I am grateful to Dr Swarnalatha G for literally taking the publication from the stage of conception to reality, going stage-by-stage through the publication process. Words are not enough to thank the WIN Leads headed by Dr Urmila Anandh and editors, Dr Anita Saxena and Dr Manisha Sahay who guided us at crucial steps. We have a young, enthusiastic editorial team with us to help with the publication. Thanks are also due to the energetic reviewers who helped us with the peer review process and completed the process in very short time periods, varying between two hours and a week.

In this issue, we present a variety of clinical materials and I am thankful to each author for the time they have spent on this. Firstly, there is a perspective article from our dynamic leader, Dr Urmila Anandh, regarding her views on the challenges ahead of the women nephrologists and the barriers for their growth. She presents her solutions for enhancing the productivity and mitigation of stress to the women in medicine. Dr Swarnalatha presents the results of a comparative analysis of the outcomes of live donor renal transplants and cadaver renal transplants. Dr Priyamvada and her co-author discuss the nuances of xenotransplantation, which is making the news these days in different parts of the world. There is an interesting case report of recurrent crescentic glomerulonephritis in a young girl. There is also an illustrative image of calciphylaxis. In view of the March month being the Kidney month, on the occasion of the World Kidney Day, there is a topical commentary on the theme of ‘Kidney Health for all’ and its implications for India.
As we present this first issue, we are aware of the numerous challenges ahead. We intend to get our journal indexed in some of the prominent indexing sites and for this we need quality publications. Funds are a very prominent challenge. But hope runs eternal and we are hopeful to face the challenges one-by-one and turn them in our favour. In this context, it would serve us well to remember these immortal lines by the ancient Indian poet Kalidasa in ‘Salutations to the dawn’.

Look well to this day,
For it and it alone is life.
In its brief course
Lie all the essence of your existence:
The Glory of Growth
The Satisfaction of Achievement
The Splendor of Beauty
For yesterday is but a dream,
And tomorrow is but a vision.
But today well lived makes every yesterday a dream of happiness,
And every tomorrow a vision of hope.

Dr Anupama Y J
Editor-in-Chief, IJKD
PERSPECTIVE:
Women in Nephrology: The Journey, Barriers, Challenges and the Future

Urmila Anandh

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Introduction

In 1849 when Miss Elizabeth Blackwell (of British origin) became the first lady to get a medical degree from Geneva Medical College (New York) in United States of America, there was a letter to the New England Journal of Medicine (NEJM) stating that “it is much to be regretted that she has been induced to depart from the appropriate sphere of her own sex, and led to aspire to honours and duties, which by the order of nature and the common consent of the world devolve alone upon men”.¹ This statement reminded me of the article which the Editor -in-Chief of this journal had written in the Women in Nephrology (India) newsletter in which she stated that pioneering lady medical professionals in India also had to struggle to get acceptance.² I will not be surprised if the sentiment expressed in the NEJM letter in the nineteenth century is still prevalent in some of our colleagues’ mindset, especially when it concerns women doctors practising in specialities which are still considered as exclusive male domains.

Nephrology, a relatively young subspeciality of medicine was dominated by male professionals in its earlier years. Over the years, gratifyingly, more and more young women are taking the plunge and are studying to become nephrologists. This is despite the fact that nothing much has changed in society to facilitate their pursuit of this demanding speciality. This article traces the journey of women nephrologists and the barriers and challenges they faced and continue to face. It also tries to look at measures which will improve the lot of women who take up nephrology as their profession.
Women in Nephrology - The Journey

As far as mankind’s existence is known, the task of caring was the responsibility of a woman. The first known healthcare workers were the shamans, (shamanism is a spiritual healing process dating back to 17000-25000 years ) in whom majority were women. The role of women in healthcare was not emphasized in medical texts as most of the authors were males.Metrodora (c 200-400 CE) was a woman Greek physician who discussed about etiology and symptomatology of diseases in her book “On the Diseases and Cures of Women”. Even though her textbook was widely referenced, she limited her expertise to women healthcare.

In ancient India, medical practice was the domain of priests. As this was a male dominated profession, absence of the mention of female medical practitioners is to be expected. The only mention of a female vaidya is that of Rusa whose work on Ayurveda was translated into Arabic on the order of Harun al Rashid in the eighth century. Also, in ancient India, medical education began after the age of maturity, which the women students could not pursue since they were married off by that age.

In the last two hundred years women were often excluded from studying medicine and when they did there was a lot of consternation and uproar. Despite these adverse circumstances, women took up medicine and allied subjects like physiology, immunology and genetics in the beginning of the 20th century. Nephrology was formally recognised as a subspecialty of medicine in the late 1950s and early 1960s. Even before the speciality got its formal recognition, it is worthwhile to note that there were many pioneering women scientists who worked tirelessly in the field of renal physiology between 1918 and 1960. The works of Marian Minor Crane, Anna Josephine Eisenman , Pauline Merrit Hald, Lois L. McKay, Grace Medes, Gladys Cameron, Alma Elizabeth Hiller, Phyllis Adele Bott, Muriel Combes MacDowell and Margaret Mylle were only recognised in 1999. In the last 60 to 70 years of the existence of nephrology as a specialty, women nephrologists have made seminal contribution in the progress of this speciality. The following names were recognised by the International Society of Nephrology (ISN) for their work in the development of this subspeciality:

1. Dr Josephine Briggs for her work in the renin angiotensin system, diabetic nephropathy, blood pressure at the National Institutes of Health (NIH), USA.
2. Dr Renee Habib, a pioneer in nephron-pathology in France who helped establish nephrology as a specialty.
3. Dr Vidya N Acharya, the first woman nephrologist in India, who did pioneering work in kidney diseases and helped establish one of the oldest nephrology departments in Mumbai, India.
4. Dr Hai Yan Wang, the head of the nephrology department in Peking University First Hospital since 1983. She is instrumental in developing the nephrology services in China and is the editor of many Chinese nephrology journals.
5. Dr Mona Al-Rukhaimi, a strong leader in nephrology in the middle east (UAE) and an advocate of ethical practice of transplantation.
6. Dr Saraladevi Naicker, a pioneering nephrologist from South Africa who created the first training programme for nephrology in Africa. Her initiatives have led to the development of nephrology services all over Africa.
7. Dr Batya Kristal, the first woman head of department of Nephrology in Israel. She is the founder of Israel’s National Kidney Foundation.
8. Dr Priscilla Kincaid-Smith, the first woman President of International Society of Nephrology, is known for her work on analgesic nephropathy. She has been a towering inspiration for women nephrologists worldwide.

It would be extremely difficult to collate all the names of women nephrologists who have enriched this speciality by their work. The list is not complete, but it is an honour to mention Agnes Fogo (the current President of ISN), Vivette D’Agati (nephropathology), Gabriella Moroni and Liz Lightstone (Lupus Nephritis), and Sharon Moe and Teresa Adragao (vascular calcification) for their contributions over the years in this speciality. These pioneers have constantly encouraged us and the younger generation to take up this exciting but demanding speciality despite numerous hurdles.

**Women in Nephrology - Today**

Even though women continue to collaborate and contribute to the development of nephrology, till now there have been only three women Presidents in the history of ISN, an organization which is more than 60 years old. The first President was in 1972, followed by a hiatus of more than 43 years when Dr Adeera Levin was appointed as the next woman President of ISN in 2015. The American Society of Nephrology (ASN) was founded in 1966 by 17 men. The ISN was founded by Prof Jean Hamburger and the initial meetings and committees had very little female representation. Today women make up almost 40% of the nephrology workforce. This change over the years is commendable and mostly because of the changing attitudes of both the students and their mentors.

Dr Alfonso Palma, a senior Spanish nephrologist who has witnessed the slow but steady increase in the representation of women in nephrology says “when students would come to ask me about the speciality after sitting their Internal Medical Resident exam, the men always asked me if you could earn money working in nephrology, but the women never asked about this, they had more of an interest in the patient. Nephrology is an unusual speciality because it requires a great deal of effort, a lot of dedication, a lot of studying, a lot of work…. And it is not very well paid. Kidney patients consume you. If they die under your care it leaves a huge mark on you and this is something a lot of people can’t tolerate, although women can”.

The inclusion of more women in various strata of nephrology workforce bodes well for the speciality. To encourage and enhance their participation, we need to look at the barriers and challenges faced by young nephrology trainees and develop systems that remove/reduce these challenges and help facilitate a hassle-free fellowship program.

**Women in Nephrology: Barriers and Challenges**

In ASN and other organizations where the representation of women nephrologists are progressively increasing (25%-36%), leadership positions still are mostly the domain of men. In fact, creating an ecosystem where women automatically reach higher echelons and break the glass-ceiling is not the only challenge faced by us. We need to continuously evolve and develop infrastructure and systems which will encourage young women medical graduates to pursue nephrology. For this to happen we need to understand the barriers and challenges faced by these young women.

In many countries, it takes more than 5 years to graduate as a nephrologist after your with the primary medical school training. This is the period...
when women contemplate motherhood and to pursue their training, they often restrict their desire to become one. This ‘deferred parenthood’, so as to complete their training is described in many studies.8 Having a baby during training is fraught with difficulties. Sometimes leave taken during pregnancy may lead to termination of training contracts and often extension of the training duration. There are global discrepancies of maternity leave duration and reimbursement. Then, there is the guilty feeling of leaving the department under-staffed. Returning to work after delivery is often very stressful as the long hours of nephrology training is often not compatible with child care centre working hours. Often the mother misses out-of-work hours meetings and this negatively affects her career advancement.9 Maintaining a work life balance is difficult at this stage. This leads to feelings of low self-worth. Female physicians have a higher divorce rate than their male counterparts, especially those who work longer hours.10

Women nephrologists face numerous hurdles in career advancements and professional growth. Numerous studies have reflected on the gender disparities in remuneration and grant approvals in the speciality.11 A third of nephrology articles have women as primary authors and majority (80%) of peer reviewers are males.12 Women often skip conferences because of lack of on-site childcare facilities and exclusion of children from the conference venue.

The challenges of women nephrologists attaining leadership positions has been already alluded to before.

Women in Nephrology: The Journey

Women in Nephrology: The Journey

Women in Nephrology: The Journey

Summary and Conclusions

From the early years of nephrology, women have played a major role in the growth and expansion of this speciality. Now, they are increasingly
becoming a substantive part of the nephrology workforce. Their unusual qualities make them well suited for this difficult speciality. Addressing their issues and challenges will help not only them but the speciality as a whole. By removing barriers and prioritizing gender parity, inclusion of women nephrologists will ensure an efficient and effective workforce.

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COMMENTARY
‘Kidney Health for All’ - Implications for India
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On March 10, 2022, the world will celebrate the 16th World Kidney Day (WKD). It is a joint initiative of the International Society of Nephrology (ISN) and the International Federation of Kidney Foundations - World Kidney Alliance (IFKF-WKA) and is celebrated globally with the aim of improving kidney health and reducing the burden of kidney disease.¹ The theme for WKD 2022 is ‘Kidney Health for All’. It is important to remember that while kidney disease is common and harmful, it is usually preventable. It affects the lifestyle of the individual patient and also impacts the family and the society at large. By promoting ‘Kidney Health for All’, it is intended that the world recognises the deleterious socioeconomic impact of kidney diseases and employs kidney healthy practices which will go a long way in reducing the burden of kidney diseases in the community. In this article, an attempt is made to elucidate the challenges in the diagnosis and care of patients with Chronic Kidney Disease (CKD) in India.

CKD is a common condition with the prevalence of 8-16% in the global population.² It affects approximately one in every ten individuals and much of the morbidity of CKD is due to the associated cardiovascular (CV) events such as myocardial infarction, heart failure, stroke and arrhythmias. There is also an increased risk of death from CV events and sudden cardiac death is particularly common. The prevalence of CKD is gradually rising and so also is the mortality. Globally, the all-age mortality from CKD increased 41.5% from 1990 to 2017 and the all-age prevalence increased 29.3%.³ There is also a huge component of loss of Disability adjusted life years (DALY) due to CKD.

The prevalence and the risk factors for CKD however tend to differ among the developed and the developing countries. While lifestyle diseases such as diabetes, hypertension and obesity predominate in the developed countries, the causes are much more varied and multidimensional in lower and low-middle income countries (LMICs).⁴ Tropical infections such as leptospirosis, malaria cause acute kidney injury, as a sequelae of which there is persistence
of kidney damage. Climate change with rising global ambient temperature, growing uses of agrochemicals are other postulated causes. Low birth weight, unclean water, lack of sanitation, malnutrition and lack of health literacy are other major drivers of the high prevalence of CKD. In addition, there is also the influence of poverty and illiteracy on healthcare accessibility and availability. The inequality of health care services and the ignorance drive people to presentation at an advanced stage of the disease and with complications. This in turn enhances the healthcare expenditure in the already poor people turning it into a vicious cycle.

Healthcare in India and the burden of noncommunicable diseases:

India is a vast country with a great variability in the people, landscapes, density of population, literacy rate and health care facilities across the country. While 70% of the Indian population is said to reside in the villages, the healthcare services are predominantly concentrated in the urban areas. There is a nationwide public health system organized at various levels that is almost entirely free to users. However, 82% of the outpatient services and 58% of inpatient services are provided by the private sector, which comes at a significant cost, ill afforded by the country’s poor. Further there is a paucity of medical professionals working in the rural areas. It is estimated that 74% of the doctors work in urban areas. The infrastructure of existing hospitals in rural areas is also not adequate. Thus the people may have to resort to fraudulent healers, informal healthcare providers or sometimes, traditional healers for their health needs.

India faces a huge burden of diseases which has now shifted from communicable diseases to noncommunicable diseases and they account for 60% of all deaths in recent times. The age adjusted prevalence of diabetes is 9.6% with the prevalence being greater in urban areas. It is estimated that a staggering 53% have undiagnosed diabetes. A recent meta-analysis reports an increase of prevalence in both rural and urban India from 2.4% and 3.3% in 1972 to 15.0% and 19.0% respectively in the years 2015-2019. The prevalence of hypertension is about 30% and the gap in prevalence between urban and rural India is slowly reducing. A study from rural areas near Shimoga, for example, reported an age-adjusted prevalence of 30%. The Fourth District Level Household Survey reported hypertension in 25.3% with greater prevalence in men (27.4%) than women (20.0%). This translates into 207 million persons with hypertension in India. With a huge population burden (estimated at 1.39 billion in 2021), it is imperative that the onus of the primary mode of control of diseases, including kidney disease, should be by focusing on preventive efforts. A national programme for control of NCDs called the National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular diseases and Stroke (NCPDCS) was launched in 2010, but it did not include a policy for CKD, until recently. Population based screening for diabetes and hypertension is an integral part of the NPCDCS programme.

Hurdles in diagnosis and management of CKD in India

The rising prevalence of CKD in India is a well-known phenomenon. The earlier studies reported a prevalence of 0.89% -1.39%, while the multi-centric SEEK study recorded a prevalence of 17.2%. It is, however, difficult to objectively compare various figures available from various studies on the prevalence of CKD. The studies offer varied prevalence rates, depending on the time period in which the study was conducted and
the different defining criteria employed for the diagnosis of CKD. In addition, there are regional differences with some areas showing a dramatic increase in cases of CKD compared to others. There are hotspots of CKD along the east coast of India, where the reported prevalence of CKD is very high, almost 18%.14 The diagnosis of CKD, though simple, has its pitfalls too. Lack of standardization in methods of estimation of creatinine between laboratories and differences in equations estimating Glomerular filtration rate is another impediment for comparison of prevalence among regions.13 There is no eGFR estimating equation validated for the Indian population. There is no national registry for documentation of CKD and its various socio-demographic characteristics with early efforts at such a cause quickly petering off. All these are hurdles to our understanding of the distribution of the disease in the country. At the primary level too, the practitioners who attend to the vast majority of the people with various ailments are less oriented to kidney disease and diagnose them late. Late referral to nephrologists, delay in diagnosis of kidney dysfunction in patients with long standing diabetes/hypertension and indiscriminate use of nephrotoxic medications are other factors that complicate kidney care.

Challenges in the management of CKD in India

There are currently very few qualified nephrologists (rough estimate is around 1850 nephrologists for a population of 1.3 billion) and mostly in the urban areas.15 The delayed referral to nephrologists also adversely affects the care of patients. It is reported that only 20-30% patients achieve the recommended blood pressure and glycemic targets and reflects poor physician practices. The availability of renal replacement therapy (RRT) is also mainly concentrated in urban areas and many have to travel long distances to reach dialysis centers. It is estimated that only about 10% of patients with end stage kidney disease (ESKD) can afford to be on long term dialysis and discontinuation of therapy is common. Although many public hospitals now have haemodialysis units under the Pradhan Mantri National Dialysis Programme (PMNDP), the rising numbers of ESKD can barely be accommodated in these centers. Reports suggest that peritoneal dialysis as the initial RRT option is cost-effective compared to haemodialysis, but this is yet to translate to routine clinical practice.17 Renal transplantation is available in mostly private hospitals and the deceased donor transplantation program has only barely taken off at a few centers.

Kidney Health for all - what can be done?

This year’s WKD theme- ‘Kidney Health for all’ is an all-inclusive goal to ensure that kidney health is equally accessible to all, overcoming the regional, national, racial and gender inequalities. It is essentially an adaptation of the 17 Sustainable Development Goals (SDGs) that had been formally adopted by all United Nations member countries in 2015.18 Education is the cornerstone to ensure that everyone has a basic understanding of the need for evaluation and management of early kidney disease. Improved health in the family as a whole with more focus on the health of the mother and the child, improving health literacy and improving opportunities to build a better workforce are other strategies. Quality education is the key to reduce inequality and poverty. Improving the nutritional status, provision of clean water and better sanitation promotes health. Community health workers, auxiliary nurse midwives and Accredited Social Health Activists (ASHA) may be trained to screen for diabetes, hypertension and provide basic health education to rural population.19 They could be taught to monitor the health status...
of patients with CKD. Promoting gender parity is important to ensure equal opportunities to access healthcare. Better antenatal care results in healthy babies with lower risk of CKD in later life.\textsuperscript{19} Avoidance and better control of preeclampsia also reduces risk for later development of CKD for women. Regular screening at community level for diabetes and hypertension and ensuring adequate control goes a long way in prevention of CKD. Ensuring equitable distribution of RRT facilities with quality care that is accessible and affordable is a priority for countries and a suitable policy be drafted by policymakers in this regard.

**Conclusions:**

Health is a fundamental right of all individuals on this planet and the WKD serves to remind the practitioners of kidney care, their responsibilities in ensuring the deliverance of good quality kidney care to patients. Efforts at kidney awareness are made all over the world by conducting various activities which serve to gradually bring awareness to people and promote kidney health. Co-ordinated efforts among various stakeholders are important to ensure this goal.

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MINI-REVIEW:
XENOTRANSPLANTATION

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ABSTRACT
Xenotransplantation is propounded as a viable solution to address the severe organ shortage. Pigs are a likely source of organs. However, there are immunological and non-immunological challenges that need to be addressed. A primary initial concern was hyperacute rejections. The advances in genetic engineering have permitted the production of genetically modified pigs, removing the multiple carbohydrate antigens responsible for vascular rejections. Triple Knock Out (TKO) animals with genes knocked out for the carbohydrate antigens galactose-α1,3-galactose (α-gal), N-glycolyneuraminic acid (Neu5Gc) and the SDa blood group has helped in overcoming hyperacute rejections. Human transgenes for inflammatory mediators, coagulation components, and complements are added to TKO animals to improve graft outcomes. Xenotransplantation is now rapidly moving from bench to the bedside. In 2021, three porcine kidneys were successfully transplanted to brain dead recipients. Early 2022 witnessed the first successful pig heart transplant to a live human host. Experimental data on cellular rejections in xenografts is minimal. The long term hemodynamic compatibility and function of xenografts in humans remain unknown. With the current developments, more human data on xenotransplantation will likely emerge.

Key Words:
Keywords: Xenograft, Pig -to-human transplant, alpha 1,3-galactosyl transferase, hyperacute rejection
Introduction

Kidney transplantation is the best available treatment for End-stage renal disease (ESRD), in the present times. However, there is a constant imbalance between demand and the supply of organs for renal transplants. Cadaveric organs pose additional concerns. Brain death induces an autonomic storm, humoral, metabolic and immunologic changes in all organs. Following brain death, there is an upregulation of inflammatory cytokines and chemokines, enhanced HLA expression, leucocytic infiltration to tissues and generation of a procoagulant milieu. Many patients often die waiting for an organ. There is a need to explore alternate sources to meet the ever-increasing demand for organs. The World Health Organization (WHO) defines xenotransplantation as “any procedure that involves the transplantation, implantation or infusion into a human recipient of either: (i) live cells, tissues, or organs from a non-human animal source; or (ii) human body fluids, cells, tissues or organs that have had ex vivo contact with live non-human animal cells, tissues or organs”. Apart from providing a steady supply of organs, xenotransplantation avoids the harmful effects of brain death on target organs and the sociocultural barriers for a deceased organ transplant.

ANIMAL SOURCES FOR XENOTRANSPLANTATION

Xenotransplantation is not entirely a new concept. The non-human primates (NHP) are phylogenetically closer to humans. Hence the initial experimentation started with NHP as a potential organ source. In the 1960s, while human-human kidney transplant was in its infancy, Reemtasa et al. transplanted Chimpanzee kidneys to 13 patients. All were lost early due to rejections or infections, barring one patient who survived for nine months. Autopsy studies showed histologically normal kidneys. However, these experiments were not carried forward due to the poor overall success. Many old-world monkeys like Baboons and Rhesus monkeys have been used in preclinical models. However, though physiologically and immunologically related, there are potential problems for NHP as a source of organs. The constraints include the organ size disparity, the transmission of xenozoones, longer times for reaching maturity, longer gestation times, and a limited litter. Besides, blood type compatibility and lack of genetically modified animals are also significant limitations. Pigs are an alternate source for organs in xenotransplantation. Pigs have the advantage of larger litter size, shorter time to maturation, and lesser organ size disparity. ABO blood group compatibility is not a significant concern, and pigs are less vulnerable to transmit infections through graft. Advances in the field of somatic cell nuclear transfer and genome editing, particularly CRISPR-Cas9, have permitted multiple genetic modifications in pigs, eventually facilitating human cross transplants.

BARRIERS FOR XENOTRANSPLANT

1. IMMUNOLOGICAL

Xenoreactive natural antibodies

A fully vascularised pig kidney is more severely rejected than human allografts due to the genetic disparity between the human and pig. The xenograft may be dismissed by i) hyperacute xenograft rejection, ii) acute humoral xenograft rejection, or iii) acute cellular rejection.

Hyperacute rejections (HAR) occur due to circulating preformed antibodies. The
binding of donor-specific antibodies to the endothelial cells of graft leads to activation of the complement proteins and cell lysis, leading to disruption of graft vasculature and graft loss. The recent developments in genetic engineering have facilitated the removal of many target pig antigens, which predispose them to hyperacute rejections. The first xenograft described is galactose-α1,3-galactose (α-gal) epitope on pig tissue, resulting from the enzyme called α1,3-galactosyltransferase (GGTA1). This oligosaccharide is expressed on all mammalian tissues barring humans and non-human primates. Primates and humans develop antibodies in neonatal life; the possible antigen source is gut bacteria. However, GGTA1 knockout (GTKO) pig organs were rejected when transplanted to primates, implying the presence of other antigens. The other oligosaccharide antigens include N-glycolyneuraminic acid (Neu5Gc) and the SDa blood group. The enzymes responsible for producing these antigens are Cytidine monophosphate-N-acetylneuraminic acid hydroxylase (CMAH) and β-1,4N-acetyl galactosaminyltransferase (B4GALNT2).

Even when TKO organs prevented hyperacute rejections, AHXR is still reported in animal models. In vitro, human studies have shown that sera of sensitised patients can mount a humoral immune response to TKO pig cells. It is believed that the anti-HLA antibodies in the serum cross-react with class 1 swine leukocyte antigens (SLA class 1). This cross-reactivity suggests the presence of one or more shared epitopes between HLA 1 and SLA 1. Similarly, SLA Class 2 antibodies were detected in 45% of allosensitised human sera and 25% of sensitised sera.

Cell-mediated immune response

If the xenograft survives the challenge of HAR and AHXR, cellular rejections are still possible. Cellular rejection may result from innate immune mechanisms or adaptive immune mechanisms. Cells contributing to cellular rejection include macrophages, neutrophils, T cells, and B cells. Human NK cells have a high affinity for attacking xenografts. The potential mechanisms include:

- The Fcγ portion of circulating antibodies bound to the xenograft endothelial cells can attach to the Fcγ II receptors on NK cells
- The oligosaccharides on the xenografts can stimulate the lectin receptors on NK cells
- The SLA class 1 molecule on xenografts have a very low affinity to interact with the inhibitory receptors on human NK cells (KIR, ILT2, and CD94.) This would accelerate the activation of NK cells damaging the donor cells.

The non-galactose antigens often mediate acute humoral xenograft rejections (AHXR).
• NK cells may be involved in the presentation of xenoantigens to host immune cells

T cells also play a crucial role in acute xenograft cellular rejection. Like allotransplantation, two pathways are implicated. Pig antigen-presenting cells (APCs) directly activate donor T cells in the direct pathway. Donor APCs are mostly migratory leukocytes or donor endothelial cells. The indirect pathway involves the porcine antigens being presented by recipient APCs. Activation of T cells leads to CD4+ T-cell stimulation, B-cell activation, and antibody production. Studies have shown T cell responses against xenoantigen are stronger than alloantigen. However, data on AXCR from animal experiments is limited, as grafts often do not survive the humoral rejections.

Genetic engineering techniques to produce pig organs that prevent AXCR are in infancy; no cross transplantation data is available from animal experiments. The potential molecular targets include costimulatory molecules cytotoxic T-lymphocyte-associated protein 4 immunoglobulin (pCTLA4-Ig) and programmed cell death ligand 1 (PD-L1). Attempts to knock out the porcine CTLA4-Ig were successful; however, the GTKO/ pCTLA4-Ig pigs were highly susceptible to infections. Transgenic pigs expressing human CTLA4-Ig have been developed recently. Transgenic pig tissues with the human PD-L1 are available but have not entered the clinical testing phase. Another potential target is introducing the human variant of the class II transactivator (CIITA-DN) to pig tissues, which leads to reduced expression of SLA class molecules. Recently, TKO animals with SLA class 1 gene edits are have been successfully produced in the laboratory.

Role of complement

Complement plays a significant role in the events that unfold following xenotransplant. Human tissues possess complement regulatory protein (hCRP) that resists the cell damage caused by complement activation. The capacity of pig CRPs to bind human complement is suboptimal. Complement plays a part in innate immune response, humoral response, ischemic reperfusion injury, and coagulation cascade activation. Activation of the complement cascade results in tissue damage, hyperacute rejections and thrombotic microangiopathy (TMA).

2. NON IMMUNOLOGICAL

Molecular incompatibilities can occur between the human and porcine proteins regulating coagulation cascade and inflammatory pathways. When there is damage to endothelial cells, tissue factor (TF) is released, which activates the extrinsic complement pathway. Other coagulation factors further amplify the coagulation cascade, leading to thrombin activation. The porcine thromboregulatory molecules - viz thrombomodulin (TBM), endothelial protein C receptor (EPCR), and thrombin-activatable fibrinolysis inhibitor - interact inefficiently with various human coagulation components. Hence, human antibody binding to porcine endothelial cells and subsequent complement activation leads to unregulated coagulation and organ damage. The TKO animals can be modified further to express human transgenes (hTGs), for hCRPs (CD46, 55 & 59), coagulation pathway regulatory proteins (e.g., thrombomodulin and endothelial protein C receptor) and self-recognition receptors.
3. BIOETHICAL ISSUES

Xenotransplant remains a controversial topic despite the benefits it offers. A significant concern with xenotransplantation is the transmission of porcine endogenous retroviruses (PERVs). Safe xenotransplantation would need PERV-C-free animals with low expression of PERV-A, and PERV-B. There is a concern of low-level viremia, which may escape the detection limits of standard testing and get transmitted to human hosts. Theoretically, if transferred to humans, PERV’s might be capable of reaching epidemic proportions as humans lack immunity against the viruses. The collective risk to society due to the transmission of infectious agents remains an unresolved concern. Animals rights activists have often criticised the xenotransplantation experiments, as it goes against the principle of animal welfare. Genetic experimentation with animals brings civil society and science to crossroads; deontological arguments like playing God and creating “Frankensteins” needs to be addressed and clarified. Such attitudes from the general public combined with the long and uncertain post-transplant course may lead to psychological sequelae to the recipients. Most governments strictly regulate xenotransplantation due to the genetic experimentation and uncertainties involved with the procedure.

INDUCING IMMUNOLOGIC TOLERANCE IN XENOTRANSPLANT

The porcine xenografts generate a robust T and B cell response in primates. Hence inducing a state of immunologic tolerance would be essential to make xenotransplantation a reality. Two methods are being tested towards induction of tolerance – transplantation of donor thymus issue or inducing mixed chimerism. Thymus transplant can be either done by placing a vascularised thymus lobe to the host or as a composite along with the xenograft. The thymus can be placed under the renal capsule, in the kidney, and tissue can be vascularised. Animal experiments have shown that both methods induce tolerance across HLA class 1 and 2 barriers. Induction of microchimerism involves harvesting the bone marrow progenitor cells from the genetically modified source animals and transplanting them to the potential recipient. Although mixed chimerism has been successfully demonstrated in concordant species, cross-species experiments with primates pose significant challenges. Engraftment rates were lower due to macrophage-mediated destruction of porcine cells. Also, the administration of species-specific growth factors may be needed to facilitate engraftment.

EXPERIENCE WITH HUMAN XENOTRANSPLANTS

The first clinical-grade porcine kidney transplant with a human decedent model was reported from the University of Alabama, USA. The experiment fully simulated clinical kidney transplantation. After native kidney nephrectomy, the 57-year-old braindead male was given both porcine kidneys from 10 GE pigs- a clinical-grade pig designed for human transplantation. The mutations include targeted insertions of two human complement inhibitor genes (hCD55, hCD46), two human anticoagulant genes (hTBM, hEPCR), two immunomodulatory genes (hCD47, hHO1), and knock out for GGTA1, β4GalINT2, CMAH and growth hormone receptor. The pig kidney did not express the ABO blood group antigens.
The immunosuppressive regimen included rabbit Antithymocyte globulin (175 mg on days 0,1 and 2), Rituximab (1800 mg day 0), Tacrolimus, mycophenolate and methylprednisolone. The warm ischemia time was 28 and 29 minutes for the right and left xenografts; cold ischemia times were four h and five h 37 minutes for the right and left xenografts. The right kidney produced urine at 23 minutes, and the experiment was terminated at 77 hours. There were no changes in creatinine clearance, possibly attributed to the microcirculatory shock due to brain death. Initial kidney biopsies showed evidence of TMA, which did not progress in the subsequent biopsies. The New York University performed two successful kidney xenotransplants in cadaveric recipients. The donor was GalSafe™ Pigs. The kidney was placed in the lower limb; along with the kidneys, the thymus was also transplanted for inducing immunologic tolerance. Subsequently, The first successful porcine to human heart transplantation was performed in January 2022 the technical details are not published at the time of writing this article.

Conclusions:
With genomic alterations in source animals, human xenotransplantation has become a reality. The successful performance of four xenotransplants –one live and three deceased- has opened a new avenue in the history of transplantation. The significant barriers of xenotransplant - hyperacute and accelerated humoral rejections - could be avoided with appropriately modified animals and immunosuppressive regimens. However, ongoing challenges include cellular rejections, intermediate and long-term graft survival and potential transmission of xenozoonoses. Mechanistic problems are another concern. The porcine organs and vasculature are more fragile and accustomed to much lower blood pressures than humans. The long term hemodynamic consequences and the optimal function of xenografts remain unknown.

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References:


Comparison of Outcomes of Live and Deceased Donor Renal Transplantation-A Retrospective Study from a single center in South India

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ABSTRACT
Background: Renal transplantation is the treatment modality of choice for patients with end-stage renal disease (ESRD). Living donors constitute the majority of the organ donor pool in India. Deceased donation program is only slowly evolving in the country. In this study, we aimed at comparing the outcome of live and deceased donor renal transplantation at our institute.

Methods: This is a single-center, retrospective, observational study of renal transplant recipients from January 2010 to April 2016 conducted in a tertiary care centre in South India. The clinical profile, graft dysfunction, graft survival and patient survival rates of renal transplant recipients were analyzed.

Results: Of 210 recipients, live donor renal transplant (LDRT) recipients were 176 (83.80%) and deceased donor renal transplants (DDRT) were 34 (16.19%). Delayed graft function was common in DDRT (64.7%) compared to LDRT (3.40%). Graft dysfunction episodes were commoner in...
DDRT (1.04 episodes/patient/year) compared to LDRT (0.43 episodes/patient/year). Higher rejection rate was seen in LDRT (25.56%) compared to DDRT (8.82%) with mean duration of follow up of 3.37±1.80 years and 2.14±1.12 years respectively. Modification of immunosuppression and noncompliance were the risk factors for rejection. Death censored graft survival rates at 6 months, 1 year and 5 years in DDRT were 98.9%, 97.2%, and 92.6% respectively and at 6 months, 1 year and 3.26 years in LDRT were 100%, 97%, and 94% respectively. Patient survival rates at 6 months, 1 and 5 years in DDRT were 94.3%, 91.5% and 86.4% respectively, and in DDRT patient survival rates at 6 months, 1 and 3.26 years were 91.2% 85.3% and 79.4% respectively. Though the patient survival rate was better in LDRT compared to DDRT, it did not reach statistical significance. Overall mortality rate was 14% and infection was the commonest (77.74%) cause of mortality. Mortality rates in LDRT and DDRT were 13.63% and 20.58% respectively.

Conclusions: Live donors constitute the majority of the organ donor pool. DGF is commonly seen in DDRT. Rejection rate was higher in LDRT, with noncompliance and modification of immunosuppression being the risk factors. There is no difference in the patient and graft survival between LDRT and DDRT.

Key words: Deceased donor, Graft dysfunction, Graft rejection, Graft survival, Patient survival

Introduction: Renal transplantation is the treatment modality of choice for patients with end-stage renal disease (ESRD). The short-term and long term renal transplant outcomes have improved markedly during the last few decades due to improved surgical techniques, better immunosuppressive medications, prevention and treatment of infections. Despite improved outcomes, only a few ESRD patients have option of transplantation due to the paucity of donors. Deceased donation is slowly picking up in India resulting in expansion of the donor pool. There are very few studies comparing the outcomes of LDRT and DDRT from India. The present study was undertaken to compare the outcomes of LDRT with that of DDRT and to determine the various factors influencing the graft and patient survival in LDRT and DDRT.

Material and Methods: This is a retrospective, observational study of patients who underwent renal transplantation from January 2010 to April 2016 in a Nephrology unit at a large, tertiary care hospital in South India. Patients who were on regular follow up a minimum of 6 months were included in the study. Recipients who were lost to follow up (n=30) that is, those who were following up with local nephrologists (n=20) and those whose complete data was not available (n=10) were excluded from the study.

Donor and recipients were selected according to standard guidelines. All patients were given 3 consecutive doses of 1 gram intravenous Methylprednisolone (IVMP) and maintenance triple immunosuppression with Tacrolimus (0.1mg/kg/day and if induction was given at 0.08mg/kg/day), Mycophenolate Mofetil (MMF) (600 mg/m2/dose twice a day) and Prednisolone 20mg a day. Tacrolimus dose was tapered according to serum drug levels which were monitored on a monthly basis for the first six
months and as and when required subsequently. Dose of steroid was tapered from 20mg/day to 10 mg/day at the end of 6 months and continued thereafter.

Induction therapy was given in case of spousal and deceased donor transplantation with Basiliximab (two doses of 20 mg each on day 0 and 4) or Antithymocyte globulin (ATG) at a cumulative dose of 3mg/kg over 3-4 days. Patients who were given induction and anti-rejection therapy were given prophylaxis with Valganciclovir 450 mg orally daily, Fluconazole 150 mg daily and Cotrimoxazole once daily for 3 months. All the patients were followed regularly, with monthly investigations of complete blood picture, complete urine examination, blood sugars, liver and renal function tests, lipid profile, urine culture and sensitivity, 24 hour urine proteins, renal graft doppler and DTPA renogram. Serological investigations like Cytomegalovirus (CMV) DNA, Hepatitis C RNA and Hepatitis B DNA Polymerase chain reaction were performed in patients with elevated liver transaminases. Data on all the graft dysfunction episodes were collected and analyzed. Renal biopsy was done in patients in whom pre and post renal causes were excluded. Findings of biopsy were documented and treated accordingly. Rejections, defined as per Banff criteria, were treated with escalation of baseline immunosuppression and 3 doses of 1gram IVMP. In steroid resistant cellular rejection ATG for 3-5 days at the dose of 1mg/kg/d was given, and in steroid resistant humoral rejection 5 to 6 plasmapheresis sessions and/or Rituximab (375 mg/m²) were given. Data pertaining to recipient; blood group, age, gender, native kidney disease, duration of dialysis, mode of dialysis, blood transfusions prior to transplant, previous transplant, CMV status, immunosuppression protocol received and compliance to therapy were taken. Number of graft dysfunction episodes, cause of dysfunction, treatment given and response to therapy were analyzed. Various factors influencing the graft and patient survival were analyzed. Surgical complications if any were documented. Death censored graft survival and patient survival were analyzed at 6 months, 1 year and 5 years. Data pertaining to donor; age, sex, blood group, live donor renal transplantation (LDRT) / deceased donor renal transplantation (DDRT), donor relation to recipient, cold ischemic time, warm ischemic time and CMV status were taken for analysis.

Definitions: Immediate graft function (IGF): Patient had brisk diuresis after anastomosis of donor and recipient blood vessels.

Slow graft function (SGF): Patient had diuresis after anastomosis, but there was slow decline in serum creatinine. There was no requirement of dialysis after transplantation.

Delayed graft function (DGF): Patient had anuria after anastomosis and need for dialysis within the first week after renal transplantation.

Acute graft dysfunction: Defined as an elevation in the level of serum creatinine by more than 0.3 mg/dl or increase by 25% from the baseline.

Rejection, both cellular and antibody mediated were defined according to Banff 2013 criteria. Patient survival was calculated from date of transplantation to date of death or date of last follow up.
Graft survival censored for death with a functioning graft (death-censored graft survival) was calculated from the date of transplantation to the date of irreversible graft failure signified by return to long term dialysis or retransplantation or the date of last follow up during the period when the transplant was still functioning. In the event of death with a functioning graft, the follow up period was censored at the date of death.

Noncompliance was defined as stoppage or missing of all or single immunosuppressive medications.

Modification of immunosuppressive therapy was defined as change of either tacrolimus/MMF to everolimus because of side effects to tacrolimus/MMF or after protocol biopsy, or decrease of dosage.

Dehydration was defined as improvement of graft function with administration of intravenous fluids.

Statistical analysis: Statistical analysis was done using SPSS 17 Software (IBM, Chicago, IL). Continuous variables were expressed as mean and standard deviation (SD). Categorical variables were expressed as proportions. Univariate and multivariate analysis were done to assess the influence of various factors influencing the outcome. Cox-Regression analysis was done to estimate the hazard risk at 95% Confidence interval. P-value < 0.05 was considered as statistically significant. Kaplan-Meier survival analysis was done to estimate graft and patient survival at 6 months, 1 year and 5 years.

Results: A total of 240 patients underwent renal transplantation during this period in the unit, out of which 210 renal transplant recipients were included in the study. Patients who were in follow-up with the local nephrologists and whose data was incomplete were excluded from the study. Overall, LDRT constituted 83.80% compared to DDRT of 16.19%.

Baseline characteristics of patients are shown in table-1. There was a higher preponderance of female donors in LDRT compared to males in DDRT. Recipients in DDRT had longer vintage on dialysis and cold ischemic time compared to LDRT which is statistically significant. Most common form of native kidney disease was chronic glomerulonephritis (CGN) 38.57% followed by CKD of unknown etiology, chronic interstitial nephritis (CIN), diabetic nephropathy, polycystic kidney disease.
Delayed Graft Function: DGF was significantly higher in DDRT (64.7%) compared to LDRT (3.4%). There was no significant difference in the etiology of DGF in LDRT and DDRT. Acute tubular necrosis (ATN) was the most common cause of DGF in both LDRT (66.66%) and DDRT (50%) followed by rejections [LDRT (33.33%), DDRT (25%)]. Acute interstitial nephritis was seen only in DDRT (25%). The risk factors for DGF were prolonged cold ischemic time, DDRT and longer vintage on dialysis prior to transplantation (P<0.05).

Graft Dysfunction: In this study, there were a total 192 graft dysfunction episodes seen in 122 patients. The most common cause of graft dysfunction was acute rejections, seen in 48 (25%) episodes, followed by ATN (20.31%), sepsis (17.18%), dehydration (11.45%) and calcineurin inhibitor (CNI) toxicity (8.33%), (table 2). The incidence of graft dysfunction was more in DDRT (1.04 episodes/patient/year) compared to LDRT (0.43 episodes/ patient/year). The most common cause of graft dysfunction was rejection (28.66%) in LDRT whereas it was dehydration (31.4%) in DDRT. However, 42.45% and 43.75% of recipients in LDRT and DDRT had recovered renal graft function respectively. Mean serum creatinine in patients with persistent graft dysfunction was 2.28+0.90 mg/dl. Renal biopsy was done to analyze 127(66.14%) graft dysfunction episodes in 89 (42.38%) patients. Of which 32 (35.95%) patients underwent second biopsy in view of persistent graft dysfunction and third biopsy in 6 (6.74%) patients. On analysis of 2nd biopsy findings, in patients with ATN in the first biopsy 33.33% had rejection and 26.66% had CNI toxicity.
Table-2: Distribution of acute graft dysfunction episodes, their etiology and outcome

<table>
<thead>
<tr>
<th>Graft dysfunction etiology</th>
<th>Total number of events, N (%)</th>
<th>LDRT, N (%)</th>
<th>DDRT, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rejection</td>
<td>48(25%)</td>
<td>45(28.66%)</td>
<td>3(8.57%)</td>
</tr>
<tr>
<td>Acute tubular necrosis(ATN)*</td>
<td>39(20.31%)</td>
<td>33(21.01%)</td>
<td>6(17.14%)</td>
</tr>
<tr>
<td>Tacrolimus toxicity</td>
<td>16(8.33%)</td>
<td>13(8.28%)</td>
<td>3(8.57%)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>33(17.18%)</td>
<td>26(16.56%)</td>
<td>7(20%)</td>
</tr>
<tr>
<td>Acute interstitial nephritis(AIN)</td>
<td>10(5.20%)</td>
<td>9(5.73%)</td>
<td>1(2.85%)</td>
</tr>
<tr>
<td>Others#</td>
<td>46(23.95%)</td>
<td>31(15.78%)</td>
<td>15(42.8%)</td>
</tr>
<tr>
<td>Total events</td>
<td>192(100%)</td>
<td>157(100%)</td>
<td>35(100%)</td>
</tr>
<tr>
<td>Total number of patients with events</td>
<td>122</td>
<td>106</td>
<td>16</td>
</tr>
</tbody>
</table>

*Only patients with renal graft biopsy proven ATN were considered. Clinically presumed ATN were not included.

#Others include gastroenteritis, dehydration secondary to decreased fluid intake, cortical, papillary necrosis, BKV nephropathy, Native kidney disease recurrence.

Rejection: Of 210 transplant recipients, 48 rejection episodes were seen in 42 recipients. In LDRT, 45 episodes were in 39 recipients with mean follow-up of 3.37±1.80 years and 3 episodes in 3 DDRT with mean follow up of 2.14±1.12 years. Recipients in LDRT had higher rejection rates (25.56%) compared to DDRT (8.82%). In LDRT, higher rejection rate was seen in recipients with spousal donors (36.58%) followed by siblings (29.03%) and parents (13.59%). Among various types of rejection, antibody mediated rejection was common 60.41%, followed by cellular rejection (35.41%) and combined cellular and antibody mediated features (4.16%) In LDRT, 45.45% rejection episodes occurred during the first month of transplantation compared to 33.33% in DDRT. Modification of immunosuppressive medications within 3 months prior to rejection episode, prolonged cold ischemic time, and noncompliance to therapy were significantly associated with rejection (table-3). Absence of induction therapy, donor age, recipient age did not influence the rejection. Only 3 recipients developed rejection in DDRT, hence risk factor for rejection in DDRT could not be assessed.
Graft survival: Kaplan-Meier survival analysis was used to compare the graft survival rates between LDRT and DDRT by log rank test. Mean duration of follow up of LDRT was 1215.9+ 649.5 days and in DDRT 771.9+ 404.7 days. There was no significant difference in the graft survival between the LDRT and DDRT at 6 months and 1 year. Death censored graft survival rates at 6 months, 1 year and 5 years in LDRT were 98.9%, 97.2%, and 92.6% respectively. In DDRT, death censored graft survival rates at 6 months, 1 year and 3.26 years were 100%, 97%, and 94% respectively (Figure -1).

It was observed that patients without graft dysfunction at 6 months had higher risk of graft loss (P Value of 0.001) which was statistically significant. Patients with rejection and UTI episodes had 8 and 4 times higher risk of graft loss (P Value of 0.0001 and 0.009 respectively) which was statistically significant.

Patient survival: Kaplan-Meier survival analysis for patient survival showed no difference in LDRT and DDRT. Patient survival rates at 6 months, 1 year, 5 years in LDRT were 94.3%, 91.5% and 86.4% respectively and in DDRT, patient survival rates at 6 months, 1 year and 3.26 years were 91.2%, 85.3% and 79.4% respectively (figure 2). Though the patient survival rates were better in LDRT compared to DDRT, it did not reach statistical significance (P value by Log rank was

Table-3 : Analysis of risk factors for rejection

<table>
<thead>
<tr>
<th>Factors</th>
<th>Rejection (n=42 patients)</th>
<th>No rejection (n=168 patients)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean donor age (years)</td>
<td>41.09+ 9.81</td>
<td>43.9+ 8.98</td>
<td>0.154</td>
</tr>
<tr>
<td>Mean recipient age (years)</td>
<td>32.39+ 11.65</td>
<td>31.69+ 10.85</td>
<td>0.724</td>
</tr>
<tr>
<td>Donor (Deceased vs Live) n(%)</td>
<td>3(8.82%) vs 39 (22.15%)</td>
<td>31(91.17%) vs 137 (77.84%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Recipient blood group (O:A)</td>
<td>36.4%:33.3%</td>
<td>42.9%:17.5%</td>
<td>0.263</td>
</tr>
<tr>
<td>CIT(mean) minutes</td>
<td>75.35+ 73.23</td>
<td>145.35+ 185.86</td>
<td>0.03</td>
</tr>
<tr>
<td>Induction n(%)</td>
<td>19(45.23%)</td>
<td>59(35.0%)</td>
<td>0.631</td>
</tr>
<tr>
<td>Modification of IS n (%)</td>
<td>20(22.2%)</td>
<td>5(2.8%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Noncompliance n(%)</td>
<td>20(44.44%)</td>
<td>Nil</td>
<td>0.001</td>
</tr>
<tr>
<td>Prior blood transfusions n(%)</td>
<td>51.5%</td>
<td>55.9%</td>
<td>0.639</td>
</tr>
<tr>
<td>DGF/SGF n(%)</td>
<td>6(18.2%)</td>
<td>35(19.8%)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

CIT-Cold ischaemic time; DGF-Delayed graft function; SGF-slow graft function; IS-immunosuppression
The most common cause of patient mortality was infections (77.41%) followed by sudden cardiac death in 16.12% and cerebrovascular accident (CVA) in 6.45%. In DDRT, 100% mortality was due to infections compared to 70.83% in LDRT. Age of recipient, fungal infections and graft dysfunction predicted higher risk of mortality which were statistically significant (P=0.006, 0.000, 0.001 respectively).

Discussion:
In our study, LDRT constituted 176(83.80%) and DDRT 34(16.19%) of the transplants in the study period. This is unlike the situation in developed countries. Data from the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipient, showed that live donors constituted 32.35% compared to deceased donors, which was 67.65%. The incidence of DGF was low (3.4%) in LDRT in our study compared to other studies, and the incidence of DGF in DDRT was high in contrast to other studies. This could be because of longer cold ischemic time in DDRT in our study.

Longer duration of dialysis, prolonged cold ischemic time and DDRT were statistically significant risk factors for DGF in our study. This was similar to the findings by Perisamy et al. Although, the importance of older donor age and low donor GFR have been described as risk factors for DGF in many trials, we did not observe its significance in our study. Similar to the study by Han et al. the most common cause of DGF was ATN in our study. The incidence of graft dysfunction episodes were more in DDRT (1.04 episodes/patient/year) compared to LDRT (0.43 episodes/patient/year). In our study, 35.95% of patients with graft dysfunction underwent a second biopsy in view of persistent graft dysfunction. Mean time to second biopsy was 3.84+ 2.795 months. Patients with ATN in the first biopsy, subsequently showed rejection in 33.33%, and CNI toxicity in 26.66%, suggesting that ATN may be the initial presentation of rejection or CNI toxicity. To our knowledge none of the studies have analyzed the second biopsy. In our study rejection episodes were higher in LDRT (25.56%) compared to 8.82% in DDRT. The reasons for high rejection rates in LDRT could be due to a larger sample size of LDRT, non-availability of HLA-D antigen mismatch and use...
of CDC method of lymphocyte cross-match. Longer duration of follow up in LDRT compared to DDRT and early tapering of immunosuppressive medications in view of low immunological risk in LDRT compared to DDRT are other factors that may have contributed. Better compliance to immunosuppressive medications could be one of the reasons for lower rejection rates in DDRT as they had to be on dialysis for 37.17±25.48 months prior to the transplantation. However, the rejection rates in both LDRT and DDRT were low in our study compared to other studies. There was no significant difference in the graft survival between the LDRT and DDRT in our study. This was unlike the study by Nemati et al., which showed better 3 year graft survival in LDRT than DDRT. The graft survival rates in our study both in deceased donor and live donor transplants were better than other studies. There was no statistically significant difference in the patient survival between LDRT and DDRT. However in a study by Nemati et al., the patient survival in DDRT was much lower than compared to LDRT.

Mortality rate in our study was 14.76%. Mortality rates in LDRT and DDRT were 13.63% and 20.58% respectively. Similar to the study from developing countries, our study also showed that the most common cause of mortality was infections (77.41%) followed by sudden cardiac death in 16.12% and CVA in 6.45%. However, studies from developed countries, showed cardiovascular events as the most common cause of mortality.

Our study has several strengths. There are very few studies from India which have analyzed the outcomes of kidney transplant with respect to the type of donors. This study is an attempt to fill this knowledge gap. The analysis of second transplant kidney biopsy in those with persistent graft dysfunction has also not been described in studies from India to the best of our knowledge. However, there are a few limitations too. It was a retrospective study. The sample size and the mean duration of follow up was lesser in the DDRT group compared to LDRT. HLA-D antigen matching was not done and the serological method of HLA typing was used. Lymphocyte cross match was done by the CDC method only.

**Conclusion:** Although kidney transplantation has seen a tremendous surge all over India over the last few years, live donors still constitute the majority of donor pool in India, and the deceased donation is only recently increasing in several parts of the country. DGF was commonly seen in DDRT, while the rejection rate was higher in LDRT and was the common cause of graft dysfunction in LDRT. Noncompliance and modification of immunosuppression were the risk factors for rejection in LDRT. There is no difference in the patient and graft survival between LDRT and DDRT.

**Sources of funding:** Nil

**Conflict of interest:** None

**References:**


8. Analysis of patient and graft survival. ndt .oxford journals .org/content /17/ suppl_4/60.


CASE REPORT:
Recurrent Crescentic Infection Related Glomerulonephritis: a rare presentation

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Sreejith Parameswaran1, Rajesh Nachiappa Ganesh2
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ABSTRACT
Infection Related Glomerulonephritis (IRGN) is an immune-mediated disease caused by non-renal infections. The most common histopathology is diffuse endocapillary proliferative glomerulonephritis with neutrophilic infiltrate. IRGN presenting as crescentic glomerulonephritis is exceptionally uncommon. We describe a 17-year-old girl, with no prior comorbidities who presented with recurrent crescentic IRGN. The first episode was in 2014; she made a complete recovery with immunosuppression. She developed a repeat episode of crescentic Infection-Related Glomerulonephritis in 2019, which was also treated with immunosuppression. This case report presents an extremely rare presentation of recurrent IRGN with crescents.

Keywords:
Post-Infectious Glomerulonephritis, Recurrent Crescentic glomerulonephritis, Subepithelial humps, Recurrent Infection-related Glomerulonephritis, C3 glomerulopathy.
Introduction

Infection-related glomerulonephritis (IRGN) is an immunologically mediated glomerular disease that is triggered by an extra-renal infection. Although in the past, it was almost exclusively related to streptococcal infection in children, nowadays, it is recognized to be caused by a broader spectrum of organisms encompassing bacteria, viruses, fungi, and parasites. The infection may be discovered at the time of IRGN diagnosis in up to 45% of the patients. Fever could be absent in 20-30% of the individuals contributing to a delay in diagnosis.1 The disease is severe compared to children with almost 25% requiring renal replacement therapy and only 40-50% showing complete recovery of renal function.2 The most frequent histopathological feature of Postinfectious Glomerulonephritis is diffuse endocapillary proliferation with neutrophilic infiltrates. Crescentic glomerulonephritis is seen in less than 5% of the presentations.3 Recurrent crescentic IRGN is extremely rare. We describe a 17-year-old girl who presented with two episodes of crescentic IRGN and showed response to immunosuppressive therapy.

Case description:

A 17-year-old girl presented in 2014 with a history of fever for five days associated with chills and rigors, followed by acute onset generalized body swelling, which started in the periorbital region and progressed to the rest of the body. She also complained of reduced urine output and multiple episodes of vomiting. Her serum creatinine on admission was 8.2mg/dl. Urine examination showed 300 crenated RBCs/hpf and 2+ albuminuria with 24-hour urine protein being 1.8grams/day. Kidney biopsy was performed after one sitting of haemodialysis. It showed nine glomeruli; of which, seven (78%) showed cellular crescents. There was diffuse endocapillary proliferation with dense neutrophilic infiltration in an exudative pattern in the viable glomeruli. One glomerulus showed segmental endocapillary proliferation. Immunofluorescence showed no glomeruli. ANA and ANCA were negative, and serum C3 level was low, normal C4 level, and the ASLO titer was <200 IU/ml. A screen for infections was negative. She was given Pulse methylprednisolone followed by 1mg/kg of prednisolone and monthly cyclophosphamide infusions for six months. Cyclophosphamide was considered as there were >50% crescents in the kidney biopsy and it was timed in the secretory phase of menstrual cycle. Fertility preserving methods were discussed with the patient before starting cyclophosphamide but she was unwilling due to cost restraints. Steroid dose was gradually tapered to 5mg daily by the beginning of 3rd month. Her urine output gradually improved, and eGFR (CKD-EPI) improved from 7ml/min/1.73m² at presentation to 61ml/min/1.73m² at four months. Following six doses of cyclophosphamide, she was initiated on Azathioprine maintenance for two years. The patient was off immunosuppression after June 2017. At the time of withdrawal of immunosuppression, her eGFR (CKD-EPI) was 64ml/min/1.73m², 24-hour urine protein was <140 mg /day, and urine sediments were inactive.

By the end of 2018, a few dysmorphic RBCs were documented, and by 2019 she developed subnephrotic proteinuria.

In December 2019, she developed a short febrile illness following which she noticed similar complaints as in the initial episode. Investigations revealed dialysis requiring renal failure. ANA and ANCA were negative during this admission as well, and the serum C3 and C4 levels were 20.6mg/dL (Reference interval:90-180mg/dL) and 43.90mg/dL (Reference interval:10-40mg/dL) respectively. She underwent two sessions of
hemodialysis followed by a renal biopsy which showed 18 glomeruli, of which six were globally sclerosed. The remaining viable glomeruli were enlarged and showed diffuse endocapillary proliferation with neutrophilic infiltration and irregular membrane thickening. Nine glomeruli showed cellular crescents, of which three were circumferential, and 6 were segmental cellular crescents (Figure 1A-C).

Immunofluorescence showed strong staining for IgG (3+) and C3(2+) with IgG>C3. Electron microscopy showed electron-dense deposits in mesangial, paramesangial, and subendothelial regions of the glomerular capillaries and several large subepithelial humps( Figure 2).

Fig 1A – Section shows renal cortex with two glomeruli, both of which one shows cellular crescents and the second glomerulus shows exudative pattern with dense neutrophilic infiltration. Haematoxylin and Eosin stain, x 200

Fig 1B – Section highlights the glomerulus which is globally enlarged with diffuse endocapillary proliferation and dense neutrophilic infiltration. Haematoxylin and Eosin stain, x 200

Fig 1C – Section shows coarse granular deposits of IgG along glomerular capillary basement membrane, DAKO monoclonal antibody for IgG, Fluoresceine isothiocyanate stain, x 400.
Table 1. Renal function, Hemoglobin, proteinuria, serum albumin and treatment received during the clinical course and Follow-up

<table>
<thead>
<tr>
<th>Timeline</th>
<th>Serum Creatinine (mg/dL)</th>
<th>CKD-EPI eGFR (ml / 1.73m2)</th>
<th>Hemoglobin (g/dL)</th>
<th>Urine Dipstick albumin</th>
<th>Urine RBC /hpf</th>
<th>Serum Albumin (g/dL)</th>
<th>Treatment</th>
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<td>First presentation</td>
<td>8.2</td>
<td>7</td>
<td>8.1</td>
<td>1+</td>
<td>300 crenated RBC</td>
<td>3.6</td>
<td>IV Cyclophosphamide and Steroids</td>
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<tr>
<td>(November 2014)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First discharge</td>
<td>2.0</td>
<td>36</td>
<td>9.6</td>
<td>1+</td>
<td>10-20</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>(December 2014)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>1.29</td>
<td>61</td>
<td>9.2</td>
<td>Absent</td>
<td>Absent</td>
<td>3.8</td>
<td>Azathioprine (started after completion of 6 pulses of cyclophosphamide) and Steroid maintenance</td>
</tr>
<tr>
<td>2016</td>
<td>1.20</td>
<td>66</td>
<td>10.8</td>
<td>Absent</td>
<td>Absent</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>2017</td>
<td>1.24</td>
<td>64</td>
<td>11.7</td>
<td>Absent</td>
<td>Absent</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td>2018</td>
<td>1.09</td>
<td>75</td>
<td>11.9</td>
<td>1+</td>
<td>5-10 crenated RBC</td>
<td>3.7</td>
<td>ACE inhibitors</td>
</tr>
<tr>
<td>2019</td>
<td>1.29</td>
<td>61</td>
<td>11.2</td>
<td>24 hour urine protein: 680mg</td>
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<td>4.5</td>
<td>ACE Inhibitors</td>
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<tr>
<td>Second presentation</td>
<td>6.3</td>
<td>9</td>
<td>10.1</td>
<td>2+</td>
<td>200 - 250 crenated RBC</td>
<td>2.7</td>
<td>IV Cyclophosphamide and Steroids</td>
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<tr>
<td>Second Discharge</td>
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<td>9.0</td>
<td>2+</td>
<td>17-20</td>
<td>3.0</td>
<td></td>
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<td>(January 2020)</td>
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</tr>
<tr>
<td>February 2020</td>
<td>2.49</td>
<td>27</td>
<td>9.2</td>
<td>2+</td>
<td>25-30</td>
<td>3.3</td>
<td></td>
</tr>
</tbody>
</table>
Given the recurring fever, LM, IF and EM findings, the possibility of IRGN was considered. Blood culture, dental evaluation, chest x-ray and transesophageal echocardiography were done to evaluate for occult source of infection and were noncontributory. She was pulsed with methylprednisolone and given 1mg/kg of prednisolone and re-initiated on monthly cyclophosphamide injections (total cumulative dose of 6.75 gm). Her renal functions improved to a serum creatinine of 2.2mg/dl at the time of her last follow up in February 2020. Table 1. summarizes the renal function, hemoglobin, proteinuria, serum albumin, and treatment throughout the clinical course of the patient.

**Discussion:**

Infection-related glomerulonephritis (IRGN) is an immune-mediated phenomenon commonly caused by non-renal infections. ‘Post-streptococcal’ glomerulonephritis (PSGN), which occurs in children, is the prototype infection-related glomerulonephritis. However, the past few decades have seen a shift in the epidemiology and outcomes of IRGN. A majority of these cases occur in adults, especially the elderly and the immunocompromised. The sites of infection are also heterogeneous in comparison to the typical post-streptococcal glomerulonephritis. The typical presentation of Post streptococcal glomerulonephritis is with acute nephritic syndrome occurring within 1-6 weeks of a skin or upper respiratory tract infection characterized by new-onset hematuria, proteinuria, edema, and hypertension and decreased renal function often occurring within few days. In a majority of the cases, there is a complete recovery of renal function within a few days to weeks following resolution of infection. Acute Infection-related glomerulonephritis in adults also presents commonly as an acute nephritic syndrome. The upper respiratory tract is the most common site in young adults, whereas the skin is the most common site in elderly patients. Infections at other locations including lungs, heart, urinary tract, teeth/oral mucosa, bone, and deep-seated visceral and somatic abscesses, have been implicated. The infection could be sub-clinical and discovered only at the time of IRGN diagnosis in up to 45% of the patients and fever being absent in 20-30% of the individuals leading to a delay in diagnosis. The disease in adults is severe compared to children with almost 25% requiring renal replacement therapy and only 40-50% showing complete recovery of renal function. Elderly patients with IRGN tend to have much severe disease, with most patients having renal failure ‘ab initio’. Post-infectious GN associated with sporadic infections tends to have a worse prognosis, with up to 60% of adults developing chronic kidney disease. These patients often have multiple comorbidities like diabetes, malignancy, diffuse vascular disease, and alcohol abuse. A small proportion of patients may continue to have hematuria and proteinuria. Persistent activation of the Alternate complement pathway (AP) is believed to be responsible in such cases. The pathogenesis of IRGN is understood to be due to the glomerular deposition of immune complexes, which may either form in circulation or in-situ. SH Nasr et al. in their study utilized at least three of
the following criteria to make a diagnosis of IRGN: 1) clinical or laboratory evidence of infection preceding or at the onset of glomerulonephritis 2) depressed serum complement 3) endocapillary proliferative and exudative glomerulonephritis 4) C3 dominant or codominant immunofluorescence staining and 5) hump-shaped subepithelial deposits on electron microscopy. In one of the studies done by SH Nasr et al., it was found that out of the 86 patients, 37%, 41%, and 22% had satisfied five, four, and three criteria, respectively. Our patient had presented with fever on both occasions. However, an active infection could not be found; the diagnosis was based on the renal biopsy finding of diffuse endocapillary proliferation with neutrophilic infiltrate, C3 co-dominant immunofluorescence staining, subepithelial humps in electron microscopy and a low serum complement C3.

The presentation of IRGN as crescentic glomerulonephritis is rare. The commonest histological pattern seen with IRGN is diffuse endocapillary proliferation with numerous intracapillary neutrophils, followed by focal endocapillary proliferative GN and mesangioproliferative GN. Membranoproliferative GN is the least common histological pattern of injury. Small, focal crescents are common in IRGN and are not considered as an adverse prognostic marker. However, crescentic glomerulonephritis with ≥50% crescents are rare. The data on management and long-term sequelae of crescentic IRGN is limited. Husseini et al. followed up 23 cases of postinfectious crescentic GN for a mean period of 40.1±28.9 months. The median age was 12.35 years (range 4-55 years). The commonest histological pattern was diffuse endocapillary proliferative and exudative GN. Supportive hemodialysis was required in 65% of the patients. Patients with rapidly progressive renal failure were treated with intravenous methylprednisolone at a dose of 10mg/kg/day for five days followed by oral steroids at 1mg/kg/day for four weeks and tapered after that. Younger patients were found to have a significantly better renal prognosis. The persistence of nephrotic range proteinuria and hypertension on follow up were found to be adverse prognostic factors for renal dysfunction. Among the histopathological variables, the number of crescents was the only significant variable affecting the renal function. Sakthirajan et al. reported a series of 47 crescentic IRGN patients with a mean follow up of 9.9±4.2 months. The mean age was 42±13.5 years. Complete renal recovery was seen only in 25.5%, progression to chronic kidney disease in 40.4%, seven patients reached end-stage renal disease, and nine patients died during follow-up. Pulse steroids followed by oral steroids for 8-12 weeks were used in 78.7% of the patients. Hemodialysis was required in 53.2% of the patients. On univariate analysis, MRSA infection, unidentified source of infection, non-isolation of organisms, presence of interstitial fibrosis, and tubular atrophy in renal biopsy and requirement of hemodialysis were found to be significant risk factors for poor renal outcome. The role of immunosuppression in the management of IRGN has not been evaluated in a randomized prospective clinical trial. Though steroids are frequently used in the management, none of the studies in which statistical analysis was performed found a beneficial effect on outcome. Baikunje et al. did a retrospective analysis of nine adult patients of post-infectious glomerulonephritis with crescents. The mean MDRD eGFR at presentation was 30.28ml/min/1.73m². All patients treated with steroids had better renal outcomes with a mean MDRD eGFR of 74ml/min/1.73m² [range:58-99] at a mean follow up of 22.65 months. Among patients not treated with steroids, two were left with significant renal impairment (mean MDRD eGFR 23.5 mL/min/1.73 m² [range 19–28]) at a mean follow up of 15.5 months. The evidence for additional immunosuppression with agents like cyclophosphamide and rituximab is unclear and remains anecdotal. Our patient was treated with Steroids and Cyclophosphamide in view
of crescentic glomerulonephritis and showed a complete recovery in the first episode. However, in the second episode, she had an incomplete recovery of renal function.

The novelty of our case lies in the presentation as recurrent crescentic IRGN. The recurrence of IRGN raises the possibility of an underlying disorder of complement pathways that could have predisposed the patient to a second episode and makes a case for testing for an underlying complement pathway abnormality. Also, our patient was treated with immunosuppression for two years following the first episode. On stopping immunosuppression, she was found to have a recurrence of sub-nephrotic range proteinuria during follow-up with one of the urine evaluations revealing active sediments (Table 1). She further went on to develop another episode. The closest differential diagnosis of IRGN is C3 glomerulonephritis. A detailed workup of the complement system was not possible in our case due to financial constraints. Sethi et al. described a group of PIGN patients with persistent hematuria and proteinuria, a defect in the alternate complement pathway leading to persistent activation and excessive deposition of complement proteins and breakdown products in the glomeruli resulting in the development of persistent proliferative glomerulonephritis. Recurrent RPGN after kidney transplant is a known entity. However, data on the repeated episodes of RPGN in the native kidneys is very sparse with only a few case reports published till date. One case report describes recurrence of anti GBM

Table 2. PIGN, Atypical PIGN, C3GN versus our case: a comparison of histopathology (Adapted from Reference 7)

<table>
<thead>
<tr>
<th>Microscopy</th>
<th>PIGN</th>
<th>Atypical PIGN</th>
<th>C3GN</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LM</td>
<td>Diffuse proliferative, less commonly mesangial proliferative, or crescentic</td>
<td>Diffuse proliferative, less commonly mesangial proliferative, or crescentic</td>
<td>Membranoproliferative and less commonly mesangial proliferative</td>
<td>Diffuse proliferative, crescentic, Exudative</td>
</tr>
<tr>
<td>IF</td>
<td>Bright mesangial and capillary wall C3, usually with Ig’s (garland pattern)</td>
<td>Bright mesangial and capillary wall C3, usually without Ig’s. If present IgG (trace to 1+)</td>
<td>Bright mesangial and capillary wall C3, usually without Ig’s</td>
<td>Bright mesangial and capillary wall C3 and Ig deposits</td>
</tr>
<tr>
<td>EM</td>
<td>Numerous subepithelial humps, few mesangial, and subendothelial deposits</td>
<td>Numerous subepithelial humps, many mesangial, and subendothelial deposits and ± intramembranous deposits</td>
<td>Many mesangial and subendothelial deposits, ± few intramembranous, and subepithelial humps</td>
<td>Mesangial, paramesangial and subendothelial deposits with several large subepithelial humps</td>
</tr>
</tbody>
</table>
disease, ANCA associated crescentic GN and immune complex RPGN after stable remission for 1 year.\textsuperscript{12} Table 2 highlights the histopathological features of PIGN, Atypical PIGN, C3GN, and compares it with our case.

It is prudent to evaluate for defects in the complement system in cases of IRGN with persistent hematuria, proteinuria, worsening renal dysfunction, or recurrent crescentic glomerulonephritis.

**Source of funding:** None

**Conflict of interest:** Nil

**References:**


IMAGES IN NEPHROLOGY

Calciphylaxis

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Figure 1: Clinical photograph of the Skin lesions
A 55-year old gentleman with diabetic chronic kidney disease on regular haemodialysis for the past three years, sought advice for painful skin lesions on the left leg. There was no history of fever, trauma or insect bite. His other comorbidities were obesity, ischemic heart disease, hypertension, HCV seropositive status and left subclavian vein stenosis with severe venous hypertension. His medications included nifedipine, clonidine, sodium bicarbonate, periodic erythropoietin and iron sucrose injections. On evaluation, he had a 2x4 cm necrotic ulcer covered with eschar over the left leg two inches above the lateral malleolus and two smaller necrotic areas 0.5x0.5 cm above the medial malleolus (Figure 1). Dorsalis pedis and posterior tibial arterial pulsations were not felt in both legs. His lab results were as follows: Haemoglobin-7.4 g/dl, serum creatinine-10.5mg/dl, calcium-10.5 mg/dl, phosphorus - 4.1 mg/dl (Ca*P product 41.1mg^2 / dl^2), albumin - 4.1 g/dl, alkaline phosphatase-163 IU/l, parathyroid hormone -276.8 pg/ml(normal-10-65 pg/ml). X-ray of the left foot showed extensive calcification of the blood vessels. Histopathologic examination of skin biopsy revealed extensive calcification in the subcutaneous tissue with calcific plugs in the

Figure 2: Skin biopsy of the lesion demonstrating calciphylaxis(HE, 40x)

1. Stratified squamous epithelium
2. Calcification in the subcutis
3. Calcification in the blood vessels
4. Calcification of the walls along with calcific obliteration of the lumen
dermal vessels confirming calciphylaxis (Figure 2). He was treated with intensification of dialysis against low calcium concentrates, cinacalcet and antibiotics. Sodium thiosulfate was not available and not given. The lesions worsened despite these measures. He succumbed to intractable sepsis ten weeks later.

Calciphylaxis or calcific uraemic arteriolopathy (CUA) is a chronic progressive syndrome of arteriolar media calcification, thrombotic ischemia, and necrotic ulceration. It is mostly seen in patients with advanced chronic kidney disease on haemodialysis. It may rarely be seen in renal transplant recipients with functioning kidneys. Few cases are reported even in non-uraemic settings such as alcoholic liver disease, connective tissue disease and malignancies. The pathogenesis is unclear. Disturbances in calcium-phosphorus metabolism are mostly implicated. Hyperparathyroidism, increased serum phosphorus, increased calcium x phosphorus product >70 mg²/dl², female sex, obesity, diabetes, vitamin D therapy and warfarin use are some of the factors associated with calciphylaxis. Lesions start with tender red areas developing into indurated plaques or nodules. Patients may subsequently develop an eschar followed by frank ulceration, gangrene or sepsis. Proximal pattern of involvement with lesions abdomen, thigh and buttocks carries a worse prognosis. Rarely, penis, breasts and ear lobules may become necrotic. The treatment is not well-defined. Parathyroidectomy, oral calcimimetics, sodium thiosulfate are some of the measures that have been employed with variable success. Aggressive wound debridement has been advocated and hyperbaric oxygen may be useful in healing of ulcers. The condition is associated with significant morbidity and mortality. 80% of the affected patients die of sepsis or organ failure, usually within a year. Our patient was obese and diabetic, but parathyroid hormone levels were within acceptable range for the level of kidney function. His calcium phosphorus product was also within the recommended range for dialysis patients. The cause for the lesions was not clear. High index of suspicion in patients with CKD is necessary for early diagnosis and limitation of morbidity.

References:
Indian Journal of Kidney Diseases (IJKD)

Manuscript Submission guidelines:
The journal considers the following categories of manuscripts: Original Articles, Reviews of basic and clinical topics of interest, Case reports, Letters to the editor, Images of unusual cases/biopsies/radiological images/electrocardiogram and invited commentaries and editorials. Requirements for different types of manuscripts accepted by IJKD are as follows.

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<th>No of References</th>
<th>No of Tables</th>
<th>No of Figures</th>
<th>Abstract word limit</th>
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Manuscript preparation:
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- There should be the following FIVE files related to manuscript:
  1. Covering letter
  2. Title page
  3. Main body of manuscript
  4. Figure(s)
5. Copyright form

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- Images with identifiable patient indicators are not accepted.

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