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AZATHIOPRINE ASSOCIATED WITH INTRAHEPATIC CHOLESTASIS IN A PATIENT WITH TWIN PREGNANCY AFTER A SECOND KIDNEY TRANSPLANT

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ABSTRACT

Introduction: Most pregnancies in women after a kidney transplant result in a live birth, but kidney functions should be stable for one year before conception. For immunosuppression modification occurring before pregnancy, azathioprine is used because it is considered safe for major congenital malformations during pregnancy. However, there may be an association between exposure to azathioprine during pregnancy and the onset of an unusual, early and severe form of intrahepatic cholestasis.

Case description: A young patient with a twin pregnancy after a second kidney transplant experienced intrahepatic cholestasis. There was a wide range of differential diagnosis. A battery of tests was requested including autoimmune markers, virology, and imaging. The conclusion that azathioprine was contributing to intrahepatic cholestasis with pregnancy was reached after exclusion of all other differentials.

Conclusions: Complications of pregnancy after a kidney transplant include hypertension, pre-eclampsia, deterioration of graft function up to rejection, but also unusual side effects of immunosuppression medication.

KEYWORDS

Kidney transplant, azathioprine, pregnancy, intrahepatic cholestasis

LEARNING POINTS

- A twin pregnancy after a second kidney transplant is rare.
- In addition to bone marrow suppression and elevation of liver enzymes, azathioprine can contribute to intrahepatic cholestasis of pregnancy.
- Complications of pregnancy after kidney transplant include hypertension, pre-eclampsia, deterioration of graft function up to rejection, but also unusual side effects of immunosuppression medication.

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INTRODUCTION

Most pregnancies in women after a kidney transplant result in live birth[1]. Pregnancy after kidney transplant might affect women's health and foetal outcomes, with higher risk of abortion, foetal growth restriction and even neonatal death. Rates of pre-eclampsia in patients with a kidney transplant were almost six times higher compared to the general US population (21.5% vs. 3.8%)[2]. Other complications include hypertension, deterioration of graft function, urinary tract infections and the possibility of transplant rejection. Twin pregnancy after a renal transplant is rare with high risk of adverse maternal and foetal outcomes[3]. Among the immunosuppression medications for kidney transplantation, short-acting glucocorticoids, azathioprine and calcineurin inhibitors are considered relatively safe for the risk of major congenital malformations during pregnancy. Common side effects of azathioprine include bone marrow suppression leading to leukopenia and thrombocytopenia, and megaloblastic anaemia[4]. Also, azathioprine can cause a moderate elevation of liver enzymes. There may be an association between exposure to azathioprine during pregnancy and the onset of an unusual, early and severe form of intrahepatic cholestasis[5].

A few case reports have also observed cholestasis even after it has been used for a year[6,7]. Intrahepatic cholestasis in pregnancy (ICP) is characterised by unexplained maternal pruritus, increased serum bile acid concentration over 10 µmol/l and spontaneous relief after delivery. ICP occurs most of the time during the third trimester and its incidence is 0.7% to 1.5%[8].

In addition, twin pregnancies with ICP had a higher risk for adverse perinatal outcomes than singletons, which was associated with higher bile acid level[6,7].

CASE DESCRIPTION

A young woman with a second kidney transplant presented with elevated liver enzymes on her routine blood test during follow-up in the kidney transplant clinic.

She had a second kidney transplant in March 2018 from a living, unrelated donor. She had post-transplant diabetes and was on oral sulphonyl urea drugs. The cause of end-stage kidney disease was not clear; she was discovered to have bilaterally shrunken kidneys with no family history of kidney disease.

Her other medications were tacrolimus 1 mg twice a day, azathioprine 75 mg once a day (she was intolerant to mycophenolate mofetil (MMF) and mycophenolate sodium (MPS) due to gastrointestinal side effects) and prednisolone

Blood tests	First presentation	2 weeks later	20th week of gestation	1 week after azathioprine reduced	1 week after azathioprine stopped	6 months after delivery
Creatinine (mg/dl)	0.57	0.6	0.5	-	-	0.52
Trough tacrolimus (ng/dl)	12.4	6.5	4.5	-	4.7	5
ALT (U/l)	153	89	74	70	64	47
AST (U/l)	149	55	47	46	48	38
Total bilirubin (mg/dl)	1	-	4.5	4.5	2.2	Normal
Direct bilirubin (mg/dl)	-	-	3.8	-	1.8	Normal
Gamma GT (U/l)	20	-	45	-	-	-
CMV PCR	Negative	-	Negative	-	-	-
Hep A	Negative	-	-	-	-	-
Hep B	Negative	-	-	-	-	-
Hep C	Negative	-	-	-	-	-
HCV PCR	Negative	-	Negative	-	-	-
ANA	Negative	-	Negative	-	-	-
AMA	Negative	-	Negative	-	-	-
ASMA	Negative	-	Negative	-	-	-
Anti-LKM	Negative	-	Negative	-	-	-

Table 1. Liver tests and kidney function tests throughout the pregnancy

5 mg once a day. Kidney functions were normal –creatinine 0.57 mg/dl, serum alanine aminotransferase (ALT) 153 U/l and serum aspartate aminotransferase (AST)149 U/l; the trough level of tacrolimus was 12.4 ng/dl.

In light of increased liver enzymes, more blood tests were requested. The cytomegalovirus (CMV) polymerase chain reaction (PCR) came back negative. Hepatitis A, B and C antibodies were negative. HCV RNA was undetectable. Total bilirubin and gamma-glutamyl transferase (GGT) were normal. Antimitochondrial antibody (AMA) and antinuclear antibody (ANA) were both negative. An abdominal pelvic ultrasound showed normal liver size and no other abnormality was detected. Complete blood count was normal: haemoglobin (Hb) 13.8 g/dl, white cell count (WCC) 6.8, platelets (PLT)198. Clotting was normal. Hepatologists advised a switch from drugs to basal insulin and short-acting insulin before meals. Tacrolimus was reduced to 1 and 0.5 mg and trough levels came down to 6.5 ng/dl.

Two weeks later, liver enzymes slowly came down but did not normalise (ALT 89 U/l and AST 55 U/l). She was referred to the hepatology team to follow liver enzymes.

She came to the kidney transplant clinic during follow-up when 6 weeks pregnant. The pregnancy was not planned; she was using only barrier methods for contraception. She already had a child that she conceived and delivered after her first kidney transplant.

Human chorionic gonadotropin (hCG) levels were very high considering the gestation age, and an 11-week ultrasound showed a dichorionic-diamniotic twin pregnancy. Twins run in the maternal side of her family. She was scheduled for a monthly follow-up in the obstetric nephrology clinic. She had stable kidney functions during her visits. In the 20th week of gestation, she complained of yellowish discoloration of the skin and itching. More investigations were carried out.

Total bilirubin level was 4.5 mg/dl (77 µmol/l) with direct bilirubin 3.8 mg/dl (65 µmol/l); the GGT result was 45 U/l. The abdominal pelvic ultrasound was normal, and the liver did not show any intra- or extrahepatic biliary obstruction.

Liver enzymes were ALT 74 U/l and AST 47 U/l. A repeat of the autoimmune panel (ANA, AMA, ASMA and Anti-LKM Ab) came back negative again. Thiopurine methyltransferase (TPMT) was not available and could not be done. Toxoplasma gondii was negative. Serum and urine copper levels, and thyroid hormones were within the reference range. She had not recently started any herbal or other medication. The patient had no history of biliary tract disorders such as gallstones, cholecystitis, cholangitis, or biliary tract cysts, and her first pregnancy was uneventful. She refused a liver biopsy for fear of complications.

A joint hepatology/obstetric review diagnosed intrahepatic cholestasis of pregnancy. She was advised to start ursodeoxycholic acid three times a day and cholestyramine, and reduce azathioprine, if possible, with follow-up of kidney and liver function tests. Azathioprine was reduced to 50 mg once a day with no improvement; bilirubin remained at 4.5 mg/dl (77 µmol/l) 1 week later.

As per the obstetric team plan, she had regular antenatal ultrasounds which showed normal foetal development, and cardiotocography (CTG). There was fear that high bilirubin would affect foetal development; the patient was counselled and informed that azathioprine might be contributing to ICP. Eventually, a decision was made to stop azathioprine. She continued tacrolimus and a higher dose of corticosteroids, 15 mg once a day with very close attention to her kidney functions.

One week later, total bilirubin came down to 2.2 mg/dl in 37.6 umol/l and direct bilirubin to 1.8 mg/dl (30.8 µmol/l). Bilirubin levels and liver enzymes normalised after another month. The rest of pregnancy was uneventful, and the patient delivered healthy twins, a boy and a girl, by lower segment C-section at 37 weeks as planned by the obstetrics team.

After delivery she commenced mycophenolate sodium (MPS) and 6 months after delivery she still had normal kidney functions with creatinine 0.52 mg/dl, normal liver enzymes and no proteinuria.

During the 10-month toddler health check the children appeared healthy, with normal physical and neurological development.

DISCUSSION

In pregnancy after transplant both mother and baby can experience complications related to the mother's underlying disease and immunosuppressive medication. Potential complications include hypertension, pre-eclampsia, deterioration of graft function, urinary tract infections and the possibility of transplant rejection.

In this case, there was initial elevation of liver enzymes even before pregnancy. That was thought to be probably the effect of high tacrolimus levels. Although there was an improvement in liver enzymes after reduction of the tacrolimus dose, the levels still did not normalise. This prompted extensive blood tests to exclude viral hepatitis and other autoimmune causes of liver disease.

During the 20th week of gestation, the patient developed intrahepatic cholestasis. In some cases, ICP can lead to intrauterine foetal death, spontaneous abortion and induce prematurity. According to a recent study, there is a 1%–2 % greater risk for ICP with bile acid above 40 mol/l, which is considered related to poor foetal outcomes[10].

Patients who have ICP frequently have premature labour and delivery. This happens because bile acids increase the uterus' sensitivity to oxytocin. About 20% to 40% of ICP pregnancies end in pre-term labour spontaneously[11].

There is also a risk of respiratory distress and meconium excreted in the amniotic fluid in this disorder. The patient was counselled about the effects of high bilirubin on the baby.

Pregnancy is a state of immunological tolerance associated with decreased immune activity of lymphocytes, which creates tolerance to the foetus and may benefit the kidney allograft. However, there is a possibility that the antigenic

stimulus provided by the foetus may trigger graft rejection as well[12]. Having said that, acute rejection rates are similar to the general transplant population – about 9.0% during pregnancy and 1.3% postpartum[13]. There is no data on rejection during pregnancy after a second kidney transplant. The decision to stop azathioprine was not taking lightly, the patient was counselled and was aware of the risks of kidney rejection while being on dual immunosuppression.

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