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Case Study

First, do no harm: surgical management of von Hippel Lindau syndrome

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Introduction

Von Hippel Lindau (VHL) syndrome is an inherited condition that is associated with retinal and central nervous system haemangioblastomas, as well as renal and pancreatic cysts (Varshney et al., 2017). The renal cysts have a significant likelihood of neoplastic change, and act as a pre-malignant pathological finding prior to the development of clear cell renal carcinoma.

VHL syndrome occurs due to mutations in the VHL gene (Varshney et al., 2017). This encodes a protein implicated in the regulation of hypoxia pathways. Due to its role as a tumour suppressor, VHL syndrome is inherited in an autosomal dominant fashion, although 20% of cases are thought to arise from de novo mutations, with no prior family history.

In the UK, patients with VHL are routinely surveilled annually under a watch and wait approach, as is typical for familial endocrine tumour disorders. Surgical intervention is advised when renal masses reach more than 3cm in diameter (Schmid et al., 2014), due to the minimal chance of metastasis in a tumour below this size.

Physical examination has a limited role in the detection and management of renal cell carcinoma (RCC). Although the palpation of an abdominal mass or cervical lymphadenopathy should always lead to the inclusion of RCC in the differential diagnosis, radiological imaging is necessary to detect the disease. The classic triad of frank haematuria, loin pain and abdominal mass is only seen in 6-10% of cases (Lee et al., 2002; Patard et al., 2003) and is typically associated with advanced, metastatic disease that is not suitable for surgical intervention. Aberrant renal function may be detected through blood work up, but 50% of RCC are asymptomatic prior to incidental diagnosis. 30% of patients may also exhibit paraneoplastic syndromes upon presentation.

Patient history

PM is a 55 year old female patient who has been under routine annual surveillance via MRI for renal cell carcinoma and other VHL-associated lesions since her VHL diagnosis in 1994, following an identical diagnosis in her sister. PM had a retinal lesion ablated approximately 20 years ago and had previously undergone a right radical nephrectomy (RN) due to multiple RCCs in 1998, as well as enucleation of cysts in the left kidney in 1999. Her sister died in 1996 aged 36 years from RCC. Their father died of renal cancer, and four of PM's six children have also been diagnosed with VHL syndrome.

In September 2019, new renal lesions were detected via MRI screening in her remaining kidney; one parapelvic lesion, and one interpolar lesion. Numerous cysts were also apparent. The disease appeared to be localised but was of a significant size such that a partial nephrectomy (PN) was indicated. The patient's kidney function was biochemically normal prior to admission.

Surgical background

Nephron sparing surgery, or partial nephrectomy (PN), is recommended by the European Association of Urology (Ljungberg et al., 2015) in all cases of localised RCC, as opposed to radical nephrectomy (RN). There is no benefit to the patient in terms of oncological outcomes from the more radical surgical approach (Patard et al., 2008; Van Poppel et al., 2011), and PN is significantly more likely to be associated with preservation of eGFR, maintenance of low creatinine levels post-operatively, and an increase in patient-reported quality of life – this would particularly be the case in this patient who had a solitary kidney prior to surgery (Poulakis et al., 2003; Thompson et al., 2008; Jang et al., 2016). As such, a PN would be the ideal course of action in PM's case. However, the larger of the two detected tumours lay in the renal hilum, meaning that the tumour could not be removed without sacrificing a significant amount of renal parenchyma. RCCs are highly vascularised, as is the kidney itself, making urological surgery a risky manoeuvre, even when good access is obtained. In the case of poor access to the site of the hilar tumour, a renal auto-transplant and bench surgery to remove both tumours were planned.

The first renal auto-transplant was performed in 1963 by James Hardy (Hardy, 1963) in the case of high ureteral injury during aortic surgery, with the kidney then implanted in the ipsilateral iliac fossa of the patient in question. Combining renal auto-transplant with bench surgery provided an avenue for significant progression in challenging urological surgical cases. Bench surgery offers a bloodless operating field; the ability to protect the kidney from ischaemia through hypothermia; and most crucially, increased access to the kidney itself. Uniting this technique with vascular allografts expanded the possibilities open to surgeons dealing with renovascular pathology, and case reports throughout the 1980s detail the successful treatment of renal arterial aneurysms and stenosis (Novick, Jackson and Straffon, 1990) in this way. Renal autotransplants are currently indicated in the case of renovascular and ureteral pathology, as well as for the surgical management of multiple RCCs in the same kidney (Azhar et al., 2015).

Indeed, renal autotransplantation with bench surgery has been found to preserve glomerular function in 80% of patients in a retrospective study of 100 open PNs at two UK centres (Ray et al., 2006), although this is clearly a challenging procedure. The same study identifying an intraoperative/early complication rate of 36%, and 24% of patients with one kidney prior to the operation required dialysis post-operatively. Full assessment of the literature is complicated by the fact that autotransplant is carried out for a multitude of different diseases; Ray et al found that outcomes appeared to be worse for patients with VHL, but with such a rare condition, and a rare surgical procedure, it is hard to reliably assess this conclusion on a larger scale.

Operative report

Although an open PN was the initial operative plan, due to the previously described location of tumours in this kidney a renal auto-transplant and bench surgery were a likely outcome prior to the operation. After the kidney had been mobilised intra-operative ultrasound imaging of the hilar tumour confirmed the requirement for bench surgery to gain access and the operating team adjusted course.

Bench surgery to remove both tumours which had been identified through surveillance was successful. The surgeon also removed numerous large, superficial pre-malignant cystic lesions, in an attempt to give the patient the longest possible recurrence-free survival. However, during the cyst removal it was felt that multiple of these cysts had already undergone significant neoplastic change. The removal of several cysts revealed further adjoining cysts, making the reconstruction of the kidney a fine balance between preserving sufficient nephron bulk to retain function, and removing as much neoplastic tissue as possible.

In an additional complication, upon dissection of the kidney it turned out that the renal artery was bifurcated. This meant that this artery had to be reconstructed during the bench surgery to enable a successful anastomosis with the external iliac artery.

Points for discussion

Partial nephrectomy vs. radical nephrectomy in the face of additional lesions detected mid-operation

Mid-operative decision making was a crucial part of this case. At one point during the bench surgery, there was consideration of whether to perform a RN due to the scale of malignant change detected. However, the patient had expressed a strong desire to remain off renal replacement therapy (RRT). In addition to taking patient values into consideration, the clinician must consider that RRT carries its own significant morbidity and mortality (Bray et al., 2014). In terms of best patient outcomes, there is a clear motivation to avoid the need for RRT in any form.

The opposing argument, however, is that the surgeon may have left malignant lesions in the kidney. Even if those lesions present at the time of surgery were removed, the genetic predisposition to RCC in this individual in combination with the presence of numerous pre-malignant cystic lesions, means that there is a significant likelihood that the disease will recur, and it is particularly difficult to survey the remnant kidney with follow-up imaging after this kind of radical surgery. Regardless of this, no metastatic lesions had been reported in a screening report prior to surgery, and it was felt that preserving the kidney offered the patient the best chance at a decent number of years with a good quality of life (i.e., off RRT).

Peri-operative complications in urological surgery

For patients such as PM a renal auto-transplant offers the chance of years of disease-free, independent survival – without the constraints and morbidity associated with RRT. On the other hand, major surgery such as this is not without its own risks. Indeed, PM's recovery has not been straightforward thus far, and is a useful case study for the surgical student in potential complications.

Although recovery was progressing as planned day 1 post-operation, by day 2 the patient's right leg was a source of acute pain, accompanied by muscle weakness and bruising. An urgent CT demonstrated no thrombus, but instead a partial occlusion of the distal external iliac vein and artery due to the pressure of blood flow through the vessels of the transplanted kidney. One dose of dalteparin was used prophylactically given the increased likelihood of a thrombus forming in the right leg due to reduced perfusion. Despite continued monitoring by examination and Doppler, no further intervention was required. The limb hypoperfusion resolved spontaneously.

PM then underwent three episodes of pulmonary oedema as a result of fluid overload. These necessitated her moving back onto ICU immediately after her initial transfer to the ward, and were treated with frusemide, limited fluid intake and haemofiltration. After she had stabilised from these episodes, non-specific changes were found on her ECG. An echocardiogram confirmed hypokinesia of the anterior cardiac wall, and she was referred to cardiology for angioplasty. This confirmed the presence of severe occlusion in the left anterior descending artery, which was subsequently stented with a good angiographic result. Due to the later requirement for percutaneous coronary intervention (PCI), these episodes of pulmonary oedema were likely multifactorial due to both fluid overload and reduced cardiac output due to restricted cardiac perfusion.

Delayed graft function (DGF) of the re-implanted kidney also occurred, necessitating haemofiltration. To transfer the patient from ICU to the transplant ward, she needed to be able to tolerate dialysis in case of a decline in kidney function. An initial attempt at dialysis resulted in a hypotensive episode, and thus delayed her transfer to the ward. An improvement in kidney function has prevented further dialysis requirement thus far. All in all, these complications significantly delayed ward transfer and eventual discharge and underline the importance of pre-operative fitness.

Smoking: an additional risk factor for RCC development in an already pre-disposed patient

Another point for discussion around this case is that PM is a long-term smoker. This is a significant part of her history for RCC – smoking is a key risk factor for RCC development, and is also a factor which is likely to have contributed to her vascular disease and post-operative complications (Ljungberg et al., 2015). Addressing this has the potential to improve her outcome and recovery if further surgery or treatment for VHL-associated lesions is required in future, which is a significant possibility.

Conclusions

PM has already surpassed the average lifespan of women with VHL syndrome by seven years, and the technological advances of modern urological and transplant surgery have given her a significant chance at more years of a dialysis-free life. In surgery more so than medicine, we accept from the outset that we will be doing a harm to the patient to cure them of an ill. And indeed,

when a surgery is successful, the cure can be absolute. In this case, the potential for harm was significant. Due to its vascular nature, urological surgery is risk-laden. When a patient has only one kidney, the risks of that patient being left dependent on RRT – an outcome the patient was explicitly averse to - are heightened.

When considering lessons that can be learnt from this case, it is important to note that the patient was well in herself prior to referral for surgery, and her kidney function was more than adequate. As such, she understandably feels that VHL itself does not impact her day-to-day life, but the surgical interventions required to treat lesions that are picked up by screening do. This is especially the case for a patient being treated in a specialist centre far from home. Enabling her to leave hospital after a successful surgery and full recovery has thus far required the collaboration of multiple surgical firms and health care practitioners, and her path from this point onwards. However, the RCCs in her kidney would have likely eventually metastasised and become difficult to manage effectively. The autotransplant has hopefully managed this episode of VHL-associated malignancy and preserved kidney function.

In this case, the harm of surgery is almost certainly worth it for the cure, but only if the patient recovers and regains her former quality of life. As surgical techniques advance and we become more able to perform challenging but life-extending surgeries such as this, we must ensure that post-operative care is equally optimised to promote recovery and enable patients to reap the benefits of modern surgery. In the instance of rare disorders and equally rare surgical procedures, this requires the collaboration of international centres to fully evaluate the literature and determine best practice guidelines not only for the procedure itself, but for key supportive measures required during the recovery process.

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Consent
The patient has consented to the publication of this case study.

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