

The Course of Pregnancy in a Patient with Nail-Patella Syndrome

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Abstract

Introduction: The nail-patella syndrome is a rare autosomal dominant condition with high penetrance. Pregnancy in such a patient is rare and we believe this to be the first report of a live birth occurring in a patient with nail-patella syndrome. **Clinical Picture:** A 25-year-old patient presented in her first pregnancy with nephrotic syndrome associated with characteristic bone abnormalities and nail dysplasia and was later diagnosed to have nail-patella syndrome. In her second pregnancy, the course of her pregnancy was complicated by further deterioration of renal function with superimposed pre-eclampsia resulting in early delivery at 28 weeks. **Conclusion:** Such pregnancies should be regarded as high risk and managed jointly with the renal physician in a tertiary care centre to ensure an optimal outcome to the mother and baby.

Ann Acad Med Singapore 2002; 31:349-52

Key words: Bone abnormalities, Nail dysplasia, Pregnancy outcome, Renal complication

Introduction

The nail-patella syndrome (NPS) is a rare autosomal dominant disorder defined by the association of nail dysplasia, bone abnormalities and, frequently, renal disease. We report the course of pregnancy in a patient with such a condition.

Case Report

A 25-year-old woman, who had no past medical history, was booked for antenatal care and delivery for her first pregnancy in 1997. Her pregnancy was uneventful until the 29th-week of gestation when she presented with gross pedal oedema associated with proteinuria and was diagnosed to have nephrotic syndrome. The blood pressure remained normal and the pregnancy continued uneventfully until term and resulted in a normal vaginal delivery of a healthy 2.3-kg baby boy. Post-delivery, she continued to have persistent non-selective proteinuria and was empirically treated with prednisolone 15 mg od. The nephrotic syndrome did not remit and further addition of cyclophosphamide 50 mg od to the treatment regimen was necessary. She did not have episodes of gross haematuria and remained normotensive. Urinalysis revealed 3+ proteinuria without microscopic haematuria. The 24-hour urinary protein

excretion was 3.64 g/day and there were hypoalbuminaemia (serum albumin 16 g/L) and hypercholesterolaemia. The serum creatinine was 85 μ mol/L and the creatinine clearance was 69 mL/min. Urea, electrolytes and liver function tests (except the albumin level) were normal. A screen for antinuclear and anti-double stranded DNA antibodies was negative. A kidney, ureter and bladder (KUB) X-ray was performed and revealed the incidental presence of bilateral iliac horns (Fig. 1). X-rays of both knees also showed an absent left and a hypoplastic right patella (Fig. 2). Physical examination revealed bilateral ankle oedema, absent left patella, fixed flexion deformity of both elbows with prominent olecranon processes and koilonychia of both thumbs and index fingers. There was no family history of renal disease or family members with nail or joint abnormalities. Her clinical features were consistent with that of NPS.

She consented to a renal biopsy and the specimen was studied for light, immunofluorescence and electron microscopy (EM). On light microscopy, 5 of 15 glomeruli available on the specimen were globally sclerotic while 4 others showed segments of sclerosis associated with capsular adhesions and tubular atrophy. Another glomerulus displayed a segmental increase in mesangial cells (four

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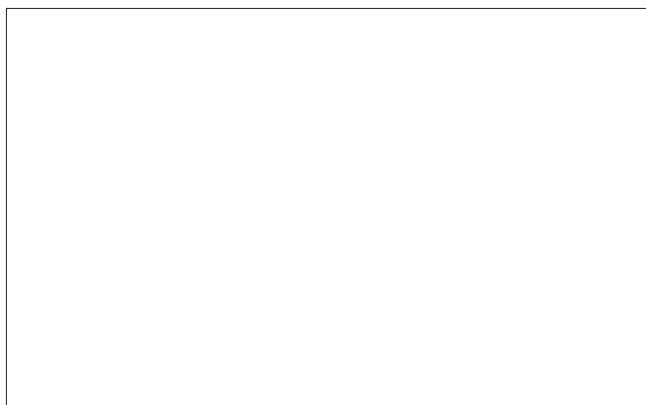


Fig. 1. X-ray showing the characteristic iliac horns of nail-patella syndrome.

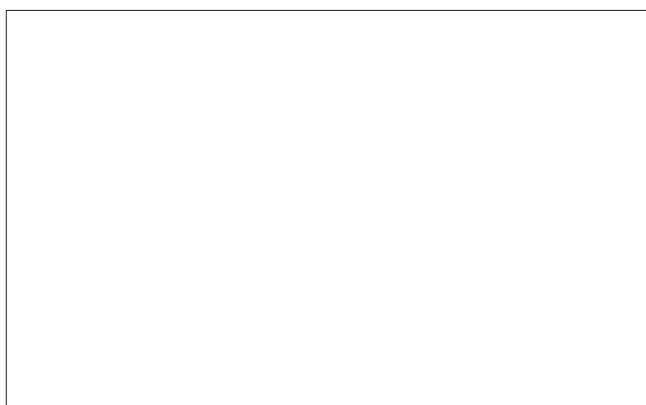


Fig. 2. Anterior-posterior bilateral knee X-ray demonstrating absent left knee patella and hypoplastic right knee patella.

cells) and matrix. Immunofluorescence revealed granular 2+ immunoreactivity for IgA in the mesangium with 1+ staining in a segmental distribution along the glomerular capillary walls with a similar distribution for IgM. Electron microscopy showed a glomerulus with irregular thickening of the glomerular basement membrane. Black collagen fibrils, mainly in the subendothelial region and occasionally in the basement membrane, were demonstrated on the phosphotungstic acid (PTA) stain. Large electron dense paramesangial deposits were seen together with collagen fibrils. The microscopic features were those of combined NPS with IgA nephropathy.

The patient conceived again in 1999 and booked early at 6 weeks of amenorrhoea for antenatal care. This second pregnancy was jointly managed with the renal physicians. Her blood pressure at booking was normal and urine revealed 4+ proteinuria. Baseline renal investigations revealed a serum creatinine level of 164 $\mu\text{mol/L}$, creatinine clearance of 28 mL/min and a 24-hour urine protein of 2.65 g. In view of the significant nephropathy, the patient was counselled regarding the possibility of worsening renal function with continuation of the pregnancy. The option of pregnancy termination was discussed but she elected to

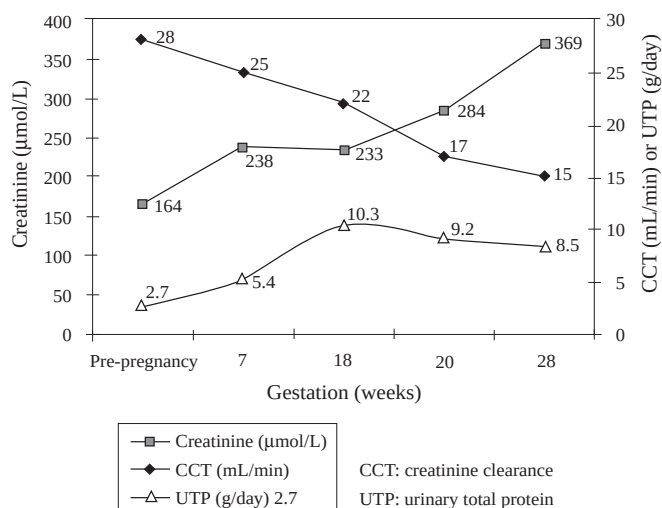


Fig. 3. Serial renal function tests during pregnancy.

continue with the pregnancy. She continued to be on maintenance prednisolone 10 mg od. Amniocentesis at 16 weeks at the patient's request revealed a normal female karyotype and no structural anomalies were noted during a fetal anomaly ultrasound scan at 20 weeks' gestation. Methyldopa was added when she developed hypertension with a blood pressure of 150/120 mm Hg at 23 weeks. She did not have symptoms of fulminant pre-eclampsia. Her renal function had by then significantly deteriorated with the serum creatinine being 369 $\mu\text{mol/L}$, creatinine clearance 15 mL/min, and a 24-hour urine protein of 10.3 g (Fig. 3).

Her blood pressure continued to worsen and she required larger doses of antihypertensive drugs. She developed preterm labour at 27 weeks which was temporarily inhibited with intravenous salbutamol to allow the administration of intramuscular dexamethasone to accelerate fetal lung maturity. Ultrasound scan showed that there was no intrauterine growth restriction of the fetus and the estimated fetal weight was 740 g. A decision was made to terminate the pregnancy at 28 weeks in view of the deteriorating renal function and poorly-controlled hypertension suggestive of superimposed pre-eclampsia. Labour was successfully induced with vaginal dinoprostone with a normal vaginal delivery of a 945-g baby girl with Apgar scores of 6 and 9 at 1 and 5 minutes of life, respectively. In the postpartum period, the mother's blood pressure normalised with only marginal improvement in renal function.

Discussion

Nail-patella syndrome, also known as hereditary onychosteodysplasia (HOOD), is a rare autosomal dominant pleiotropic connective tissue disorder affecting both mesenchymal and ectodermal tissue. It was first described by Chatelein¹ in 1820, and the hereditary nature of the

syndrome was observed by Little² in 1897. The disease has a high degree of penetrance but variable expression.³ It is characterised by onchodysplasia of the fingernails or nailbed dysplasia (most prominent on the thumb and index finger) and V-shaped lunulae or hypoplasia, absent or hypoplastic patellae, iliac horns and deformation or subluxation of the radial head. The first two findings are essential for the diagnosis.⁴ The presence of the posterior iliac horns is pathognomonic and has been observed in only 70% of cases. Our patient also had positive staining by PTA (phosphotungstic acid) of clusters of cross-banded collagen fibrils within the glomerular basement membrane and this too is pathognomonic of the diagnosis.

The genetic defect is localised on chromosome 9q34.1.⁵ The previous belief that NPS was associated with abnormalities of the COL5A1 gene which is responsible for collagen V synthesis is now refuted as COL5A1 is located on chromosome 9q34.3.⁶ Nephropathy is a known serious associated complication. The nephropathy is characterised on electron microscopy by collagen-like deposition in the glomerular basement membrane and presents clinically as proteinuria and nephrotic syndrome. The clinical relevance is determined by the course of the renal disease. The nephropathy may progress to end-stage renal failure in approximately 30% of cases, leading to decreased life expectancy.⁷ Other extraosseous manifestations, such as glaucoma and microcornea, have been described.⁸

The first described case of NPS and pregnancy in the medical literature developed pre-eclampsia at 22 weeks, leading to intrauterine fetal death at 24 weeks.⁹ The nephropathy had begun clinically during the course of gestation and persisted as isolated proteinuria in the puerperium before developing nephrotic syndrome 18 months later. This is similar to our patient who developed nephrotic syndrome late in her first pregnancy. That pregnancy, however, progressed uneventfully. The course for the second pregnancy was more dramatic. There was a progressive deterioration in renal function and proteinuria culminating in early onset development of hypertension suggestive of superimposed pre-eclampsia. Investigations for liver function, thrombocytopaenia and evidence of coagulopathy were used to distinguish superimposed pre-eclampsia from progressive renal deterioration. Fetal surveillance (with cardiotocography, biophysical profile and Doppler ultrasound assessment of umbilical blood flow) is necessary to monitor fetal well-being. Early delivery was indicated in this patient because of the worsening renal function and superimposed pre-eclampsia. Given the high risks of the clinical condition to both the mother and fetus, delivery in a tertiary institution with good neonatal support was crucial.

From a histological point of view, the combination of IgA and NPS in this woman is very unusual¹⁰ and would suggest a very poor renal outcome. Indeed, the only marginal improvement in renal function following the delivery of the second pregnancy suggests that, in addition to pre-eclampsia, there was indeed further renal deterioration during the pregnancy. It is also possible that the physiological changes of pregnancy itself may have accelerated the deterioration. This combination of renal pathologies is probably coincidental as IgA nephropathy is the commonest glomerulonephritis in Singapore (accounting for 45% of all primary glomerulonephritis).¹¹

The risk for women with NPS to have an affected child who will develop renal failure cannot easily be deduced from published pedigrees. Looij et al¹² estimated that for a patient with NPS from a family in which NPS nephropathy occurs, the risk of having a child with NPS nephropathy is about 1:4. The risk of having a child in whom renal failure will develop is about 1:10. Renal abnormalities have been studied in an aborted fetus from a woman with NPS, and intrauterine renal biopsy and ultrasonography revealing renal anomalies in fetuses affected by NPS have been reported, providing possible avenues for prenatal diagnosis of NPS. Women with NPS should therefore receive pre-conception counselling. Baseline renal assessment including a pre-pregnancy renal biopsy is the most important arbiter on the likelihood of a successful pregnancy outcome. Genetic counselling with respect to the inheritance of NPS in the fetus and the issue of possible accelerated renal deterioration with pregnancy should also be discussed. These pregnancies should be managed as high-risk pregnancies in tertiary centres with maternal-fetal medicine, renal medicine and neonatal specialists, given the need for regular surveillance of renal function and obstetric complications of early onset superimposed pre-eclampsia and intrauterine growth restriction.

In conclusion, we believe that we are the second to report a pregnancy complicated by the NPS, and indeed the first with 2 live births. The likelihood of a successful pregnancy outcome is dictated by the severity of renal disease at the outset of pregnancy and its subsequent course. Superimposed pre-eclampsia would necessitate early delivery. Successful management requires a multi-disciplinary approach, with preconception counselling and a planned pregnancy after the nature of nephropathy has been defined by a renal biopsy.

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