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• CASE REPORT •

Multiple immune disorders in unrecognized celiac disease: a case report

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Abstract

We reported a female patient with unrecognized celiac disease and multiple extra intestinal manifestations, mainly related to a deranged immune function, including macroamilasemia, macrolipasemia, IgA nephropathy, thyroiditis, and anti-b2-glicoprotein-1 antibodies, that disappeared or improved after the implementation of a gluten-free diet.

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INTRODUCTION

Celiac disease (CD), the most common life-long food sensitive enteropathy in humans, is characterized by malabsorption, chronic inflammation of small intestine mucosa, villous atrophy and crypt hyperplasia, which occur as a consequence of the ingestion of wheat gluten or related rye and barley proteins[1, 2]. CD is strongly associated with HLA-DQ2, coded by the DQA1*0501 and DQB1*02 alleles, and/or the DQ8 (DQA1*03, DQB1*0302 alleles), but a role of non-HLA genes has also been postulated[2,3]. The current prevalence of celiac disease has increased from 1:1 000 to 1:300 inhabitants, or even more[4]. Typical symptoms include chronic diarrhea, abdominal distension, and failure to thrive[2,5]. However, only few patients with CD show clinical malabsorption, while most patients have subtle symptoms, if any[6]. Therefore, the disease is clearly under diagnosed[2,7]. The recent introduction of tests for IgA anti-endomysial antibodies and the anti-tissue transglutaminase test has proved promising with a sensitivity and specificity of over 95 %[2, 8, 9].

Celiac disease may be associated with a wide range of diseases[2, 8], including thyroid, dermatological and lympho-proliferative disorders, mainly intestinal lymphomas[2]. Furthermore, there is a greater than expected prevalence of immune disorders in CD patients[2, 10-12] as well as of CD in patients with autoimmune diseases[13-15].

The current report dealed with a female patient with unrecognized CD and recurrent miscarriage, macroamilasemia, macrolipasemia, IgA nephropathy, and thyroiditis that disappeared or improved when a correct diagnosis was made and the patient was given a gluten-free diet.

CASE REPORT

A 34 years old, non drinker, non smoking woman, was admitted to the third Medical Clinic, Careggi University Hospital, Florence because of hyper-amilasemia and hyper-lipasemia of unknown origin. The patient had acute meningitis at the age of three. At age of 23, she was admitted to hospital because of syncope, referred to acute gastroenteritis complicated by metabolic acidosis; laboratory evaluation performed on that occasion showed iron deficient anemia, polyclonal hypergammaglobulinemia, elevated erythrocyte sedimentation rate (ESR), reduced C3 levels and circulating antinuclear antibodies (1:80), that led to suspicion of a not otherwise specified collagen disease. Iron deficiency was unresponsive to supplement of oral iron, while it improved following intravenous therapy. The patient had two spontaneous abortions when aged 30 and 31 years, respectively, both at the 16th week of gestation. During admission because of the second abortion, a thorough investigation was performed that was negative for potential causes of fetal demise, including fasting glucose, basal FSH, LH and estradiol levels on day 3 of a natural cycle, TSH and prolactin levels, antinuclear antibodies, antibodies against infectious agents, hysterosalpingography and genetic karyotyping of the couple. On that occasion, she was found to have hyperamilasemia and hyperlipasemia, together with the previously reported laboratory alterations; so further investigations were performed including CT, which turned out to be negative for any pancreatic disease.

At the time of admission to our hospital unit, physical examination was completely negative. Routine blood analysis showed anemia (Ht: 32.8 %, Hb: 11.2 g/dL), thrombocytosis (452 000 platelets/mL), high ESR (124 mm/h), low plasma albumin (3.05 g/dL), and high levels of IgA (1 100 mg/dL) and IgM (369 mg/dL) with no monoclonal component. The patient also had low ferritin (<9 mg/mL) and tetrahydrofolate levels (1.9 ng/ml; normal range 3-17 ng/mL). A coagulation study showed the presence of lupus anticoagulant (Table 1). Enzyme studies confirmed a remarkable increase of serum amylase (1 196 IU/L), pancreatic isoamylase fraction (798 IU/L), and serum lipase (1 650 IU/L). On the other hand, urinary amylase excretion was normal (120, normal value <1 500 IU/day), and ultrasound examination of the pancreas was normal. A chromatographic assay was therefore performed at another Institution (Ospedali Riuniti, Padova, Italy), which demonstrated the presence of macroamylasemia and macrolipasemia.

Our patient had iron-deficient anemia, which was refractory to oral iron supplementation, a well known presenting sign of CD[2, 6, 16], together with low albumin and tetrahydrofolate levels. In addition, she had macroamylasemia and macrolipasemia which could be associated with CD[17]. Therefore, a search was performed for circulating anti-gliadin, anti-endomysial and anti-transglutaminase (TTG) antibodies. Detection of these antibodies (Table 1) led us to perform upper gastrointestinal tract endoscopy and duodenal biopsy, which confirmed the diagnosis of CD. A gluten free diet was therefore introduced.

Due to the patient's clinical history of repeated abortions and the results of coagulation studies, other autoantibodies such as anti-thyreoglobulin (1:40) and anti-β2-glicoprotein-1 antibodies (24 UI/mL) were detected. Further characterization of the latter antibodies showed that IgG was 6.3 (normal range < 9) and IgM 48.7 (normal range < 5) IU/mL. All parameters of thyroid function were within the normal range.

Urinalysis showed glomerular proteinuria (0.7 g/day), microscopic hematuria, hyaline and granular casts; creatinine clearance (74 mL/min) was reduced with respect to the patient's age. These results raised the suspicion of IgA nephropathy, but the patient did not consent to undergo kidney biopsy. HLA analysis revealed the presence of HLA DQB1*-02. The main laboratory data during the first admission at our unit and the follow up are shown in Table 1.

Table 1 Main results of laboratory studies in baseline conditions and after implementation of gluten free diet

Parameter (normal values)	Baseline determinations	Gluten free diet	
		6th month	24th month
Serum amylase (IU/L) (< 220)	1196	146	132
Serum lipase (UI/L) (< 200)	1650	39	ND
Ig A (mg/dL) (60-318)	1100	119	155
Immunocomplexes (meq/mL) (< 5)	6.5	ND	ND
Antigliadin antibodies IgA (%) (< 7)	96.9	5.8	ND
Antigliadin antibodies IgG (%) (< 12)	61	18.5	ND
Antiendomysial antibodies	Positive	Positive	ND
Anti-transglutaminase antibodies (UI/L) (<8)	20.5	ND	ND
Anti-thyreoglobulin antibodies (ND)	1:40	ND	ND
Total b2 GP 1 antibodies (IU/mL) (< 4 IU/mL)	24	ND	ND
Lupus anticoagulant	Positive	ND	ND
Creatinine clearance (mL/min) (70-120 mL/min)	74.07	88.05	107
Protein excretion rate (mg/24h)	322	2268	320

IU=international units; ND=not detectable.

After six months of controlled gluten free diet, the patient's body weight increased 12 kg; laboratory investigations demonstrated normalization of serum amylase, serum lipase and immunoglobulin levels; antigliadin, anti-β2-glicoprotein-1 and anti-thyreoglobulin antibodies were no longer detectable, but antiendomysial antibodies were still present. Endoscopy showed a normal appearance of duodenal mucosa, and duodenal biopsy revealed a partial recovery of duodenal morphology. Due to the persistence of proteinuria (2.3 g/day), microscopic hematuria and hyaline and granular casts, a kidney biopsy showed that it was IgA nephropathy.

After 18 months of gluten-free diet, antiendomysial antibodies disappeared; creatinine clearance increased (Table 1), but proteinuria further worsened (2.9 g/day, Table 1), and albumin levels were still low.

After 24 months of gluten-free diet, a new duodenal biopsy showed complete recovery of villous architecture. Renal function further improved and proteinuria markedly decreased (Table 1). Amylase, lipase, and immunoglobulin levels were within the normal range. Anti-β2-glicoprotein-1, anti-thyreoglobulin, antigliadin, antiendomysial and anti-TTG antibodies were undetectable. A coagulation study was normal (Table 1).

DISCUSSION

The increased prevalence of immune disorders in patients with CD is well recognized[2, 10-12]. The association between CD and other immune disorders may be due to the sharing of a common genetic background, such as HLA antigens. However, in a very large study, involving 909 patients with celiac disease, Ventura and his associates[12] found that the development of immune disorders in CD was clearly related to the duration of exposure to gluten. It is also interesting to note that multiple immune diseases in CD patients are uncommon. In the study of Ventura *et al.*[12], only 15/909 patients had two kinds of immune manifestations and only one patient had three kinds of immune manifestations.

In this report, we described a female patient with unrecognized CD, who developed several clinical and/or sub clinical immune diseases.

Macroamylasemia with or without macrolipasemia occurs in approximately 0.4 % of general population and about 2.5-5.9 % of patients have hyperamylasemia[18, 19]. It may be either an isolated, benign condition without pathological significance or may be associated with underlying diseases such as lymphoma, AIDS, carcinoma, liver disease and autoimmune disorders. The macroamylase complex is formed by amylase bound with serum proteins, commonly IgG and/or IgA. This molecule is too large to be filtered by the kidney and excreted in the urine, so it accumulates in plasma, whereas urinary amylase is normal or even low, a finding that should point to the correct diagnosis. Similarly, the macrolipase complex is a macroenzyme formed by association of polyclonal IgA with lipase. The incidental finding of macroamylasemia, if unrecognized, directs the diagnostic work-up to the pancreas and patients undergo unnecessary examinations and even surgery. Some case reports dealed with the occurrence of macroamylasemia with or without macrolipasemia in adult and pediatric patients with CD [20-23]; in the large study by Rabsztyn *et al.*[17], 21 out of 124 newly diagnosed CD patients (16.9 %) had macroamylasemia. Interestingly, serum macroamylase usually remained elevated despite strict gluten free diet[17], and only in few cases, macroamylasemia and macrolipasemia disappeared after gluten free diet[22, 23], as it occurred in our patient.

IgA nephropathy is the most common glomerulonephritis and is considered a relatively benign disease. However, longitudinal follow-up studies demonstrated that about 20 % of patients would progress to end stage of renal disease within 20 years from its onset. Patients with IgA nephropathy often have circulating IgA-antigliadin antibodies. However, lack of IgA-antireticulin, IgA-antiendomysium antibodies or jejunal mucosal atrophy suggests that most of these patients do not have latent CD [24-26]. On the other hand, oral immunization with gliadin can induce IgA nephropathy in mice[27]. Data on the association between CD and IgA nephropathy in humans are controversial, and only few cases of IgA nephropathy had definite CD and showed remission or improvement of renal disease after gluten withdrawal[28, 29]. In our patient, the effect of gluten free diet on proteinuria was delayed, since this parameter showed increments at the 6th and the 18th month, despite the disappearance of antigliadin antibodies and normalization of IgA levels.

Patients with insulin-dependent diabetes mellitus, autoimmune thyroid disease, Addison's disease, and alopecia aerata are at increased risk of CD. A recent study addressed whether patients

with more than one autoimmune endocrine disorder were even more susceptible to CD or had celiac-type mucosal inflammation. Seven out of the 62 patients studied (11 %) were found to have CD; in addition, 2 had minor villous deterioration and 5 had an increased density of mucosal intraepithelial gamma-delta+ T-cells. HLA-DQ2 or DQ8 alleles were found in all subjects with mucosal changes[30]. The association of CD with autoimmune thyroiditis has been proved. A study in 172 patients with autoimmune thyroiditis found a 10-fold higher prevalence of CD in this population than expected[31]. The Authors concluded that the association of CD with autoimmune thyroid disease was not surprising as they shared common immunopathogenesis and suggested that it was advisable to screen patients with autoimmune thyroid disease for CD as there might be an increased risk for gluten intolerance[31]. In our patient, anti-thyreoglobulin antibodies disappeared after six month of gluten free diet. This finding confirmed that autoimmune thyroid disease and CD may share a common pathogenetic mechanism and that the disappearance of the immunological activation due to intestinal inflammation may lead to normalization of concomitant immune disorders.

Antiphospholipid antibodies, the most commonly detected of which are lupus anticoagulant, anticardiolipin and anti-β2-glycoprotein-1 antibodies, are associated with the so-called antiphospholipid syndrome, a syndrome of arterial and venous thrombotic disease, thrombocytopenia, and fetal wastage[32, 33]. Antiphospholipid antibodies are found in young, apparently healthy subjects with a prevalence of 1-5 %. Their prevalence increases with age, especially among elderly patients with coexistent chronic diseases, and is even higher in patients with autoimmune diseases. Untreated patients with CD also have an increased prevalence (about 14 %) of anticardiolipin antibodies[34, 35], a phenomenon that Di Sabatino *et al.*[35] found that an increased susceptibility of peripheral blood lymphocytes would undergo Fas-mediated apoptosis which resulted in immunogenic exposure of phospholipids with subsequent production of autoantibodies. As we know, lupus anticoagulant was observed in one patient[36], while the female patient reported here had both lupus anticoagulant and anti-β2-glycoprotein I antibodies which disappeared within 6 months after the introduction of gluten free diet.

Untreated CD in women resulted in a 8.9-fold increase in the relative risk of pregnancy miscarriage and in an about 30 % reduction of the baby's birth weight. Both miscarriage frequency and babies' low birth weight would normalize in response to gluten free diet[37, 38]. Antiphospholipid antibodies were also associated with an unusually high proportion of pregnancy losses after the 10th week of gestation[32, 33]. Our patient therefore had two different risk factors for abortion, both related to untreated CD. Unfortunately, it was not possible to establish whether the gluten-free diet corrected her miscarriage tendency, since until now the patient did not wish to plan a new pregnancy.

In conclusion, we found a high prevalence of immune diseases and a large number of organ-specific autoantibodies in a patient with CD. Although both CD and the other manifestations of a deranged immunity might be explained on the basis of a common genetic predisposition to this kind of disorders, some findings suggest that CD itself is responsible for the initiation of the immunological response. Indeed, persistent stimulation by some proinflammatory cytokines, such as interferon γ and tumor necrosis factor α, could induce further processing of autoantigens and their presentation to T lymphocytes by macrophage-type immunocompetent cells. As a matter of fact, the prevalence of immune diseases among patients with CD seems proportional to the time of exposure to gluten[12], and many immune alterations disappear following the recognition of CD and appropriate treatment, just as it occurred in our patient.

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