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CASE REPORT

Lupus in a patient with cystinosis: is it drug induced?

FK Eroglu, N Besbas, F Ozaltin, R Topaloglu and S Ozen
Department of Pediatric Nephrology-Rheumatology, Hacettepe University Faculty of Medicine, Turkey

A 9-year-old girl with a diagnosis of cystinosis since 2 years of age, on cysteamine therapy, presented with complaints of serositis and arthritis, and laboratory tests revealed high antinuclear antibody titers with hypocomplementemia. Kidney biopsy was not consistent with lupus nephritis. With prednisolone treatment her complaints resolved and creatinine level decreased, but on follow-up, serological features of systemic lupus erythematosus (SLE) continued. Six years after cessation of prednisolone, lupus features were reactivated, with positive antihistone antibodies and ANCA. Coincidence of cystinosis and SLE is very rare, and to the best of our knowledge this is the fourth case reported in the literature. Physicians should be aware that cystinosis patients may have some autoimmune manifestations with features of true or drug-induced lupus. In the light of this case, pathophysiology and treatment are discussed. *Lupus* (2015) **24,** 1452–1454.

Key words: Cystinosis; cysteamine; lupus; childhood

Introduction

Cystinosis is an autosomal recessive lysosomal storage disease, caused by mutation in the *CTNS* gene that codes for a transport protein, cystinosin. Cystine accumulates in lysosomes and causes organ dysfunction, especially in kidneys, eyes and endocrine organs. Nephropathic cystinosis presents with infantile-onset renal tubular Fanconi syndrome, and untreated patients progress to end-stage kidney disease within the first decade of life. An aminothiol compound, cysteamine, which forms a disulfide bond with cystine and removes it from lysosomes, is the mainstay of treatment of cystinosis.[1]

Systemic lupus erythematosus (SLE) is an autoimmune disorder caused by host immune dysregulation and environmental factors. SLE may be associated with drugs in 10% of cases. Concurrence of cystinosis and SLE has been reported in the literature, but there is conflict over whether this concurrence is a coincidence of true lupus and cystinosis[2,3] or a drug-induced lupus caused by cysteamine.[4] Here we report a cystinosis patient who had atypical hematuria and proteinuria complicated by synovitis, serositis and serological features of SLE.

Case report

Our patient was admitted to our clinic in November 1998 when she was 2 years of age, with complaints of delayed closure of anterior fontanel and bilateral genu valgum deformity. She is the second child of first-degree consanguineous parents. Her laboratory work-up revealed hypocalcemia, hypophosphatemia and metabolic acidosis. Urine analysis showed mild proteinuria, glycosuria and aminoaciduria. Bone marrow aspiration and eye examination showed accumulation of cystine crystals and confirmed the diagnosis of cystinosis. Cysteamine hydrochloride (90 mg/kg/day), phosphorus and bicarbonate solution was started. She was also administered calcitriol because of rickets, evident on distal metaphyses of radius and ulna.

Five months later, she had urine cloudiness. Urinalysis showed +3 proteinuria and microscopic hematuria with dysmorphic erythrocytes. Creatinine and albumin levels were normal. Renal ultrasound was normal. Microscopic hematuria was attributed to hypercalcuria (5 mg/kg/day), and hydrochlorothiazide was started in 2001.

Correspondence to: Fehime Kara Eroglu, Department of Pediatric Nephrology-Rheumatology, Hacettepe University Ihsan Dogramaci Children's Hospital, 06100, Sihhiye, Ankara, Turkey.
Email: fehimekara@yahoo.com
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Cysteamine hydrochloride was changed to cysteamine bitartrate, and the dose was decreased to 70 mg/kg. On follow-up, microscopic hematuria and proteinuria (500–700 mg/day) were persistent.

In 2005, when she was 9 years old, while taking the same dose of cysteamine bitartrate, she complained of episodic chest pain and swelling of her right ankle and knee. She had high ESR (54 mm/h) and C reactive protein levels (1.61 mg/dL, normal <0.8 mg/dL). Joint fluid culture yielded no microorganisms, and microscopy was normal with no cystine crystals. Laboratory examination revealed low complement levels (C3 69 mg/dL, normal lower limit 79 mg/dL; C4 11.7 mg/dL, normal lower limit 16 mg/dL), positive ANA (1/640), and high anti-dsDNA (2.9 IU/mL, normal <1.1 IU/mL) titer with significant proteinuria, 1200 mg/day. Kidney biopsy was done with a suspected diagnosis of SLE, but showed mesangial matrix increase without mesangial proliferation; of 15 glomeruli, two had total and two had segmental sclerosis; there was tubular atrophy, fibrosis and cystine crystals in tubules. Direct immunofluorescence staining was negative. Kidney biopsy was not found to be consistent with SLE, but since she had active arthritis, prednisolone (1 mg/kg/day) and hydroxychloroquine were started. Her complaints subsided, urine microscopy normalized with no hematuria, and proteinuria decreased to 800 mg/day. Prednisolone was gradually tapered and stopped in 2006 after one year of treatment. Microscopic hematuria and proteinuria recurred after cessation of prednisolone, and enalapril was started. From 2007 to 2012, her glomerular filtration rate decreased from 80 to 36 mL/1.73 m^2, creatinine increased from 0.44 mg/dL to 1.56 mg/dL, and proteinuria persisted at around 1400 mg/day.

In September 2012, while taking 60 mg/kg cysteamine bitartrate, she had pancytopenia with positive direct Coombs test, antinuclear antibody (ANA) titer of 1/1000, anti-dsDNA titer of 5.3 mg/dL, low complement levels (C3 68, C4 13 mg/dL) and positive lupus anticoagulant test. Antihistone antibody titer (31 IU/mL, normal <25/IU/mL) and indirect immunofluorescence antibody test for ANCA were also positive. Her creatinine level had increased to 2.13 mg/dL, while her leukocyte cystine level was normal (0.33 nmol cystine/mg protein). Kidney biopsy showed similar glomerular findings with increased thickness of intima and media of arterioles. Since she had hematological findings, prednisolone treatment (1 mg/kg/day) was started again. Three months later, her creatinine had decreased to 1.86 mg/dL and hematologic values were normal, but during prednisolone tapering creatinine again increased to 2.36 mg/dL. At last visit, in November 2014, she still had high ANA (1/1000), anti-dsDNA titer (535 IU/mL, normal <300 IU/mL) and low complement levels (C3 68 mg/dL, C4 13 mg/dL). She is still on low-dose prednisolone, enalapril and cysteamine treatment with a baseline creatinine level of 2.3 mg/dL.

Discussion

Drug-induced lupus (DIL) is a lupus-like syndrome, temporally related to continuous drug exposure, which resolves upon drug discontinuation. Findings include skin manifestations, arthritis, serositis, ANA and antihistone antibody positivity, but there are currently no standard diagnostic criteria for DIL.[5] To date, there have been three reported cases in the literature that had SLE features on cysteamine treatment. There are two main reasons for regarding these patients as suffering from drug-induced lupus caused by cysteamine: first, decrease of ESR and autoantibodies after cessation of cysteamine therapy, and second, antihistone antibody positivity.[4] They had common features, such as serositis, synovitis and ANA positivity, consistent with DIL, but also had some distinctive features that may be associated with cysteamine-induced autoimmunity, such as nephritis (proteinuria, microscopic hematuria or creatinine increase), anti-dsDNA positivity, hypocomplementemia, and vascular activation (such as lupus anticoagulant and antiphospholipid antibody positivity, thrombotic microangiopathy in kidney biopsy), which are inconsistent with classic DIL.[2–4] Our patient was taking the recommended dose of cysteamine. Furthermore, arthritis and other hematologic features have not been reported as side effects in a large cohort of patients with cystinosis.[6]

Drug-induced vasculitis (DIV) is another entity that may explain symptoms associated with cystinosis and lupus features. This entity is associated with similar drugs, such as hydralazine, propylthiouracil and penicillamine, which cause DIL, and has common symptoms, such as myalgia, arthralgia and kidney involvement (hematuria, proteinuria and creatinine increase).[7] Our patient and the patient reported by Ahmad et al. also had ANCA antibodies, which are a common feature of DIV, and this patient's renal biopsy had

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necrotizing features and faint immune staining showing features of ANCA-associated vasculitis.[2] Unfortunately, we could show neither necrotizing features nor immune deposition, which may be due either to focal features of the disease or to sampling error.

DIL and DIV share common features and possibly have a common pathogenesis. Jiang et al. hypothesized that lupus-inducing drugs have the capacity to be oxidized by the extracellular myeloperoxidase/hydrogen peroxide system of activated neutrophils and become cytotoxic. These reactive drug metabolites may induce autoimmunity by presenting autoreactive lymphocytes with abnormal forms of self-material released during premature cell death.[8] Cysteamine has been used as a free oxygen radical scavenger in several studies and has been shown to react with oxygen and generate hydrogen peroxide at low concentrations, but at higher concentrations it eliminates hydrogen peroxide, thereby protecting cellular DNA based on dosage.[9] This could also be a potential mechanism for cysteamine-induced autoimmunity.

There is no standard approach to the treatment of DIV or DIL.[7] Treatment should be individualized and decided according to organ involvement. Duration of treatment should also be individualized. If the triggering drug needs to be continued, there is a high risk of relapse and chronicity, so, to avoid side effects of steroids and treatment of symptoms such as chronic arthritis, other immunosuppressive drugs, such as azathioprine, mycophenolate mofetil and methotrexate, have been used.[10] In our case, it would have been difficult to stop cysteamine, which is the crucial treatment for cystinosis. Therefore, we gave prednisolone, whereupon her complaints resolved but serological features persisted.

Another potential problem is recurrence after transplantation. Most cystinosis patients require kidney transplantation, and cysteamine is continued after transplantation to protect organs from cystine deposition and prevent organ failure. If cysteamine triggers autoimmunity, there may be a high potential for recurrence after transplantation. Although immunosuppressive drugs are also effective against lupus, autoimmune manifestations and serology should be monitored carefully.

Conclusion

In view of these four cases, cystinosis patients may have some autoimmune manifestations with features of true or drug-induced lupus. Pathophysiology is not clear and treatment is challenging. Physicians should be aware of this entity in the case of cystinosis patients who have serositis, hematologic and vascular involvement, or atypical renal features.

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