CASE REPORT

Bronchiectasis and Focal Segmental Glomerulosclerosis in Rheumatoid Arthritis

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ABSTRACT

A 28-year-old male patient who was a nonsmoker presented with bilateral symmetrical polyarthritis and polyarthralgia, suggestive of rheumatoid arthritis (RA), along with shortness of breath, fever and cough, suggestive of chronic renal failure and nephrotic range proteinuria. The chest radiograph was suggestive of panacinar emphysematous changes with bilateral central bronchiectasis. The patient reported that two of his brothers had died in their third decade because of renal failure. Renal biopsy showed focal and segmental glomerulosclerosis (FSGS). FSGS with panacinar emphysema and bronchiectasis is a rare entity in RA patients, and considering the possibilities of a familial pattern of FSGS, transient receptor potential cation channel 6 channelopathy was the most valid diagnosis.

Key words: Bronchiectasis, focal and segmental glomerulosclerosis, rheumatoid arthritis, transient receptor potential cation channel 6 channelopathy

INTRODUCTION

Transient receptor potential cation channel, subfamily C (TRPC6), is a Ca^{2+} permeable nonselective cation channel that is gated via phospholipase C-activating receptor.[1] Six TRPC6 gene mutations are causally linked to late-onset focal segmental glomerulosclerosis (FSGS), a human proteinuric kidney disease.[1,2] In addition to FSGS, a specific TRPC6 channel has also been causally linked with hypersecretion of mucus, inflammation of the airway, immunomodulation, productive cough and hypoxia-induced pulmonary vasoconstriction.[3] Pharmacological blockade of TRPC6 is biologically sound and represents a new therapeutic approach with regard to FSGS and other proteinuric diseases. Here, we present a possible case of TRPC6 channelopathy together with a very rare association with panacinar emphysema, central bronchiectasis and rheumatoid arthritis (RA).

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CASE REPORT

A 28-year-old nonsmoker, nondiabetic, hypertensive male patient from Bangladesh, who was a manual laborer, presented at our tertiary care hospital. The patient complained of polyarthritis and polyarthralgia involving small and large joints of both upper and lower extremities for a period of 9 months along with shortness of breath, continuous low-grade fever and cough with expectoration for 4 months. Dyspnea was initially of Modified Medical Research Council (MMRC) Grade 1 but progressed over the next few months to become MMRC Grade 3 at the time of presentation to the hospital. The fever was a continuous low-grade fever of approximately 38°C, relieved only by medication and not associated with any chill and rigor. A cough was productive with a moderate

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amount of purulent expectoration. The patient had a history suggestive of allergic rhinitis and frequent lower respiratory tract infection since childhood. He had a total of eight brothers and no sisters. Two of his brothers had died due to renal failure of undiagnosed etiology in their third decade of life.

The patient was hypertensive, had bipedal pitting edema, but no peripheral lymphadenopathy or engorged neck vein. On auscultation, there were bilateral diminished vesicular breath sound and biphasic crepitations over the infrascapular, interscapular and infraaxillary areas.

The patient was euglycemic, had a high white blood cell count (11,200/mm^3) and the red blood cell morphology was normochromic normocytic. The hepatic profile showed hypoproteinemia. His renal profile showed a progressive rise of serum urea and creatinine level (serum creatinine 2.04 mg/dl upon presentation, reaching up to 3.92 mg/dl during 1 month of his admission). Urine for routine and microscopic examination showed 3+ albuminuria, presence of granular cast and pus cells. Urine culture did not yield any organism, but the 24-h urinary excretion measurement showed gradually increasing proteinuria that reached nephrotic range (1.725 g/24 h at presentation, 7.200 g/24 h after 3 weeks and >10 g/24 h after 5 weeks). Serum electrolyte showed hyperkalemia (serum potassium 5.4 mg/dl) and normal sodium level (136 mg/dl).

His sputum for Ziehl–Nielsen stain was negative. Sputum gram stain and culture did not reveal any organism. Chest radiography showed bilateral hyperinflated lung field, right lower zone bronchiectatic changes and a scalloped appearance of the right diaphragmatic outline due to bullae [Figure 1]. A high-resolution computed tomography thorax showed panacinar emphysema with bilateral central bronchiectatic changes [Figure 2]. An abdominal ultrasound showed reduced kidney size and loss of corticomedullary differentiation with features of chronic renal parenchymal disease. An electrocardiography showed sinus tachycardia, while an echocardiography showed Grade 1 diastolic dysfunction and a spirometry revealed obstructive pattern postbronchodilator improvement of forced expiratory volume in 1 second by 80 ml and 5%.

The collagen profile showed that serum antinuclear antibody was negative (titer 1:40) and RA factor was positive (titer >640 IU/ml). Serum anticyclic citrullinated peptide was positive with titre >200 U/ml (n <20 U/ml) and C-reactive protein 0.2 mg/dl (normal). Blood total eosinophil count was 270/mm^3, total IgE count 359.9 IU/ml, aspergillus-specific IgG 9.57 IU/ml (equivocal) and aspergillus-specific IgM 8.01 IU/ml (equivocal). Blood α1 antitrypsin was 1.21 g/l (normal), blood for PR3-ANCA was negative with titer 3.58 U/ml (n < 6) and MPO-ANCA was negative with titer 4.10 U/ml (n < 6). An ophthalmological examination showed no lenticonus and pure tone audiometry showed no sensorineural hearing loss. Arterial blood gas analysis showed pO_2 80 mmHg, pH 7.41, pCO_2 44 mmHg, HCO_3 26.8 mmol/L and hematocrit 30%. Therefore, it appeared to be a multisystemic disorder: RA with pulmonary and renal involvement in the form of bronchiectasis, panacinar emphysema and chronic renal failure of unknown etiology with nephritic range proteinuria.

A renal biopsy revealed FSGS with chronic tubulointerstitial nephritis, arterial/arteriolar hyalinosis with acute tubular injury [Figure 3]. There was minimal mesangial IgM deposition and no IgA-IgG deposition. C3, C1q was negative and kappa and lambda light chain was negative.

After all investigations, it was determined that the patient had the following: panacinar emphysema with central bronchiectasis, RA, nephrotic range proteinuria due to FSGS and a family history of sibling death in the third decade of life due to renal failure of undiagnosed etiology.

After a multidisciplinary consultation, the patient was put on 60 mg oral prednisolone, 1000 mg salazopyrin and 50 mg losartan. Methotrexate was avoided due to nephrotoxicity. The patient showed an improvement in the initial week, but after 7–10 days, there was further deterioration in the renal function. The steroid dose was increased to 80 mg/day and a dose of 500 mg/day oral cyclophosphamide was added. Gradually, he developed respiratory distress with features of type 2 respiratory, failure, for which he was put on invasive ventilation. However, the patient did not respond to the treatment, his condition deteriorated and, subsequently, he passed away.

DISCUSSION

FSGS is very uncommon in RA and also cannot be correlated with lung involvement.[4] Table 1 shows inherited causes correlating FSGS with other systemic diseases.[5]

Considering the inheritance pattern and age of presentation of the patient, TRPC6 channelopathy

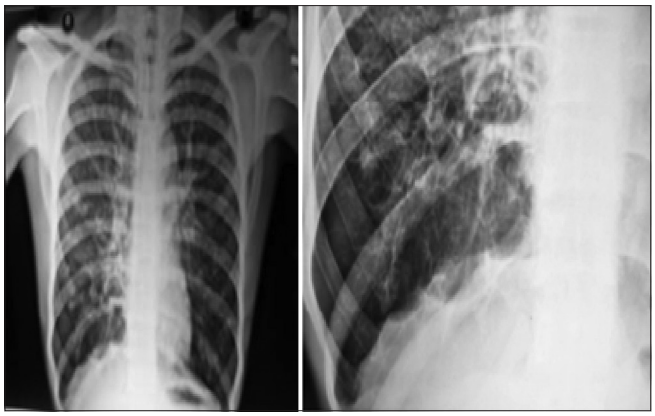

Figure 1: Chest radiography showed bilateral hyperinflated lung field, right lower zone bronchiectatic changes and scalloped appearance of the right diaphragmatic outline due to bullae

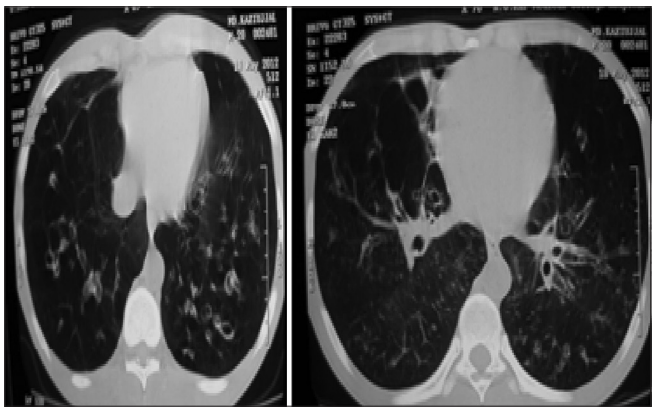

Figure 2: High-resolution computed tomography thorax showed panacinar emphysema with bilateral central bronchiectatic changes

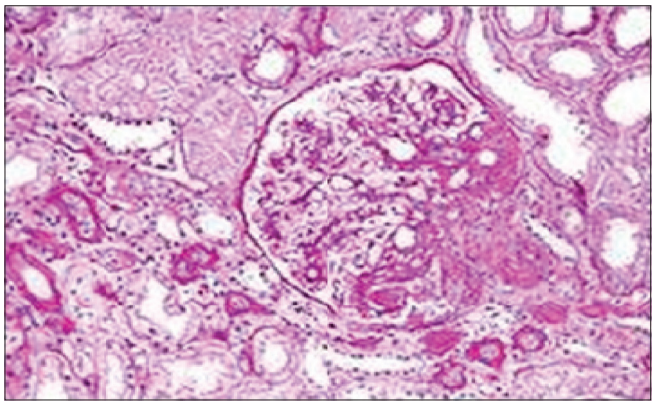

Figure 3: Renal biopsy revealed focal and segmental glomerular sclerosis with chronic tubulointerstitial nephritis

appears to be the most likely diagnosis. Late-onset FSGS associated with TRPC6 mutation is clearly different from early-onset FSGS. In late-onset FSGS, initially, the foot processes of the podocytes and glomerular slit diaphragm are well-developed and functional, but their integrity is lost between childhood and late adulthood.[1,2,6] Despite extensive search, we found only a single reported case of polycythemia vera with bronchiectasis and nephritic range proteinuria; in that case, renal biopsy showed cellular variant segmental proliferative glomerulonephritis. Despite treatment with prednisolone and immunomodulator mycophenolate mofetil, no evidence of a decrease in proteinuria was seen and kidney function progressively deteriorated.[7]

The concomitant presence of RA, bronchiectasis with panacinar emphysema and the FSGS variant of renal pathology with an inherited pattern of disease in a family is very a rare occurrence. Genetic analysis could not be conducted either locally or from outside for reasons beyond our control.

TRPC6 is a Ca^{2+}-permeable nonselective cation channel gated via the phospholipase C-activating receptor. The original missense mutation resulted in proline in the first ankyrin repeat of TRPC6 being changed to glutamine at amino acid 112 (P112Q).[5] This missense mutation resulted in enhanced plasma expression of heterologously expressed TRPC6. This also results in increased inward current responses and inward calcium movement induced by G protein-coupled receptors signaled via PLC-beta.[1] Calcium signal transduction pathways are modified by inflammatory environment generated by allergic responses. This, in turn, causes bronchial hyperresponsiveness that is typically associated with asthma.[8] In the smooth muscles of the airway, regulation of homeostatic calcium levels are associated with numerous functions such as adhesion, cell proliferation, contraction and survival.[9] Allergic reactions (acute and chronic) such as those occurring in asthma result in alteration of intracellular cytoplasmic calcium concentrations, which in turn initiates a cascade of events eventually leading to reversible airflow limitation and a loss of lung function.[10]

An experimental study revealed that the immunosuppressive agent FK-506 can inhibit TRPC6 activity *in vivo,* producing a long-lasting clinical benefit in FSGS patients, a disease with a poor prognosis.[4] Pharmacological blockade of TRPC6 may open up a new gateway in therapeutic interventions of proteinuric kidney diseases and pulmonary diseases such as chronic obstructive pulmonary diseases and asthma and those characterized by excessive pulmonary vasoconstriction.[4]

Interestingly, treatment with sildenafil was found to induce increased TRPC6 expression. It has been found that in vascular cells, protein kinase G activation causes phosphorylation on threonine 69, which in turn markedly suppresses the activity of TRPC6 channels,

Table 1: Currently known genes that cause inherited nephrotic syndrome and FSGS

Name	Associated disorder	Chromosomal location	Pattern of inheritance	Clinical features	Structure/function
Nephrin (NPHS1)	Finnish type congenital nephrotic syndrome	19q13	AR	Massive proteinuria in utero with high mortality rate	Transmembrane adhesion protein within the slit diaphragm of the podocyte
Podocin (NPHS2)	Steroid-resistant nephrotic syndrome	1q25-q31	AR	Proteinuria between 3 months to 5 years of age with rapid progression to ESRD	Structural protein that recruits nephrin and CD2AP to lipid rafts in the slit diaphragm
Alpha-actinin 4 (FSGS1)	Hereditary FSGS	19q13	AD	Adult onset FSGS with variable age of onset and severity	Actin-binding protein that binds actin to the podocyte cell membrane
TRPC6 (FSGS2)	Hereditary FSGS	11q21-22	AD	High-grade proteinuria in third to fourth decade with ESRD in 60% within 10 years of diagnosis	Relatively nonselective cation channel associated with nephrin, odocin and CD2AP at slit diaphragm
CD2AP (FSGS3)	FSGS	6p12	Haploinsufficiency	FSGS	Scaffold protein that interacts with the cytoplasmic domain of nephrin

Table adapted from Mukerji *et al*.[5] FSGS – Focal and segmental glomerulosclerosis; TRPC6 – Transient receptor potential cation channel 6; CD2AP – CD2-associated protein; AR – Autosomal recessive; AD – Autosomal dominant; ESRD – End-stage renal disease

and thus TRPC6-mediated Ca^{2+} influx.[11] In animal studies, phosphorylation of TRPC6 due to inhibition of cyclic guanosine monophosphate (cGMP)-selective PDE5 by sildenafil has been demonstrated to have anti-hypertrophic effects in mice.[12-14] Further, this PDE5 inhibition by sildenafil resulted in the suppression of Ca^{2+} influx in rat neonatal cardiomyocytes. These events, in turn, lead to suppression of endothelin-1-, diacylglycerol analog- and mechanical stretch-induced hypertrophy.[12] However, more *in vivo* studies are required to consolidate the above-mentioned phenomenon.

This case is worthy of reporting because of its rarity.

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Conflicts of interest

There are no conflicts of interest.

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