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IgG4-RD Case Conversations: Retroperitoneal Fibrosis with Refractory Ureteral Involvement

Dr. Campi:

Good evening. My name is Riccardo Campi. I'm a Consultant Urologist at the Unit of Urological Robotic Surgery and Renal transplantation of Careggi University Hospital in Florence, Italy.

Dr. Vaglio:

And my name is Augusto Vaglio. I'm a nephrologist, and I'm a Professor of Nephrology at the University of Florence, and I work at the Meyer Children's Hospital in Florence.

Dr. Campi:

These are our conflicts of interest.

Dr. Vaglio:

So this case is a case of retroperitoneal fibrosis with a very difficult to treat ureteral involvement. This is a case of a patient a 67-year-old male. He was a university professor, and he was admitted to the emergency in August 2018 for abdominal pain, lumbar pain, and vomiting. His past medical history was remarkable for smoking. He was a former smoker, 22-pack-years as cumulative smoking exposure. He had no allergies. He just had a Thalassemia trait, hypertension, which was well controlled by drugs, psoriasis, and gastroesophageal reflux disease. And it was taking at the time of admission, he was taking proton pump inhibitors and bisoprolol.

So lab tests showed that he had an acute kidney injury with a very elevated serum creatine, which was 11 mg/dL. He underwent imaging and specifically an abdominal ultrasound and CT scan, which was without contrast because of the acute renal injury. And both examinations showed bilateral hydronephrosis, no stones, no abdominal masses, there were no suspicion of tumors, but there was a suspicion of a periaortic and especially periliac tissue. And the main problem, the main issue was, of course, to perform a urinary diversion.

So the problem here is whether to get this diversion using ureteral stents or nephrostomy tubes. Therefore, I would like to ask Riccardo if he is in favor of either technique.

Dr. Campi:

Thank you, Augusto. I think from a urological perspective, we have two options. As you mentioned, ureteral stents are better for the patients in terms of quality of life during urinary diversion, but in this case, with a suspected periaortic and iliac tissue and severe hydronephrosis by acute kidney injury, I think bilateral nephrostomy is the best option to release the upper urinary tract. Let the urinary tract come back to standard anatomy and then study in elective condition the patient to understanding where the problem is, where is the obstruction, and go on with the diagnostic pathway. So I would be in favor of bilateral nephrostomies, actually.

Dr. Vaglio:

So you think that bilateral nephrostomy also allows you to perform a pyelography, which is useful to detect the stenosis.

Dr. Campi:

Yes, indeed. Yeah, you can do that at the time of placement of bilateral nephrostomy, but you can also do it later after elective imaging,

as we will see in this case.

Dr. Vaglio:

So the patient came to our hospital, the nephrostomies were in place. They were draining clear urine, and there was a greater output from the left kidney. There was progressive resolution of acute care injury, and so the patient regained a good clinical condition and good performance status. So the point was, at the time, to get a definitive diagnosis of the disease and to manage the urinary diversion, especially considering that the patient probably would not be fit with a bilateral nephrostomy in place. So preserving renal function and quality of life at the same time was one of our priorities.

So we decided to do an MRI and CT urography. The MRI of the abdomen showed the presence of a tissue which surrounded both common iliac arteries and the ureters as well. This was quite inhomogeneous on MRI, and the primary suspicion was that of retroperitoneal fibrosis. And here you will see some images of the CT urography, which confirmed the presence of a periliac tissue which was bilateral. It encased both common iliac arteries and the ureters as well. The right kidney was of smaller size. Can you confirm this, Riccardo, and can you have a look also the nephrostomy tubes that were correctly placed? So the these imaging findings supported the diagnosis of retroperitoneal fibrosis.

Dr. Campi:

yes, in this case, my comment from a urological perspective, would be that we can just see the difference in the two kidneys in terms of parenchymal volume, I would say. So the right kidney is hypoplastic, where the left kidney is hypertrophic. So this means that this condition is really impacting on renal function by also impacting on the anatomy of the kidneys. The nephrostomies are in place, and serum creatinine came back to almost normal values, but we have these suspected tissue that may represent the cause of obstruction in this case.

So my question for you, Augusto, would be what's your decision-making strategy in this case? Would you add additional imaging or diagnostic tests to provide the definitive diagnosis?

Dr. Vaglio:

Yes, sure. I think this case can be studied using metabolic imaging techniques such as the positron emission tomography. We could also consider a biopsy, and of course, we will have to test some laboratory parameters. So what we did is to perform an FDG PET scan, and actually this imaging showed that the tissue that we saw on MRI and CT had a high metabolic activity, and the degree of activity was compatible with a suspected inflammatory disease. Whereas we tested autoimmune or immune profile, and there were no positive autoantibodies. The screening for malignancies was negative. There was a just a slight increase in serum IgG4, the level was 150 with a normal value below 135, and the complement fractions C3 and C4 were within the normal ranges.

So the problem is, in such a case, should we do a biopsy, or should we – or can we avoid a biopsy? This is a problem with patients with retroperitoneal fibrosis, because the biopsy can be a risky procedure and sometimes cannot yield a sufficient amount of tissue for definitive diagnosis. So generally, we rely on imaging findings such as CT and MRI. We consider FDG PET. And we also consider the clinical phenotype of the patient. So generally, patients with retroperitoneal fibrosis who have no clear etiologies are classified based on these grounds, based on these findings, as idiopathic.

And this disease belongs to the spectrum of IgG4-related disease. And to classify the disease as IgG-4 related, we should follow this algorithm which was proposed by a joint initiative of the American College of Rheumatology and the EULAR, the European Society of Rheumatology, and was published in 2020. So the patient, our patient, had the entry criterion for this algorithm, which was the presence of a typical lesion within the IgG4-related disease spectrum. And this was retroperitoneal disease. The patient had no exclusion criteria, so he had no criteria that made this diagnosis improbable or unlikely.

And then we have the possibility to, or to apply this algorithm, we should score the weight of each of these items, of each of these findings, to understand whether the patient can be classified as IgG4-related or not. So our patient scored 12. The score of 12 comes from 4, which was for the mildly elevated, and 8 for the presence of retroperitoneal fibrosis on imaging. So two important items which, however, were not sufficient to reach the cutoff of 20; therefore, the disease could not be clearly classified as IgG4-related. But the problem is that in the score, we should also consider the biopsies, and this patient did not undergo a biopsy, so we cannot rule out the possibility that this was an IgG4-related disease. Actually, this is very common in patients with idiopathic RPF idiopathic retroperitoneal fibrosis, because most of them, especially for the risks related to the biopsy procedure, do not undergo a biopsy. So generally, the diagnosis really relies on what we said before. So clinical findings, imaging findings, and PET scan.

So the problem now, once we have diagnosed the disease as idiopathic, we have tried to rule out all the possible etiologies. We have tried to classify the disease as IgG4-related or not. The problem is to treat the disease. In this case, the patient has a severe bilateral

involvement of the ureters. So there are two main choices. The first is whether we could use a conservative approach. We follow an approach based on the urethral diversion, using stents or nephrostomy tubes plus systemic therapies. Or on the other hand, we could use a surgical approach, first by performing ureterolysis, and then see whether or not to treat the patient with immunosuppressive therapy.

So what we did is follow a conservative approach. So we placed bilateral stents and this allowed us to remove the nephrostomy tubes, and we started systemic therapy with steroids and mycophenolate mofetil. The patient also tested positive for a tuberculosis test, and so he received prophylaxis with Isoniazid before and also during the first months of immune suppressive therapy.

And this treatment was quite effective in terms of reduction of the retroperitoneal mass. As you can see, after treatment, we have a significant decrease in the thickness of the periliac tissue. We can also see, you can confirm probably, Riccardo, but we can also see on the left-hand side of the figure that the stents are correctly placed. But nevertheless, despite the improvement in terms of a reduction of the mass and despite the presence of urethral stents bilaterally, there is a significant hydronephrosis, and this is a problem now.

Dr. Campi:

Yes, indeed. Yes indeed.

Dr. Vaglio:

So overall, we treated the patient with immune suppressive therapy. We removed the nephrostomy tubes. We have the stents in place. We regularly tried to remove the stents, but we had to replace them because there was significant obstruction. So despite the very good clinical condition that the patient resumed, we have now to address the issue of refractory ureteral involvement. And this is the problem that we have to face now.

So now I think the urologist is the main actor in this phase, but we, of course, we discussed the different options, but I leave the stage to Riccardo for the discussion of this phase of treatment.

Dr. Campi:

Thank you, Augusto. I think this is the main learning point here is that, at this time of the therapeutic journey of the patient, we need a multidisciplinary approach. Because if you look back to the case, the urologist or the surgeon in general, could have thought to intervene right at the time of diagnosis and I think it would have been perhaps a mistake from a therapeutic point of view, because treatment actually achieved the favorable results in terms of reduction of the periliac tissue. But of course, we have the problem of refractory hydronephrosis despite the improvement at the ureteral level. So now the problem is to discuss with the patient the two options of lifelong stents or nephrostomy tubes, meaning a conservative management versus surgery that is, of course, carries out risks of complications and impact on quality of life.

So at this point, I think my general opinion is that a multidisciplinary, multispecialty approach and collaboration is really key to individualized care toward value-based care, meaning achieving the best outcomes with the patient preference and goals discussed between the specialists. So really shared decision-making is key in these patients at this stage of treatment.

We have to explain, as a urologist and surgeons, we have to explain that the intervention of ureterolysis plus or less reimplantation and omentoplasty as some specific risks that should be really understood by patients. And patients should be aware of the expectations of surgery, in terms of the probability of treatment and relief from symptoms and improvement of quality of life.

From a surgical point of view, we have also to discuss with the patient the surgical approach. We have an open traditional approach through a midline laparotomy that is, of course, more invasive. And then we have recently developed minimal invasive techniques, laparoscopic and robotic techniques. From a purely surgical technique perspective, we have to consider that we not only have to do bilateral ureterolysis with omentoplasty and intraperitonealization of the ureters, but also in special cases, to reimplant ureters in case it's ureterolysis is not enough. However, regardless of the choices, the goals of surgery remains to relieve the symptoms, prevent further renal impairment, and improve patients quality of life.

In our case, 15 months after diagnosis, we performed a robotic-assisted laparoscopic bilateral ureterolysis with omentoplasty. For those of you who are not familiar with surgical concepts, in simple words, omentoplasty means that the ureters are wrapped with omentum tissue coming from the stomach, basically, and the omental tissue carries with it the vascularization that allows these this flap to become vital for the ureter, and also at the same time, achieves an intraperitonealization, meaning that this is a separation of the tissue from the retroperitoneal space to the intraperitoneal space. As you can see in these two snapshots from a robotic surgical intervention, the miniaturization of the instruments allows the surgeon to be very gentle and very precise in the dissection. And also in the second image, you can see the omental flap that is wrapped around the ureter, around the ureter with a bit of tissue. And this allows the separation of the ureter from the extraperitoneal cavity.

During surgery, actually, and I give the speech back to Augusto now, we have the possibility to do a biopsy to send some tissue for histopathological analysis. And this is what showed in our case.

Dr. Vaglio:

So the histopathology that we could also see in this picture is a mixture of chronic inflammation. So you can see that there are many mononuclear cells which are mixed with large bands of collagen, and therefore, this is a fibroinflammatory disease. And these are basically the main features of idiopathic retroperitoneal fibrosis. And when this is IgG-4 related, we can detect a significant proportion of plasma cells which are positive for IgG4. In our case, there was no evidence of a significant increase in infiltrating IgG4-positive plasma cells. This is mainly for two possible reasons. The first is that the majority of patients with isolated retroperitoneal fibrosis lack significant infiltration of IgG4-positive plasma cells. But nevertheless, the spectrum of the disease that this entity belongs to is the same.

The second point which can account for the lack of a chronic and IgG4-rich plasma cell infiltrate is that this is a late stage of the disease. So if the biopsy had been performed before treatment, this was probably - this would have probably allow us to see a more realistic histopathological picture of the disease itself.

So basically, what we had from surgery was not only the treatment of this refractory ureteral disease or ureteral involvement, but also the possibility to have a biopsy, which confirmed the benign nature of the disease and demonstrated that there was still some degree of inflammation together with fibrosis.

Dr. Campi:

So looking at the postoperative course and follow-up, in the immediate postoperative period, the patient developed a thoracic pain and an EKG suspected for myocardial infarction, and the patient was transferred to the cardiology unit for monitoring. Fortunately, conservative management was enough, and no procedures were performed. And the patient came back to the urology unit and finally was discharged on postoperative day 5 with bilateral ureteral stents correctly in place, preserved renal function with an EGFR of 80 mL/minute, and removal of the ureteral stents happened 1 month after surgery.

Dr. Vaglio:

So the long-term follow-up of the patient who is regularly seen at our clinic, and now we are 4 years after diagnosis, shows that the patient is doing well. He has a moderate degree of chronic kidney disease, and this is expected in some way, because we showed that he had a hypoplastic right kidney, and then, you know, the refractory hydronephrosis. So for some time, the patient was exposed to an obstructive uropathy. So it's not surprising to see that he had serum creatinine of 1.6 mg/dL, which corresponded to an EGFR of about 50. But anyway, his clinical condition was stable and his kidney function was stable as well. On ultrasound, the right kidney was smaller, and there was no hydronephrosis, and there was no recurrence of retroperitoneal disease on CT or MRI, and we did not detect any other organ involved by a possible IgG4-related disease.

So to summarize, this case shows a very difficult-to-treat aspect of IgG-4 related disease, which is retroperitoneal fibrosis, which in most cases, involves the ureters. In some patients, this can be overcome just by medical immune suppressive therapy, but in some other cases, after an initial conservative approach based on stent placement or a nephrostomy tube placement plus immune suppressive therapy, we need to treat the refractory ureteral obstruction using surgery.

And I think that really the discussion between the nephrologist or the internal medicine or the rheumatologist that takes care of the medical part of the case, and the urologist and the patient himself has been key in the proper management of the case.

Dr. Campi:

I completely share with you, Augusto, the concept that multidisciplinary approach and decision-making is key. My opinion is that we should discuss these patients since the very beginning of the patient journey, because, of course, it's an integration of medical therapy and surgery. As always, surgery must be placed at the right time in the therapeutic pathway, not too early and not too late. So identifying the perfect timing for surgery and also individualize and discuss the expectations for surgery is a key factor to achieve favorable outcomes and also to respect patient preference and values that have been elicited in shared decision-making.