Autoimmunity in inflammatory bowel disease: a case of ulcerative colitis with diabetes mellitus, autoimmune hepatitis and autoimmune hypothyroidism

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SUMMARY: Najafi M, Zamani MM, Rezaei N, Sabbaghian M. Autoimmunity in inflammatory bowel disease: a case of ulcerative colitis with diabetes mellitus, autoimmune hepatitis and autoimmune hypothyroidism. Turk J Pediatr 2012; 54: 651-653.

Ulcerative colitis (UC) is a form of inflammatory bowel disease, which occasionally can be associated with autoimmune disorders. Herein, a two-year-old male infant with UC under sulfasalazine therapy is presented, who consequently developed type I diabetes mellitus, autoimmune hepatitis and autoimmune hypothyroidism. Although presence of concurrent autoimmune diseases with UC is a rare condition, it could highlight the role of immune-related mechanisms as a pathogenesis of disease.

Key words: autoimmune diseases, autoimmune hepatitis, diabetes mellitus, ulcerative colitis.

Pediatric inflammatory bowel disease (IBD) is a group of disorders with unknown pathogenetic etiologies, which are thought to be caused by interactions between the genetically susceptible host and environmental factors[1-3]. Ulcerative colitis (UC) is a form of IBD that is characterized by hemorrhagic-ulcerative inflammation of the large bowel, which starts from the rectal mucosa with continuous spreading to its proximal parts[1,4].

The association of several immune diseases has been reported in pediatric IBD patients. It has been shown that autoimmune hepatitis (AIH) and UC may coexist[5]. The association of type I diabetes mellitus (T1DM) and UC was reported and has led to several genetic investigations for this coexistence[6,7], while presence of autoimmune thyroiditis (AIT) in patients with UC was also documented[8].

However, to our best knowledge, there is no report of the combination of several autoimmunity disorders in a pediatric patient with UC. Herein, a male toddler is presented with an overlapping syndrome of UC and AIH, T1DM, and autoimmune hypothyroidism.

Case Report

A 23-month-old male infant was referred to a tertiary hospital with fever and tonic-clonic seizure attack. There was no history of autoimmunity in his family; prenatal, natal and postnatal history did not show any considerable medical points. Phenobarbital was initiated.

He was brought to the same hospital 20 days later with fever, productive cough, edema, skin macular eruptions, mild diarrhea, non-suppurative conjunctivitis, and cervical lymphadenopathy. Abdominal sonography showed hepatomegaly (87 mm). Further laboratory studies, including liver enzymes and liver function tests, were all normal.

On the suspicion of anti-epileptic hypersensitivity syndrome, phenobarbital was discontinued and methyl prednisolone and ceftriaxone were started until the sepsis work-ups were completed. The patient's symptoms continued. In addition, increased levels of erythrocyte sedimentation rate (ESR: 83 mm/h) and C-reactive protein (CRP +4), leukocytosis and anemia (white blood cells [WBC]: 16,500/mm^3, polymorphonuclear cells: 66%, lymphocytes: 30%, hemoglobin: 9.3 g/dl, platelets: 283,000/

mm^3), and desquamative skin lesions, especially in the extremities, were detected.

Intravenous immunoglobulin (IVIg) was started considering Kawasaki vasculitis. The symptoms were consequently relieved, and further evaluations did not show any other finding. Cardiac echocardiography showed normal cardiovascular status with no vegetation. Blood, urine and cerebrospinal fluid cultures and viral examinations for cytomegalovirus (CMV), Epstein-Barr virus (EBV), human immunodeficiency virus (HIV), hepatitis A and B, and rheumatic disease (anti-nuclear antibody [ANA], anti- dsDNA, rheumatoid factor [RF]) were all negative. Immunodeficiency work-up including serum Ig levels, flow cytometry, and nitroblue tetrazolium test were also normal.

Two weeks later, the child was brought to the same hospital with progressive diarrhea (5-20 times a day), abdominal distention and edema in the extremities. There were many WBC and red blood cells (RBC) in the high-power field on the stool exam. Microbial and virologic examination, parasitological tests, and toxicologic test for *Clostridium difficile* were all negative. Upper gastrointestinal (GI) series did not show any pathologic findings. In colonoscopy, erythema with ulcers, loss of normal vascular pattern, and friability of the mucosa in the distal colon were seen. In colonoscopy, ulcerative inflammation of the rectal mucosa with continuous spreading to the left colon was seen, while inflammation was limited to the colon and did not show any involvement of the terminal ileum. The biopsy report showed infiltration of lymphomononuclear cells, eosinophils and some neutrophils in the lamina propria and superficial mucosa, which showed a reduced number of goblet cells without any ulceration. There were crypt abscesses, but no intramural lesions were seen. The results of biopsy were compatible with a diagnosis of early UC. Sulfasalazine (40 mg/kg/day in 4 dosages) was started, and the diarrhea decreased, but the patient remained unwell.

He was referred to the Children's Medical Center Hospital, the Pediatrics Center of Excellence, affiliated with Tehran University of Medical Sciences, Iran. Liver aspartate transferase (SGOT), alanine transferase (SGPT), alkaline phosphatase (ALP) and gamma glutamyl transferase (GGT) were increased, to 70 IU/L, 230 IU/L (normal ranges: <45 IU/L), 447 IU/L (normal range: <145 IU/L) and 266 IU/L (normal range: < 51 IU/L), respectively; other liver tests were normal. Anti-smooth muscle antibody (ASMA), anti-mitochondrial antibodies (AMA), ANA, and anti-liver kidney antibody (antiLKM) were all normal, while tissue transglutaminase antibody (TTG), antigliadin, and endomysial antibody were negative. IgG level was raised to 10.3 g/L, while other Ig levels were <1.5 g/L. Abdominal sonography showed hepatomegaly (90 mm) with little increased parenchymal echogenicity, without dilated ducts, and normal gallbladder wall thickness.

Liver biopsy revealed low-grade and low-stage hepatitis (histological activity index [HAI] score: stage 1-2 and grade 3-4 and Scheuer score: stage I, grade I), with no evidence of sclerosing cholangitis. In the histologic study, interface of peri-septal hepatitis with a predominantly lymphoplasmacytic necrotic and inflammatory infiltrate, with central-portal bridging necrosis, was seen, together with biliary changes. According to the International Autoimmune Hepatitis Group (IAIHG) modified scoring system[9], the child was categorized as probable AIH with pretreatment score of 11. For controlling both IBD and AIH, mercaptopurine was started as 5 mg/kg/day in one dosage.

Other laboratory studies showed increased blood glucose (blood sugar [BS]: 422 mg/dl) and HbA1C of 7.3% (normal range: 6.3%-7.7%). Therefore, insulin therapy was also started simultaneously, once the diagnosis of T1DM was made.

Thyroid function tests (TFTs) were also abnormal; the child was planned for TFT again one month later, once he was discharged with mercaptopurine, prednisolone and insulin. After one month, TFT showed increased thyroid stimulating hormone (TSH: 6 mIU/L) test and low thyroxin (T4=3.5) levels; therefore, hypothyroidism was diagnosed and levothyroxine was administered, while increased levels of anti-thyroglobulin antibody (700 IU/ml, normal range: 5-100 IU/ml) and anti-thyroid peroxidase250) IU/ml; > 70 IU/ml is considered positive) were detected.

Regular follow-up visits every three months were advised. After three years of therapy with

mercaptopurine (1/6 of 50 mg tablet daily) and low-dose prednisolone (5 mg daily), IBD and AIH were under control. The last colonoscopy biopsy showed mild focal crypt distortion and no activity (quiescent phase of IBD). T1DM and hypothyroidism were under control with insulin (6 units neutral protamine Hagedorn [NPH] and 4 units regular both morning and evening) and levothyroxine (25 μg daily), respectively.

Discussion

Irritable bowel disease (IBD) is thought to result from an inflammatory response to environmental factors in a genetically susceptible host. Epidemiological evidence strongly implicates genetic factors in IBD susceptibility. This is reflected from family studies that identify a much higher incidence of IBD in individuals with a positive family history. There is also evidence that infectious agents may be aggravating factors in IBD.

Immunosuppressant agents are the basic treatments of IBD and especially UC. Certain microbial diseases are likely causes for the UC presentation; thus, ruling out these infectious diseases is essential for the diagnosis of UC. To achieve this aim in our young case of UC, we performed a large study including virologic examinations (CMV, EBV, HIV, hepatitis A and B), parasitological tests, and toxicologic test for *Clostridium difficile*, which were all negative.

Although presence of concurrent autoimmune diseases with UC is a rare condition, it could highlight the possible conditions and complications associated with this GI disorder and could show dysregulation of the immune system as a pathogenesis of disease. Studies on this issue may simplify genetic research about the IBD etiology as well. Recent studies have shown that some genes, including PTPN22 and CTLA4, which are considered as important risk factors for human autoimmunity, are associated with UC[10,11].

A number of studies have investigated association of these autoimmune diseases, such as T1DM and UC[7], while others searched AIH and its association with other autoimmune diseases[12].

A very recent report suggested inflammatory colitis associated with autoimmune liver disease, as a distinctive phenotype, while they claimed different clinical features from those of classical UC[13]. However, further multi-center studies are needed to compare clinical and laboratory findings between pediatric patients with UC and autoimmune disorders and those with isolated UC.

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