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CLINICAL VIGNETTE

Common Variable Immunodeficiency (CVID) in a Treated Lymphoma Patient: Which Came First, the Lymphoma or the CVID?

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Introduction

Common variable immunodeficiency (CVID) is a disease which causes a reduction in immunoglobulins, particularly immunoglobulin G (IgG), leading to immunosuppression and recurring infections.¹ In addition, patients with CVID are more susceptible to lymphoproliferative diseases such as lymphoma.² We describe a case of concomitant CVID and lymphoma, in which the diagnosis of CVID was delayed for years due to confounding factors from chemotherapy and immunosuppression from the patient's treatment for his lymphoma.

Case

A 49-year-old male was seen in Hematology in 2015 complaining of recurrent upper respiratory infections (URIs). He had been previously diagnosed with cold agglutinin hemolytic anemia and grade IIIA follicular lymphoma two years prior and completed 6 rounds of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). He was considered to be in remission, and had been on rituximab maintenance therapy every 3 months for the following 1.5 years. During treatment, labs showed decreased immunoglobulin levels (Table 1), with immunoglobulin A (IgA) of 13 mg/dL (reference range 47-310 mg/dL), immunoglobulin G (IgG) 320 mg/dL (reference range 600-1340 mg/dL), and immunoglobulin M (IgM) 93 mg/dL (reference range 50-300 mg/dL). Rituximab was discontinued, with the reasoning that the patient did not qualify for 2 years of therapy since studies did not include cold agglutinin patients.

Patient was subsequently seen 9 months later, and continued to complain of recurrent URIs. Immunoglobulin levels were rechecked, and showed IgA <4, IgG 257, IgM 66. At that time, his immunosuppression was thought to be due to residual effects of R-CHOP or rituximab. He was diagnosed with selective deficiency of IgG, and started on monthly intravenous immunoglobulin (IVIG). Patient symptomatically improved and IgG levels increased to 651 after IgG levels were back to baseline, IVIG was discontinued.

However, the patient developed recurrent URI's and one year later IgG was rechecked and found to be 253. His continued immunosuppression was again attributed to residual immuno-

suppression from rituximab. Patient was given 3 more months of IVIG, with resolution of his recurrent infections.

On August 2019, patient returned and stated that his recurrent URIs had returned. He subsequently, presented to the emergency department on November 2019 after noticing a new, enlarging right axillary mass. Physical exam revealed a hard, rubbery, golf ball-sized lesion. CT chest, abdomen and pelvis demonstrated new right axillary lymphadenopathy measuring up to 2.4 cm and mild splenomegaly measuring 14 cm but no other pathologically enlarged lymphadenopathy. Although the patient denied any B symptoms, this was concerning for recurrence of his lymphoma. Biopsy showed mixed acute and chronic inflammatory cells, and was interpreted as granulomatous inflammation. Flow cytometry showed no immunophenotypic abnormalities. The axillary swelling and lymphadenopathy subsequently resolved without any intervention. This was confirmed by repeat imaging, making recurrent lymphoma highly unlikely, and raising concerns about etiologies. He was referred to infectious diseases but did not make an appointment.

On follow up appointment in November 2019, patient was restarted on IVIG due to low immunoglobulins, with IgA <5, IgG 217, IgM 44. He received IVIG another four months with symptomatic improvement and increase of IgG to 550.

Six months after stopping IVIG, his IgG was rechecked and found to be 313. Although he had not had any URIs, patient was given IVIG from October 2020 to December 2020, due to the flu season and COVID-19 surge.

On May 2021, patient's immunoglobulin levels were rechecked, and were found to be low again with IgA <5, IgG 329, IgM 43, IgE <2. Due to his persistently low IgG levels 6 years after his chemotherapy and rituximab had ended, an underlying primary immune deficiency was thought to be the cause and was diagnosed with common variable immune deficiency, and restarted on IVIG.

Discussion

Common variable immunodeficiency (CVID) is a type of primary immunodeficiency characterized by reduced levels of IgG and either IgA or IgM, leading to immunosuppression and recurring infections. Per guidelines from the European Society for Immunodeficiencies and the Pan American Group for Immunodeficiency in 1999, CVID should be considered in a patient who has a marked decrease of IgG (at least 2 standard deviations below the mean for age), a marked decrease in at least one of the isotypes IgM or IgA, and fulfills all of the following criteria: onset of immunodeficiency at greater than 2 years of age, absent isohemagglutinins and/or poor response to vaccines, and defined causes of hypogammaglobulinemia have been excluded according to a list of differential diagnosis.^{1,2} The incidence of CVID is estimated to be between 1 in 50,000 to 1 in 25,000, which makes it the most common immunodeficiency.³ There is often a delay between onset and diagnosis, with one study in Europe finding a median diagnostic delay of 7.2 years when age of onset is less than 10 years of age, and 3.1 years when age of onset is greater than 10 years of age. This delay in diagnosis is likely because CVID is considered to be a diagnosis of exclusion.² The standard of care treatment for CVID is immunoglobulin replacement with IVIG.⁴

In addition to increased incidence of infection, CVID is associated with a greater risk of autoimmune diseases, chronic lung disease, bronchiectasis, gastrointestinal inflammatory disease, malabsorption, granulomatous disease, liver disease, and lymphoma.^{5,6} These increased risks are thought to be due to immune dysfunction. One study estimates that the standardized incidence ratio of lymphoma to be 12:1 in CVID patients compared to the general population, though no specific screening guidelines exist for CVID.⁷

Diagnosing CVID in this patient was a challenge due to his initial lymphoma diagnosis, followed by his chemotherapy and rituximab treatment which led us to initially thought his immunodeficiency was due to residual effects of his treatment. However, the patient continued to have low IgG levels after stopping IVIG, with recurrence of infections requiring multiple reinstitution of IVIG courses over 6 years period after completion of therapy. Studies have shown that patients

receiving R-CHOP chemotherapy can take more than two years to recover their IgG levels, with 85.2% of patients having 70% restoration and 51.9% of patients having 90% restoration of their IgG levels two years after treatment. However, no patients had developed hypogammaglobulinemia that persisted for more than two years.⁸ Rituximab treatment is also known to lower IgG levels, with 19.3% of patients with previously normal IgG levels developing hypogammaglobulinemia after 18 months of therapy.⁹ In patients receiving chemotherapy and rituximab, B-cell recovery can take up to 18-24 months, while B-cells recover in 6 months after rituximab alone.¹⁰

A case series reported 17 patients with persistent hypogammaglobulinemia for 5 months to 12 years after rituximab therapy, requiring treatment with IVIG. Those patients were thought to have underlying immune deficiency such as CVID. However, none had IgG levels checked prior to rituximab therapy, making it unclear if these patients already had hypogammaglobulinemia prior to rituximab treatment.¹⁰

We believe our patient, likely had previously undiagnosed CVID, and then subsequently developed lymphoma. Although it was initially thought that his immunosuppression was due to his chemotherapy and rituximab, his persistently low IgG levels requiring multiple courses of IVIG over 6 years is not consistent with medication-induced immunosuppression, as we would expect his IgG levels to have recovered this long after immunosuppressive therapy was stopped.

This case study shows that in lymphoma patients with persistent hypogammaglobulinemia after chemotherapy and rituximab, it is important to consider CVID as a pre-existing diagnosis. Delays in diagnosis could lead to potentially severe infectious complications, which could be avoided by providing IVIG therapy. We believe that patients with newly-diagnosed lymphoma with frequent recurrent infections, should have immunoglobulin levels checked prior to initiating treatment. More research is required to determine the true incidence of undiagnosed CVID patients who present with lymphoma, as well as the incidence of prolonged immunosuppression caused by rituximab in previously immunocompetent patients.

Table 1: Timeline of Notable Events and Immunoglobulin Levels Over Time

Date	IgA (ref range 47-310 mg/dL)	IgG (ref range 600- 1340 mg/dL)	IgM (ref range 50-300 mg/dL)	IgE (ref range 0-114 mg/dL)	On IVIG
February 2014	Finished 6 rounds of R-CHOP				
February 2014- September 2015	Received rituximab every 3 months				
April 2014	13	320	93		No
June 2016	<4	257	66	<2	No
Aug 2016-Jan 2017	Received monthly IVIG				
October 2016		1256			Yes
December 2016		651			Yes
March 2017		625			No
August 2017		303			No
November 2017		253			No
November 2017- January 2018	Received monthly IVIG				
February 2018		845			Yes
November 2019	<5	217	44		No
December 2019- April 2020	Received monthly IVIG				
June 2020		550			No
October 2020		313			No
October 2020- December 2020	Received monthly IVIG				
December 2020		1129			Yes
May 2021	<5	329	43	<2	No

Legend:

IgA: immunoglobulin A

IgG: immunoglobulin G

IgM: immunoglobulin M

IgE: immunoglobulin E

IVIG: intravenous immunoglobulin

R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone

Red boxes: lab value below reference range

Blue boxes: labs obtained while patient receiving IVIG

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