CASE REPORT

A 'Full House' Glomerulopathy in a Patient with Multiple Lentigines Syndrome: A Case Report

KK Hoe[1], N Smith[2], EN Barton[3], AK Soyibo[1]

ABSTRACT

*Multiple lentigines syndrome (MLS) is an autosomal dominant disease which is usually diagnosed clinically by the presence of characteristic features. The molecular genetic testing is an adjuvant diagnostic tool to identify the mutation of particular genes such as PTPN11 genes, RAF1, BRAF or MAP2K1 genes. This syndrome was formerly known as LEOPARD syndrome or Noonan syndrome with multiple lentigines. 'LEOPARD syndrome' is an acronym of characteristic features (**L**entigines, **E**lectrocardiographic conduction abnormalities, **O**cular hypertelorism, **P**ulmonary stenosis, **A**bnormalities of the genitalia, **R**etardation of growth, and **D**eafness). There was no previous case report about any glomerulonephropathy in association with MLS. We present a case of a patient with MLS with recurrent nephrotic syndrome who was found to have histologic evidence of 'full house' glomerulopathy.*

Keywords: 'Full house' glomerulopathy, LEOPARD syndrome, multiple lentigines syndrome, Noonan syndrome with multiple lentigines

Glomerulopatía 'full house' en un paciente con síndrome de lentigos múltiples: un reporte de caso

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RESUMEN

*El síndrome de lentigos múltiples (SLM) es una enfermedad autosómica dominante que de modo general se diagnostica clínicamente por la presencia de rasgos característicos. La prueba genética molecular es una herramienta de diagnóstico auxiliar utilizada para identificar la mutación de genes específicos tales como los genes PTPN11, RAF1, BRAF, o los genes MAP2K1. Este síndrome se conocía anteriormente como síndrome del leopardo o síndrome de Noonan con múltiples lentigos. El síndrome toma su nombre del acrónimo en inglés LEOPARD, que describe sus rasgos característicos (**L** lentigos; **E** conducción electrocardiográfica de las anormalidades; **O** hipertelorismo ocular; **P** estenosis pulmonar; **A** anormalidades de los genitales; **R** retardo del crecimiento; y **D** deafness, 'sordera' en inglés), y que fuera introducido por Gorlin* et al *en 1969. No existía ningún reporte de caso*

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anterior sobre glomerulonefropatía asociada con SLM. Presentamos el caso de un paciente con SLM con síndrome nefrótico recurrente en el que se halló evidencia histológica de glomerulopatía 'full house'.

Palabras clave: Glomerulopatía 'full house', síndrome del leopardo, síndrome de lentigos múltiples, síndrome de Noonan con múltiples lentigos

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INTRODUCTION

Multiple lentigines syndrome (MLS) is an autosomal dominant disease which is usually diagnosed clinically by the presence of characteristic features. This syndrome was formerly known as LEOPARD syndrome or Noonan syndrome with multiple lentigines. 'LEOPARD syndrome' is an acronym of characteristic features (**L**entigines, **E**lectrocardiographic conduction abnormalities, **O**cular hypertelorism, **P**ulmonary stenosis, **A**bnormalities of the genitalia, **R**etardation of growth, and **D**eafness) which was introduced by Gorlin *et al* in 1969 (1). The characteristic features of MLS include brown skin spots (lentigines), cardiac conduction defect with hypertrophic cardiomyopathy, pulmonary stenosis, short stature, ocular hypertelorism, abnormal genitalia, and hearing defect. It is not necessary to have all of the characteristic features to diagnose MLS. Lentigines are disperse flat brown macules most commonly seen on the face, neck and upper part of the body with sparing of the mucosa (2). They are quite similar to skin freckles, but they are not sensitive to sunlight. There have been approximately 200 cases of MLS patients in the world. The first case of MLS was reported in 1936, and associated cardiac abnormality and short stature were included among the clinical features of MLS in 1962 (3). The 'full house' immunofluorescent pattern means detection of IgA, IgM, IgG, C1q and C3 deposits on immunofluorescent microscopy.

There was no previous case report about any glomerulonephropathy in association with MLS. We present a case of a patient with MLS with recurrent nephrotic syndrome who was found to have histologic evidence of 'full house' glomerulopathy.

CASE REPORT

In July 2015, a 15-year-old male was referred to the Internal Medicine team of the University Hospital of the West Indies, Kingston, Jamaica, because of intermittent cramps to his calves for two years and intermittent generalized oedema for one year. His pre-admission urinalysis and urine microscopy showed albumin 4+, blood 1+ and 3–6 red blood cells/hpf. Blood investigations showed a decrease in total protein of 48 g/L and albumin of 27 g/L. The serum urea and creatinine were elevated at 11.9 mmol/L and 286 mmol/L respectively. The result of spot urine protein to creatinine ratio was 2.57 mg/mg.

Past medical history was significant for the presence of cardiac murmur at the age of 15 months. At that time, he weighed 12 kg (50th percentile), and his height was 82 cm (25–50th percentile). His echocardiogram showed concentric left ventricular hypertrophy along with increased trans-aortic pressure suggestive of outflow obstruction. He was assessed as having hypertrophic obstructive cardiomyopathy at such a young age. A two-dimensional echocardiogram was repeated when he was 10 years old. It revealed severe hypertrophic cardiomyopathy without evidence of outflow tract obstruction. An electrocardiogram revealed left axis deviation, QTc 498 mm which was prolonged and features of left ventricular hypertrophy. Of note, two paternal aunts had similar cardiac problems, and the patient's father had cardiac disease but was never investigated.

The brownish flat skin macules and freckles appeared over the palms, soles of the feet, anterior upper chest and axilla when he was 11 years old. Eventually, he was assessed as having MLS (LEOPARD syndrome) based on the presence of multiple lentigines, hypertrophic cardiomyopathy, hypertelorism and growth delay (borderline). Of note, his baseline hearing test was normal bilaterally.

Because of abnormal renal indices found in the screening tests done when he was 15 years old for intermittent oedema, he was admitted to the Nephrology service for further evaluation. Clinically, he had mild lower limb pitting oedema on admission with pale mucous membranes and hypertrophic lips, and there were widespread brownish skin patches over his entire body including his face, tongue, palms and soles. Additional findings of bilateral transverse palmar creases (formerly known as Simian creases) were noted (Figs. 1–4). Of note, the

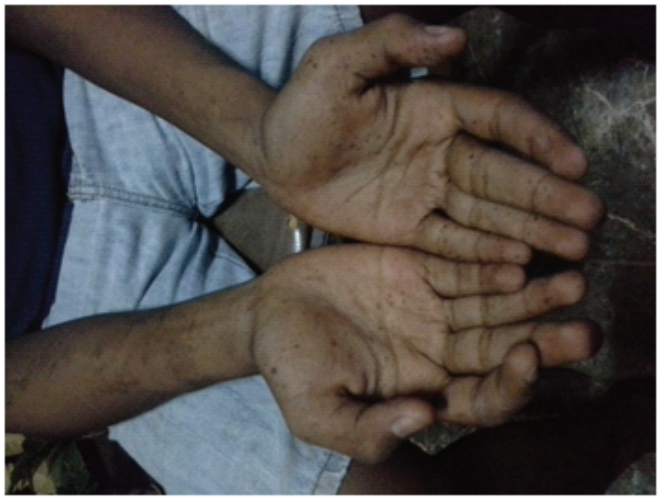

Fig. 1: Widespread light to dark brownish macules (lentigines) over the palms.

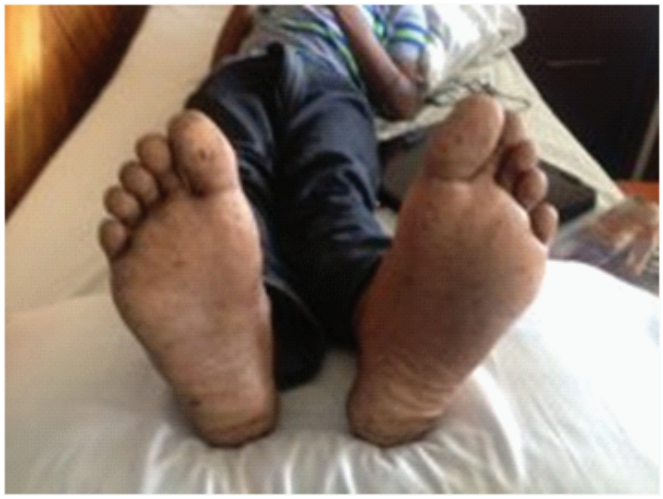

Fig. 2: Widespread light to dark brownish macules (lentigines) over the soles.

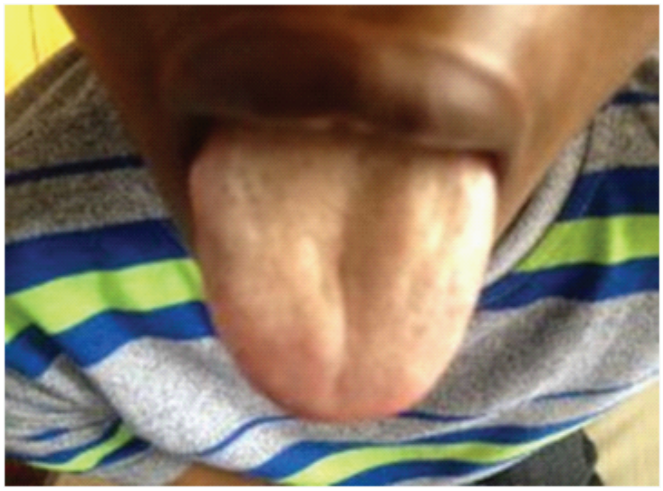

Fig. 3: Hypertrophic lips with lentigines on the tongue.

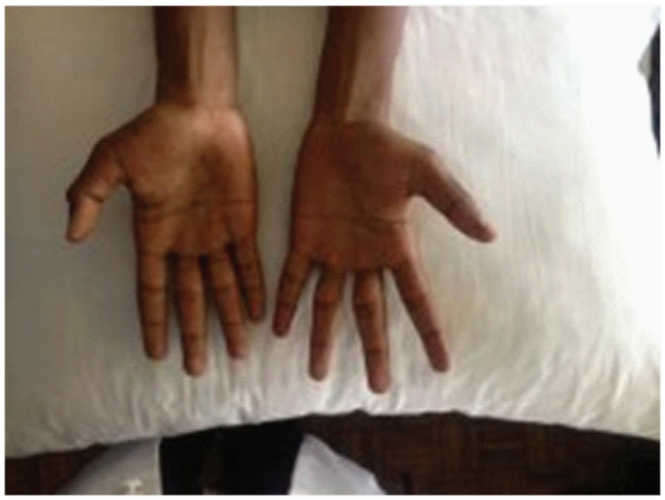

Fig. 4: Bilateral Simian creases.

transverse palmar crease (Simian crease) is associated with some of the genetic syndromes such as cri du chat syndrome (chromosome 5), Klinefelter syndrome, Wolf-Hirschhorn syndrome, Noonan syndrome (chromosome 12), Patau syndrome (chromosome 13), Edward's syndrome (chromosome 18) and Down syndrome (chromosome 21).

He also had 3/6 ejection systolic murmur best audible at the left lower sternal edge which was louder on expiration. His blood pressure (BP) was elevated for his age, with systolic BP in the range of 120–140 mmHg and diastolic BP in the range of 65–85 mmHg. His kidneys were not ballotable. There was no clinical evidence of undescended testes or hypospadias.

His renal ultrasound revealed that his kidneys were hyperechoic with loss of the corticomedullary differentiation. No renal mass, hydronephrosis or calculus was seen. The right kidney measured 8.9 cm, and the left kidney measured 9.9 cm. Findings were noted to be consistent with those of the renal parenchymal disease. A renal biopsy was subsequently done.

A histology report on light microscopy stated that there were 21 glomeruli, 15 of which were globally sclerosed with hyalinosis. There was focal, mild increase in his mesangeal matrix and no increase in his mesangeal cellularity. The glomerular capillaries were otherwise patent without endocapillary hypercellularity. Tubules were dilated and contained hyaline and granular casts. The tubular epithelium exhibited marked degenerative and regenerative changes. A moderate interstitial mononuclear inflammatory cell infiltrate was present. There was severe (approximately 50%) interstitial fibrosis and tubular atrophy. Immunofluorescence study was significant for fine granular segmental staining of the glomerular capillary walls for IgG (2–3+), IgA (trace), IgM (1+), C3 (2–3+), C1q (2+), kappa (2+) and lambda (2+).

This immunofluorescence pattern of staining was highly suggestive of lupus nephritis. However, subsequent antinuclear antibody, double stranded DNA and rheumatoid factor were all negative. Serum C3 and C4 were also within the normal range.

The patient was assessed as having non-lupus 'full house' glomerulonephritis (GN) with MLS. The decision was made to treat his non-lupus 'full house' GN with corticosteroid and mycophenolate mofetil. However, the chronicity shown on renal biopsy was unfavourable for the significant positive outcome in this patient. Despite receiving treatment with intravenous methyprednisone 500 mg daily for three days followed by oral prednisone 0.5 mg/kg/day along with oral mycophenolate mofetil 500 mg twice a day, his estimated glomerular filtration rate based on serum creatinine (eGFRcreat) gradually declined (Table). Other medications he received were metoprolol, caltrate D, febuxostat, Hb fortex, frusemide, folic acid and resonium A (polystyrene sulfonate).

Table: Monthly progression of renal dysfunction and complete blood count over the course of admission and follow-up, July to October 2015

Results	July	August	September	October
Na+ (mmol/L)	136	138	135	137
K+ (mmol/L)	5.0	5.5	5.2	5.6
Cl (mmol/L)	108	108	109	110
HCO3 (mmol/L)	21	16	16	16
BUN (mmol/L)	11.9	10.8	11.3	14.6
Creatinine (μmol/L)	286	380	468	506
eGFR (ml/minute)	33	25	19	17
Calcium (mmol/L)	2.02	1.92	1.8	1.7
Magnesium	2.1	0.67	0.72	0.75
Phosphate	1.6	1.5	1.6	1.6
Albumin	27	25	27	30
Haemoglobin (g/dL)	10.8	11.0	9.8	10.5
White cell count	3.0	4.6	4.2	4.5
Platelet	285	315	317	353

DISCUSSION

Multiple lentigines syndrome manifests with markedly variable expressivity. No single finding is pathognomonic, and only few patients have all major features. Kim *et al* proved that missense mutations in PTPN11, a gene encoding the protein tyrosine phosphatase SHP-2 located at band 12q2, were the major underlying cause of this genetic syndrome (4), accounting for 80% of MLS (5). The inappropriate synthesis of melanin due to SHP-2 mutation seemed to be the underlying cause of lentigines (6). The absence of these particular gene mutations has been reported in a small number of patients with MLS, and the cause of that is still unknown.

Left ventricular hypertrophy usually occurs in the inferior part of the left ventricle. Pulmonary stenosis is seen in up to 20% of individuals with MLS. The index case was diagnosed first with hypertrophic cardiomyopathy of the left ventricle when he was one year old which was followed by the development of lentigines at the age of 11 years onward.

Although 50–75% of those patients have short stature, the height of the index case remained at 50th percentile for his age. He had no deafness which was seen in approximately 20% of the cases.

Male patients of MLS can be associated with genital abnormalities, most commonly undescended testes (cryptorchidism) and, to a lesser extent, hypospadias. They may have decreased fertility. Female patients may present with delayed puberty and atrophy or agenesis of the ovaries.

The 'full house' nephropathy is usually suggestive of lupus nephritis. However, since the late 1990s, cases of 'full house' nephropathy without clinical and laboratory evidence of lupus have been recognized as non-lupus 'full house' nephropathy. Some of these cases later developed systemic lupus erythematosus [SLE] (7). Although an assumption was made that the 'full house' nephropathy could be an imminent presentation of SLE, it remained inconclusive as not all the follow-up cases transformed to full-blown lupus. A study on non-lupus 'full house' glomerulopathy among 24 cases showed membranous nephropathy as the most common glomerulopathy (46%), followed by membranoproliferative GN (12.5%), post-streptococcal GN (12.5%), anti-C1q nephropathy (4%) and unclassified mesengeal GN [4%] (8). Another study assumed environmental factors as probable underlying aetiologic agents and recommended close follow-up for the development of SLE (9). The index case had no clinical or laboratory evidence of SLE at that point, but he had a higher chance to develop SLE in the future; an extended period of surveillance was warranted. There were a few more individual case reports of 'full house' nephropathy with negative serology for SLE; these cases were treated as lupus nephritis or at least kept under surveillance for SLE (10–12).

CONCLUSION

Multiple lentigines syndrome, which is also known as Noonan syndrome with multiple lentigines or LEOPARD syndrome, can be associated with immune mediated 'full house' glomerulopathy. It was not clear whether the activation of autoantibodies in this case was directly related to the genetic defect of MLS. 'Full house' nephropathy

can progress rapidly to advanced nephropathy if diagnosis and treatment are delayed. It strongly indicates that prompt diagnosis and early treatment of 'full house' nephropathy are mandatory, whether it is lupus or non-lupus. Since the majority of non-lupus cases have turned to lupus 'full house' nephropathy with time, an extended period of surveillance is necessary.

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