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Case Management Strategies for Patients with ADPKD – Part 1

Announcer:
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Dr. Chebib:
Hello, and welcome to this webcast titled, "Optimizing the Care for Patients with ADPKD – Case Management Strategies, Part 1." I am Fouad Chebib, an Assistant Professor of Medicine at the Mayo Clinic, Florida, and I'm joined today by my colleague, Dr. Pranav Garimella. Dr. Garimella, please introduce yourself.

Dr. Garimella:
Hi. I'm Pranav Garimella. I'm an Associate Professor of Nephrology at the University of California San Diego. In this webcast today, we're going to review several common cases and provide insights into practical evidence-based management, and strategies to achieve optimal outcomes in patients with PKD.

Dr. Chebib:
Before we get started, let's review our learning objectives. Upon conclusion of this educational activity, participants should be able to summarize a practical approach to diagnose and treat pain in ADPKD, identify characteristics of atypical kidney cystic diseases, review best practices and identification and management of intracranial aneurysms in ADPKD, and describe the role of tolvaptan in patients with ADPKD, age 55 and older.

Let's start with our first case. I have a patient who is 28-year-old female, who's coming in with an acute pain, mostly on the right flank side but she also tells me that she has also a right upper quadrant pain as well. I'm curious what's your approach in a patient with ADPKD, who has such an acute pain.

Dr. Garimella:
Thank you, Fouad. As you know, this is a pretty common presentation in patients with polycystic kidney disease and unfortunately so.

And, as with all cases, it depends on how the patient presents. In your case, it's an acute pain, so this is something that has happened probably over the course of hours or days, and that narrows the differential diagnosis down to a few things at the top of the list that I'd like to start off with. As with most people, people with PKD can also have infection-related pain, so the first thing I want to rule out that's probably the most important thing to consider is whether or not this patient has an infection that needs timely antibiotic treatment.

Dr. Chebib:
Absolutely.

Dr. Garimella:
So, what I first look for is, is there anything to suggest an infection? Does this patient have a urinalysis to suggest something? Do they

have any blood in their urine? Do they have anything to suggest inflammation? And so those would be the first things that I would like to understand, as I branch down the treatment p – algorithm.

Dr. Chebib:
Yeah, so she has no fever and we got her CRP and it's normal CRP – not elevated. And then her urinalysis is bland with no pyuria and no dis – no urinary symptoms, no dysuria.

Dr. Garimella:
Okay. So, so that's good. So that tells me that, you know, the likelihood of a urinary tract infection in this person is very low. And you gave me another clue that I would say, that she had pain in her flank, and also in her you know the right upper quadrant, which makes me think that perhaps this is something that could be spanning both areas, and common things being common in polycystic kidney disease I'm now beginning to think of either a cyst that may have ruptured or a cyst that's enlarged, that could be pressing upon it. And so, this could also be a cyst on the liver that could be presenting with symptoms, so now I'm thinking along more cyst-related pain rather than an infection.

Dr. Chebib:
Yeah, that's a great point that it's important to rule out any other, non-cystic causes of pain, and that it seems that she has also cyst rupture. So she tells you now that after she had all this acute pain, she started having gross hematuria. So, but she's in a lot of pain and what would you recommend? Should she go to the emergency department for an abdominal imaging?

Dr. Garimella:
Right. So again, it depends on how much of pain control is acutely needed, and as long as we've ruled out an infection you know, I usually tend to avoid sending patients to emergency rooms if possible. So having them come back from an urgent care visit to our PKD program or something, the next day, would probably be what I would recommend, if it sounds like the patient could make it there. And I'd try to get some kind of imaging at that point. You know, if I can get an ultrasound early on, fine, but otherwise a non-contrast CT sometimes is a good option, because one other thing that patients also have that can present with blood without an infection is kidney stones.

Dr. Chebib:
Mm-hmm.

Dr. Garimella:
And patients with PKD, as you probably have seen, have a lot of kidney stones as well. So that's what I'm thinking about next. How about you? Where would you take this?

Dr. Chebib:
Yeah, so with cyst bleeding, typically it kind of resolves on its own, so a lot of times we ask them to rest, to hydrate themselves very well. Sometimes they might require a little bit more of IV pain medications or coming in into the hospital, if the bleeding is not stopping after few hours or a couple of days. Unfortunately, there's not a lot of other options to stop the bleeding. Most of the times we wait for it to stop on its own. Sometimes we do some interventions with embolization. We've had some success with that. Otherwise, we've had couple of cases where we used tranexamic acid and that was helpful but those are in severe cases.

Dr. Garimella:
That's interesting. And, you know, like you've seen some of these patients, even when the hematuria resolves, they tend to have chronic pain you know, even after this acute episode resolves, once in a while every few months, and every few weeks, there's a flareup of pain. How do you typically approach someone who comes in now with chronic pain?

Dr. Chebib:
Yeah, that's a big deal in ADPKD patients. A lot of our patients with ADPKD live with chronic pain, and many times we – it's kind of disregarded. You know, we know it's from ADPKD, but we don't have too many options, and – and the patients feel they're not heard, so it's important first to acknowledge that PKD causes pain. It's not in the patient's head, it's true pain. And pain is complex, so – and especially with chronic pain – so we try to approach it in a multidisciplinary approach.

There's a lot of conservative management that we can do including heat pads, some Tylenol, sometimes even in acute pain we can use two or three days of NSAIDs, which is acceptable although as nephrologists, we don't like NSAIDs, but in the acute setting, I think it's acceptable to use two to three days with good hydration. The chronic pain situation – it becomes more challenging, because we don't wanna use a lot of the pain medication. Sometimes we need to use some narcotics. And then we go into procedures. Have you done any procedures for chronic pain interventions?

Dr. Garimella:
Yeah, that's a great thing, because again most people tend not to want procedures. But if you could actually identify, perhaps, one or two cysts that may be culprit lesions, I think targeting those would probably be most beneficial. In patients who have generalized multiple large cysts, targeting a single cyst may end up getting you a procedure that actually doesn't resolve the pain. But if you can target them cyst aspiration is an option sometimes there is a recurrence of the fluid in the cysts, but foam sclerotherapy, perhaps, would be a good option. There's been some data recently published over the last two or three years, showing about – up to about 70-80% reduction in pain at follow-up after foam sclerotherapy, so it's definitely something that can be considered.

And there are newer technologies that, perhaps, you know some large PKD centers may be using, especially in conjunction with anesthesia, and regional pain management and, you know, we've had our colleagues in anesthesia consider the placement of implantable pain control devices. I don't know what your experience is with that?

Dr. Chebib:
Yeah, we're exploring that with our colleagues in anesthesia and trying to use some successful experiences in pain other than PKD, and they're trying to apply it to PKD. We sometimes use celiac plexus block to ensure that the pain is coming from from that kidney. We also do some renal derivation sometimes, and then if all these fail, then we start trying to do some innovations such as these implantable devices, but it's kind of a stepwise approach. It's complex, it's important to have a good relationship with the patient, and have a – kind of a team with your anesthesiologist, pain clinic and try to help them with such a debilitating disease. There's also tolvaptan that has been shown to improve pain by 17% or in 17% of the patients in TEMPO 3:4, there was a good improvement with tolvaptan, so that's potentially an option. If they are eligible otherwise, that would be a good option.

Dr. Garimella:
Great. This is a really complex topic, as you just, you know…

Dr. Chebib:
Yes.

Dr. Garimella:
…nicely summarized there.

Dr. Chebib:
Great, well, thank you, and we'll move on to our next case.

Dr. Garimella:
Absolutely. Alright, so Fouad, one of the things that sometimes strikes me as surprising is once in a while you get these patients who don't seem to have a very large cystic burden, or they are – they – they're older. They have a decreased GFR, and they have some family history of having cystic kidney disease. Very often, cystic kidney disease is attributable off the bat to off the bat to ADPKD, but, you know, these patients have not often had a genetic diagnosis and they come in, you do an imaging study, and their cysts – there are cysts, but their kidneys aren't as enlarged as you would expect, perhaps, for someone with that degree of GFR impairment. How do you approach such cases?

Dr. Chebib:
Yeah, those are very important cases to recognize, because now that we have treatments for autosomal dominant polycystic kidney disease, it's important to really have an accurate diagnosis. So as you mentioned similar patients might have a family history of kidney failure, kidney cysts, and then it's kind of an autosomal dominant, and so someone would come and they would tell you, "My mother and my grandmother reached kidney failure in their 60s, 70s." They had cysts, they called them polycystic kidneys because that was the only diagnosis at the time. And now we're realizing that not all kidney cysts are due to ADPKD. So there's the PKD1 mutations, PKD2 mutations, but there is still about 10-15% of patients who don't have PKD1 or PKD2, and there's a group that we're try – that are now through genetic testing, we're understanding there is potentially GANAB mutations and other ADPKD mimickers. So, where you're mentioning that the kidney cysts or the kidney size is not congruent with the GFR, meaning that that patient had doesn't have huge kidneys, so their total kidney volume is on the smaller side although they have bilateral kidney cysts perhaps, but their – their kidney length is probably either smaller, or to a normal size, and then their GFR is - is much sma – much lower than what you expect with a cystic burden. So always, when you're trying to match the cystic burden to the GFR, it's important to kind of put it in context, so do these cysts are causing such a low GFR? There's another process.

So, there are entities that are closer to the ADTKD – so the autosomal dominant tubulointerstitial kidney disease – where these patients would have kidney cysts. They have an autosomal dominant inheritance – so family history, but they have more of interstitial fibrosis leading to that lower GFR. So these patients you would have, again, bilateral kidney cysts, low GFR, they might have gout high uric

acid, they might have family history of early gout. They might have low magnesium, some genitourinary malformations – so things like ADTKD due to MUC1 mutation, HNF1 beta with also early onset diabetes. And there is this new entity called DNAJB11-associated disease that can cause bilateral kidney cysts, and it's kind of in between ADPKD, ADPLD and ADTKD. So it has polycystic livers, polycystic kidneys, and more often interstitial fibrosis component, and these patients kind of have good GFR up till they reach their 50s and 60s, and then all of a sudden they just kind of really accelerate their kidney dysfunction.

Dr. Garimella:
I can see why that can be very confusing, with something like ADPKD Type 2, which similarly presents, but then you have more typical presentation on imaging. So, would you recommend genetic testing often to patients who have non-congruent findings on imaging and GFR?

Dr. Chebib:
Yes, absolutely. So this is one absolute indication to obtain a genetic testing. Having a panel of cystic genes to look for PKD1, PKD2, and all these new genes that are being discovered, and also look at polycystic liver disease genes, and then the autosomal dominant tubulointerstitial kidney disease genes. Those are very important and then the main way of diagnosing these patients through genetic testing.

Dr. Garimella:
Understood. That great, you know, the atypical, I think, cases are really important. Once in a while, we also see cases with atypical – and by atypical, I mean unilateral cyst enlargement, or sometimes asymmetric cyst enlargement with one side more than the other. Is the prognosis for these similar to what you would see in ADPKD type 1 or type 2?

Dr. Chebib:
Yeah, those are, again, also very interesting cases, where just – either they're asymmetrical so either one kidney is all cystic and the other kidney has one or two cysts, or half of the other kidney has cysts and then the other kidney is very cystic. So these patients actually do much better. They are called focal ADPKD, or atypical ADPKD, Mayo imaging class 2A. Yeah, so typically, these patients do do very well. They have very good prognosis, and since they have a preserved on either a portion or a whole kidney, then they do very well from kidney function standpoint.

There is, however, a – a Mayo imaging 2B, and those patients have bilateral kidney cysts. They have ADPKD, but they have atrophic kidneys and these patients don't do as well. They might have vascular disease, and for all 2A and 2B patients, they – it's about 5% of all ADPKD patients.

Dr. Garimella:
So, I think you brought up the important Mayo Clinic classification which is really what everyone hears about, is the Mayo Class 1A to 1E, which is for typical ADPKD, and that's how we re-stratify patients and decide on, either disease-modifying therapy or other interventions. So, thank you for bringing up atypical PKD.

Dr. Chebib:
Alright. So moving to the next case. So ADPKD is a systemic disease and it has many extrarenal manifestations. And one very serious es – extrarenal manifestation is intracranial aneurisms. So, one of our patients is a 29-year-old female who comes into our clinic. She has ADPKD, but has been diagnosed recently and she comes in having family history of ADPKD in her father, who had intracranial aneurism and required an intervention. So she is a little bit worried, and she is asking you what to do and how to approach it

Dr. Garimella:
Yeah. This is, I think thankfully, a well-recognized phenomena, both amongst nephrologists and perhaps even family care practitioners and others now, that intracranial aneurisms tend to cluster in ADPKD. So the prevalence of intracranial aneurisms is anywhere between four to six times higher in the PKD population than it is in the general population and they tend to cluster. So, if someone has a family history, the likelihood that they have it, or if their – one of their siblings or someone would have it – would be higher than in the general population, if someone had it. And we have certain criteria, and one of the reasons why we screen for aneurisms is that in PKD patients, these aneurisms tend to occur at earlier ages. They tend to rupture about a decade or so earlier than the general population, and aneurism rupture can lead to significant comorbidities if not. So we want to identify and try and intervene. So in this case, for instance, where this woman has a family history of her father having an aneurism, I think it is an absolute indication to screen her, doing an MRI with an angiogram, to make sure that there is no aneurism at this time.

Dr. Chebib:
Great. Yes, that's what we would recommend, as – is obtaining a brain imaging, typically we would obtain a brain MRA as you mentioned. So this patient had no intracranial aneurism. Would you recommend a repeat MRA in – and how often would you repeat

that?

Dr. Garimella:
So that's asking a very good question. And that's because we don't have very high quality data on how often and, you know, to repeat. Now, if we found an aneurism, that's a slightly different approach, because neurosurgeons tend to repeat imaging, usually one or two times in a year at first. If that's stable, then they push that out, to maybe every year, and then every three years. But in somebody who doesn't have an aneurism, but has a family history, they're probably still at an increased risk of developing aneurisms, and so people have tried to model this out using different retrospective data sets, cost of effective analysis, and the consensus recommendations right now seem to be about repeating it once every five years or so. And I think that seems to be acceptable to most patients, because they want that reassurance as well, that they don't have something ticking that could be devastating if it ruptures.

Dr. Chebib:
Absolutely. Repeating every five years with the high-risk patients. Who else do you think is a high-risk patient, that we should screen?

Dr. Garimella:
So in people who don't have a family history or who don't have, you know new onset headaches – that's obviously very concerning, so if someone has new onset headaches or any kind of visual changes, neurological changes, you want to image them. But outside of that, I think the the other populations that we would like to screen are those who have high-risk occupations – pilots, bus drivers, people whose life – who have other people's lives depending on their jobs. If you are undergoing high-risk surgery and you have a history of PKD, for instance, so if you are undergoing cardiac surgery, vascular surgery, large intraabdominal or hepatic surgery, where you're getting general anesthesia, and you want to make sure that they don't have an aneurism that could rupture. I think that those are populations. The one other condition where I would perhaps screen, is if a patient is being put on systemic anticoagulation. Let's say they have atrial fibrillation and they need to put on it. Whether just being on an anticoagulation increases the risk of rupture, we don't know, but definitely if it ruptures, I think controlling that becomes a lot more complicated, so it's worthwhile considering whether you want to screen those populations as well.

Dr. Chebib:
And then you mentioned, kind of repeating imaging if we find an aneurism. So, how often would you repeat the imaging, if we find an aneurism in ADPKD patients?

Dr. Garimella:
Again this is extrapolated really from a lot of the newer surgical literature, where they've studied aneurisms and their recurrence, so most often, we try and repeat an imaging six months after the first initial imaging, and then about 12 months later, and if both those are stable and don't require an intervention, then probably annually for the first two or three years, and then maybe every second year or so, is usually what my colleagues in neurosurgery would recommend. And they have far more expertise in dealing with this and following up imaging sizes, so I would defer to them.

Dr. Chebib:
Excellent. Yeah, that's what we do, is once we discover them, we do the monitoring and then we do the referral to our neurosurgeons, who have done great. And in fact, we looked at our experience at Mayo Clinic and we screened about 812 patients who as pre-symptomatic screening, so mostly before a big surgery, or before their kidney transplantation, or if they are at high risk, and we found that the prevalence was about 9.3%, so about 75 patients had aneurisms. And then on follow-up there was no rupture, thankfully, so we tell our patients that it's reassuring that there's no rupture, so even if we discover these patients discover these aneurisms in the prescreening – pre-symptomatic screening, then if we follow them serially we can do interventions to – such as clipping and coiling, and then we can prevent we can prevent the rupture.

Dr. Garimella:
Alright, Fouad, so let me just introduce our final case, and this is something that I have often encountered in clinic where we have patients over the age of 55 or 60, who are sometimes referred especially since the advent of tolvaptan's approval from the FDA. And they are often asking me if they are qualified, and I'm wondering how you approach these cases?

Dr. Chebib:
Yeah, this is a great point. Right now in the practical guide we recommend tolvaptan for patients at risk of rapid progression, age 18 to 55 with EGFR 25 and above. So, Mayo imaging class 1C, 1D, 1E. So this is not controversial, and this is based on data from TEMPO 3:4 and REPRISE data. However, in REPRISE data, the patients in the group of above 55 to 65 – the placebo the placebo group had a GFR about 2.5 ml per minute per year as a GFR rate of decline or slow. And by definition, it's more on the slow progression, so the placebo was in a slow progression phase or status, and then tolvaptan did not show an effect on this population. However, there's emerging data such as the NKF poster last year, that showed pooled data and pooled analysis of patients who are above 55 to 65, and

there is still some benefit for patients who are between 55 to 65, but there's – we should have very good evidence that they have rapid progression, so such as…

Dr. Garimella:
How would you identify these rapid progressors?

Dr. Chebib:
Yes, well, so typically is in addition to having probably Mayo class 1C and 1D, because 1E most likely they've already been on dialysis. So if they're 1C or 1D, and then they have a historic GFR decline above 3 ml per minute per year, over a good average of time, I think these patients would benefit from tolvaptan, so there's this emerging data. And then we owe it to our patients to slow their disease progression, even if they're 55 to 65, because any additional years off dialysis is very precious, and our patients – even if they're in their 60s, they're still very young, so we…

Dr. Garimella:
Absolutely.

Dr. Chebib:
We need to everything possible. Of course, in addition to treating well their blood pressure through ACE inhibitors and ARBs, and then having good hydration, avoiding any nephrotoxins and all the general CKD care as well.

Dr. Garimella:
Excellent, so don't rule someone out just because they were older than what the trial included. Absolutely. Then the hope is in the next few years, we're gonna have also additional treatments that we can offer to our patients, so we'll base this off trials – the clinical trials and their results.

Dr. Chebib:
Excellent. Thank you so much for that discussion. Thank you.

Dr. Garimella:
Alright. So now that we're at end, let's briefly cover what we've gone over today. Pain – as we know it in PKD – is a complex condition. It could encompass everything from stones to infections to cyst ruptures, and essentially needs a multidisciplinary approach and a patient centric approach to treat.

Dr. Chebib:
Absolutely. Then we covered in our second case how do we identify atypical kidney cystic diseases including ADTKD, ADPLD and other atypical ADPKD patients, such as focal ADPKD or Mayo class 2. And then the role of genetic testing to identify and diagnose these patients accurately.

Dr. Garimella:
We then discussed the importance of screening for aneurysms, in what patient populations we use this, what the follow-up of these should be, and again, the importance of neurosurgical referral early on, when detected.

Dr. Chebib:
Perfect. And in our last case, we described how we manage patients with ADPKD who are above 55, and then the controversy and the shared decision to start tolvaptan, and there is emerging data that there is a benefit to use tolvaptan in this age group, 55 to 65, when they have evidence of rapid progression. Well, I would like to thank you, Dr. Garimella, for joining me in this webcast today.

Dr. Garimella:
Thank you.

Dr. Chebib:
We hope you find this presentation useful in your clinical practice, and thank you for your time and attention.

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