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Review

# Lymphoproliferative disease and cancer among patients with common variable immunodeficiency

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ABSTRACT

Innate immune deficiencies are a heterogeneous group of genetically inherited diseases affecting the innate and adaptive immune systems that confer susceptibility to infection, autoimmunity, and cancer. This review discusses the latest insights into the links between common variable immunodeficiency (CVI) and malignancies.

Although Ig therapy greatly reduces the number of infections and enhances survival, it does not appear to address the development of cancer, especially lymphoma. The reasons for the increased susceptibility to lymphoid malignancies are unclear. These include genetics, immune dysregulation, radiosensitivity and chronic infections such as *Helicobacter pylori*, EBV, human herpes virus type 8 and cytomegalovirus.

Further studies will allow us to better stratify the risk for cancer in these patients, and teach us to better prevent these complications and to better treat them.



**Contents**



## 1. Introduction

Usually, researchers divide host defense into two harmonizing compartments: innate and adaptive. These work together to efficiently prevent, control, and when necessary destroy the broad range of pathogens that challenge vertebrates. While T- and B-cell-mediated adaptive immunity needs DNA rearrangement and amplifies its response upon re-exposure to the same antigen, resulting in long-lasting specific immunity, the innate system is preformed in the germline. Innate immunity comprises epithelial and mucosal barriers, natural antimicrobial products, pattern-recognition receptors, and cytokines.

Innate immune deficiencies are a heterogeneous group of genetically inherited diseases affecting the innate and adaptive immune systems that confer susceptibility to infection, autoimmunity, and cancer. Although we have an inclination to combine immune deficiencies into subgroups based on cell types or compartments (T cells, B cells, NK cells, complement, phagocytes), these compartments synergistically interact, creating the complex entity known as the immune response [1].

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Common variable immunodeficiency (CVI) is a clinically significant immune defect [2,3]. It is a heterogeneous group of disorders, characterized by hypogammaglobulinemia [4], and the incapacity to make specific antibodies in response to immunization [5]. Defects in cellular immunity, which occur in approximately one third of patients, likely contribute to their susceptibility to conventional and opportunistic pathogens.

CVI is the most common symptomatic primary antibody disorder in adults, with monogenic causes identified in less than 10% of all cases. Although there are no clear-cut data on the prevalence of CVI, prevalence ranging from 1:10,000 to 1:50,000 or 1:100,000, is estimated [6–8].

Presentation is variable, both in terms of clinical features and patient age, although patients usually present with recurrent bacterial infections. CVI may also present with characteristic non-infective complications. Based on the complications, distinct clinical phenotypes have been proposed.

In an effort to elucidate the association between all disease-related complications and prognosis, a large European cohort of CVI patients (with an average follow-up of 25.6 years) was studied [2]. Five phenotypes were defined: infections only, autoimmunity, polyclonal lymphocytic infiltration, enteropathy, and lymphoid malignancies. Diverse phenotypes were associated with different survival times: those subjects without disease complications (infections only) surviving longer than those with autoimmunity (relative risk (RR) of mortality, 2.5), enteropathy (RR, 3.0), polyclonal lymphocytic infiltration (RR, 4.0) and, not unexpectedly, lymphoma (RR, 5.5). Polyclonal lymphocytic infiltration (in lung, lymph node, spleen or unexplained granuloma) was associated with a 5-fold increased risk of lymphoid malignancy occurring late in the disease ($P = 0.007$). High polyclonal IgM levels were found to correlate with the development of lymphoma in this series [2].

More recently Cunningham-Rudles pointed out that CVI consists of 2 phenotypes, one in which infections are the characteristic and another in which impressive inflammatory and/or hematologic complications also develop, including lymphadenopathy, splenomegaly, autoimmune cytopenias, enteropathy, and/or granulomatous disease. These phenotypes appear to be stable, are related to immunologic and inflammatory markers, and are predictive of outcomes [9].

Although Ig therapy greatly reduces the number of bacterial infections and likely enhances survival, it does not appear to address the characteristic inflammatory complications and the development of cancer, especially lymphoma.

In fact, a higher frequency of malignancy has been reported in these patients [10–16]. The incidence in CVI is around 11–13% and usually occurs during the fifth or sixth decade of life, with a risk 12–18 times higher than the general population [17]. In 2002, a combined study from Denmark and Sweden, using national cancer and immunodeficiency registries, found a increased incidence of 12-fold [13].

The most common sites of involvement are the gastrointestinal tract and the lymphoid tissues.

In fact, there is no doubt about the significantly higher incidence of gastric cancer in patients with CVI [18].

## 2. CVI and gastric cancer

*Helicobacter pylori* infection and pernicious anemia are risk predictors for gastric cancer in the general population and probably in patients with CVI. Dhalla et al. performed a review of the literature for gastric cancer and conducted a cohort study of gastric pathology in 116 patients with CVI under long-term follow-up. Regardless of the presence of pernicious anemia or *H. pylori* infection, patients with CVI have an increased risk of gastric cancer and are therefore

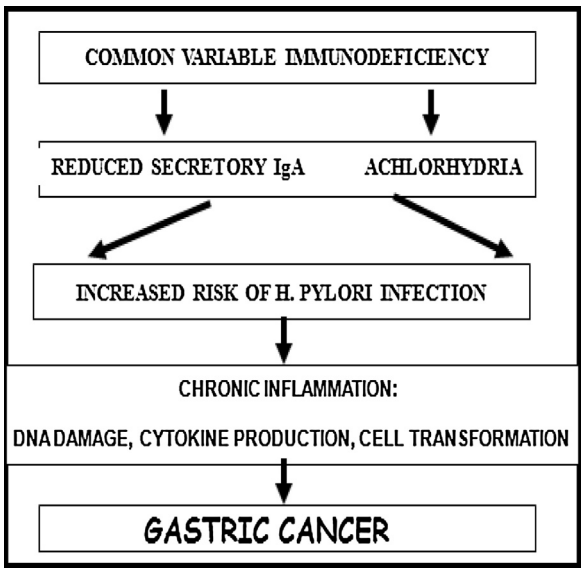


**Fig. 1.** Mechanisms of gastric cancer in CVI patients.

a high-risk population [19], and there are some reports of gastric cancer presenting at a young age in patients with CVI.

The increased risk of gastric cancer in patients with CVI was recognized in 1985, when a prospective study of 220 patients with CVI followed for 11 years reported a 47-fold increased risk [20]. In a different study, patients with CVI also have a 10-fold increased risk of gastric cancer [13], while in one study, 16% of 120 patients with CVI in the Immunodeficiency Cancer Registry had gastric adenocarcinoma [10]. A multi-center study using Scandinavian cancer and disease registries reported a SIR of 10.3 (95% CI 2.1–30.2), but no increased risk in family members of patients with CVI [13]. This suggests that the increased risk of gastric cancer in CVI relates to the immunodeficiency rather than to genetic traits or *H. pylori* virulence shared with relatives.

Nevertheless, outcome studies of large CVI cohorts followed for medians of 11 and 7 years, respectively, found only four cases of gastric carcinoma in 472 patients [4,12], indicating that the absolute risk is low (about 1% per decade). A different study [21], showed an even lower SIR of 6.1 (95% CI 1.26–17.84). While variability in prevalence from different locations is not surprising, the considerable differences, especially over time, suggest that environmental factors are important [22].

The mechanisms underlying an increased frequency of gastric cancer in CVI are not understood (Fig. 1). Specific antibodies (secretory immunoglobulin IgA) have been shown to kill *H. pylori* in vitro, and the absence of such antibodies in patients with CVI [23] may contribute to the risk.

However *H. pylori* infection does not seem to be more frequent than in the general population, and although there are no formal studies, gastric pathology does appear to be more frequent. In 1999 an Italian group studied gastric pathology in a cohort of 65 patients with CVI after finding that more than 50% had dyspeptic symptoms. Upper gastrointestinal endoscopy revealed that 14 of 34 patients had *H. pylori* infection, 80% of which was associated with chronic atrophic gastritis. In this series, two of 34 had neoplasia (one adenocarcinoma and one high-grade dysplasia), consistent with an increased risk of gastric cancer in CVI [24].

Furthermore, achlorhydria, which compromise defense against *H. pylori* infection in CVI patients, suggests a different cause for gastric cancer.

De Petris et al. determined the morphological features of CVI-associated gastric adenocarcinoma (CAGA) and of the background