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Biopsy-Defined Adult Celiac Disease and Selective Immunoglobulin A Deficiency

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Abstract Celiac disease has been associated with selective IgA immunoglobulin deficiency. A celiac disease cohort of 234 biopsy-defined adults (including 73 males and 161 females) from a 30-year period from 1982 to 2011 was reviewed. A total of 7 with selective IgA immunoglobulin deficiency were noted, or about 3%. All were female with an initial positive biopsy for untreated celiac disease. All had characteristic small intestinal biopsy features of severe histopathological adult disease and additional biopsies demonstrated a histopathological response after 1 to 10 years on a strict gluten-free diet. For 6 of the 7, diagnosed at ages 24 to 40 years, follow-up biopsies were either normal or showed only minimal epithelial lymphocytosis. In addition, a 71 year old female had a limited but definite histopathological response to a gluten-free diet. Although there was no microscopic evidence for a malignant lymphoma, added biopsies for molecular gene re-arrangement studies revealed a monoclonal lymphocyte population suggesting an occult or cryptic T-cell lymphoma. Gastric and colonic biopsies showed no abnormalities or evidence of epithelial lymphocytosis. In all of those tested, IgA antibodies to tissue transglutaminase were detected, occasionally even at high levels. In these, a gluten-free diet serological response was detected. Together, these findings demonstrate a heterogeneous serological response to a gluten-free diet in adult celiac disease accompanied by selective immunoglobulin deficiency.

Keywords: *IgA deficiency, celiac disease, immunodeficiency, tissue transglutaminase, duodenal biopsy*

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1. Introduction

Immunoglobulin A deficiency is the most commonly detected form of selective immunoglobulin deficiency with an estimated prevalence in Caucasians of approximately 1 in 500 persons [1]. Most individuals are asymptomatic, although a concern persists that administration of blood products containing anti-IgA antibodies may lead to a severe, even fatal, transfusion reactions and should be avoided [1,2].

Primary IgA deficiency was first described in 1963 in 2 healthy individuals [3] and most laboratories define IgA deficiency in a male or female more than 4 years of age as a serum IgA concentration of less than 7 mg per dL or 0.07 g per liter, (but a normal serum IgG and IgM) where other causes of hypogammaglobulinemia have been excluded [1]. IgA deficiency may be secondarily caused by different medications or even other disorders that are reversible with discontinuation of the medication or resolution of the disorder [1]. Interestingly, some viral infections (eg., congenital rubella, hepatitis C and Ebstein-Barr) have been reported to cause persistent IgA deficiency [4]. Most adults are believed to have a permanent disorder [5], but spontaneous remission may also occur [6]. In contrast, children with IgA deficiency may often have a delay in production. And so, care has been urged with age-related IgA measurements [7]. Primary IgA deficiency is believed to result from defective terminal B-lymphocyte differentiation leading to reduced serum and mucosal IgA production [8,9] and, occasionally, may be associated with a number of autoimmune disorders, the most common being celiac disease with some suggesting a prevalence of 1 in 200, or more [1]. In celiac disease, serological detection of IgA antibodies ordinarily used in screening or case finding for celiac disease may not be as effective leading some to suggest use of IgG antibodies in this setting.

In a recent report [10], duodenal endoscopic biopsies were used as a screening tool for histopathological changes characteristic of untreated adult celiac disease in a symptomatic referred patient population. In this group of 9665 patients evaluated during a period of 30 years, a total of 234 patients with celiac disease, or 2.4%, were positive including 73 males and 161 females. In the present report, findings in 7 with celiac disease and selective IgA deficiency are now described.

2. Methods

All patients were referred for evaluation of symptoms, including abdominal pain and bloating, diarrhea and/or weight loss to the author in a teaching hospital setting. After an overnight fast, most patients were administered intravenous sedative and topical xylocaine spray before the procedure. Some requested that the procedure be done without sedation. Biopsies were routinely obtained from

the stomach and descending duodenum to confirm visible macroscopic findings, including normal or abnormal appearing mucosa, and exclude any microscopic findings that may account for symptoms. In some patients, additional biopsies were also obtained from the duodenal bulb or more distal duodenum. Endoscopic biopsies were obtained using regular pinch forceps and placed in fixative (eg., Bouin's, formalin) after careful orientation on mesh or filter paper with "the mucosal surface up" in the endoscopy suite. Routine histopathological processing through the biopsy core was performed as previously noted [11,12] and interpreted by experienced endoscopic biopsy pathologists. All biopsies reported to be consistent with adult celiac disease were also independently reviewed at that time by the author investigator as a second trained observer of mucosal biopsy material [11,12].

Patients with biopsies consistent with celiac disease were evaluated by a dietitian and treated with a gluten-free diet. Compliance with the gluten-free diet was typically monitored by clinical evaluation (along with serological studies since 2000). Most had additional biopsies within two years from initial evaluation for histological assessment to confirm improved mucosal architecture.

Initial biopsies were considered consistent with adult celiac disease only if severe or moderately severe architectural changes were defined (i.e., crypt hyperplastic villous atrophy, total or partial villous atrophy, Marsh 3) along with other changes of celiac disease, including intraepithelial lymphocytosis, as noted elsewhere [12]. Patients with minimal architectural change or epithelial lymphocytosis alone in the initial biopsies were not included because previous North American studies involving both children and adults have demonstrated that most patients with this limited severity of histopathological change do not have celiac disease [13,14].

Records were retrospectively examined to identify patients with serum IgA deficiency. In addition, biopsies obtained after initiation of a gluten-free diet were classified based on degree of architectural change and epithelial lymphocytosis [12], and other laboratory data, including follow-up immunoglobulins and serological assays, including IgA antibodies to tissue transglutaminase, were reviewed.

3. Results (Table 1)

3.1. Study Population

Seven adults in the entire celiac population of 234 (i.e., about 3%) had a severe "flat" biopsy lesion (i.e., crypt hyperplastic villous atrophy, Marsh 3 lesion) consistent with untreated celiac disease combined with selective IgA immunoglobulin deficiency. These histopathological changes were similar to findings in patients with untreated celiac disease without selective IgA immunoglobulin deficiency. Of these 7, all were females, including 6 between the ages of 24 and 40 years, while 1 elderly female was 71 years of age. All 7 were Caucasian, resident of the Canadian province of British Columbia.

3.2. Follow-up Biopsy Studies

All 7 patients were repeatedly assessed on an ambulatory basis by the investigator and a dedicated dietitian with expertise in dietary management of adult celiac disease to ensure compliance with a strict gluten free diet. Of these, all were documented to show a histological response to the gluten free diet with follow-up duodenal biopsies from 1 to 10 years after the original duodenal biopsies were done. These included 5 with subsequent normal biopsies on a gluten-free diet, 1 with moderate, but persistent, architectural changes (after 2 years) and 2 with minimal changes, including epithelial lymphocytosis only.

3.3. Follow-up Serology Studies

Of these 7 patients, 3 were originally diagnosed prior to 2000, and serum antibody studies (i.e., specifically IgA antibodies to tissue transglutaminase) were not then available for clinical use in our hospital (one of these was later tested after 2000 while on a gluten-free diet). In 4 others identified after 2000, results of follow-up studies were available. All of these studies were done after the initial biopsy studies were completed and then after variable periods on a gluten-free diet as well as at the time of follow-up biopsy on a gluten-free diet. Of these 4 patients, 2 had high serum IgA antibodies to tissue transglutaminase before initiation of a gluten-free diet, and 2 were below the upper limit of the normal range noted for normal adults without selective IgA immunoglobulin deficiency. Following treatment with a gluten-free diet, both patients with elevated IgA antibodies to tissue transglutaminase normalized.

3.4. Special Biopsy Studies

One elderly female, aged 71, only partially responded to a gluten-free diet. Repeated biopsy studies over 2 years in this patient showed benign gastric and duodenal mucosal biopsies but special gene rearrangement studies demonstrated a monoclonal T-cell population in both sites, perhaps reflecting an early phase T-cell neoplastic change without detectable histopathological features of lymphoma.

Table 1. Clinical, Pathological and Serological Features

Age (Yr)	Duod Bx	SIgA	tTG	FU Duod Bx[Yr]	FU SIgA	FU tTG
Diagnosis before 2000						
42 (1982)	Severe, M3	0.60	NA	Normal, M0[1987]	0.50,0.50	3.4, 3.1
37 (1982)	Severe, M3	0.50, 0.54	NA	Normal, M0[1992]	ND	NA
37 (1984)	Severe, M3	0.13, 0.10	NA	Mild, M1 [1985]	ND	NA
Diagnosis after 2000						
40 (2003)	Severe, M3	0.18	79	Mild, M1[2004]	0.18	6.8
24 (2007)	Severe, M3	0.48	5	Normal, M0[2008]	0.4	ND
46 (2008)	Severe, M3	0.46, 0.57	105, 89	Normal, M0[2011]	0.46, 0.47	29, 18
71 (2001)	Severe, M3	0.30	3.0	Moderate, M2[2001,2002]	0.30	3.0

Round brackets (Yr), year of first biopsy; Square brackets [Yr], yr of repeat biopsy. Abbreviations: Duod Bx, duodenal biopsy; SIgA, serum immunoglobulin A (normal, 0.7 to 4.0 g/L); tTG, tissue transglutaminase antibodies (normal, less than 20 U, Inova); FU. Follow-up; ND, not done, or NA, not available; M3, M2, M1, M0, Marsh classification equivalent to severe, moderate, mild and normal.

3.5. Family History

No patient had a known family history of celiac disease or an immunodeficiency syndrome, however, a 46 year old female reported that her mother previously died of a malignant lymphoma.

3.6. Other Clinical Disorders

These included a parathyroid adenoma, confirmed by a neck dissection after persistent hypercalcemia, pulmonary artery stenosis and onset of renal failure. In spite of prolonged follow-up, only 1 patient had a serious recorded infection, brochopneumonia necessitating antibiotic therapy.

3.7. Other Laboratory and Biopsy Studies.

Other routine blood studies, including hemograms, liver chemistry tests, iron, folic acid and vitamin B12 studies were normal. Gastric mucosal biopsies in all 7 patients were normal and 3 had colonoscopies with colonic mucosal biopsies that were normal with no evidence of gastric or colonic epithelial lymphocytosis [15,16].

4. Discussion

This retrospective review explored a 30-year clinical database of biopsy-defined celiac disease [10] that included 161 females and 73 males. Of these, 7 were detected with selective IgA deficiency, or almost 3% (i.e., females, 4.5%). This rate in this biopsy-defined celiac disease cohort examined here exceeds reported rates of IgA deficiency in this disorder of about 1 in 200 or more (i.e., about 0.5 %) [1], but is similar to the reported rate of 2.31% for selective IgA deficiency in the only other comparable long-term evaluation over 25 years in a high prevalence area [17]. It is even conceivable that the numbers with IgA deficiency in this cohort may have been higher, if serum immunoglobulins had been routinely quantitated over the entire time frame of this current evaluation extending from 1982 to 2011. Indeed, the results in this biopsy-based evaluation are very comparable to recent reported estimates of 1.9% in a different North American population that employed prospectively-collected serum samples for immunoglobulins, IgA antibodies to transglutaminase and deamidated gliadin peptide [18].

All of the celiac patients in this evaluation had characteristic biopsy changes in the duodenum before initiation of a gluten-free diet. In these, follow-up biopsies were repeated from 1 to 10 years after initiation of a gluten-free diet. A response with mucosal architectural recovery occurred in all patients, although 2 patients had persistent duodenal intraepithelial lymphocytosis [19]. In addition, 1 elderly female with IgA deficiency had persistent and ongoing architectural changes in repeated biopsies over a 2 year period on a gluten-free diet raising suspicion of a refractory or limited response. Although previous studies have suggested that histological resolution may only occur after a more prolonged period on a gluten-free diet in the elderly compared to younger patients [20,21], the results in all 7 patients support observations in a previous long-term evaluation noted earlier that there is no apparent difference in the gluten-free dietary mucosal response from celiac disease with or without immunoglobulin deficiency [17].

Although earlier long-term studies suggested that the risk of lymphoma was not increased in celiac disease with IgA deficiency [17], special molecular gene-re-arrangement studies using added biopsies in our elderly patient with selective IgA deficiency demonstrated the presence a monoclonal lymphocyte population. To date, histological evidence of an occult or cryptic malignant lymphoma was not been defined in this patient despite repeated endoscopic biopsy studies. Nevertheless, fatal T-cell lymphomas may occur, not only in celiac disease responsive to a gluten-free diet [22], but also complicating selective immunoglobulin A deficiency [23,24].

Clearly, ongoing follow-up of this high-risk patient with both celiac disease and selective IgA deficiency is required.

Immunoglobulin A deficiency is well recognized to be a cause of false-negative or falsely low determinations of IgA antibodies (i.e., either anti-endomysial or anti-tissue transglutaminase antibodies or both) used in screening or case-finding for celiac disease [1]. In this setting, use of an alternative antibody, such as IgG, or even endoscopic biopsy may be considered, if there is a high suspicion for adult celiac disease. The present evaluation, however, also documented that IgA antibodies to tissue transglutaminase were present in all patients that could be tested here with selective IgA immunoglobulin deficiency. However, in some only low levels of the antibody appeared to be detectable. Interestingly, very high levels of IgA antibodies to tissue transglutaminase were noted in some biopsy-defined celiacs with serum IgA immunoglobulin deficiency and these returned to normal levels with a gluten-free diet, confirming findings in another study and similar to the anticipated response to a gluten-free diet in adult celiac disease without IgA immunoglobulin deficiency [17]. It is not clear if this dissociation reflects an as yet to be determined heterogeneous B-cell response in adult celiac disease with or without selective IgA immunoglobulin deficiency, or simply, the presence, in some patients, of distinct gluten-dependent B-cell responsive clones. Further studies are needed.

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