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REVIEW

Epidemiology and pathophysiology of malignancy in common variable immunodeficiency?

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Abstract Common variable immunodeficiency (CVID) is a diagnostic category of primary immunodeficiency (PID) which may present with heterogeneous disorders including recurrent infections, autoimmunity, granulomatous diseases, lymphoid and other types of malignancies. Generally, the incidence of malignancy in CVID patients is around 1.5–20.7% and usually occurs during the 4th–6th decade of life. Non-Hodgkin lymphoma is the most frequent malignancy, followed by epithelial tumours of stomach, breast, bladder and cervix. The exact pathological mechanisms for cancer development in CVID are not fully determined; however, several mechanisms including impaired genetic stability, genetic predisposition, immune dysregulation, impaired clearance of oncogenic viruses and bacterial infections, and iatrogenic causes have been proposed to contribute to the high susceptibility of these patients to malignancies.

Introduction

Common variable immunodeficiency (CVID) is a diagnostic category of primary immunodeficiency (PID) that includes heterogeneous disorders defined by increased susceptibility to recurrent infection, low levels of immunoglobulin

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(Ig) in serum and impaired specific antibody responses to pathogens or vaccines.[1–4] Patients may also have a wide variety of non-infectious complications, including autoimmunity and inflammatory conditions, enteropathy, granulomatous diseases, lymphoid malignancies and different types of cancers.[5,6] Malignancy has been proposed as a distinct clinical phenotype of CVID due to underlying genetic predisposing factor which influences mortality and morbidity of patients, but it is argued that this phenotype could be a secondary consequence to viral infections or immune dysregulation.[7]

Several studies report a high frequency of malignancy in CVID patients.[8–16] Generally, the incidence of cancer in these patients is around 10% (range 1.5–20.7%, Table 1) and usually occurs during the 4–6th decade of life, with a risk 5–12 times higher than in the general population.[12,17] In two large cohorts in New York and Italy, the incidence of cancers was noted to be 15.2% and 20.7% in CVID patients, respectively.[14,18] The most common site of malignancy is lymphoid tissues.[19–21] Recent studies reported that Non-Hodgkin lymphoma (NHL) is the most frequent malignancy, followed by epithelial tumours of stomach, breast, bladder and cervix. Among epithelial tumours in CVID patients, gastric adenocarcinoma is the most prevalent cancer.[14,21–23] In fact, the cumulative incidence of cancers in CVID appears to have expanded, but the data for cancers other than lymphoma are difficult to separate out.[24] However, in the New York study the frequency of other malignancies was reported about 7%,[14] and 3% in the European Society for immunodeficiencies study.[5] In a study by the Australasian Society of Clinical Immunology and Allergy (ASCIA), the increased risks of malignancies in CVID patients compared to the population without CVID were identified as 12-fold for NHL, 7-fold for stomach cancer, 2.49-fold for leukaemia, 2.24-fold for breast cancer, and surprisingly, 146-fold for thymus cancer.[17]

In this study, we sought to demonstrate the epidemiology and aetiology of common types of malignancies in CVID patients by reviewing the most recent evidence on this topic.

Mechanisms of increased susceptibility of CVID patients to malignancy

The exact pathological mechanisms of malignancy in CVID are not fully determined; although several mechanisms have been suggested to contribute to the high susceptibility of these patients to specific types of malignancies.[16] These mechanisms include innate genetic instability and genetic predisposition, persistent activation and proliferation of the lymphoid cells during the course of infections, impaired clearance of oncogenic viruses and bacterial infections (Fig. 1).

Impaired function of immune system

Impaired immune response results in decreased clearance of oncogenic viruses and bacteria, as well as chronic antigen stimulation, chronic inflammatory response, and survival and proliferation of premalignant and malignant cells, all of which can predispose CVID patients to oncogenic mutations and malignant transformations.[25–29] The key cells of the immune system for tumour surveillance are natural killer (NK) cells and $CD8^+$ T cells, which are parts of the innate and adaptive immune response. After recognition of a tumour antigen via the T cell receptor (TCR), activated $CD8^+$ cytotoxic T cells can kill the tumour target cells. Moreover, $CD4^+$ T cells, especially T helper cell type 1 (Th1), provide ''help'' for the activation of $CD8^+$ T cells, and can display cytotoxic activity in some situations.[30–32] However, defects in CD4+ T cells and $CD8^+$ T cells immunity, which occur in approximately one-third of CVID patients, possibly contribute to their susceptibility to malignant complications.[33–35] In addition, the frequency of NK cells, as other tumour killer cells has been reported to be lower in CVID.[36,37] However, data of 801 CVID patients from the national UK Primary Immune Deficiency (UKPID) registry showed that, overt cancer is associated with significantly lower absolute $CD8^+$ T cell but not NK cell numbers, raising the question as to what extent immune senescence, especially of $CD8^+$ T cells, might contribute to the increased risk of cancers.[38]

There are multiple associations between a broad spectrum of autoimmune diseases, chronic inflammatory diseases, and cancer development.[39] It is demonstrated that the risks of all NHL increases in association with rheumatoid arthritis, Sjögren syndrome, systemic lupus erythematosus, and celiac disease.[40] All of these conditions are also associated with CVID.[41,42] In addition, the use of nonsteroidal anti-inflammatory drugs, systemic corticosteroids, and immunosuppressive medications was shown to be associated with risk of NHL in rheumatoid arthritis patients.[40]

Viral and bacterial infections

Infections with certain type of viruses and bacteria have been recognised as risk factors for several types of cancer in different ways; when some viruses directly affect the genes inside cells and cause them to grow out of control, other infectious organisms can cause long-term inflammation which leads to changes in the infected cells and in nearby immune cells, and eventually lead to cancer.[43–45] It is demonstrated that chronic inflammation can promote all stages of tumorigenesis including apoptosis evasion, sustained angiogenesis, DNA damage, limitless replication, self-sufficiency in growth signalling, and insensitivity to anti-growth signalling, as well as tissue invasion and/or metastasis.[46] In addition, some types of bacterial and viral infections can suppress patient immune system, and therefore help to the development of cancers.[47,48]

Although immunoglobulin therapy greatly reduces the episodes of infections and enhances patients' survival, it does not appear to address the development of cancer, especially lymphoma. The definite reason for the increased susceptibility to lymphoid malignancies is unclear. The proposed mechanism includes genetics, radiosensitivity, immune dysregulation, and chronic infections such as *Helicobacter pylori*, Epstein–Barr virus (EBV), human herpes virus type 8 (HHV8) and cytomegalovirus (CMV). Up to now, the strongest association between chronic bacterial infection and the development of cancer involves *H. pylori*, which is associated with increased risk of adenocarcinoma of the stomach and mucosa-associated lymphoid tissue (MALT) lymphoma.[49–52] It is suggested that the robust

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