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Authors
Narsai, Tejal
Su, Houfen
Braxton, David
et al.

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Case Report

Collagenous Gastritis in Primary Selective IgM Deficiency: Transition to EBV+ Gastric Adenocarcinoma

Tejal Narsai,1 Houfen Su,1 David Braxton,2 and Sudhir Gupta 1

1Division of Basic and Clinical Immunology, University of California, Irvine, California, USA
2Hoag Hospital, Newport Beach, California, USA

Correspondence should be addressed to Sudhir Gupta; sgupta@uci.edu

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1.Introduction

SIgMD was first described in 1967 [1]; however, only recently has it been incorporated as a primary immunodeficiency in IUIS classification [2]. SIgMD is characterized by a serum IgM below 2 SD below the mean with normal serum IgG and IgA, and exclusion of secondary causes of low serum IgM [3]. Patients with SIgMD may be asymptomatic or present with recurrent infections and allergic and/or autoimmune manifestations [4, 5]. A number of malignant disorders have been reported in patients with SIgMD [6, 7]; however, it is unclear whether there is a true increase in the prevalence of malignancy in SIgMD.

Collagenous gastroenteritis includes collagenous gastritis, collagenous sprue, and collagenous colitis and is characterized by subepithelial collagen deposition and infiltration by inflammatory mononuclear cells in the lamina propria [8–12]. Among collagenous gastroenteritides, collagenous gastritis is very rare and isolated collagenous gastritis is predominantly present in children. In adults, it is generally associated with diffused disease including collagenous colitis [13]. Kamimura et al. reviewed data on all 60 known cases of collagenous gastritis reported until 2015, and no progression of collagenous gastritis to gastric carcinoma was observed [14].

Collagenous gastritis has not been reported as a predisposing factor for gastric cancer, and collagenous gastritis has not been reported in SIgMD. Furthermore, progression of collagenous gastritis to gastric adenocarcinoma has never been reported.

We present, to the best of our knowledge, the first case of SIgMD with isolated collagenous gastritis and transition of collagenous gastritis to gastric adenocarcinoma.

2.Materials and Methods

2.1. Case Description. In 2017, a 53-year-old male was referred to us with a history of asthma and allergic rhinitis and history of recurrent upper respiratory tract infections. During his teenage years, he reported having frequent episodes of acute sinusitis. In his 30 s, he was diagnosed with an
2.4. Flow Cytometry. Approximately 1 million PBMCs were used per combination for antibody staining. 20 μl of antibody was added to PBMCs for 30 min. PBMCs were washed and fixed by 2% paraformaldehyde (PFA).

For regulatory T cells, the following surface staining cells were fixed and permeabilized by using a Foxp3 staining buffer set (BD Bioscience, San Jose, California) as per the manufacturer’s protocol. Intracellular staining with anti-Foxp3PE monoclonal antibody, and appropriate isotype control (Mouse IgG1k-PE), was used for nonspecific staining.

All flourescence minus one controls and isotype controls were stained and fixed by 2% PFA for flow cytometry. Cells were acquired by using the BD FACS Celesta (Becton-Dickenson, San Jose, CA) equipped with a BVR laser. Forward and side scatters and singlets were used to gate and exclude cellular debris. Thirty thousand cells were acquired and analyzed using FLOWJO software (Ashland, OR).

The following surface makers identified various lymphocyte subsets:

Subsets of CD4 T cells and CD8+ T cells: naïve (TN)-CD4+/CD8+CD45RA+CCR7+, central memory (TCM)-CD4+/CD8+CD45RA-CCR7+, effector memory (TEM)-CD4+/CD8+CD45RA-CCR7+, CD45RA+effector memory, and terminally differentiated effector memory (TEMRAn)-CD4+/CD8+CD45RA-CCR7-

Subsets of T follicular helper cells: cTFH-CD4+CXCR5+CD45RA-, TFH1-CD4+CXCR5+CD45RA-CXCR6-CXCR3+, TFH2-CD4+CXCR5+CD45RA-CXCR6-CXCR3, TFH17-CD4+CXCR5+CD45RA-CXCR6-CXCR3, and TFH1+TFH17-CD4+CXCR5+CD45RA-CXCR6-CXCR3+

Regulatory lymphocytes: CD4Treg-CD4+CD25+CD127- Foxp3+, CD8 Treg-CD8+CD183+CCR7+CD45RA-Foxp3+, TFR-CD4+CCR5+CD45RA-CD25highFoxp3+, and Breg-CD19+CD24+CD38+

3. Results

3.1. Subsets of CD4 and CD8 T Cells. Naïve T cells (T_N) upon activation with an antigen undergo clonal expansion and differentiation to effector cells, and at the end of immune response, they are retained as memory T cells. Based on their homing properties, expression of adhesion molecules, and chemokine receptors, memory T cells are classified into central memory (T_CM) and effector memory (T_EM) CD4+ and CD8+ T cells [15, 16]. A small population of T_EM cells reacquire CD45RA and are termed as terminally differentiated effector memory T cells (T_EMRA). These subsets differ with regard to proliferative response, cytokine production, effector properties, and sensitivity to apoptosis [15]. Therefore, we examined these subsets in our patient. CD4 T_N were decreased, and CD4 T_CM were increased (Figure 3(a)). CD8 T_N and T_CM increased, whereas T_EM was decreased (Figure 3(b)).
immunoglobulin isotype switching, and differentiation of B cells to immunoglobulin-secreting cells [17, 18]. The signature cytokine they produce is IL-21. However, based on additional cytokines produced, cTFH has been further classified into T FH1, T FH2, and T FH17 [19]. Therefore, we examined all subsets of cTFH, cTFH1, T FH14, and T FH2, whereas T FH17 was reduced as compared to control (Figure 4).

3.3. Regulatory Lymphocytes. There are 4 members of the “regulatory club” [20–24]. CD4 Treg plays an important role in immune tolerance and cancer [22]. In addition, T follicular regulatory cells (T FR) regulate the function of cTFH cells [20, 21]. In addition, CD8 Treg and Breg have also been shown to play a role in peripheral tolerance in cancer [23, 24]. Therefore, we examined all 4 regulatory lymphocytes. T FR cells and CD4 Treg were increased, whereas Breg and CD8 Treg were comparable to control (Figure 5).

4. Discussion

SIgMDis is a rare primary immunodeficiency disease characterized by low serum IgM and normal IgG and IgA; B cells with surface membrane IgM are normal [6]. We present the 1st SIgMD patient who developed collagenous gastritis that transitioned to EBV + gastric adenocarcinoma.

Collagenous infiltrative disorders of the gastrointestinal tract are characterized by subepithelial deposition of collagen bands with mononuclear cell infiltration in the mucosa [25]. In 1989, Colleti and Trainer [26] reported the first case of collagenous gastritis in a 15-year-old girl who presented with recurrent abdominal pain and bleeding. Collagenous gastritis is extremely rare; since 1989, less than 70 cases of collagenous gastritis have been reported. A few cases of collagenous gastroenteritis have been reported in primary immunodeficiency diseases [27–31]; however, isolated collagenous gastritis has been reported only in one case of hypogammaglobulinemia [32] and in one case of selective IgA deficiency [33]. Ours is the first case of collagenous gastritis in SIgMD. The pathogenesis of collagenous disorders of the gastrointestinal tract remains unclear. A role of the immune system has been proposed based on collagenous gastroenteritis in autoimmune diseases including systemic lupus erythematosus, Sjogren’s syndrome, celiac disease, and ulcerative colitis [34–39]. Freeman reported celiac disease in more than 20% of patients with collagenous colitis, a rate that exceeds the reported detection rates of celiac disease in other clinical settings [40].

In a long-term follow-up of patients with collagenous gastritis ranging from 2–16 years, no case of gastric cancer has been observed [41, 42]. However, colon cancer has been rarely recorded in collagenous colitis [43]. Also intriguing was the coincidental later development of lymphomas in 2
patients with collagenous colitis in the absence of celiac disease [40]. Previous reports have recorded Hodgkin and non-Hodgkin lymphomas, including a mycosis fungoides-type T-cell lymphoma in collagenous colitis [44–46]. Additional studies will be needed to determine if there is an increased risk for these lymphoproliferative malignancies in collagenous colitis.

Gastric cancer is the fourth most common cancer and the second leading cause of death worldwide [47]. Gastric cancer is the most common cause of death among CVID patients [48]. Epstein–Barr virus (EBV) is detected in 10% of gastric adenocarcinoma patients [49–54]. Hepatitis B virus (HBV) and Helicobacter pylori (H. Pylori) have also been implicated in gastric cancer [49]. Kamimura et al. [42] reviewed all 60 patients of collagenous gastritis reported in the world literature until 2015 with a follow-up ranging from 2–14 years. They reported 6 adults and 4 children with collagenous gastritis that were positive for H. pylori. None of the patients with collagenous gastritis have ever progressed to gastric cancer. Our patient was negative for H. pylori infection. In addition to H. pylori and EBV, other predisposing factors for gastric cancer include atrophic gastritis and pernicious anemia. Gastric malignancy has not been described in SlgMD. Gastric adenocarcinoma has been

Figure 3: (a) CD4 subsets: CD4+ subsets are characterized by different makers: naïve (TN; CCR7+CD45RA+) central memory: TCM (CCR7+CD45RA-), effector memory: TEM (CCR7-CD45RA-), T effector memory RA: TEMRA (CCR7-CD45RA+). (b) CD8 subset: CD8+ gated cells. In PBMCs, CD8+ T cells were gated and gated CD8+ cells subsets are characterized by different makers: TN (CCR7+CD45RA+), TCM (CCR7+CD45RA-), TEM (CCR7-CD45RA-), and TEMRA (CCR7-CD45RA+). Abnormal values are circled in red.
reported in patients with other primary immunodeficiencies; however, none were reported to be EBV+ [48,55–62]. Our patient was diagnosed with collagenous gastritis eight years prior to the development of EBV+ adenocarcinoma. Furthermore, at the time of diagnosis, no EBV viremia was present.

Figure 4: TFH cells: in PBMCs, CD4+ gated cells and various TFH subsets were characterized by different makers: cTFH-CXCR5+CD45RA- and TFH subsets TFH1 (CXCR3+CXCR6-), TFH1+TFH17 (CXCR3+CXCR6+), TFH2 (CXCR3-CXCR6), and TFH17 (CXCR3-CXCR6+). Abnormal values are circled in red. (a) CD4+T-cell subsets. (b) CD8+T-cell subsets.

Figure 5: Regulatory lymphocytes: CD4Treg gated CD4+ cells for CD25+CD127- and then analyzed as CD4+CD25+CD127-Foxp3+ cells. Abnormal values are circled in red. CD8 Treg: gated CCR7+CD25highCD45RA-CD8 T cells expressing CD183 (CXCR3) and FoxP3. TFR cells were characterized as TFR-CD4+CD25+CD127-Foxp3+ and Breg as CD19+CD24+CD38+.
In order to understand a role of immune responses in gastric cancer in our patient, we examined various subsets of CD4+ and CD8+ T cells and regulatory lymphocytes. Zhang et al [63] reported increased TH1 cells that promote inflammation, suppress Breg, and correlate with worse clinical outcome in gastric cancer. Our patient, who had mild course of the disease, also had increased TH1 cells, but normal Breg cells, suggesting Breg may play a role in clinical outcome of gastric adenocarcinoma. Murakami et al. [64] reported increased regulatory B cells in gastric cancer and suggested that Breg may play a role in immune evasion in gastric cancer. In contrast, Hu et al. [65] reported that IL-10-expressing B cells (Breg) were highly enriched in tumor-infiltrating B cells and were present at reduced frequencies in circulating B cells. Furthermore, they demonstrated that infiltrating B cells and were present at reduced frequencies in expressing B cells (Breg) were highly enriched in tumor-infiltrating B cells and were present at reduced frequencies in circulating B cells. Wang et al. [66] also observed that Breg suppressed TH1 CD4+ T cells (IFN-γ) and induced CD4+ Treg and suggested that increased CD4 Treg might contribute to immune escape in gastric cancer. However, in our patient, CD4 Treg was increased and Breg was comparable to control, yet he had a favorable outcome. In SlgMD, Breg and CD8 Treg are increased, whereas CD4 Treg is comparable to control [67]. Therefore, changes in regulatory lymphocytes in our patient are distinct from those in SlgMD and may suggest their role in transition of collagenous gastritis to gastric adenocarcinoma.

5. Conclusions

In summary, we described the first case of SlgMD with isolated collagenous gastritis that transitioned to gastric adenocarcinoma. Furthermore, this is the 1st case of EBV + gastric adenocarcinoma in any primary immunodeficiency. The role of immunological alterations in transition of collagenous gastric to EBV + gastric adenocarcinoma is unclear; however, regulatory lymphocytes may play a role in clinical outcome.

Data Availability

Readers can access the data supporting the conclusions of this study by requesting from the corresponding author.

Conflicts of Interest

All authors declare no conflicts of interest.

Authors’ Contributions

TN collected clinical data and wrote the manuscript. HS performed flow cytometry. SG conceived the idea, supervised HS, analyzed the data, and wrote the manuscript.

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