Case Report

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Selective IgA Deficiency with Multiple Autoimmune Comorbidities: A Case Report and Literature Review

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ABSTRACT

Individuals with Selective Immunoglobulin-A Deficiency (SIgAD) are often asymptomatic, and symptomatic SIgAD patients often have autoimmune comorbidities. A 48-year-old Han Chinese man presented with abdominal discomfort, hematochezia, and a large tumor in the anogenital region. The primary diagnosis of SIgAD was based on the patient's age, serum IgA concentration (0.067 g/L), and the evidence of chronic respiratory infection. No other immunoglobulin deficiency or evidence of immunosuppression was present. The primary diagnosis of giant condyloma acuminatum was based on human papilloma virus-6-positive laboratory results and histological characteristics. The tumor and adjacent skin lesions were resected. Hemoglobin concentration fell to 5.50 g/dL, and an emergency erythrocyte transfusion was performed. The body temperature increased to 39.8 ºC, suggesting a transfusion reaction, and 5 mg dexamethasone was administered intravenously. Hemoglobin concentration stabilized at 10.5 g/dL. The clinical signs and laboratory results indicated autoimmune hemolytic anemia, systemic lupus erythematosus, and Hashimoto's thyroiditis. Abdominal discomfort and hematochezia subsided. Though uncommon, the manifestation of multiple autoimmune comorbidities can occur in SIgAD patients. Further research is needed regarding the causes of SIgAD and the autoimmune disorders that often occur as comorbidities.

Keywords: Autoimmune Disorder; Comorbidity; Giant Condyloma Acuminatum; Selective IgA Deficiency

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INTRODUCTION

Selective IgA Deficiency (SIgAD) is the most common primary immunodeficiency (PID) (1), occurring at a rate of 1:18 550 to 1:1613 among Asians (2-4), lower than the prevalences of 1:251 in Africans (5) and 1:442 to 1:965 in Caucasians (3, 6, 7). There is no treatment for SIgAD, and clinical presentations can vary considerably (1). Though individuals with SIgAD may be asymptomatic, many are at greater risk of a variety of infections (1, 3). The immune factors that distinguish asymptomatic individuals with SIgAD from those developing such complications remain largely unclear.

Patients with SIgAD are at an increased risk of proliferative diseases, including some cancers (8-11). Malignancies of the gastrointestinal tract are most prevalent among SIgAD patients (9, 11), but cancers of lymphoid tissues, lungs, liver, pancreas, and nervous system have also been reported (10-12). Human papilloma virus (HPV) is a major cause of cancer of the oropharyngeal and anogenital regions (13). Giant condyloma acuminatum (GCA) is a rare HPV-induced cancer characterized by the aggressive growth of large non-metastatic tumors with destructive invasion of local tissues (14). Though SIgAD patients are at an increased risk of HPV infection (10), it is unclear whether they also have an increased risk of HPV-related proliferative diseases.

Around 25.5-31.7% of SIgAD patients are also diagnosed with autoimmune comorbidities (3, 15-18). Though type-1 diabetes mellitus (T1DM) (3, 16), thyroid disorders (16, 19), and inflammatory bowel disease (IBD) (17, 18) are most common globally, the prevalences of these and other autoimmune comorbidities vary by region and ethnicity (3). Epidemiological research is hampered by the relatively small numbers of SIgAD patients with such comorbidities, compared with the number of primary diagnoses of autoimmune disorders in the general population (3). Herein, we present an SIgAD case with GCA and multiple autoimmune comorbidities, as well as some features of other autoimmune conditions.

CASE REPORT

Presentation

A 48-year-old Han Chinese man presented with abdominal discomfort, hematochezia, and a large tumor on the exterior of the anogenital region (Figure 1A). The patient self-reported his history of frequent respiratory infections since birth, and the presence of the tumor for approximately 2 years. No documented individual or family medical history was available. Chest, abdominal, and pelvic CT scanning showed splenomegaly, bronchiectasis (Figure 1B), and signs of lung infection (Figure 1C), but no signs of gastrointestinal or hepatic diseases were detected. As shown in Table 1, blood analysis using a Cell-Dyn hematology analyzer (Abbott Laboratories, Abbott Park, IL, USA) showed leukocytosis and mild anemia with elevated bilirubin levels. Serum

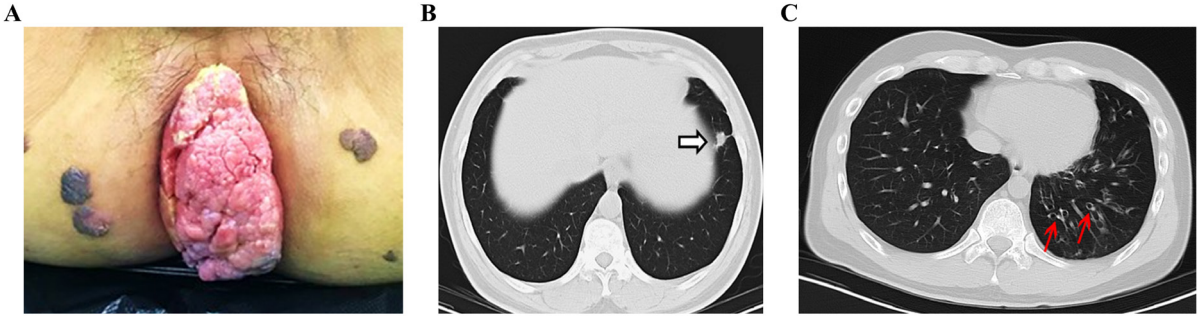

Figure 1. A) Anterior view of the anogenital region on presentation. B) Chest CT showing a nodular focus of infection in the left upper lobe. C) Chest CT showing signs of bronchiectasis in the left lung.

Table 1. Relevant laboratory results

Component	Result	Reference	Indication
Pre-operative analyses			
WBC (10^9/L)	12.1	3.5–9.5	Current infection[#]
RBC (10^{12}/L)	3.23	4.3–5.8	AHA*
Reticulocytes (%)	6.8	0.5–1.5	AHA*
Hemoglobin (g/dL)	10.0	13.0–17.5	AHA*
Total bilirubin (μmol/L)	67.7	5.1–17.1	AHA*
Conjugated bilirubin (μmol/L)	12.7	0.0–6.0	AHA*
IgG (g/L)	9.58	7.51–15.60	SIgAD*
IgM (g/L)	2.36	0.46–3.04	SIgAD*
IgA (g/L)	0.067	0.82–4.53	SIgAD*
Anti-HEV antibody, Ig class	Positive, IgM	Negative	Exposure
HPV, genotype	Positive, HPV-6	Negative	Condyloma acuminatum
Post-operative analyses			
Smooth muscle antibody (1:100)	Positive	Negative	Autoimmune hepatitis[x]
Anti-glycoprotein-210 antibody	Weakly positive	Negative	PBC[x]
Direct Coomb's test	Positive	Negative	AHA*
Anti-cardiolipin IgM (>400 MPL)	Positive	Negative	SLE*
Complement C3 (g/L)	0.47	0.79–1.52	SLE*
Complement C4 (g/L)	0.13	0.16-0.38	SLE*
Anti-TPO antibody titer (IU/mL)	94	< 9.0	HT*
CD4+/CD8+	0.29	0.68–2.47	HT*

[#]In combination with radiological findings; *In combination with clinical signs and/or other laboratory indicators; [x]Insufficient for diagnosis; White Blood Cell (WBC), Red Blood Cell (RBC), Autoimmune Hemolytic Anemia (AHA), Selective Immunoglobulin-A Deficiency (SIgAD), Hepatitis E Virus (HEV), Human Papilloma Virus (HPV), Primary Biliary Cholangitis (PBC), Systemic Lupus Erythematosus (SLE), Hashimoto's Thyroiditis (HT), Thyroid Peroxidase (TPO)

immunoglobulin analysis using a Beckman Coulter IMMAGE800 showed IgG and IgM concentrations within reference limits with a deficient concentration of IgA (0.067 g/L), which supported an SIgAD diagnosis. Serum was negative for viral antigen-specific antibodies for hepatitis B or C, but hepatitis E virus (HEV)-specific IgM was detected by ELISA (Wantai Pharmaceutical, Beijing, China), indicating a recent or current HEV infection. The HPV Genotyping Test Kit (Chaozhou Hybribio Biochemical, Guangdong, China) showed HPV6 positive. Hematoxylin and eosin staining of tumor biopsy identified numerous koilocytes, and immunostaining identified P16-, P63-, and HPV-positive keratinocytes, which supported the GCA diagnosis. Thus surgical resection was recommended. The sexually transmitted disease panel (Wantai Pharmaceutical) was negative for human immunodeficiency virus, syphilis, and gonorrhea.

Intervention

Upon initial examination, azithromycin was prescribed at 500 mg/day for 10 days for a lung infection. For mild anemia, iron, vitamin B12, and folic acid dietary supplements were recommended. Twenty-one days following the initial presentation, the patient was admitted for inpatient treatment. The large tumor and adjacent skin lesions were surgically resected. Post-operative hemoglobin level dropped to 5.50 g/dL, and the patient received an emergency transfusion of two units of washed erythrocytes of matching blood type. Approximately 12 h following the transfusion, his body temperature increased to 39.8º C, indicating a transfusion reaction. Dexamethasone (5 mg) was immediately administered intravenously, and his hemoglobin level stabilized at 10.5 g/dL.

Post-operative Assessment and Outcomes

Abdominal discomfort and hematochezia subsided post-operatively and were attributed to obstruction of the anus by the GCA tumor. Given the transfusion reaction, an extensive post-operative laboratory analysis of autoimmunity was ordered, which showed: (a) negative for anti-nuclear antibodies, Sjögren's antibodies (anti-SS-A and anti-SS-B), anti-ribonucleoprotein antibody, rheumatoid factor auto-antibodies, and anti-neutrophilic cytoplasmic auto-antibodies (P-ANCA and C-ANCA); (b) positive direct Coomb's test, which combined with splenomegaly and elevated reticulocyte count supported a diagnosis of autoimmune hemolytic anemia (AHA) and a cause of the blood transfusion reaction; (c) positive for anti-cardiolipin IgM antibodies (>400 MPL) with deficient serum levels of C3 (0.47 g/L) and C4 (0.13 g/L) complement proteins (references: 0.79–1.52 and 0.16-0.38 g/L, respectively), combined with pyrexia and AHA supported a diagnosis of systemic lupus erythematosus (SLE) (20); and (d) thyroid peroxidase (TPO) antibody titer of 94 IU/mL (reference: <9.0 IU/mL) and $CD4^+/CD8^+$ ratio of 0.29 (reference: 0.68–2.47), supporting a diagnosis of Hashimoto's thyroiditis (HT). The patient was positive for smooth muscle antibodies (1:100), consistent with the autoimmune hepatitis (21), but CT imaging did not indicate any liver pathology. In addition, the patient was weakly positive for anti-glycoprotein-210 antibodies, consistent with the primary biliary cholangitis (PBC) (22), but the CT imaging did not indicate any cholestasis. Genotype analysis showed HLA-B15 (homozygous)-[DR4, DR3, heterozygous]-[DQ4, DQ3, heterozygous] and an exon 6: c.754T>C (p.Y252H) mutation in the interleukin-10 receptor alpha subunit gene (IL10RA). At 5 days post-surgery, the patient was discharged with a referral to an outpatient Immunologist for long-term treatment of HPV and autoimmune comorbidities. Follow-up records for this patient were not available.

DISCUSSION AND LITERATURE REVIEW

Manifestations of SIgAD

Our patient presented symptoms not necessarily indicative of PID, but routine pre-operative laboratory findings supported an SIgAD diagnosis based on serum immunoglobulin levels, patient's age, the evidence of frequent respiratory infections, and the absence of immunosuppressive disorders. We did not perform an analysis of IgG subclasses to rule out common-variable immunodeficiency, but this alternative diagnosis seemed unlikely, given the lack of severe SIgAD symptoms (23). Respiratory infections are, however, the most common comorbidities in SIgAD patients (12), and CT scanning for our patient showed bronchiectasis with signs of lung infection, despite no report of respiratory symptoms from the patient. The frequency of chronic manifestations of SIgAD, including bronchiectasis progression due to recurrent respiratory infections, typically increases over time (12, 24, 25). Studies of Caucasian SIgAD patients reported a significantly higher gastrointestinal cancer risk (9), and a Chinese study found that gastrointestinal cancers occurred more often than the other types of cancers in SIgAD patients (12). However, we are unaware of any studies showing SIgAD patients at increased risk of HPV infection or HPV-related cancer. Nonetheless, case reports exist of oral and anogenital squamous cell carcinoma in SIgAD patients (26, 27).

Biological Mechanisms of SIgAD

Evidence for a genetic basis of SIgAD is conflicting (12, 28). Deletions on chromosomes 18 and 14 can result in SIgAD. However, those of chromosome 18 also cause other more severe congenital defects, and those of chromosome 14 are extremely rare (29). Among Europeans, SIgAD is associated with the human leukocyte antigen (HLA) haplotypes HLA-A1, HLA-B8, HLA-B14, HLA-DR1, HLA-DR3, HLA-DR7, and HLA-

DQ2 haplotypes of chromosome 6 (29-31) and TNFRSF13B mutations of chromosome 17 (32, 33). A study in China found that the majority of Chinese blood donors with SIgAD had HLA haplotypes similar to those found in Caucasians, albeit at a lower prevalence in the population (30).

Individuals with genotypes conferring increased risk of SIgAD often do not manifest clinical symptoms (29, 30). Therefore, congenital genetic factors alone might be insufficient to facilitate the manifestation of clinically symptomatic SIgAD, which highlights the possibility that symptomatic and asymptomatic SIgAD cases might differ based on currently unidentified biological or environmental factors. Our SIgAD patient did not have a high-risk HLA genotype. He did, however, possess a mutation in the IL10RA gene. Certain IL10RA mutations are strongly associated with IBD (34). Positive associations between Crohn's disease and the DR4 and DQ4 components of the patient's genotype have also been reported in Asian patients (35). Our SIgAD patient had no clinical or laboratory findings to support a diagnosis of IBC, Crohn's disease, or celiac disease.

Autoimmunity in SIgAD

Various autoimmune disorders are associated with SIgAD (3, 36) with 25.5% to 31.7% of SIgAD patients suffering at least one autoimmune comorbidity in their lifetime (15-17). Among adult SIgAD patients of European descent, celiac disease and T1DM are the most common autoimmune comorbidities, with prevalence ratios (PRs) of 35.3 and 10.4, respectively (18), followed in the order of descending prevalence by SLE (PR=8.9), thyroiditis (PR=8.5; hypo- and hyper-thyroiditis combined), IBD (PR=5.0; celiac and Crohn's diseases combined), rheumatoid arthritis (PR=4.5), and myasthenia gravis (PR=3.0) (18). A study in Turkey reported similar results in a much smaller SIgAD patient sample (19). In rare cases, SIgAD patients can develop antibodies against IgA, increasing the risk of transfusion reaction (1, 4). It is unlikely that anti-IgA antibodies contributed to the relatively rapid onset of the transfusion reaction in our SIgAD patient.

Autoimmune disorders are more prevalent among relatives of SIgAD patients than among those of healthy controls (16, 19). However, studies have reported conflicting results concerning whether a family history of autoimmunity or PID is associated with autoimmune comorbidities in SIgAD patients, which may reflect the confounding effects of studies with small sample sizes (3). Furthermore, though the correlations between SIgAD and several different autoimmune disorders have been demonstrated, not all autoimmune disorders occur among SIgAD patients (3). No monogenic hypothesis for the basis of autoimmunity in SIgAD has been supported substantially (3). The loci of some of the SIgAD-risk-conferring HLA haplotypes do overlap with genes associated with autoimmune disorders, including SLE, T1DM, celiac disease, and Grave's disease (37). One study found that regulatory T-cell deficiency is more common in SIgAD and certain autoimmune disorders (16, 17), suggesting that defects in immunological regulation are involved, but similar studies were unable to confirm such findings (38). Moreover, T cell-independent IgA production also occurs in mucosal immunity.

Abolhassani et al. found that, in SIgAD patients complicated by autoimmunity, 76.4% had a class-switching defect, compared with 5% of SIgAD patients without autoimmunity (16), and defective class-switching is one proposed cause of SIgAD. This finding fails to fully explain asymptomatic SIgAD, but it does represent an underlying link between SIgAD and autoimmunity. Viral infections might also contribute to autoimmunity through molecular mimicry (39). Though such a mechanism would not be specific to SIgAD, recurrent infections due to IgA deficiency could contribute to a higher rate of infection-induced autoimmunity compared with healthy people. However, though molecular mimicry

is involved in the manifestation of several well-characterized diseases (39, 40), evidence in support of viral molecular mimicry as a cause of autoimmunity is insufficient (3).

For our Chinese SIgAD patient, post-operative laboratory findings were suggestive of multiple autoimmune disorders. Previous reports have described SIgAD patients presenting such disorders primarily as singular comorbidities (3, 19, 41). Our SIgAD case received AHA, SLE, and HT diagnoses. The prevalences of autoimmune comorbidities in SIgAD are known to vary based on ethnicity and region (3, 30). Whether Asian patients are at an increased risk of such comorbidities is unknown. The patient was also positive for smooth muscle antibodies (1:100), which was consistent with autoimmune hepatitis, but the histological or imaging evidence required for that diagnosis was lacking (21). In addition, the patient was weakly positive for anti-glycoprotein-210 antibodies, which was consistent with PBC (22), but evidence of cholestasis to support that diagnosis was absent. In adult SIgAD patients, PBC and AHA occur less frequently as comorbidities than IBD, autoimmune thyroiditis, SLE, rheumatoid arthritis, and myasthenia gravis (3).

CONCLUSION

Further research is needed to identify the primary underlying cause, which might then serve as the basis for the development of novel treatment strategies. With relatively few large-scale studies of SIgAD-associated autoimmune comorbidities in the literature, physicians treating SIgAD patients must be vigilant to identify incident autoimmunity to avoid severe complications. When necessary, treatment with IgA-free blood products is recommended, and SIgAD patients should be advised to wear medical identification bracelets to reduce the risk of transfusion reaction during emergency medical treatments (1).

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AUTHORS' CONTRIBUTION

FL participated in conception and design; LH, XL, JJ, QW participated in acquisition of data; DG, YW and TL participated in analysis and interpretation of data. LH, DG, XL, JJ, YW drafted the article; QW, TL, FL revised it critically for important intellectual content. All authors read and approved the final version to be published.

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AVAILABILITY OF DATA AND MATERIALS

All data analyzed during this study are included in the manuscript.

CONSENT FOR PUBLICATION

The informed consent for publication statement has been signed by the patient.

ETHICS APPROVAL

A formal ethical review by an institutional review board was not required because this is a case report and literature review. The study conforms to recognized standards is required by referencing to the Declaration of Helsinki.

Conflict of Interest: None declared.

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