Coeliac Disease and Multiple Immunodeficiencies: Case Report of a Diagnostic Dilemma

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Abstract

Coeliac disease (CD) often coexists with other autoimmune and primary immunodeficiency diseases (PID), creating a problem in timely diagnosis and management. An unusual case of coeliac disease that was difficult to diagnose and manage because of its unusual clinical presentation. Initially diagnosed as celiac disease but showed poor response to standard therapy is reported. Frequent attacks of opportunistic infections led to immunodeficiency work-up that revealed natural killer cell (NK) deficiency with low serum IgA and IgG2 levels. The patient eventually succumbed to recurrent infections. The co-existence of PID is unusual in a patient with CD. This case report highlights the importance of investigating PID in patients with autoimmunity.

Keywords: Autoimmunity, Coeliac disease, Natural killer cell.

Introduction

Coeliac disease (CD) is an immune mediated enteropathy in which there is an abnormal response to exogenous gliadin. Tissue transglutaminase (tTG), an autoantigen in CD, deamidates gliadin and increases the pathogenecity of this protein. Clinical manifestation of CD is from mild non-specific symptoms to severe diarrhoea, malnutrition and weight loss.[1,2] The disease often coexists with other autoimmune disorders such as autoimmune thyroid disease, insulin dependent diabetes mellitus or Addison's disease.[1] Various PID are also associated with coeliac disease causing difficulties in making timely diagnosis of CD and its management.[2-4] We report an unusual case of CD with multiple immunodeficiencies that posed a diagnostic and management dilemma.

Case Report

A young man of 22 years, born out of a consanguineous marriage was admitted through emergency in the gastroenterology department, with complaints of loose motions and weight loss. At the age of 12 years he was diagnosed as a case of seronegative CD with retarded growth and history of recurrent diarrhoea usually after ingestion of gluten containing food. Gastro-intestinal biopsy reports showed partial villous atrophy. Repeat serological testing for CD in our laboratory revealed weak positive anti-tissue transglutaminase-IgA activity (Table).

Past history was significant for recurrent diarrhoea requiring antibiotics, typhoid at 11 years of age, meningitis at 15, and pneumonia at 18 years. Family history revealed that one sibling (male) out of six, died at the age of 25 years, due to recurrent upper respiratory tract infection.

Table: Post-admission test results.

Microbiological tests			
Stool D/R1	No abnormality detected		
Blood culture	Negative		
CMV2 antigenemia assay	Negative		
CMV DNA by PCR3	Positive (3 x 103 copies /ml) in plasma		
Anti-HIV4 IgG4	negative		
Anti-CMV2 IgG	positive		
Serum Immunoglobulins	Day1	Day 14th	
IgA	0.66	0.47	0.82-4.53 G/L
IgG	20.2		7.51-15.6 G/L
IgG1	18.5		3.8-9.3 G/L
IgG2	0.48		2.4-7.0 G/L
IgG3	1.12		0.218-1.76 G/L
IgG4	0.06		0.039-0.86 G/L
IgM	0.94		0.46-3.04 G/L
IgE	28		< 150 IU/ ml (for age 15 years or above)
Complement levels			
C3	0.67		0.79-1.52 G/L
C4	0.31		0.16-0.38 G/L
HLA DQ2	Present (homozygous)		
ANA	Negative		
Anti-tissue transglutaminase-IgA	6.9		Weak positive: 4-10 IU/ ml, Positive: >10 IU/ ml
Anti-gliadin-IgA	0.6		Positive: >5 IU/ ml
Anti-gliadin-IgG	0.3		Positive: >10 IU/ ml
Functional antibody tests	Pre-immunization	Post-immunization	protective antibody levels
Anti- tetanus antibody titer	0.04	1.5	> 0.06IU/ml)
Anti-diphtheria antibody titer	0.04	0.01 -0.1 IU/ml	
Anti- PCP5 IgG2 titer	nil	nil	> 4.8 mg/L
Lymphocyte subset analysis	Day 14th	At discharge	cells/µl
CD3+CD4+ T cells	1342	1104	410-1590
CD3+CD8+ T cells	2156	2065	190-1140
CD3-CD56+ (NK6) cells	14	27	90-590
CD19+ (B) cells	673	1183	90-660
Random blood sugar			
Serum folate levels	3.1		2.9-18.7 ng/ml
Vitamin B12	181		180-914 pg/ml
Thyroid profile			
TSH7	2.78		0.34-5.60 IU/ml
Free T4	0.95		0.58 – 1.64 IU/ml
Random Cortisol level	20.44		4.6-31.1 µg/dl (at 8-11 am)
U/S whole abdomen	Normal liver, pancreas, gall bladder, spleen & both kidneys. No ascitis		

Abbreviations 1= detailed report, 2= cytomegalovirus, 3= polymerase chain reaction , 4= human immunodeficiency virus, 5= pneumococcal capsular polysaccharide, 6= natural killer, 7 =thyroid stimulating hormone.

On examination, he was emaciated and dehydrated along with dark pigmentation of the skin. Height was 62 inches, weight was 27 kg and body mass index was 10.9. Initial routine investigations at the time of admission showed normochromic normocytic anaemia, leukocytosis (14.7x 10^9/L) with relative lymphocytosis (Lymphocytes = 56%, neutrophils = 36%, monocytes = 6%, eosinophils = 1.5%) and normal renal function. Erythrocyte sedimentation rate, C-reactive protein, reticulocyte counts and coagulation profile were within normal limits, however direct Coomb's test was positive. His serum albumin (2.9 g/dl) and serum calcium (6.7 mg/dl) were low, indicating malabsorption.

He was treated with intravenous fluids, partial parental nutrition and was kept on gluten free diet. Ciprofloxacin and Metronidazole were also administered to combat diarrhoea. During the treatment, patient developed neutropenia (absolute neutrophils counts = 150 cells/µl) and oesophageal candidiasis. Repeated gastro-intestinal and rectal biopsies showed Cytomegalovirus (CMV) inclusions in rectal mucosa (Figure). This raised the suspicion of cellular immunodeficiency. Anti-HIV test was found negative. Lymphocyte subset analysis revealed very low number of NK cells and high T and B cell counts. Serum IgA, IgG2 and C3 levels were found low with normal functional antibody response to Diphtheria and Tetanus vaccine but no response to Pneumococcal capsular polysaccharide vaccine (Table).

He was given Gancyclovir for 21 days. Vitamin B12 was administered intravenously on day 7 of admission. One week later he developed a maculopapular rash and was treated with methyl prednisolone for one week resulting in gradual

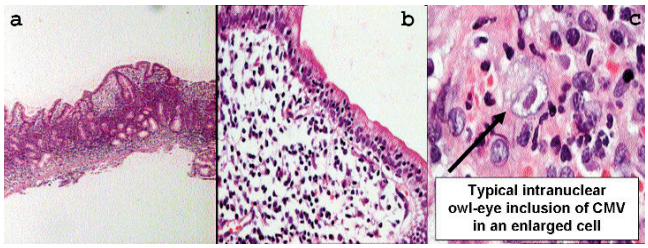

Figure: a) Low-power photomicrograph showing severe villous atrophy and crypt hyperplasia (H & E, X100). b) medium view showing moderate lymphoplasmacytic infiltrate in the lamina propria and increased intraepithelial lymphocytes (H & E, X 200). c) High-power view showing an enlarged endothelial cell with typical intranuclear inclusions (H & E, X400).

disappearance of the rash. At discharge, NK cell counts were still low with a high CD8+T cell count and normal CD4+ T cells (Table).

His NK cells remained low after two months of initial recovery and on subsequent follow-ups (25 cells/µl). Serum IgA (0.53 g/l) and C3 levels (0.62 g/l) also remained low. Available test results did not show involvement of any other endocrinopathies associated with immune dysregulation polyendocrinopathy enteropathy X-linked (IPEX)[4] (Table).

Patient was readmitted many times thereafter with diarrhea (refractory to treatment for CD) and pneumococcal pneumonia and finally succumbed to recurrent chest infections.

The final diagnosis was of refractory CD with IgA, IgG2 and classical NK cell deficiency.[5]

Discussion

Autoimmunity and PID can co-exist and create problem in patient management. Autoimmune enteropathy is often found in patients with selective IgA deficiency, common variable immunodeficiency (CVID) and IPEX,[3,4] but the role of NK cells remains undetermined.[6,7] In our case report, patient initially presented with CD which was difficult to manage along with recurrent, opportunistic infections such as candidiasis and CMV disease. A family history suggestive of PID led us to work-up for immunodeficiency. NK cell deficiency was the most likely explanation for the occurrence of CMV disease. As CMV can itself cause a decrease in number of these cells, this created a diagnostic dilemma. However repeatedly low NK cell counts found at recovery and on follow-up visits strongly suggested classical NK cell deficiency as proved by other studies.[5] Despite of treatment for CD, patient continued to have severe recurrent diarrhoea. Persistent diarrhoea and recurrent pneumococcal pneumonia were explained by the deficient serum IgG2, IgA and C3 levels, as seen in other studies,[8,9] however partially low C3 may have been a result of malnutrition in this patient.[9]

PID generally manifests itself in infancy or early childhood, however it can be diagnosed in adulthood or even later.[4,8] Diagnosis of PID is a multi-stage process that requires coordinated and sometimes extensive work-up by primary physicians and immunologists. Various factors can influence the diagnostic work-up including age, sex, family history of immunodeficiency diseases, and more importantly the type of organisms causing recurrent infections. Generally infections with extracellular organisms are seen in patients deficient in humoral immune system while intracellular organisms specify defect in cell mediated immune response.[3,4,8]

The IgA, IgG2 and C3 deficiencies are all associated with severe recurrent infections and autoimmunity, other studies also showed similar findings.[3,4,8] NK cell deficiency is associated with severe CMV and other herpes infections.[5] Their role in the pathogenesis of many autoimmune diseases is also now being recognized.[10] Therefore PID should be suspected in patients presenting with recurrent or unusual infections and autoimmune disorders.[3,4]

Conclusion

This case highlights the importance of investigating the patients with recurrent severe infections and autoimmunity for underlying immunodeficiencies. This can report suggests the existence of NK cell deficiency with low IgA and IgG2 in a patient with CD.

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