Renal angiomyolipomas in tuberous sclerosis—rare but potentially life-threatening lesions

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SUMMARY

We discuss an 18-year-old girl, diagnosed with tuberous sclerosis complex and known to have renal angiomyolipomas (AMLs) but having no regular urological follow-up, who presented with left-sided abdominal pain and haematuria on urine dipstick testing at the out-of-hours General Practitioner (GP) service. She was diagnosed as having urinary tract infection/pyelonephritis and discharged with simple analgesia and antibiotics. Subsequent imaging of her renal tract demonstrated multiple large AMLs with evidence of recent bleeding, which required arterial embolisation.

BACKGROUND

In patients with tuberous sclerosis complex (TSC), apparently innocent urinary tract infection (UTI)/pyelonephritis/ureteric colic-like symptoms may in fact belie a more serious pathology. Angiomyolipomas (AMLs), rare in the general population, are common in patients with TSC and can lead to potentially life-threatening haemorrhage. These patients should be monitored closely with regular imaging and urological follow-up. Moreover, such patients with acute symptoms should be considered for urgent radiological investigation, preferably as inpatients, and be reviewed by a urology team.

CASE PRESENTATION

We present an 18-year-old girl, known to have tuberous sclerosis, referred to our urology outpatient department by her GP. One month before, she had presented to the out-of-hours GP service with left-sided abdominal pain and was found to have haematuria on urine dipstick testing. She was discharged at that time with simple analgesia and antibiotics for a suspected urinary tract infection/pyelonephritis. Her GP arranged an ultrasound, prior to her outpatient appointment, which showed a 5.5 cm lesion in her right kidney and an 8.9 cm lesion in her left, both of which had appearances consistent with AMLs.

Diagnosed at age 6 with TSC following a referral to a dermatologist for skin lesions from birth (ash leaf macules and angiofibromas), she was being managed on Lamotrigine for epilepsy but was otherwise well, studying at college. A screening renal tract ultrasound soon after diagnosis was found to be normal, but a subsequent routine scan at age 12 showed multiple small AMLs. Despite the identification of these AMLs, her next ultrasound was 4 years later. This ultrasound at age 16 demonstrated a 5.5 cm AML; however, she had no further imaging arranged and was only seen by a Urologist following acute presentation 2 years later.

INVESTIGATIONS

An urgent CT scan was arranged at the time of her outpatients appointment (figures 1 and 2), which demonstrated various lesions in the right kidney (the largest of which measured 52×60×58 mm) and two large lesions in the left kidney (73×42×74 and 43×28×40 mm), one of which appeared to have a feeding artery, showing evidence of a recent bleed.

TREATMENT

This particular lesion in her left kidney was thought to be the source of her symptoms and so she underwent arterial embolisation to that AML (figures 3 and 4). The procedure was performed successfully, with no immediate complications.

OUTCOME AND FOLLOW-UP

She has since had no further loin pain or bleeding and is being discussed at our multidisciplinary team meetings with regard to her remaining lesions. She is due for a DMSA scan to assess renal function to inform further nephron-sparing management decision.

DISCUSSION

TSC is a rare autosomal dominant neurocutaneous condition (though 60–70% of cases are sporadic) leading to the growth of non-malignant congenital tumours in the brain, kidneys, heart, eyes, lung and skin, occurring in around 1 in 6000 to 1 in 12 000.¹ It is caused by mutations in either the TSC1 gene (chromosome 9q34) coding the protein hamartin or the TSC2 gene (chromosome 16p13) coding the protein tuberin.² These proteins are involved in regulating cell cycle progression including apoptosis via the mTOR pathway. As such, mutations in these two proteins lead to unregulated cell proliferation, manifesting as the non-malignant tumours described above.

Classically, tuberous sclerosis presents clinically as a triad of mental retardation, epilepsy and adenoma sebaceum (Vogt's triad). Dermatological lesions, such as ashleaf macules, facial angiofibromas and shagreen patches,³ in combination with neurological involvement, in particular the presence of cortical tubers on brain MRI,⁴ are often the first step towards diagnosis, as was the case with our patient. New diagnostic criteria reflect the recognised phenotypical variability and multisystem nature of TSC, using major and minor criteria.⁵ By age 11, 80% of patients will demonstrate some form of renal manifestation.^{6–7} Renal cell carcinomas remain rare, seen in around 1% of cases, Renal cysts in 17–35% but by far the most common are AMLs seen in 50–75% of cases.^{8–10}

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Figure 1 Axial CT scan, highlighting a lesion in the left kidney with mixed attenuation.

AMLs are neoplasms derived from perivascular epithelioid cells containing blood vessels, smooth muscles and mature adipose cells.¹¹ AMLs can also be found in the general population but remain rare. They are often found incidentally on radiological investigation and the symptoms are varied. A review by Nelson *et al*⁸ found the most common presenting symptoms to include flank pain (41%), palpable renal mass (11%) and haematuria (11%). Twenty per cent of patients with AMLs have tuberous sclerosis.¹² Significantly, AMLs in patients with TSC behave differently to AMLs seen in the general population. They are typically larger, more often multiple, occur at a younger age and are more likely to grow and/or haemorrhage.^{13 14} The patient in our report had AMLs recognised on ultrasound at age 12 but had never been referred to a urologist. Subsequent ultrasounds arranged sporadically during her teenage years showed the lesions to be growing, yet she had not been referred.

As described above, the main concern with AMLs is the risk of rupture, which in severe cases can lead to cardiovascular shock, with 20–30% of patients presenting in this manner.⁸ The main predictor for haemorrhage is tumour size and specifically

Figure 2 Coronal CT scan demonstrating anatomical distortion of both kidneys by large lesions, again showing mixed attenuation.

Figure 3 Radiograph pre-embolisation showing disorganised vasculature of the left AML with tiny aneurysmal-like lesions.

tumours greater than 4 cm in size. Steiner *et al*¹⁴ found that lesions with an initial diameter of 4 cm or more were more likely to grow than lesions smaller than 4 cm (46% vs 27%) and were more likely to require surgical intervention (53% vs 7%).¹⁵ The ultrasound of our patients 2 years ago demonstrated a lesion of over 5 cm in size.

Generally, the indications for intervention include acute haemorrhage and pain or size greater than 4 cm even when asymptomatic. Arterial embolisation allows nephron sparing while remaining minimally invasive and has thus become the preferred method of treating AMLs. Retrospective reviews have found the procedure to be safe and well tolerated,^{16 17} though AMLs in the TSC population appear to have a high recurrence rate, requiring repeat intervention.¹⁸ Moreover, recent studies,

Figure 4 Radiograph postembolisation showing reduced vascular flow in the AML.

while supporting arterial embolisation as a first line therapy, advocate the role of conservative management for asymptomatic lesions, particularly if they are slow growing.^{19 20} Medical therapy has previously been unavailable for the treatment of AMLs but mTOR inhibitors potentially pave the way for an alternative to surgical interventions and will hopefully prove a useful management option in the near future,²¹ particularly in cases such as this, where there are multiple large lesions. For the patient described in our report, there is no doubt that she will require lifelong surveillance and follow-up.

Owing to the rare nature of the condition, predicting prognosis for our patient is somewhat difficult. Without doubt though, caution should be used with TSC patients with renal problems. Early specialist input should be sought as soon as renal lesions are identified, demonstrated to be growing (particularly after reaching the 4 cm threshold) and certainly when they present acutely.

Learning points

- ▶ Clinicians should be especially vigilant of seemingly innocent urinary tract infection-like symptoms in patients with tuberous sclerosis as they could represent a life-threatening event.
- ▶ Early specialist input should be sought as soon as possible, particularly when lesions are identified and/or known to be growing.
- ▶ The management of multiple renal lesions may prove difficult but the priority should be the lesion causing acute symptoms.

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Competing interests None.

Patient consent Obtained.

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