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Ashwagandha and Kidney Transplant Rejection

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INTRODUCTION

Ashwagandha is an herbal product traditionally believed to have a wide array of effects including immune stimulation. This can have implications for organ transplant recipients such as rejection and possible graft loss. Here, we present the course of a kidney transplant patient who developed acute rejection requiring a graft nephrectomy after the use of ashwagandha. We recommend that organ transplant recipients should be warned of the potential adverse effects of easily available herbal medications including ashwagandha.

CASE PRESENTATION

A 69-year-old male kidney transplant recipient was admitted for evaluation of elevated creatinine. He previously had kidney failure due to diabetic nephropathy. His other history included hypertension, moderate aortic stenosis, coronary artery disease, and a history of a stroke (right-sided ischemic stroke with no residual deficits). After chronic hemodialysis for 4 years, he received a deceased donor kidney transplant in 2018. He had no identified anti-HLA antibodies (calculated panel reactive antibodies 0%) and received basiliximab induction immunosuppression followed by maintenance therapy with tacrolimus, mycophenolate sodium, and prednisone. Serum creatinine improved rapidly after transplantation with no evidence of delayed graft function and remained stable, ranging from 90 to 110 μmol/l, over the next 2 years. Tacrolimus trough levels were always in the therapeutic range (8–10 μg/l in the first 2 months, followed by 6–8 μg/l between 2 and 6 months, and 4–6 μg/l thereafter). At his last clinic visit 2 weeks before the current presentation, he was on stable doses of mycophenolate sodium (Myfortic, Novartis Inc., Basel, Switzerland) 720 mg twice daily, tacrolimus (Advagraf, Astellas Inc., Tokyo, Japan) 2 mg daily with trough level at 5 μg/l, and prednisone 5 mg daily. He remained on sulfamethoxazole-trimethoprim once a day for *Pneumocystis jiroveci* pneumonia prophylaxis. Serum creatinine was 101 μmol/l.

The patient presented to the hospital with a 3-day history of feeling unwell with nausea, anorexia, vomiting, and right lower quadrant abdominal pain. He had been anuric for 2 days. He did not have any infectious symptoms including dysuria or hematuria and reported taking immunosuppressive medications as prescribed.

Hospital Course

On examination, his blood pressure was 145/60 mm Hg, heart rate 59 beats per minute, and no peripheral edema. Serum creatinine was 1347 μmol/l with sodium of 123 mmol/l and potassium of 7.2 mmol/l. He had a severe anion-gap metabolic acidosis with a pH of 7.05, bicarbonate of 8 mmol/l, and an elevated anion gap at 28 mmol/l. His tacrolimus drug concentration was 5 μg/l, within the acceptable therapeutic range. Urine analysis showed 2+ blood, 3+ protein with <5 white blood cells per high power field, and 5 to 30 red blood cells per high power field. A nontunneled dialysis catheter was placed in the right internal jugular vein, and hemodialysis was initiated. A noncontrast computed tomography of the abdomen and pelvis demonstrated a swollen right lower quadrant transplant kidney with increase in size from 10 cm (from imaging a year prior) to 12.9 cm and surrounding

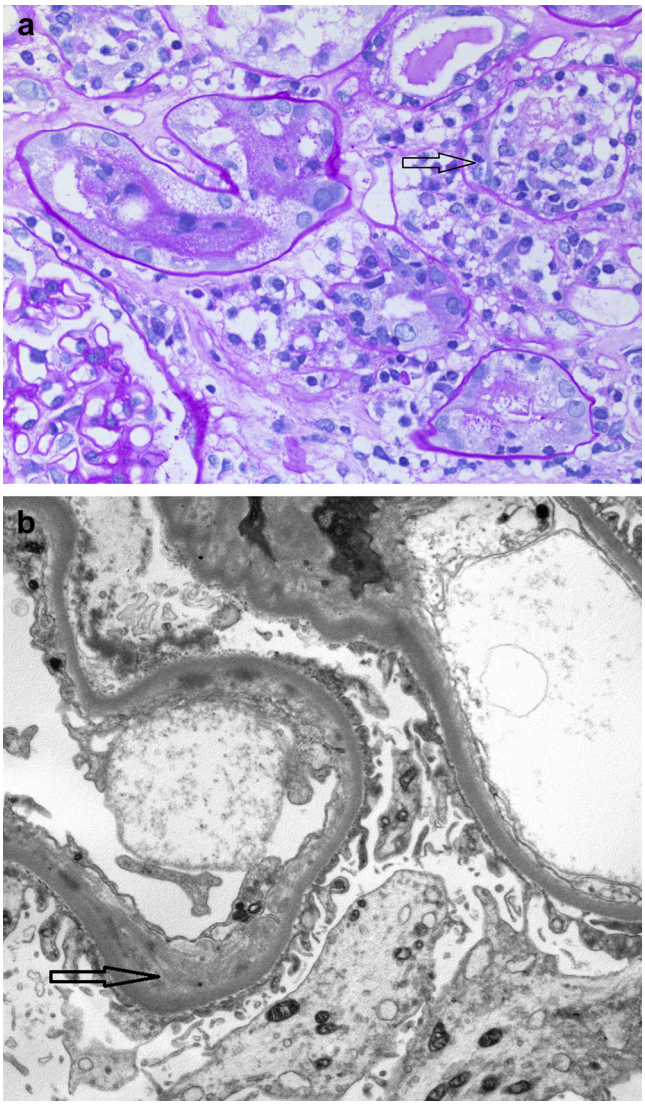

Figure 1. (a) Severe interstitial edema and inflammation, including plasma cells with severe tubulitis (arrow). A portion of normal glomerulus is found on the left lower corner (periodic acid–Schiff, original magnification ×400). (b) Glomerulus capillary loop showing expansion of the subendothelial zone by early new basement membrane formation (arrow) (transmission electron microscopy, original magnification ×11,800).

inflammatory changes. With a suspected acute rejection, empirical methylprednisolone 4 mg/kg intravenously for a total of 3 doses was given followed by high-dose oral steroid at 1 mg/kg.

Subsequent kidney biopsy revealed diffuse and severe mixed interstitial inflammatory infiltrate including a significant number of eosinophils and plasma cells, associated with prominent interstitial edema. There were numerous foci of severe tubulitis with tubular epithelial cell degeneration. There was moderate peritubular capillaritis but no glomerulitis or arteritis. Immunofluorescence showed rare (1%–5%) c4d staining in peritubular capillaries. Donor-specific antibodies were not detected. The diagnosis was severe tubulointerstitial nephritis with a differential diagnosis of drug-related acute tubulointerstitial nephritis (see below) and acute T cell–mediated rejection (Banff 2019, grade IB; Figure 1a). This was interpreted clinically as acute T cell–mediated rejection for which he received thymoglobulin for a total of 4 doses (7 mg/kg cumulative). The dose of tacrolimus was increased to achieve a trough level target between 6 and 8 μg/l. His urine output improved, but he remained dialysis dependent. On further history, it was revealed that the patient had been using ashwagandha, an herbal product, for the past 2 weeks. On deeper questioning, he had been unhappy with his muscular strength and endurance and had trawled the internet for solutions. On an internet forum, he discussed his symptoms with an alleged healthcare provider who recommended taking this supplement daily. He purchased the supplement online and had been taking 2 pills per day for 14 days before presentation.

Three weeks after his initial biopsy and still dialysis-dependent, the patient underwent a repeat graft biopsy because of ongoing dialysis requirement. Light microscopy demonstrated a very similar appearance to the first biopsy, with no glomerulitis or arteritis. C4d staining was minimal, involving <10% of the peritubular capillaries. He received 3 more doses of pulse methylprednisolone 4 mg/kg intravenously and continued oral prednisone at 1 mg/kg. Unfortunately, 3 weeks after this event, he developed symptoms of nausea, vomiting, diarrhea, and odynophagia with bicytopenia involving red blood cells and platelets. Gastrointestinal mucosal biopsy showed cytomegalovirus (CMV) mucositis extending from the esophagus to descending colon. He was started on intravenous ganciclovir. Repeat graft biopsy, performed 7 weeks after the initial biopsy, again showed acute T cell–mediated rejection (Banff 2019, grade IA), with acute tubular necrosis and CMV-positive epithelial cells in glomeruli. There was at least mild interstitial fibrosis and a significant amount of interstitial edema. Ultrastructural changes in keeping with early transplant glomerulopathy (Figure 1b) supported a diagnosis of rejection. It was considered unsafe to continue immunosuppression with severe CMV infection. He underwent graft nephrectomy and continued on maintenance dialysis. Mycophenolate and tacrolimus were withdrawn, and he was continued on a tapering dose of prednisone.

DISCUSSION

Ashwagandha (Sanskrit for "smell of the horse," scientific name *Withania somnifera*) is an herb of the Indian Ayurvedic system used as a rejuvenator.[1] It is commonly referred to as Indian ginseng or winter

cherry and is grown in some parts of the East including India, Nepal, and Yemen. It is commonly used as a household remedy in India and as a tonic and aphrodisiac in the elderly. Leading online platforms have made it widely available all over the world, and it is marketed for a variety of indications, such as an antistress remedy, anxiety relief, adrenal fatigue, difficulty concentrating, social anxiety, and promotion of an overall healthy mental state, making it a veritable panacea.[2] It is available in several forms, including vegetarian capsules, tea bags, and root powder that can be mixed with water, clarified butter, or honey. The biologically active constituents of ashwagandha include alkaloids (isopelletierine, anaferine, anahygrine), steroidal lactones (withanolides, withaferins), and saponins. Some other constituents like glycowithanolides have been reported to have immunostimulatory effects with activation of macrophages.[2] These compounds activate phagocytosis and increase activity of lysosomal enzymes in these inflammatory cells.

Animal studies have demonstrated the immunostimulatory properties of this medication. In a laboratory study from India, 80 mice were divided into 8 groups.[3,4] They were initially sensitized with a thymus-dependent antigen that was a human O group red blood cell at 20% suspension. The control mice received ashwagandha extract at a dose of 100 mg/kg, which corresponds to the usual human dose of 4 to 6 g/d. Three groups received cyclophosphamide, azathioprine, or prednisone and another 3 groups received ashwagandha extract at doses of 100 mg/kg along with either of these immunosuppressive agents. After 15 days, the mice were killed, and a blood sample was analyzed. The control group showed suppression of peripheral blood cell counts including all 3 lineages. When ashwagandha was combined with prednisone or azathioprine but not cyclophosphamide, marrow activity was restored. The group treated with ashwagandha alone had an increase in antibody titer against red blood cells, thus demonstrating an immunostimulatory effect of this drug. To our knowledge, no human studies have been performed to test the immunostimulatory effect of this herbal remedy.

The patient in this case had stable graft function for more than 2 years after the transplant. He was unsensitized and had no history of donor-specific antibodies. There was no history of prior rejection (including borderline type) or infection due to CMV or BK virus. He was compliant with clinic visits and immunosuppression all through the post-transplant period. All previous tacrolimus trough levels were within the acceptable target range. Apart from the initiation of ashwagandha about 2 weeks before the rejection episode, there was no obvious trigger for the rejection. Based on the immunostimulatory capacity of ashwagandha in mice, we propose a similar immunostimulatory effect in humans as well that triggered an acute rejection episode. Even though the dose of ashwagandha used by our patient (1 g) was lower than the usual prescribed dose (4–6 g), the immune stimulation may have been enough to trigger an episode of acute rejection.

Table 1. Teaching points

1. Herbal supplements are widely used and may lead to kidney injury through several mechanisms including tubular damage and interstitial nephritis.
2. Ashwagandha is an Indian herbal supplement that is widely available over the counter and online, with immunostimulatory effects and may lead to kidney allograft rejection.
3. Physicians taking care of kidney transplant recipients should be aware of this and routinely assess supplement use.

In a population-based study in the United States of 10,005 individuals, the prevalence of any supplement use was highest in chronic kidney disease stage 3 to 5 at about 36%, followed by 27.3% in chronic kidney disease stages 1 and 2. The most common reasons for using supplements were to improve overall health, to stay healthy, to improve bone health, and to get more energy.[5] Some of these supplements were rich in elements that have toxic effects in patients with chronic kidney disease, including potassium and phosphorous. Previous reviews described various kidney syndromes caused by supplements including hypertension (e.g., *Glycyrrhiza* sp), acute tubular necrosis (e.g., *Securida* sp, *Euphoria* sp), acute interstitial nephritis (e.g., *Uno degatta*), papillary necrosis (e.g., Chinese herbs adulterated by phenylbutazone), urinary retention (e.g., *Datura* sp), and kidney stones (e.g., Ma huang, ephedrine).[6] A 2011 survey of kidney and liver transplant recipients demonstrated that 58% of recipients were taking over-the-counter supplements.[7] Some supplements (such as St John's wort) are well-known to increase the risk of rejection through induction of CYP450 and lowering calcineurin inhibitor drug levels.[8] Drugs and supplements that cause rejection through immune stimulation are rarely reported. Infections and vaccinations have been reported to increase rejection risk; however, molecular mimicry to donor antigens cannot be excluded. Immune checkpoint inhibitors administered to kidney transplant recipients cause rejection through loss of peripheral tolerance mechanisms unrelated to a donor antigen specificity.[9] This case strongly suggests that ashwagandha nonspecifically causes immunostimulation and loss of peripheral tolerance.

The supplement ashwagandha remains widely and easily available. Over-the-counter and online sale of the drug makes it easily accessible to a large population. We recommend that kidney (and other solid organ) transplant programs and recipients should be made aware and warned of this potential adverse effect of using ashwagandha (Table 1).

DISCLOSURE

SH receives research salary support from the Department of Medicine, University of Ottawa. All the other authors declared no competing interests.

AUTHOR CONTRIBUTIONS

All authors contributed to data collection, critical evaluation of collected data, and writing the manuscript. SH had full access to the data in the study and had final responsibility for the decision to submit for publication.

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