Case Report

Focal segmental glomerulosclerosis in a girl with myelodysplastic syndrome

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Introduction

Myelodysplastic syndromes (MDS) are a group of heterogeneous clonal stem cell disorders characterized by abnormal differentiation and maturation of bone marrow haematopoietic cells. These disorders show a wide range of clinical and haematological features, and are sometimes accompanied by immunological and paraneoplastic disorders including vasculitis, autoimmune phenomena and classic connective tissue disorders [1]. Although MDS have been described mainly in adults, it has now been increasingly recognized in children [2]. However, various forms of glomerular disease associated with MDS that have been reported in adults remain rare in children [3–7]. We report here a girl with MDS accompanied by focal segmental glomerulosclerosis (FSGS). This is the first case of FSGS associated with MDS.

Case

A 15-year-old girl was referred to hospital because of generalized seizure, and a brain tumour was detected in the right frontal lobe by magnetic resonance imaging. She was referred to our hospital for treatment of the brain tumour. She had a history of leukopenia since 4 years of age. She was also noted to have microscopic haematuria (+) and proteinuria (+) just after she had contracted rubella when she was 6 years of age, although urinalysis was normal previously. Follow-up examination of urinalysis showed occult blood (+ − 1+) and proteinuria (+ − 1+). She underwent surgery for the brain tumour twice and the tumour was totally excised. On histological examination, the brain tumour was diagnosed as an oligodendroglioma.

She was referred and readmitted to our hospital because of persistent fever at 16 years of age. On admission, her height was 151 cm, weight 40 kg, physical examination was unremarkable and blood pressure was normal. Neither hepatosplenomegaly nor lymphadenopathy has been detected. Family history was negative for haematological and renal diseases. Laboratory studies showed the following: white blood cells 1900/µl (neutrophils 56%, monocytes 21%, lymphocytes 21%); red blood cells 325 × 10⁴/µl; haemoglobin 9.6 g/dl; haematocrit 29.2%; platelets 94 000/µl; serum total protein 7.3 g/dl; albumin 3.9 g/dl; blood urea nitrogen 9 mg/dl; creatinine 0.6 mg/dl; sodium 143 mEq/l; potassium 3.8 mEq/l; chloride 108 mEq/l; calcium 9.0 mg/dl; phosphorus 2.3 mg/dl; and C-reactive protein 17.8 mg/dl. Immunological studies showed the following: immunoglobulin (Ig) G 1232 mg/dl; IgA 159 mg/dl; IgM 173 mg/dl; complement C3 174 mg/dl (normal range, 68–138 mg/dl); complement C4 33 mg/dl (normal range, 12–35 mg/dl); and haemolytic complement activity 58 U/ml (normal range, 34–49 U/ml). Anti-nuclear antibody and anti-DNA antibody were both negative. Urinalysis showed proteinuria (3+) and occult blood (1+). Urine protein to creatinine ratio was 2.13. Cellulor count in the cerebrospinal fluid was normal and blood culture was negative.

She was administered antibiotics and fever declined within 10 days. However, pancytopenia persisted and bone marrow aspiration was performed. Bone marrow aspiration showed hypoplastic marrow with trilineage dysplasia, and blast cells comprised 2% of the total.
Chromosome analysis of the bone marrow showed 46, XX/45, XX, −7. The possibility of Fanconi anaemia was ruled out by a chromosomal instability test in circulating lymphocytes and skin fibroblasts exposed to mitomycin C and diepoxybutane (DEB). She was diagnosed as having MDS (category 1b: refractory anaemia with dysplasia according to the WHO classification [2]). Analysis of circulating lymphocyte subpopulations using monoclonal antibodies for the lymphocyte receptors showed increased T lymphocytes (91.1% of the total; helper T cells, 49.6%; suppressor T cells, 38.9%) and decreased B lymphocytes (2.5% of the total). Proteinuria decreased to ~0.5 g/24 h in 1 month with the decline of fever. However, proteinuria persisted at the same level thereafter, and percutaneous renal biopsy was performed 9 months later. Renal biopsy demonstrated segmental sclerosis in one of 11 glomeruli, while the remaining glomeruli showed minor abnormalities. Neither tubulointerstitial changes nor vascular lesions were evident. On immunofluorescence, there was no positive staining for either IgG, IgA, IgM, C3 or fibrinogen. Electron microscopic examination demonstrated focal fusion of the epithelial foot processes (Figure 1). After renal biopsy, she received a whole bone marrow transplantation from her HLA-matched older sister. At present, she has signs of chronic graft-versus-host disease and, although her serum creatinine level is within the normal range, mild to moderate proteinuria persists on urinalysis.

Discussion

Renal involvement in patients with MDS is rare, and there are only sporadic reports of glomerulonephritis associated with MDS. In a large series of patients with MDS, the frequency of clinical glomerular disease has been reported to be two out of 221 (0.9%) [1], four out of 825 (0.48%) [3] and five out of 125 (4%) [4] of MDS patients, respectively. A total of 19 cases of glomerular disease associated with MDS could be found in the literature to date [1,3–7]. These include nephrotic syndrome [4,6], rapidly progressive glomerulonephritis and, in histologically examined cases, membranous nephropathy [1,5], crescentic glomerulonephritis [3], atheroembolic renal disease [5], amyloidosis [3] and mesangial proliferative glomerulonephritis with and without mesangial IgA deposition [1,4,6]. Although most were adult cases, three children were included among recently reported cases [6,7]. However, FSGS accompanied by MDS has not been reported to date.

In addition to MDS and glomerulopathy, our patient presented with karyotypic abnormality of monosomy 7, and solid brain tumour, i.e. oligodendroglioma. Monosomy 7 is the most common genetic change in paediatric MDS [2], and is also seen in a wide variety of pre-leukaemic conditions in children once they evolve to MDS and acute myelogenous leukaemia (AML). These include Fanconi anaemia, congenital agranulocytosis and Schwachman–Diamond syndrome. An increased risk of MDS with monosomy 7 has also been found in children with type I neurofibromatosis. However, the association has not been reported previously either between FSGS and MDS or between FSGS and monosomy 7. Although monosomy 7 has been suggested to be a cytogenic marker for myeloid leukaemia in MDS, the association between myeloid leukaemia and FSGS is rare, and we could find only three cases of chronic myeloid leukaemia and FSGS.
all of which showed an association with interferon-α therapy [8].

Our case is the first report of MDS with FSGS. Nevertheless, the possibility exists that these two diseases occurred coincidentally and are not pathogenetically related at all. However, the annual incidence of FSGS has been estimated as 1.4–21 per million population worldwide [9], and the annual incidence of MDS was 0.5–4.0 per million children under 15 years of age [2]. Thus, among 1800 million children in the world, the annual incidence of MDS could be estimated as 900–7200, and FSGS could occur coincidentally only in 1.3–151×10⁻³ children annually among these MDS patients. These data strongly suggest some pathogenic relationship between these two diseases.

The exact aetiology of FSGS is unknown. FSGS is also known to occur secondary to various non-specific disorders. However, disorder of lymphocyte function, especially functional abnormality in T lymphocyte, has been thought to be involved in the aetiology of primary FSGS through the production of factors that increase the permeability of the glomerular basement membranes [10]. From this perspective, various immunological abnormalities including functional abnormality in T lymphocytes are commonly reported in patients with MDS [1] and, although we did not study T-lymphocyte functions in our patient before bone marrow transplantation, our patient also showed an inordinately increased T-lymphocyte subpopulation. This suggests some immunological problems also in our patient which may have been related to the onset of this type of glomerular injury. Further studies regarding the pathogenic association between glomerulonephritis and MDS are necessary. However, our case indicates that FSGS should be included in the spectrum of glomerular injury accompanying MDS.

Conflict of interest statement. None declared.

References


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