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Lymphoid Proliferations of Indeterminate Malignant Potential arising in Adults with Common Variable Immunodeficiency Disorders: Unusual Case Studies and Immunohistological Review in the Light of Possible Causative Events

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Abstract

Patients with common variable immunodeficiency disorders (CVIDs) who developed B cell lymphoproliferation of indeterminate malignant potential are described in order to raise a

discussion of the relationship between infection and lymphoproliferation in infection prone patients. Those with CVID are at risk of developing either polyclonal or monoclonal lymphoproliferation in part due to the dysregulation of their adaptive immune systems. The aetiologies of the lymphoproliferations are unknown but intriguing; the relevance of infection being particularly problematic. The patients described here demonstrate variability in preceding infection, age at presentation, response to antibiotics and other types of therapy as well as outcome. The question of treatment is also controversial; issues include whether antibiotics or chemotherapy are the first line of therapy in all patients and whether transformation to aggressive B cell malignancy is inevitable or depends on other factors and if so, the length of time for such progression.

Keywords

Common variable immunodeficiency disorders; lymphoid proliferation; lymphoma; infection

Introduction

The most frequent symptomatic primary antibody deficiencies (PIDs) are the common variable immunodeficiency disorders (CVIDs), with a prevalence of approximately 1:20,000 [1]. They comprise a heterogeneous group of diseases that have primary antibody failure in common [2]. Since CVID is a diagnosis by exclusion of secondary causes of antibody failure including lymphoid malignancies, such a diagnosis should not be made until at least two years have elapsed without evidence of an underlying lymphoid malignancy.

The incidence of malignancies, particularly of lymphoid tumours, is increased in CVID patients compared with the general population [3]. In 2002, a combined study from Denmark and Sweden, using national cancer and immunodeficiency registries, found a modestly increased incidence of 12-fold [4]. In a long-term Italian cohort of 224 CVID patients, five patients were found to develop non-Hodgkin lymphoma, with a calculated 18-fold increase in risk [5]. More recently, antibody deficiency disorders were found to be associated with a narrower range of cancers than other forms of immunodeficiency [6]. This Australian data from 1,132 PID patients showed a further reduction to a 1.6-fold increased risk. Together, these studies show an increased but relatively low incidence of lymphoma compared with other immune-compromised patients, such as HIV/AIDS patients (78-fold increase) or transplant recipient cohorts (80-fold increase) [7] in which T cell immunosuppression, resulting in oncogenic viral infections, is thought to play a causative role.

The reasons for the increased susceptibility to lymphoid malignancies are unclear [8]. It is interesting to note that those PIDs with increased risk of infection are confined to deficiencies of the adaptive system, particularly in T cells. T cell defects occur in only a small proportion of CVID patients. This has been proposed as an explanation for the increased risk of malignancy, in keeping with the increased prevalence in other groups with low CD3 numbers such as in HIV infection [7]. However, low numbers of CD3 cells in CVID patients are associated with opportunistic infections [9] and not with lymphoid malignancies, though there are low numbers of such patients in any series.

In an attempt to clarify the association between all disease-related complications and prognosis, a large European cohort of CVID patients (with an average follow-up of 25.6 years) was studied [10]. Five distinct clinical phenotypes were defined: infections only, autoimmunity, polyclonal lymphocytic infiltration, enteropathy, and lymphoid malignancies. Different phenotypes were associated with different survival times: those patients 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 surprisingly, 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 [10]; whether this is as a result of chronic infection and subsequent polyclonal lymphoproliferation is not known.

Since overall patient survival is now improved and most acute bacterial infections can be prevented with improved patient management [11], it is timely to consider whether or not there is there a link between persistent or sub-clinical infections and these complications.

In this review, we discuss three patients in whom a spectrum of lymphoproliferative lesions developed over many years, in order to illustrate some of the issues involved, including those of patient management. The first two patients show a potential link between the development of polyclonal lymphoproliferation secondary to different types of infection, followed much later by overt lymphoid malignancy.

The lymphomas that arise in patients with immunodeficiency or immune dysregulation differ from those arising in immunocompetent hosts [12]. In addition, the underlying alterations of lymphoid tissues observed in patients with immune disorders have an impact on the usual criteria for the diagnosis of lymphoma. For example, extra-nodal lymphomas arising in mucosal-associated lymphoid tissue (MALT), termed MALT lymphomas, produce prominent lymphoid infiltration of extra-nodal sites that usually lack lymphoid tissue, such as the lung or the stomach. However, patients with CVID often exhibit marked lymphoid infiltration of a reactive nature in MALT-associated sites, making the distinction between benign and malignant lymphoid proliferations ambiguous. Criteria for the diagnosis of malignancy include demonstration of a monoclonal process either by immunophenotypic or molecular means and in some cases, the acquisition of cytogenetic aberrations.

The discussion emphasizes the difficulties of estimating a prognosis following longstanding lymphoproliferation and, therefore, management in terms of chemotherapy. Three pathologists (KG, QL and ESJ) reviewed all biopsy specimens taken from the three patients.

Relationship of MALT Lymphomas with Infections

The first case demonstrates the difficulties of defining a potential relationship between persistent infection and the subsequent development of a MALT lymphoma. A 61-year-old lady presented with two short episodes of high fever, malaise, profuse sweating, anorexia and a 10-month history of multiple, transitory subcutaneous lumps on her lower limbs. Biopsy of a typical subcutaneous lump revealed a panniculitis and *Aspergillus fumigatus* was grown on culture. Chest X-ray revealed transient bilateral pulmonary infiltrates consistent with primary *Aspergillus* infection. Bronchial biopsy showed submucosal lymphoid infiltrates consistent with follicular bronchiolitis; sarcoid and malignancy were excluded. Immuno-histology of a parabranchial lymph node showed reactive lymphoid hyperplasia with sinus histiocytosis. Low levels of serum IgG (4.3 g/L) and IgA (0.3 g/L) were found, and there was a lack of specific antibodies to diphtheria, tetanus and pneumococci despite immunizations. A diagnosis of CVID was made and immunoglobulin replacement therapy was started. She had normal numbers of CD4⁺, CD8⁺, CD16⁺CD56⁺ and CD19⁺ cells in the blood. She had no relevant family history or personal infection history to suggest a T cell defect. The pulmonary infiltrates gradually reduced on IgG substitution; as the patient became asymptomatic, she refused further invasive procedures and anti-fungal agents.

Five years later, she presented with intractable wheezing, dry cough and shortness of breath. Bronchoscopy showed white nodules along the endobronchial length in the left bronchial tree. Bronchial biopsy now showed lymphoid aggregates composed mainly of B cells of kappa light chain restriction and a few scattered T cells suggesting a MALT lymphoma of bronchial lymphoid tissue. Polymerase chain reaction (PCR) was not available at that time. Peripheral lymphocyte subpopulations were now abnormal, with low B cells and reduced CD4⁺ and CD8⁺ numbers. She refused treatment other than amoxicillin (for 18 months) and replacement immunoglobulin therapy (trough IgG≈6.5 g/L) and her symptoms resolved. Over the next 9 years, she remained well and free of bacterial infections, though chest CT scan showed persistent bilateral nodular opacities and mediastinal lymphadenopathy. Peripheral T cell numbers normalized though the B cell numbers remained very low (Table I). The development of the marked but transient T cell lymphopenia may have been related to the lymphoproliferation in her chest following the previously untreated fungal infection at this site.

At 77 years, she presented with sudden, marked weight loss. Chest CT scan showed areas of increased opacification in both lung fields and prominent pulmonary consolidation in the right mid zone, increased widespread lymphadenopathy in the mediastinum, *porta hepatis* and upper retroperitoneum as well as limited ascites. A biopsy performed at the right lung base revealed a diffuse large B cell non-Hodgkin lymphoma (DLBCL), with dense CD20⁺ cells, few CD3⁺ cells and scattered mitotic figures. She refused treatment and died within months.

Evidence for a relationship between some infections and MALT lymphomas was reported some time ago with the association of chronic infection with *Helicobacter pylori* and lesions in the stomach. Immunoproliferative disease in the small intestine has been associated with *Campylobacter jejuni* [13]. Cutaneous lymphoma has been reported after *Borrelia burgdorferi* infection, ocular lymphoma following *Chlamydomydia psittaci* and spleen and liver lymphoma in association with hepatitis C virus.

Chronic viral infection and other opportunistic infections are uncommon in CVIDs [9] and associated with reduced T cell numbers. There is the possibility that these uncommon patients have an autosomal recessive form of combined immune deficiency since there is an over-representation of consanguinity in this group [14]. There are reports of defects of antigen presentation and cellular immunity in CVIDs and at least half of patients with CVID have circulating T cells specific for epitopes derived from CMV and/or EBV [15, 16]. Whether this is relevant to the development of MALT lymphomas in CVID patients remains to be seen. The gradual reduction of T cells in this patient suggests that reduced T cell immune surveillance might be implicated in the initial episode of lymphoproliferation following aspergillosis. Whether or not the antibiotic and immunoglobulin therapies helped to contain this episode and normalize the peripheral CD4⁺ count for the next 9 years remains speculation.

Reports of patients in whom MALT lymphomas were responsive to antibiotics [17] led to a search for microbial species associated with marginal zone (MZ) lymphomas [13]. In patients with primary hypogammaglobulinaemia, routine bacterial and viral cultures, PCR to detect adenovirus, CMV, HHV8, herpes simplex virus 1, enterovirus, rhinovirus, *B. burgdorferi*, *Chlamydia pneumoniae*, *Legionella* spp., *Mycoplasma pneumoniae*, *Pneumocystis jirovecii* and *Ureaplasma urealyticum* have been positive even in patients with no signs of apparent ongoing infection. However, these studies have not yielded consistent results, suggesting that a variety of organisms could be responsible for lymphocytic stimulation rather than any specific organism. Alternatively, since the viral infections are common and become latent, those findings may be coincidental.

Lenze et al. proposed that chronic exposure to a foreign antigen triggers lymphoid proliferation and increases the risk of mutations [18]. The relationship between the initial aspergillosis and the subsequent MALT lymphoma in the first case is intriguing. In retrospect, this patient should have received anti-fungal therapy at her first presentation to prevent subsequent lymphoproliferation and maybe even to treat the MALT lymphoma. Recurrent cutaneous lumps due to *Aspergillus* are most frequently associated with infection in the lung, as in this patient [19]. Cutaneous aspergillosis is rare and almost exclusively associated with severe immunocompromise [19, 20] and has not been reported previously in a patient with PID. Clinical resolution without treatment with anti-fungal agents in the presence of normal lymphocyte numbers does not exclude persistent silent infection. The subsequent development of a marked T cell lymphopenia, coincidental with the MALT lymphoma in her chest, may be related.

Difficulties in Diagnosis in CVID Patients

Diagnosis of MALT lymphoma is difficult. In many situations, the distinction between reactive and neoplastic lymphoproliferative disease can be made using appropriate morphologic, immunophenotypic and molecular studies. Sander et al. [21] reported that “tumour-like proliferations” (nodular lymphoid hyperplasia) of lymphoid tissue in lung or gastrointestinal tract were common in CVID patients, but most patients had a benign clinical course. B cell rearrangement studies might have been useful in the first case to differentiate MALT lymphoma from nodular lymphoid hyperplasia of the lung, though it is possible for both conditions to coexist in the same patient [22–24]. Whether or not this would have changed patient management is debatable.

The second case demonstrates the difficulties in diagnosis of lymphoproliferative lesions in extra-nodal sites in CVID patients. A 23-year-old man presented with intermittent severe immune thrombocytopenia (ITP) that recurred in association with viral or bacterial infections and was responsive to corticosteroid therapy. Initially, serum immunoglobulin levels were measured following a skin abscess and found to be very low (IgG, 0.6 g/L; IgA, 0.1 g/L; IgM, 0.3 g/L). He failed to make specific antibodies on test immunization, meeting the criteria for a diagnosis of CVID. He was started on replacement immunoglobulin therapy, which he continues to receive 29 years later. He had two older sisters who had died at aged 8 months and 4 years of age from “bone marrow failure”; further details were not available.

He developed autoimmune hemolytic anaemia (AHA) at the age of 35 years and responded well to high-dose corticosteroids. At this time, he developed mild intermittent gastrointestinal symptoms, including diarrhoea but not malabsorption; campylobacter and cryptosporidia were found in stools intermittently, but gastric biopsies showed no *H. pylori*. Several duodenal biopsies, done at 3–5-year intervals for potential infection showed minor villous atrophy only but no pathogens; he did not respond to a gluten-free diet despite full compliance.

Five years later, he developed small (1–2 cm) erythematous, non-itchy skin lesions consistent with cat-scratch fever but repeatedly PCR negative on biopsy. Other negative PCR tests included *Bartonella*, human herpes virus (HHV) 6 and HHV 8. The lesions stained positive for EBV (LMP-1), and immuno-histology showed dense, perivascular, dermal infiltrates of light chain-restricted small lymphocytes, consistent with MZ lymphoma. The appearance of new lesions stopped briefly on trimethoprim therapy for 3 months but then recurred transiently over the following 4 years, at 3–4-month intervals despite prophylactic antibiotics. Those lesions that were not removed surgically resolved; those that were removed showed variable light chain restriction at different times.

Oligoclonal (rather than monoclonal) rearrangement of V_H chains was demonstrated by PCR analysis in two of these biopsies.

At the age of 45 years, he presented with a markedly enlarged cervical lymph node. Excision biopsy showed altered nodal architecture with a lymphoid infiltrate with lambda light chain excess and some large B cells but the histology was not typical of large B cell lymphoma. Acutely enlarged, multiple pulmonary nodules and pleural plaques were found on CT, though bone marrow examination was normal. A clinical diagnosis of lymphoma was made, and he was treated with six courses of chemotherapy (prior to the availability of rituximab) with prophylactic acyclovir and trimethoprim. This resulted in complete resolution of the chest findings and enlarged lymph nodes. Skin lesions with unchanged histology continued to appear for the next 6 months, after which time they apparently ceased spontaneously.

He has had no skin lesions or lymphadenopathy in the subsequent 11 years. He is well, without breakthrough infections, though with intermittent loose bowels for which he receives budesonide (9 mg daily). He has developed sclerosing cholangitis though no organism has been found. Despite regular (twice yearly) monitoring, there has been no $CD4^+$ lymphopenia.

In contrast to the first case, this patient had an atypical lymphoid proliferation in the skin suggestive of MZ lymphoma. However, in contrast to MALT lymphoma, an association with EBV was shown by immunohistochemistry. Recently, Gibson et al. have described EBV-positive lymphoproliferations resembling MALT lymphoma that occur in the post-transplant setting; interestingly, most cases involve the skin and subcutaneous tissue; these unusual cutaneous lesions exhibited features resembling PTL and MALT lymphoma [25]. EBV has also been shown to be associated with some B cell lymphomas in patients with CVID, though whether pathogenic or latent in the B cells is difficult to know. Given the restriction of the skin lesions in our patient to the upper trunk, a possible aetiology was cat scratch fever though the PCR was consistently negative. There was evidence of recurring scratch marks and the lesions stopped after the cat was banished; it is even possible that another zoonotic organism was involved.

Whether or not the almost continuous corticosteroid therapy, instituted for a recurrence of ITP and subsequently AHA, was instrumental in the development of these lesions remains unclear but there were no significant changes in the numbers of circulating $CD4$ cells. ITP and AHA are relatively common complications of CVIDs (prevalence 12–15%) and are significantly associated with polyclonal lymphoproliferation ($p=0.001$) [10] but the cause of the progression is unknown at present though infection remains a possibility. The clinical phenotypes of CVID with autoimmune cytopenia and/or with lymphoproliferation have poor prognoses [10].

Therapy with antibiotics is not uniformly successful, as in this case [17]. It has been shown that MALT lymphomas lacking translocations respond to antibiotics whereas those with demonstrable translocations are antibiotic resistant [26, 27], though this has to be confirmed. Cytogenetics might have been useful in this case, as the apparent initial response to antibiotics in this patient was encouraging, and yet he progressed to frank lymphoma.

The histology of lymphoid tissue from antibody deficient patients without suspected malignancies varies from being microscopically normal to grossly abnormal. The germinal centres in lymph nodes from patients with CVID tend to lack well-developed lymphoid cuffs and without careful immunophenotypic and molecular studies, these can be mistaken for lymphoma [21]. This may have led to the apparent increased risk of lymphoma in older studies and underlines the need for expert histological opinion and review of material from all immune deficient patients for a consensual approach.

Nodular lymphoid hyperplasia is also seen in CVID patients during infection in extra-nodal sites, such as a lung or gastrointestinal tract, and may simulate lymphoma clinically [21]. Such lesions may contain small populations of monoclonal B cells, further making histological distinction between lymphoma and lymphoid hyperplasia difficult. Not only has monoclonal proliferation without progression to malignancy been reported in CVID patients [28] but a study of clonal rearrangements of immunoglobulin heavy chain (IgH) and T cell receptor showed oligoclonal lymphocyte populations irrespective of the histology [24]. This case illustrated that different clones of dysfunctional B cells in independent sites can mimic lymphoma but may not necessarily progress to frank lymphoma.

Treatment Options

A diagnosis of lymphoma in patients with CVIDs is particularly challenging and the decision to treat with chemotherapy is a clinical one. Chemotherapy was delayed in this case without adverse effect and successful treatment only instituted once symptomatic widespread lesions were detected. Lymphoma was diagnosed clinically in this case and the local nodal architecture was destroyed by infiltration by atypical monoclonal B cells in the lymph node biopsy some 5 years after the initial skin lesions had presented in a variety of places in the skin. Treatment with chemotherapy, dictated by clinical and radiological considerations, may not have been necessary; it might be that rituximab alone might have been sufficient.

The final case illustrates a different clinical decision: to treat with antibiotics rather than chemotherapy. A 32-year-old woman presented with a history of multiple upper respiratory infections and chronic cough. Past medical history was significant for genital chondyloma and *Varicella zoster*. A CT of the chest showed bronchiectasis with lung nodules and diffuse lymphadenopathy. Transbronchial biopsy of the lung nodules revealed marked chronic and mild acute inflammation, focal lymphocytic and inflammatory cell infiltrates with foamy macrophages; staining for acid-fast bacilli, fungus and pneumocystis were negative. Biopsy of an axillary lymph node showed non-specific reactive hyperplasia. She had mild thrombocytopenia, low immunoglobulin levels and normal numbers of peripheral CD4⁺ and CD8⁺ cells. A diagnosis of CVID was made and IVIg therapy started. She continued to have multiple respiratory tract infections; daily prophylactic antibiotics, inhaled corticosteroids and long acting beta agonists were commenced.

Eight years later, CT of the abdomen showed extensive retrocrural and retroperitoneal lymphadenopathy with a suspicious mass arising from the left kidney. Core needle biopsy showed features suggestive of MZ lymphoma, though IgH gene rearrangement analysis was equivocal. Repeat endobronchial biopsy showed reactive lymphoid hyperplasia consistent with follicular bronchitis; lymphoid infiltrates were composed of CD3⁺ cells and CD19⁺ cells in a follicular arrangement; scattered plasma cells were polyclonal. *Haemophilus influenzae* was grown from the bronchoalveolar lavage. The nature of the lung disease was both obstructive and restrictive. A decision to follow the lymphoma clinically without chemotherapy was made. Repeat CT scans of the neck, chest, abdomen and pelvis revealed that lesions have been stable overall and the patient has shown some improvement in lung function 5 years later. She remains clinically well on antibiotic prophylaxis (clarithromycin, 1 week/month).

This patient demonstrates the difficulties in determining the appropriate therapy for an apparent MZ lymphoma even once it has spread beyond the initial mucosal site. The findings of inflammation and reactive changes only in the lung (on two occasions, 8 years apart) and local lymph node histology suggest an infective cause, supported by positive microbiology. The subsequent development of MZ lymphoproliferation at a remote site, the kidney, was unusual but not unknown in CVID. This case provides further support for

observing MALT lymphomas without resorting to chemotherapy without apparent ill effects in selected antibody deficient patients.

Discussion

The inherent genetic instability of lymphocytes and sustained activation and proliferation of the lymphoid system during infections increases the risk of malignant transformation. This is particularly marked in chronic infection, immunodeficient and autoimmune conditions that are recognized risk factors for lymphomas [13] and are frequently found together in the context of CVIDs [2]. The recent finding from the Australian register that CVIDs are more likely than genetic T cell deficiencies to be associated with lymphoid malignancies is interesting [6]. The proportion of patients with T cell abnormalities is low in those with spontaneous rather than familial CVID [9] and suggests that underlying B cell dysregulation may account for the increased risk of malignancy. Furthermore, low CD4 counts were not found to be predictive for the development of lymphoma in the Northern European study [10] but only raised polyclonal serum IgM levels. The development of lymphoproliferation may have more to do with B cell instability than failure of T cell surveillance in CVIDs.

The finding that genes involved in lymphoproliferation are significantly associated with particular subgroups of CVID patients in the recent genome-wide association, and gene copy number variation study supports this theory [29]. Genes were found to be significantly associated with the subsequent development of lymphoma, including PFTK1 that is constitutively expressed at high levels in B cell lymphomas. A significantly high number of patients were found to have duplications in a gene for initiation of DNA replication, namely ORC4L, which is associated with B cell lymphoproliferative disorders. However, such studies are in their infancy and need to be confirmed before they can be used as predictors of clinical phenotypes in CVIDs.

Although chronic infection does induce lymphoproliferation, it is unlikely that this alone is sufficient to provoke malignant change. However, chronic stimulation (with or without persistent infection) in the setting of a dysfunctional adaptive immune system increases the risk of malignant proliferation. The absence of detectable pathogenic material in immunocompetent and immunodeficient patients with a lymphoid malignancy suggests that such a stimulus is not always necessary [30]; in the presence of lymphoid dysregulation, transformation to uncontrolled clonal proliferation may be a rare chance event.

The natural history of MALT lymphoma is usually indolent but there is evidence that some progress to DLBCL [31] as in the first case. Rates of transformation in the general population range from 3% to 19% [32]. At what stage and why transformation occurs is not clear. Non-Hodgkin lymphomas may develop from nodal and extranodal lymphoid tissues. A distinct subset of low-grade extra-nodal lymphomas arising from B cells of the MZ has been recognized [33]. There are three distinct lymphomas deriving from MZ B lymphocytes: splenic MZ lymphomas, extra-nodal MZ lymphoma of MALT type (commonly referred as MALT lymphoma) and nodal MZ lymphomas. Although many aspects of their histology and molecular pathogenesis are distinct, these entities share a number of common features, the most striking being their possible association with chronic antigenic stimulation by microbial and/or auto antigens.

Marginal zone B cells are a bridge between the innate and adaptive immune responses to pathogens; they participate in T cell-independent “innate-like” immune responses to microbial pathogens, proliferating rapidly on activation and producing IgM in a primary antibody response [13]. The recent finding that higher serum IgM levels are associated with polyclonal lymphocytic infiltration as well as lymphoid malignancy in CVID patients [10] is

supportive of their role in the complication of extra and intranodal polyclonal lymphoproliferation.

Conclusions

Since there is increased susceptibility of patients with CVIDs [10] to lymphoproliferation following any chronic antigenic stimulation, it is important to reduce the infective load of all pathogens. There is a need to continue to search for pathogens by all available means: in biopsies by specific staining for pathogens, by fluorescent in situ hybridization and in blood by measurement of viral loads by PCR. The role of immuno-histology is changing but detection of CD5, CD23, CD10 and now cyclin D1, to define mantle cell malignancy, is important, and there will be new markers.

Cytogenetic alterations are common and although finding of translocations is interesting, they do not appear to guide therapy in all cases [33], require viable cells and such studies have been largely superseded by PCR. The role of PCR to detect monoclonality is uncertain, since oligoclonal proliferation is common in many primary immune deficiencies. A finding of monoclonality is thought to be helpful to support subsequent treatment with chemotherapy. PCR has enabled studies at the single-cell level for cellular origin and viral integration. However, we have known for a long time that monoclonality of B cells does not imply invasive malignant behaviour since MGUS is common in older patients and yet less than 50% develop overt life-threatening malignancy over 30+ years [34]. A multi-step pathogenesis is involved in invasive malignant diseases of all types. The risk of a diagnostic dilemma is reduced by the favourable prognosis of these “low-grade” lymphomas and their tendency to remain localized to the primary site for a long time. The “watch and wait” policy to avoid the complications of chemotherapy in patients who were already suffering from a primary immune deficiency appears to have been satisfactory in these three cases, in whom there was no progression for 9, 5 and at least 5 years, respectively. Chemotherapy was successful when it was indicated clinically in the second case. The significance of large lymphocytic cells in an extra-nodal MZ lymphoma requires further studies.

It is important to continue to search for prognostic factors that are related to each clinically phenotype of CVID, in order to identify the minority of patients that are particularly susceptible to malignancy. Raised polyclonal IgM levels remain the only prognostic indicator at present [10]. Genome-wide screens are in their infancy but have shown promise [29]. Treatment for lymphoproliferation in the absence of prognostic indicators remains a difficult decision and therefore must be tailored with careful consideration to what ultimately is in the patient's best medical and personal interests. Chemotherapy was delayed in these cases without adverse effects, and successful treatment for lymphoma only instituted in the second case once symptomatic, widespread lesions were detected.

We can speculate that the increased risk of uncontrolled lymphoproliferation in a small proportion of CVID patients may result from a combination of division of lymphocytes during frequent infections and the underlying dysregulation of the adaptive immune system. It is possible that lymphoid malignancy in these patients may be restricted to those with particular susceptibility genes, perhaps those shared with immunocompetent individuals with lymphoma. Whether or not infection plays a triggering role, treating all infections in CVID patients is important to reduce the time of cellular proliferation; the finding of latent pathogens may be incidental or pathogenic.

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Table I

Lymphocyte subpopulations during patient follow-up

Age (years)	Total lymphocyte Count $\times 10^9$ (NR, 1.0–2.8 $\times 10^9$)	B cells Count $\times 10^9$ (%) (NR, 0.4–1.0 $\times 10^9$)	T cells Count $\times 10^9$ (%) (NR, 0.9–1.5 $\times 10^9$)	T CD4 Count $\times 10^9$ (%) (NR, 0.7–1.3 $\times 10^9$)	T CD8 Count $\times 10^9$ (%) (NR, 0.4–0.8 $\times 10^9$)
61	1.20	0.10 (9%)	0.90 (75%)	0.60 (50%)	0.30 (21%)
66	0.49	0.04 (9%)	0.31 (64%)	0.23 (47%)	0.08 (17%)
68	0.48	0.05 (12%)	0.25 (56%)	0.18 (41%)	0.06 (19%)
71	0.61	0.06 (14%)	0.39 (64%)	0.28 (46%)	0.10 (17%)
75	0.87	0.07 (8%)	0.60 (69%)	0.40 (46%)	0.20 (23%)

NR normal range