Lymphoma in common variable immunodeficiency: interplay between immune dysregulation, infection and genetics

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Purpose of review

Common variable immunodeficiency represents the largest group of primary immunodeficiency patients. The variable clinical manifestations include an increased susceptibility to chronic infections, granulomatous disease and the lymphoproliferative predisposition to develop lymphoma. This review discusses the latest insights into common variable immunodeficiency and uses common variable immunodeficiency as a model to examine the links between immunodeficiency and chronic infections in causing lymphoma.

Recent findings

Newly identified disease genes within the common variable immunodeficiency population, have advanced the understanding of human immunodeficiency and the molecular basis of B-cell biology. Refined laboratory techniques have better defined this heterogeneous condition by classifying the underlying B-cell and T-cell abnormalities. New sensitive methods have also identified the presence of persistent infections that may play a role in the development of lymphoma.

Summary

There are several reasons for an increased risk of lymphoma in common variable immunodeficiency patients. These include genetics, immune dysregulation, radiosensitivity and chronic infections such as *Helicobacter pylori*, human herpes virus type 8 and cytomegalovirus. Chronic infections may enhance the development of lymphoma in an antigen specific manner. The interaction between chronic infections and the development of lymphoma is still unclear but studies to clarify this may lead to prevention measures and lymphoma reduction strategies.

Keywords

common variable immunodeficiency, cytomegalovirus, granulomatous variant, *Helicobacter pylori*, human herpes virus type 8, lymphoma, radiosensitivity, transmembrane activator and calcium-modulating ligand interactor

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Introduction

Common variable immunodeficiency (CVID) is the most common adult onset primary antibody-deficiency syndrome. The diagnosis of CVID is based on low levels of IgG/IgA immunoglobulin, recurrent respiratory tract infections or failure to respond to any vaccination, and exclusion of other known causes of antibody deficiencies. This definition however, masks the true complexity of the condition. The spectrum of manifestations includes immune dysregulation such as autoimmune diseases, granuloma formation, and the predisposition to malignancies. Various means to dissect this heterogeneous disorder, including the definition of genetic mutations causing the CVID phenotype [1] and grouping patients according to differences in B-cell differentiation [2], have all led to better classification and clinical management of this condition. Lymphoma is among the more severe complications of CVID [3]. This is despite improved immunoglobulin replacement, surveillance of infections and prescription of antibiotics in many primary immunodeficiency (PID) centres. Whereas chronic infections, persistent inflammatory autoimmune disease and chronic antigenic stimulation have been suggested to explain the predisposition to lymphoma [4], their relative contribution and exact mechanism in CVID is unknown. In this article, we will discuss recent advances in our understanding of the genetic and immunological aspects of CVID and explore the interplay between immunodeficiency and infections in the development of lymphoma by reviewing new information on this topic.

The granulomatous variant disease in common variable immunodeficiency: a harbinger of lymphoma?

About 10% of CVID patients have lymphoproliferative manifestations, including lymphadenopathy, splenomegaly and interstitial lung disease. This combination is often known as the 'granulomatous variant' as tissue histology often shows noncaseating granulomas with no evidence of infection; these characteristics are in many ways similar to sarcoidosis. The nature of the interstitial lung disease is variable and includes lymphocytic interstitial pneumonia, granulomatous disease and lymphoid hyperplasia [5]. One study of CVID patients with granulomatous lymphocytic interstitial lung disease (GLILD) demonstrated decreased survival (13.7 years vs. 28.8 years) [6]. The causes of mortality included respiratory failure, liver failure and malignant transformation. In another cohort of patients with GLILD, two out of five patients developed lymphoma [5].

In order to segregate the more severe CVID phenotypes such as the granulomatous variant from less complicated patients, certain groups have used flow cytometry to develop classification schemes based on lymphocyte differentiation patterns. The two most popular B-cell classifications are based on the numbers of memory B cells and levels of undifferentiated B cells [7,8]. In the Piqueras classification, patients with no CD27+IgMneg memory B cells (group MB0) had a higher prevalence of granulomatous disease, splenomegaly and lymphoid proliferation. In the alternative Warnatz classification, patients with less than 0.4% of CD27+IgMneg.IgDneg but greater than 20% of CD21neg peripheral B cells (group Ia) have a higher incidence of splenomegaly and autoimmune cytopenias.

In another study, high levels of the soluble form of a lymphocyte activation marker, soluble CD30 (sCD30), which is a member of the tumour necrosis factor (TNF) receptor superfamily, was shown to be associated with splenomegaly and a reverse ratio of CD4+/CD8+ T cells in CVID patients [9]. In the same report, out of 25 CVID patients, the patient with the highest sCD30 serum level developed mucosa-associated lymphoid tissue (MALT) lymphoma at the age of 17 years [9]. On the basis of this observation, the authors suggested sCD30 as a prognostic marker in patients with splenomegaly.

The concept of classifying CVID by lymphocyte surface markers was recently extended to T cells by Giovanetti *et al.* [10•]. They found that CVID patients with CD4+CD45RA+CD62L+ naïve T cells in the lower third quartile (group 1) had more severe clinical scores and splenomegaly ($r=-0.68$ and $r=-0.76$, respectively). CVID patients with low or very low naïve T cells (group 1 and 2) also had impaired production of new thymic emigrants (CD4+CD31+ T cells), increased CD4+ T-cell activation, proliferation and apoptosis. Levels of naïve T cells were significantly associated with the Warnatz B-lymphocyte classification. In particular, CVID cases with a more severe loss of naïve CD4+ T cells had more severe memory B-cell depletion. In another recent study [11•] the proportions of regulatory T cells (CD4+CD25highFoxP3+) cells were markedly decreased in CVID patients with splenomegaly ($P=0.02$) but the decrease in CVID patients with granulomas was not significant ($P=0.373$).

Transmembrane activator and calcium-modulating ligand interactor is the commonest genetic defect associated with the common variable immunodeficiency phenotype

The genetic inheritance of CVID is complex and variable, with both autosomal recessive and autosomal dominant patterns [12]. In many families IgA deficiency and CVID occur together. Previous linkage studies showed susceptibility loci at the HLA locus on chromosome 6p, and on chromosomes 4p, 12p and 16q [13,14]. Overall, it has been estimated that about 10% of CVID patients display a familial inheritance [15]. The most significant advance is the identification of four genes involved in the pathogenesis of this condition by candidate gene analysis. Mutations are observed in the genes encoding the TNF superfamily receptor transmembrane activator and calcium-modulating ligand interactor (TACI) [16,17]; the B-cell activation factor of the TNF family receptor (BAFF-R) [18]; the CD19 B-cell antigen [19]; and the costimulatory molecule inducible costimulator (ICOS) [20]. The B-cell genes TACI, BAFFR and CD19 affect B-cell development directly, whereas ICOS deficiency causes impaired T-cell help rendering B cells unable to undergo immunoglobulin class switching within the germinal centre. Only TACI mutations have been found in significant numbers of CVID patients, as ICOS, CD19 and BAFF-R mutations are very rare. Of these four genetic causes, only TACI deficiency is associated with autoimmunity and lymphoproliferative disease. All genetic defects have been reviewed recently [1,21]; therefore, we will discuss only TACI and its relevance to lymphoproliferation.

Mutations in *TNFRSF13b* encoding TACI have been identified in approximately 10% of CVID patients [16,17]. TACI is a member of the TNF receptor super family, especially expressed on marginal zone B cells. TACI interacts with its ligands BAFF and APRIL (a proliferation inducing ligand), which are two related members of the TNF ligand family secreted by antigen-presenting cells. Whereas BAFF is known to be central to

B-cell survival [22], APRIL provides a survival signal to plasma cells and seems to be involved in the class switch recombination to IgA [23]. Both TACI and BAFF-R are part of a complex signalling network that promotes B-cell survival and production of IgG and IgA. TACI signals through TRAF-2, TRAF-5 and TRAF-6 and through CAML. TRAF activation results in activation of nuclear factor kappa B (NFkB) and JUN amino terminal kinases, though CAML ligation leads to NF-AT and AP-1 activation. TACI knockout mice have an expansion of peripheral B cells and an impaired T-cell independent type II response [24]. Their B cells are hyperresponsive to mitogenic stimuli and immunoglobulin production indicating that TACI is a negative regulator. Genetic inactivation of TACI in mice leads to a systemic lupus erythematosus (SLE) like disorder with B-cell hyperplasia, autoantibodies and a fatal glomerulonephritis. A striking feature is that 15% of these mice develop lymphoma. Mice with heterozygous mutations have a normal B-cell phenotype.

Interestingly in humans, both homozygous and heterozygous mutations in *TNFRSF13b* encoding TACI are found in CVID. The peripheral B-cell phenotype in humans does not show any hyperreactivity; instead, there is reduction in B-cell numbers, especially CD27+ memory cells. The most frequent lymphoproliferative manifestation of TACI mutation in humans is splenomegaly and enlarged tonsils. There is one published case of lymphoma in a TACI patient with an A181E mutation, whose mother (not investigated) also died of lymphoma [17], but we are aware of two additional cases of B-cell lymphomas in patients with heterozygous TACI mutations (Dr Salzer, personal communication). A search for TACI mutations in 119 SLE patients in Freiburg and Hanover by sequence analysis showed no segregation of any of the TACI variants to the SLE phenotype [25].

Lymphoma in common variable immunodeficiency

The association between CVID and malignancy was first noted in two separate surveys of CVID cohorts. Kinlen *et al.* [26] reported a 30-fold increase in the risk of lymphoma and a 47-fold increase in the risk for stomach cancers, though Cunningham-Rundles [27] reported a 259-fold increase in lymphoma. The striking incidence of lymphoma has been reconfirmed in a more recent report using cancer and immunodeficiency registry data from Denmark and Sweden [28]. They showed a more modest 12-fold increase in the risk of lymphoma. It is tantalizing to suggest that the reduction in relative incidence of lymphoma could be due to more modern practices; this possibility is also further supported by a recently completed multicentre prospective follow up study of 224 CVID patients in Italy [29••]. That study yielded four cases of non-Hodgkin's lymphoma (NHL) over 5 years with a calculated 18-fold increase in risk. Together, these four studies of approximately 1000 CVID patients show an increased incidence of over 10 times the risk of the healthy population. Intriguingly this figure is comparable with figures for HIV/AIDS (78-fold increase) and transplant recipient patient cohorts (eight-fold increase) in a meta-analysis recently published [30].

The lymphomas that occur in association with CVID are more likely to be of B-cell origin than of T-cell origin. The predominance of NHL over Hodgkin's disease also reflects that Epstein–Barr virus (EBV) has not been found in the majority of cases. In a multicentre UK-based retrospective study on lymph node biopsies taken from primary immunodeficiency patients (PID) [31], 16 out of 19 samples positive for lymphoma were from CVID patients. The majority of lymphoma samples were NHL with only one case of Hodgkin's disease, and EBV was not found in any of the samples by in-situ hybridization. Follow-up of patients who developed lymphoma showed that only 37% were alive at the conclusion of the above study. This is consistent with data from the immunodeficiency cancer registry that also showed that NHL is the most frequent malignancy in PID [32].

The diagnosis of lymphoma in patients with CVID and other primary antibody deficiencies is quite difficult. The histology of lymphoid tissue from antibody deficiency patients without suspected malignancy varies from being microscopically normal to grossly abnormal. Stimulation by an infection may result in an atypical lymphoid hyperplasia often indistinguishable from lymphoma by ordinary light microscopy [33].

In 1992, Harris *et al.* [34] reviewed 30 nodal and extranodal lymphoid lesions from 17 patients with CVID. The biopsies were classified into four groups: malignant lymphoma (two cases); atypical lymphoid hyperplasia (eight cases); reactive lymphoid hyperplasia (14 cases) and chronic granulomatous inflammation (six cases). The two malignant lymphomas were diagnosed using histologic criteria. In one neoplasm, EBV was identified in the tumour cells by in-situ hybridization. The cases of reactive lymphoid hyperplasia and chronic granulomatous inflammation had no atypical architectural, cytologic, or immunohistochemical features. The cases of atypical lymphoid hyperplasia were of particular interest, as these patients had either widespread involvement or massive disease. The diagnosis of lymphoma was considered likely by the clinicians and, in three cases, the histologic slides were originally interpreted as malignant lymphoma by the referring pathologists. Although the architecture of these lesions appeared to be effaced on haematoxylin and eosin-stained sections, immunohistochemical analysis

demonstrated preserved architecture with florid expansion of B-cell and T-cell compartments. In addition, clinical follow-up of these patients was benign, and gene rearrangement analysis in three lesions revealed no evidence of clonality. The authors of this study conclude that the majority of lymphoid lesions in patients with CVID are benign and that immunohistochemical and gene rearrangement studies are particularly helpful in the assessment of cases of atypical lymphoid hyperplasia [35].

However, the validity of clonality as a marker of lymphoma in antibody deficiency was refuted by Gompels *et al.* [31] when they reviewed lymph nodes biopsies from 29 patients with CVID. They demonstrated that the evidence of clonality in biopsy material is insufficient to determine malignancy as monoclonal proliferations have been reported in these patients without progression.

Bacterial infection and mucosa-associated lymphoid tissue lymphoma in common variable immunodeficiency

After assignment of extranodal marginal zone lymphoma (low grade B-cell lymphoma of MALT type) as a separate and distinct entity in the new WHO classification of lymphoid malignancies [34], some of the low grade small cell NHL in CVID cohorts were reexamined and more accurately ascribed to this subtype. For example, five out of 22 (23%) in Cunningham-Rundle's cohort mentioned earlier were of MALT type; since then, there have been a total of eleven reported cases of marginal zone lymphoma in CVID in the literature [36,37]. The majority of cases involved the lung (five out of 11) with the remainder affecting the parotid gland (three cases), sinuses, orbital cavity and stomach (one case each). This contrasts with the location of MALT in non-CVID cohorts in which the stomach is the most common site [38]. This is surprising considering that *Helicobacter pylori*, which is implicated in the aetiology of MALT, is common in CVID patients. The single reported CVID case of *H. pylori*-associated MALT had responded to antibiotic treatment [37]. Other infections have been implicated in MALT lymphoma including *Campylobacter jejuni* [39,40]. In the general patient population, eradication of *H. pylori* by antibiotic treatment leads to a complete remission of low-grade associated gastric MALT lymphoma in most cases [41]. On the basis of this observation, the concept evolved that MALT lymphoma development is associated with antigen driven inflammation. The antigen recognition and subsequent drive could occur directly through the B-cell receptor of tumour B cells or indirectly through cytokines secreted by reactive T cells [42]. The first hypothesis is discredited by a recent study by Lenze *et al.* [43], which showed that the majority of MALT lymphoma immunoglobulins showed no reactivity against any specific antigens including *H. pylori*.

Viral infection and lymphoma in common variable immunodeficiency

As indicated earlier, patients with CVID may have T-cell defects with an increased susceptibility to viral infections. It is tempting to link chronic viral infections to many of the complications of CVID including the development of lymphoma. Wheat *et al.* [44] made an important finding of the presence of human herpes virus 8 (HHV-8) in six out of nine CVID patients with granulomatous and lymphomatous interstitial lung disease (GLILD). They used a combination of methods to identify HHV8, including analysing genomic material from mononuclear cells from peripheral blood by nested and real time quantitative PCR (QRT-PCR), and staining tissue with latency associated nuclear antigen-1 (LANA1). During the course of the study within the GLILD cohort, one patient developed NHL and one patient developed MALT lymphoma. In the NHL patient, HHV8 was found at high copy numbers by QRT-PCR (>15 000) in the malignant lymph node, implicating HHV8 in the development of NHL. However, the role of HHV8 in the patient with MALT lymphoma was equivocal as HHV8 was only found using QRT-PCR. We have investigated the peripheral blood of 50 CVID patients from our cohort at the Royal Free Hospital, London for HHV8 by PCR and have found no positive results. This may be due to the higher cut off used by our virology laboratory compared with the positive results from Wheat *et al.* [44] with a range of 12.3–43.5 copies/μg of DNA. Further work is underway to confirm the role of HHV8 in CVID complications.

In a different study, Raeiszadeh *et al.* [45] investigated the role of another herpes virus, cytomegalovirus (CMV), in CVID patients. They found that CVID patients had a large proportion (13-fold increase) of CD8+ T cells specific for CMV derived peptides compared with control patients. Among the CMV specific T cells, there was an increased proportion of late memory T cells (CD27neg CD28neg) with most of these cells expressing perforin and CD57+. In the six CVID patients expressing a high frequency of perforin positive T cells to CMV derived peptides (>55%), three had colitis and one of these patients later developed NHL. These six patients also had a higher incidence of splenomegaly and granulomatous complications than the CVID group with a lower frequency of perforin positive T cells (Drs Raesizadeh and Webster, personal communication).

From infection to cancer in common variable immunodeficiency

Chronic occult infections such as *H. pylori*, CMV and HHV8 may predispose CVID patients to developing NHL. However, this link is circumstantial and convincing

evidence is only documented in case reports [37,44,45]. Nevertheless, it is generally recognized that antigenic stimulation predisposes to cancers [46]. In the presence of *H. pylori* extracts, T cells from MALT lymphoma patients are able to sustain the proliferation of malignant B cells *in vitro*, by a CD40–CD40L dependent processes [47].

As recognized by many tumour models, multiple hits are needed to induce a clone of malignant cells. The acquisition of genetic abnormalities could stem from release of oxygen free radicals released by neutrophils in the setting of recurrent bacterial infections and subsequently driven indirectly by cytokines released by reactive T cells.

Plausible mechanisms of cancer enhancement include aberrant signal transduction that influences malignant conversion or reduced cancer surveillance. Perhaps CVID patients are more prone to malignant transformation because of innate dysregulation of B-cell homeostasis mediated by host constitutive factors such as BAFF-R signalling. BAFF expression is shown to be upregulated during infection [48]. BAFF levels are also shown to be increased as tumours of NHL patients become more aggressive [49], and blocking BAFF and APRIL results in apoptosis of NHL B cells [50]. NHL tumours also secrete BAFF and express BAFF-R, pointing to the possibility of an autocrine circuit propagating survival of cancer cells [51]. BAFF signalling involves NFκB activation and up-regulation of NFκB targets Bcl-2, Bcl-xL and Mcl-1 in NHL [43] and B-CLL [52]. Likewise, MALT lymphomas that develop in the context of prolonged lymphoid proliferation are also associated with an elevated antigen-specific expression of proteins that are involved in IKK and NFκB activation, namely Bcl-10 and MALT1 [53].

Management considerations to reduce risk of lymphoma

The cornerstones of treatment for CVID are immunoglobulin replacement and prophylaxis with antibiotics. The rationale for immunoglobulin replacement is to treat and prevent acute and respiratory infections by encapsulated bacteria. An extension of this practice is prescribing prophylactic antibiotics for recurrent bacterial infections such as *Haemophilus influenzae*. This treatment regimen, however, will not eradicate chronic infections such as CMV, HHV8 or *H. pylori*. To address this issue, we have started screening all our CVID patients for *H. pylori* by stool-antigen testing and treating positive results with triple therapy consisting of amoxicillin, metronidazole and lansoprazole. As for CMV and HHV8, infection surveillance is complex and the rationale for treatment is uncertain. The interpretation of the infection status from peripheral blood viral load is difficult whereas detection of viral antigens in tissue samples requires special expertise and is invasive. Further studies are needed to clarify the role of CMV and HHV8 in causing CVID complications such as chest, gut and liver inflammation.

Common variable immunodeficiency and radiosensitivity

The investigations of a complicated CVID patient often entail frequent radiological tests such as computed tomography (CT). An often-neglected consideration is the possibility of an increased radiosensitivity in CVID patients. There are only two published reports on this topic, but both Palanduz [54] and Vorechovsky [55] showed that cells taken from CVID patients after X-ray irradiation display a higher rate of chromosomal aberration compared with healthy controls. In the Vorechovsky study, the patient with the highest chromosomal radiosensitivity subsequently went on to develop lymphoma. As the exact level of 'safe' radiation exposure in CVID patients is unknown, clinicians should consider a risk–benefit assessment when ordering CT scans. Radiologists are advised to use the lowest possible radiation necessary to obtain a sufficient resolution required for management decisions.

Conclusion

CVID is a complex disease with an increased risk of lymphoma. Over the past few years, a significant amount of research has uncovered several key aspects of the disease. Among the most significant recent breakthroughs is the discovery of monogenic defects such as ICOS deficiency and TACI deficiency among the CVID cohort, throwing light upon the molecular basis of this disease. Other advances include studies of the more severe CVID granulomatous variant which showed severe underlying B and T-cell defects and the presence of chronic viral infections such as HHV8 and CMV. The association between lymphoma and CVID could reflect myriad factors including genetics, immune dysregulation, chronic infections and radiosensitivity. As infection is a modification factor, further work is needed to confirm its role in causing disease and to evaluate the efficacy of treatment in preventing the development of complications such as lymphoproliferative disease.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 432–433).

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