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GRANULOMATOUS DISEASE in COMMON VARIABLE IMMUNODEFICIENCY#

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Abstract

Granulomatous disease occurs in 8-22% of patients with common variable immunodeficiency (CVID). We examined the clinical and immunologic information of all 37 of 455 (8.1%) CVID subjects with this complication. The median age at diagnosis of CVID was 26 (2 - 59). 14 had granulomas 1 - 18 years before diagnosis of CVID. In 6 detection of granulomas coincided with this diagnosis; for 17, granulomas were documented later. 54% had lung granulomas, 43% in lymph nodes and 32% in liver. 54% of the group had had autoimmune diseases, mostly immune thrombocytopenia and hemolytic anemia. 24% had had a splenectomy. Nineteen (51.3%) required steroid treatment for granulomas; other immune suppressants were used in some. Over 25 years 28.5% died (median age 37.5), but not significantly more when compared to our CVID patients without granulomas (19.8%). Those with lung granulomas had similar mortality to those with granulomas in other tissues.

Introduction

Common variable immunodeficiency (CVID) is characterized by hypogammaglobulinemia, defective antibody responses and recurrent infections [1;2;3;4;5]. Recurrent pulmonary infections especially for patients with delayed diagnosis or inadequate immune globulin replacement [6;7;8;9;10], can lead to bronchiectasis, respiratory failure and cor pulmonale, some of the most significant causes of both morbidity and mortality in this immune defect [1;2;3;6;7]. While hallmark of CVID is that of a B cell defect, many patients also have variable T-cell abnormalities including cytokine defects, poor lymphocyte proliferation[1;11;12] and dendritic cell defects [13;14;15]. Mutations in selected genes are known to lead to the CVID phenotype, including the inducible co stimulator (ICOS) [16;17;18;19] and CD19 [17;18]. The role of mutations in the *TNFRSF13B* gene encoding TACI (Transmembrane activator and calcium modulator and cyclophilin ligand interactor) although demonstrated in a significantly increased number (8%) of patients [20;21] is somewhat less clear as the same mutations can be found in healthy family members [22;23]. In order to classify CVID subjects, a number of

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reports have used various immunological characteristics, particularly B cell functions in response to selected activators *in vitro*. Most recently, enumeration of peripheral blood switched memory B cells has been used as an indicator of immunologic capacity also showing significant clinical relevance [24;25;26;27;28].

The development of granulomatous disease or autoimmunity in CVID are two of the most problematic of clinical conditions, as some form of immune suppression may be required for adequate treatment. The granulomatous changes, or what is reported to be “sarcoidosis” is not infrequently diagnosed years prior to the recognition of hypogammaglobulinemia and in these cases, greatly delays the recognition of the immune defect and the revision of the diagnosis to CVID with granuloma [29;30;31;32;33]. Alternatively, those with known CVID may be found to have granulomata when a tissue is biopsied at a later date. Although granulomas can be found in many organ systems, lungs are the most prominent location [31;33]. In some patients an intense lymphoid infiltration accompanies the granulomata leading what has been termed “granulomatous lymphocytic interstitial lung disease” (GLILD) [33;34] the presence of which may be associated with a poorer outcome [34]. For unclear reasons, granulomatous disease is often found in association with autoimmunity, in particular, immune thrombocytopenic purpura (ITP) or autoimmune hemolytic anemia (AIHA) [31]. These episodes may occur years before the discovery of granulomas in any tissues. Here we outline the clinical and immunological data of 37 CVID patients in whom granulomas were documented in one or more organ systems and compare the mortality of these subjects to other CVID subjects.

METHODS

Patients

The clinical and immunologic information of a total cohort of 455 patients with CVID were surveyed. The diagnostic criteria for CVID included reduced serum IgG, IgA, and/or IgM by two or more confidence intervals below the normal ranges for ages and antibody deficiency, verified by lack of protective titers to vaccine antigens, based on laboratory reference values. [1;2;4]. Subjects who had other causes of congenital or acquired hypogammaglobulinemia were excluded. Serum IgG, IgA and IgM levels at the time of diagnosis, before immunoglobulin replacement, were obtained. Of the group, current medical information was available for 370 subjects; this included 76 subjects who had died in the follow-up period of 25 years. For those patients in whom granulomas had been diagnosed, a review of medical records and pathology reports was performed to verify the finding of granulomas and determine the tissues involved. The results of additional tests, such as pulmonary functions and radiological studies, including those obtained in the course of our evaluations, were reviewed and additional tests obtained where required.

Other Immunologic studies

T cell proliferative responses to mitogens (phytohemagglutinin, concanavalin and pokeweed mitogen) were determined by standard methods and compared to results for the laboratory controls. For more recently referred subjects, the percentages of T, B cells, total memory B cells (CD27+CD19+) and isotype switched memory B cells (CD27+IgM- IgD- CD19+) were quantitated by flow-cytometry, using freshly isolated peripheral blood mononuclear cells. Subjects with 0.4% or fewer of isotype switched memory B cells, as based on the number of peripheral blood mononuclear cells, were considered to be Group 1 while those with greater than this number as Group 2 subjects, as previously described [24;26;27] For comparison, normal controls of age 18 or older (n=35) had levels of isotype switched memory B cells between 18.2% and 31%.

Statistics

The median levels of serum immunoglobulins were determined. For patients whom the immune globulin levels were defined as less than a given number, the whole number under this level was used, such as 6 mg/dl in place of < 6.7 for calculations. The Mann-Whitney test was done to compare lymphocyte proliferation results between subjects with granuloma and those without. The Chi square test was used to determine differences between the incidence of autoimmunity in CVID subjects with and without known granulomas; this test was also used to determine differences between the mortality of subjects with granulomas as compared to all other CVID subjects not found to have such lesions. The log rank test was performed to determine if patients with known pulmonary granulomas had increased mortality as opposed to those with granulomas elsewhere. (Prism 4; Graph Pad Software).

RESULTS

Patients and Location of Granulomas

Of the 455 subjects with CVID, 37 subjects (8.1%) had been found to have granulomas in one or more tissues. This group consisted of 29 (78%) Caucasian, 5 (14%) African American, 2 (5%) Hispanic and 1 (3%) Asian patients. For the group as a whole, 92% are Caucasian, 2.7% African American, 4% Hispanic and 1% are Asian patients. Of these, two had family history of CVID or IgA deficiency. The age of these patients at the time of diagnosis with CVID ranged between 2 to 59 years (median 26); 24 out of 37 (64.8%) were female (Table-1). (For the group of CVID subjects as a whole, 57.5% were female.) Granulomas had been detected in 14 of these patients, 1 to 18 years before the diagnosis of CVID was established. In 6 patients of the group, the detection of granulomas coincided with the diagnosis of the immunodeficiency; in the remaining 17, granulomas were found after the diagnosis of CVID. Granulomas were documented in the lungs in 20 of these subjects (54%) and 12 (60%) also had granulomas in other organs, the liver and the lymph nodes being the most common (Table-1). The other locations in the order of frequency were lymph nodes (16), liver (12), skin (7), spleen (5), bone-marrow (2), brain (2), retina (2), small bowel (1) and kidney (1). On lung biopsy, 6 subjects of the group (cases 5,8,13, 14, 28 and 36) had a dense lymphocytic infiltrate in the lungs and were diagnosed as having lymphocytic interstitial pneumonia. Four patients (cases 1,12,19, 22) also were also found to have a lymphoid infiltration accompanying the granulomas found on liver or spleen biopsies. Subject 29 was found to have granulomas on skin biopsy done after an acute antibiotic-induced drug eruption; he has no other known granulomas. The granulomas in various organs were very large, as for one subject in whom the spleen and surrounding mesenteric tissues formed a granulomatous mass (Figure 1, subject 15) or multiple, as for subject 19 who had numerous granulomas studding the surface and interior of the spleen (Figure 2.) Some granulomata were solitary, as shown for Subject 26 in whom only one granuloma was found in the bone marrow examination done for ITP (Figure 3). An organism was not identified in any case using standard stains and cultures.

Pulmonary Status—Twenty two patients (59%) have had moderate to severe respiratory symptoms with chest radiographic abnormalities including nodular changes, bronchiectasis and/ or diffuse interstitial changes leading to reduced vital capacity and impaired diffusion capacity of carbon monoxide. One of these had a bilateral lung transplantation and 3 others had been considered for this procedure. One of these subjects (#19) has severe hepatopulmonary syndrome and hepatic transplantation has been considered. While 7 subjects (19%) had neither clinically significant chronic respiratory symptoms nor radiological or functional evidence of pulmonary disease, the remaining have either localized bronchiectatic changes or other interstitial abnormalities with retained lung functions.

Laboratory studies

Serum immunoglobulin levels at diagnosis and peripheral lymphocyte phenotypes are shown on Table-2. Median IgG, IgA and IgM levels for the group were 210 mg/dl, 6 mg/dl and 19 mg/dl, respectively. Six of the 29 (20.6%) patients investigated had an inverted CD4+/CD8+ T cell ratio. While lymphocyte proliferative studies also were not performed in each case, 24 of the 33 tested (72.7%) had reduced T cell responses to at least one of these mitogens. (On Table 2, shown as underlined values.) Comparing these lymphocytes responses to other CVID subjects in this group who did not have granulomas, lymphocyte proliferation analyses were not significantly different. For 22 subjects, the percentage of isotype switched memory B cells (CD27+ IgM-IgD-) was obtained; these revealed very low levels (0.4% or fewer) for 20 of these subjects; 9 had switched memory B cell percentages of 0%. Two others of the group had more than 0.4% [24].

Autoimmunity, Medical Treatment and Splenectomy

Twenty of these 37 (54 %) patients had one or more episodes of autoimmunity. Ten of these subjects had a history of ITP, 4 had had AIHA, 5 patients had had both ITP and AIHA at different times. (Table-3). Four subjects (Cases 2,10,30,35) had multiple episodes of these autoimmune cytopenias. In contrast, for the 418 other patients, with no known granulomas, one or more autoimmune conditions were known for significantly fewer subjects, 76 subjects (18%) ($p=0.001$) (This includes predominantly ITP and/or AIHA (55 subjects), but also rheumatoid arthritis (8), insulin dependent diabetes (3), alopecia totalis (3), anti-IgA antibodies (3), systemic lupus erythematosus (2), vasculitis (2), juvenile rheumatoid arthritis (1), primary biliary cirrhosis (2), pernicious anemia (2), neutropenia (2), thyroiditis (2) and myasthenia gravis (1). Steroids, either orally or intravenously, were given to 19 of the 37 patients to treat acute autoimmune disease (Table 3.) Splenectomy was performed in 9 (24.3%) of these patients, either for uncontrolled autoimmunity, splenic enlargement (2), or suspicion of lymphoma (1). One subject received rituximab (Case 2) with resolution of autoimmunity. Nineteen patients (51.3%) had also been given steroids, with or without other therapies, for reducing or controlling granulomas in lungs, nodes, liver, brain or skin. Seven of these subjects were also given one or more additional immune suppressants: hydroxychloroquine (5 subjects), cyclosporine (3 subjects), azathioprine (2 subjects), methotrexate (2 subjects), infliximab (1 subject), and etanercept (1 subject) were also used either alone or in different combinations. None of these additional therapies was of clear benefit in the treatment of granulomatous disease. (Table-3). (In contrast of the 418 subjects with no known granulomas, splenectomy had been performed in 20 subjects, 5% of the group.)

Mortality

Ten out of the 35 (28.5%) patients with granulomas for whom current information is known, have died, at median age of 37.5 years, over the 25-year follow-up. (Table-4). Seven of these patients died of respiratory failure related to granulomatous lung disease and one died of liver failure stemming from granulomatous liver disease. Of the group who died, LIP had been found in one. (#28) One patient died shortly after lung transplantation due to surgical complications. One patient, not on any immune suppressants, died of progressive multifocal leukoencephalopathy (PML). The differences in mortality between patients with pulmonary granulomas as compared to subjects with granulomas elsewhere, was not significant ($p=0.230$.) For the total group of 455 subjects, current follow-up was known for 370 subjects. Using this group as the denominator, we did not find a significant difference in mortality for subjects with granulomas as compared to those without, of which 19.8% died in this interval ($p=0.68$).

DISCUSSION

Granulomatous disease occurs in between 8 to 22% of subjects with CVID [1;30;31;33;35] an association still not commonly recognized by physicians [29;30;31]. In fact when granulomas are discovered first, the diagnosis of CVID is often delayed as the patient is considered to have uncomplicated sarcoidosis. Tissue biopsy may be required not only for diagnosis of granulomas but also to differentiate these lesions from other complications such as lymphoid hyperplasia or lymphoma, which also occur in CVID [36;37]. Lungs, lymph nodes and spleen are the most commonly affected sites, although other organs such as skin, liver, bone-marrow, kidney, gastrointestinal tract and brain can be involved [30;31;32;33;38;39;40;41;42]. In our cohort, lungs were the primarily affected site, followed by lymph nodes and liver. In six of our subjects, a lymphocytic interstitial infiltrate accompanied the granulomas, a combination that may contribute to respiratory insufficiency and death [33;34]. A recent study reported a median survival of 13.7 years for CVID patients with granulomatous/lymphoid interstitial infiltrates, as compared to 28.8 years in those who did not have this complication [34]. In our cohort, 10 patients (of the 35 for whom we have current data) died in the follow-up period of 25 years; only one of whom also had LIP. Six of these were complicated by respiratory insufficiency resulting from granulomatous interstitial lung disease although pneumonia was a precipitating cause in five. We could not verify that patients with known granulomas in lungs had a shorter survival than those who had granulomas in other tissues. This difference may be due to the bias introduced by the choice of tissue that was examined; if granulomas were found in an enlarged lymph node or liver, the lungs may not have been biopsied as well, unless a clinical reason required this procedure. In addition, the mortality for these subjects with granulomas was not significantly different from the mortality for the other members of the CVID group in whom granulomas were not found (19.8%.) This is likely to be due to the nature of this cohort of subjects, as it is now clear that patients with non-infectious complications, potentially over-represented in this population, have an increased mortality when compared to subjects who have only recurrent infections [3].

For unclear reasons, granulomatous changes are associated with autoimmunity in CVID [31]. In this cohort, more than half had been diagnosed with an autoimmune condition, ITP or AIHA being the most common. This is very significantly increased in comparison to the percentage of autoimmunity (18%) known in the remaining CVID population, not specifically noted to have granulomas [36]. CVID subjects with granulomas or autoimmunity are also likely to have a significant deficiency of isotype switched memory B cells [24;25;26;27] suggesting that most profound lack of B cell maturation is likely to be associated with the abnormal genetic, cellular or cytokine environment that supports granulomata formation. T cell defects in CVID have also been associated with the formation of granulomas in tissues, including an expansion of CD8⁺ T cells and lack of CD4⁺ T cells with defective T cell proliferative responses [31;43] as shown for many of the subjects examined here.

In general, granulomas are known to develop in response to microbial or insoluble agents. Since the lungs are commonly involved in CVID, the search for an environmental antigen triggering this reaction is always worthwhile. The granulomas in CVID are usually of non-caseating nature, although caseating granulomas have also been reported [30;31;44] raising the possibility of an infectious etiology as the original trigger. A case of CVID with granulomatous and lymphoproliferative disease following an acute *Toxoplasma gondii* infection has been reported in a 12 year-old girl [45]. The human herpes virus 8 (HHV8) has been observed in pulmonary samples and bone marrow of some CVID patients with granulomatous lymphocytic interstitial lung disease [46]. However, in most patients no microorganism has been identified, as for the subjects reported here, although in time molecular techniques may shed more light on such lesions. In the case of patient 29 here, granulomas

were only found on skin biopsy done for an acute antibiotic drug reaction, suggesting that granulomas can be formed in subjects with CVID, in other settings of inflammation.

In sarcoidosis, a model for understanding granuloma formation, the cardinal histologic feature of granuloma is an excess of CD4+ T cells, potentially enriched in oligoclonal alpha beta T cells; these appear to interact with antigen presenting cells to initiate the granulomatous tissue reaction [47]. Activated CD4+ T cells produce both IL-2 and INF-gamma, also leading to TNF-alpha production [47;48]. Cultured alveolar macrophages release high levels of TNF-alpha in sarcoidosis, which is correlated with disease progression [49]. TNF-alpha has been shown to highly expressed within granulomas in tuberculosis [50]. The crucial role of TNF-alpha in the maintenance of granuloma formation has been demonstrated in several experimental models which indicate that in the absence of TNF or TNF receptors, there is defective granuloma formation, due to inefficient dendritic cell function and/or lack of cellular infiltration essential for containing the infection [51;52;53]. The role of IFN-gamma in central necrosis has also been suggested, but its overall role in the development of granulomatous disease is unclear [51]. Cytokine abnormalities have been previously noted in CVID. T cell INF-gamma secretion was upregulated in some patients especially in subjects with reduced numbers of naive CD4+ T cells [43;54]. While intracellular IL-12 was increased in monocytes in one study of subjects with CVID [55], IL-12 production by monocytoic DCs was found defective [13;14]. As TNF-alpha plays an important role in granuloma in model systems and possibly human diseases, this cytokine has attracted the most attention in CVID. From older data, 11 of 24 CVID patients with reduced CD4+ T cell counts, increased neopterin levels and splenomegaly, had significantly elevated serum levels of TNF-alpha and both forms of soluble TNF (p75 and p55) receptors (sTNFRs) [56]. Mullighan reported granulomas in 20 of 90 patients with CVID (22%); 8 of these 20 (40%) had an unusual TNF-alpha allele (TNF +488A) [35] but increased TNF-alpha production was not actually examined in these patients. Another factor potentially enhancing the formation of granulomas in CVID might result from the defective TLR9 signaling shown to occur in this immune defect [57] as TLR9 knockout mice have increased granuloma formation on challenge with mycobacterial antigens [58].

Appropriate treatment of granulomas in CVID presents a particular challenge, as some form of immune suppression may be required, always undesirable in the presence of an existing immune defect. Unfortunately immunoglobulin replacement has shown little effect in controlling granulomatous changes, however, with one exception [38]. When immunosuppressive therapy is required in clinical grounds, steroids have been the first choice, however, additional agents may be needed if the dose of steroid required is more than desirable or the length of treatment is prolonged. Hydroxychloroquine may be an alternative treatment due to inhibitory effect on monocyte-macrophage activation, antigen presentation and TNF-alpha release [59]. Cyclosporine has also been used successfully in some patients for LIP [60], and was used for two subjects in this series with unclear benefit. TNF-alpha -blocking agents (infliximab and etanercept) have attracted particular attention because of the putative role of TNF-alpha in granulomatous disease in CVID, and beneficial effects noted in some cases of sarcoidosis [61;62]. These therapies have also been used with some success in case reports of cutaneous [41] or systemic [63;64] granulomatous diseases in CVID. However, which subjects should be given this therapy, and when, remains unclear; collection of further data on this subject is required. It was given to two of our subjects with no improvement. Mycophenolate mofetil (CellCept) may be an alternative option especially in patients diagnosed with granulomatous and lymphocytic infiltrations as it may exert a preferentially suppressive effect on activated T cells, inhibits expression of adhesion molecules and inhibit nitric oxide (NO) synthesis [65]. However, immunosuppressive therapy may expose patients to a risk of opportunistic infections and possibly malignancy, a risk in CVID [1;36;66]. In pulmonary granulomatous lymphocytic lung disease, lung transplantation has been performed (as for case #6 here) however granulomas can recur in the transplanted lung [9]. Although hypercalcemia

is common in sarcoidosis presumably due to increased 1,25-dihydroxyvitamin D3 production by activated macrophages [67], it appears unusual in subjects with CVID with granulomas, with few exceptions [40] and case #14-here]. In these cases, steroids or hydroxycloquine can reduce the serum calcium. While the presence of granulomas can promote tissue damage leading to the need for intervention, it should be noted that 7 subjects in this cohort, with granulomas documented in tissues 1 to 18 years previously, have never required any treatment.

In summary, granulomatous disease is a relatively unusual complication of CVID and is still poorly recognized. The causes of this tissue reaction remain unknown, as the cellular and cytokine abnormalities are still not well elucidated. Where required on clinical grounds, the best therapeutic approach is to control the inflammatory cascade by using immunosuppressive and/or antiinflammatory agents as sparingly as possible. Clinical trials to gather sufficient data on subjects with this complication, coupled with additional investigation of the pathogenesis, may help to better guide therapeutic options.

References

- [1]. Cunningham-Rundles C. Common variable immunodeficiency. *Curr Allergy Asthma Rep* 2001;1:421–9. [PubMed: 11892068]
- [2]. Geha RS, Notarangelo LD, Casanova JL, Chapel H, Conley ME, Fischer A, Hammarstrom L, Nonoyama S, Ochs HD, Puck JM, Roifman C, Seger R, Wedgwood J. Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. *J Allergy Clin Immunol* 2007;120:776–94. [PubMed: 17952897]
- [3]. Chapel H, Lucas M, Lee M, Bjorkander J, Webster D, Grimbacher B, Fieschi C, Thon V, Abedi MR, Hammarstrom L. Common variable immunodeficiency disorders: division into distinct clinical phenotypes. *Blood* 2008;112:277–86. [PubMed: 18319398]
- [4]. Conley ME, Notarangelo LD, Etzioni A. Diagnostic criteria for primary immunodeficiencies. Representing PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies). *Clin Immunol* 1999;93:190–7. [PubMed: 10600329]
- [5]. Chapel H, Cunningham-Rundles C. Update in understanding common variable immunodeficiency disorders (CVIDs) and the management of patients with these conditions. *Br J Haematol*. 2009
- [6]. Busse PJ, Farzan S, Cunningham-Rundles C. Pulmonary complications of common variable immunodeficiency. *Ann Allergy Asthma Immunol* 2007;98:1–8. [PubMed: 17225714] quiz 8-11, 43
- [7]. Burton CM, Milman N, Andersen CB, Marquart H, Iversen M. Common variable immune deficiency and lung transplantation. *Scand J Infect Dis* 2007;39:362–7. [PubMed: 17454905]
- [8]. Martinez Garcia MA, de Rojas MD, Nauffal Manzur MD, Munoz Pamplona MP, Compte Torrero L, Macian V, Perpina Tordera M. Respiratory disorders in common variable immunodeficiency. *Respir Med* 2001;95:191–5. [PubMed: 11266236]
- [9]. Thickett KM, Kumararatne DS, Banerjee AK, Dudley R, Stableforth DE. Common variable immune deficiency: respiratory manifestations, pulmonary function and high-resolution CT scan findings. *Qjm* 2002;95:655–62. [PubMed: 12324637]
- [10]. Quinti I, Soresina A, Spadaro G, Martino S, Donnanno S, Agostini C, Claudio P, Franco D, Maria Pesce A, Borghese F, Guerra A, Rondelli R, Plebani A. Long-term follow-up and outcome of a large cohort of patients with common variable immunodeficiency. *J Clin Immunol* 2007;27:308–16. [PubMed: 17510807]
- [11]. North ME, Ivory K, Funauchi M, Webster AD, Lane AC, Farrant J. Intracellular cytokine production by human CD4+ and CD8+ T cells from normal and immunodeficient donors using directly conjugated anti-cytokine antibodies and three-colour flow cytometry. *Clin Exp Immunol* 1996;105:517–22. [PubMed: 8809143]
- [12]. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. *Clin Immunol* 1999;92:34–48. [PubMed: 10413651]

- [13]. Bayry J, Lacroix-Desmazes S, Kazatchkine MD, Galicier L, Lepelletier Y, Webster D, Levy Y, Eibl MM, Oksenhendler E, Hermine O, Kaveri SV. Common variable immunodeficiency is associated with defective functions of dendritic cells. *Blood* 2004;104:2441–3. [PubMed: 15226176]
- [14]. Cunningham-Rundles C, Radigan L. Deficient IL-12 and dendritic cell function in common variable immune deficiency. *Clin Immunol* 2005;115:147–53. [PubMed: 15885637]
- [15]. Scott-Taylor TH, Green MR, Eren E, Webster AD. Monocyte derived dendritic cell responses in common variable immunodeficiency. *Clin Exp Immunol* 2004;138:484–90. [PubMed: 15544626]
- [16]. Grimbacher B, Warnatz K, Peter HH. The immunological synapse for B-cell memory: the role of the ICOS and its ligand for the longevity of humoral immunity. *Curr Opin Allergy Clin Immunol* 2003;3:409–19. [PubMed: 14612664]
- [17]. van Zelm MC, Reisli I, van der Burg M, Castano D, van Noesel CJ, van Tol MJ, Woellner C, Grimbacher B, Patino PJ, van Dongen JJ, Franco JL. An antibody-deficiency syndrome due to mutations in the CD19 gene. *N Engl J Med* 2006;354:1901–12. [PubMed: 16672701]
- [18]. Kanegane H, Agematsu K, Futatani T, Sira MM, Suga K, Sekiguchi T, van Zelm MC, Miyawaki T. Novel mutations in a Japanese patient with CD19 deficiency. *Genes Immun* 2007;8:663–70. [PubMed: 17882224]
- [19]. Grimbacher B, Hutloff A, Schlesier M, Glocker E, Warnatz K, Drager R, Eibel H, Fischer B, Schaffer AA, Mages HW, Kroczeck RA, Peter HH. Homozygous loss of ICOS is associated with adult-onset common variable immunodeficiency. *Nat Immunol* 2003;4:261–8. [PubMed: 12577056]
- [20]. Salzer U, Chapel HM, Webster AD, Pan-Hammarstrom Q, Schmitt-Graeff A, Schlesier M, Peter HH, Rockstroh JK, Schneider P, Schaffer AA, Hammarstrom L, Grimbacher B. Mutations in TNFRSF13B encoding TACI are associated with common variable immunodeficiency in humans. *Nat Genet* 2005;37:820–8. [PubMed: 16007087]
- [21]. Castigli E, Wilson SA, Garibyan L, Rachid R, Bonilla F, Schneider L, Geha RS. TACI is mutant in common variable immunodeficiency and IgA deficiency. *Nat Genet* 2005;37:829–34. [PubMed: 16007086]
- [22]. Pan-Hammarstrom Q, Salzer U, Du L, Bjorkander J, Cunningham-Rundles C, Nelson DL, Bacchelli C, Gaspar HB, Offer S, Behrens TW, Grimbacher B, Hammarstrom L. Reexamining the role of TACI coding variants in common variable immunodeficiency and selective IgA deficiency. *Nat Genet* 2007;39:429–30. [PubMed: 17392797]
- [23]. Zhang L, Radigan L, Salzer U, Behrens TW, Grimbacher B, Diaz G, Bussel J, Cunningham-Rundles C. Transmembrane activator and calcium-modulating cyclophilin ligand interactor mutations in common variable immunodeficiency: clinical and immunologic outcomes in heterozygotes. *J Allergy Clin Immunol* 2007;120:1178–85. [PubMed: 17983875]
- [24]. Warnatz K, Denz A, Drager R, Braun M, Groth C, Wolff-Vorbeck G, Eibel H, Schlesier M, Peter HH. Severe deficiency of switched memory B cells (CD27(+)IgM(-)IgD(-)) in subgroups of patients with common variable immunodeficiency: a new approach to classify a heterogeneous disease. *Blood* 2002;99:1544–51. [PubMed: 11861266]
- [25]. Piqueras B, Lavenu-Bombléd C, Galicier L, Bergeron-van der Cruyssen F, Mouthon L, Chevret S, Debre P, Schmitt C, Oksenhendler E. Common variable immunodeficiency patient classification based on impaired B cell memory differentiation correlates with clinical aspects. *J Clin Immunol* 2003;23:385–400. [PubMed: 14601647]
- [26]. Wehr C, Kivioja T, Schmitt C, Ferry B, Witte T, Eren E, Vlkova M, Hernandez M, Detkova D, Bos PR, Poerksen G, von Bernuth H, Baumann U, Goldacker S, Gutenberger S, Schlesier M, Bergeron-van der Cruyssen F, Le Garff M, Debre P, Jacobs R, Jones J, Bateman E, Litzman J, van Hagen PM, Plebani A, Schmidt RE, Thon V, Quinti I, Espanol T, Webster AD, Chapel H, Vihinen M, Oksenhendler E, Peter HH, Warnatz K. The EUROclass trial: defining subgroups in common variable immunodeficiency. *Blood* 2008;111:77–85. [PubMed: 17898316]
- [27]. Sanchez-Ramon S, Radigan L, Yu JE, Bard S, Cunningham-Rundles C. Memory B cells in common variable immunodeficiency: clinical associations and sex differences. *Clin Immunol* 2008;128:314–21. [PubMed: 18620909]
- [28]. Ko J, Radigan L, Cunningham-Rundles C. Immune competence and switched memory B cells in common variable immunodeficiency. *Clin Immunol* 2005;116:37–41. [PubMed: 15925830]

- [29]. Arnold DF, Wiggins J, Cunningham-Rundles C, Misbah SA, Chapel HM. Granulomatous disease: distinguishing primary antibody disease from sarcoidosis. *Clin Immunol* 2008;128:18–22. [PubMed: 18486555]
- [30]. Fasano MB, Sullivan KE, Sarpong SB, Wood RA, Jones SM, Johns CJ, Lederman HM, Bykowski MJ, Greene JM, Winkelstein JA. Sarcoidosis and common variable immunodeficiency. Report of 8 cases and review of the literature. *Medicine (Baltimore)* 1996;75:251–61. [PubMed: 8862347]
- [31]. Mechanic LJ, Dikman S, Cunningham-Rundles C. Granulomatous disease in common variable immunodeficiency. *Ann Intern Med* 1997;127:613–7. [PubMed: 9341059]
- [32]. Kanathur N, Byrd RP Jr, Fields CL, Roy TM. Noncaseating granulomatous disease in common variable immunodeficiency. *South Med J* 2000;93:631–3. [PubMed: 10881789]
- [33]. Morimoto Y, Routes JM. Granulomatous disease in common variable immunodeficiency. *Curr Allergy Asthma Rep* 2005;5:370–5. [PubMed: 16091208]
- [34]. Bates CA, Ellison MC, Lynch DA, Cool CD, Brown KK, Routes JM. Granulomatous-lymphocytic lung disease shortens survival in common variable immunodeficiency. *J Allergy Clin Immunol* 2004;114:415–21. [PubMed: 15316526]
- [35]. Mullighan CG, Fanning GC, Chapel HM, Welsh KI. TNF and lymphotoxin-alpha polymorphisms associated with common variable immunodeficiency: role in the pathogenesis of granulomatous disease. *J Immunol* 1997;159:6236–41. [PubMed: 9550427]
- [36]. Cunningham-Rundles C. Hematologic complications of primary immune deficiencies. *Blood Rev* 2002;16:61–4. [PubMed: 11913998]
- [37]. Cunningham-Rundles C. Autoimmune manifestations in common variable immunodeficiency. *J Clin Immunol* 2008;28(Suppl 1):S42–5. [PubMed: 18322785]
- [38]. Pujol RM, Nadal C, Taberner R, Diaz C, Miralles J, Alomar A. Cutaneous granulomatous lesions in common variable immunodeficiency: complete resolution after intravenous immunoglobulins. *Dermatology* 1999;198:156–8. [PubMed: 10325463]
- [39]. Krupnick AI, Shim H, Phelps RG, Cunningham-Rundles C, Sapadin AN. Cutaneous granulomas masquerading as tuberculoid leprosy in a patient with congenital combined immunodeficiency. *Mt Sinai J Med* 2001;68:326–30. [PubMed: 11514920]
- [40]. Meyer A, Lachmann HJ, Webster AD, Burns A, Thway K. Hypercalcemia in a patient with common variable immunodeficiency and renal granulomas. *Am J Kidney Dis* 2005;45:e90–3. [PubMed: 15861342]
- [41]. Lin JH, Liebhaber M, Roberts RL, Dyer Z, Stiehm ER. Etanercept treatment of cutaneous granulomas in common variable immunodeficiency. *J Allergy Clin Immunol* 2006;117:878–82. [PubMed: 16630948]
- [42]. Misbah SA, Spickett GP, Esiri MM, Hughes JT, Matthews WB, Thompson RA, Chapel HM. Recurrent intra-cranial granulomata presenting as space-occupying lesions in a patient with common variable immunodeficiency. *Postgrad Med J* 1992;68:359–62. [PubMed: 1630981]
- [43]. North ME, Webster AD, Farrant J. Primary defect in CD8+ lymphocytes in the antibody deficiency disease (common variable immunodeficiency): abnormalities in intracellular production of interferon-gamma (IFN-gamma) in CD28+ ('cytotoxic') and CD28-('suppressor') CD8+ subsets. *Clin Exp Immunol* 1998;111:70–5. [PubMed: 9472663]
- [44]. Hatab AZ, Ballas ZK. Caseating granulomatous disease in common variable immunodeficiency treated with infliximab. *J Allergy Clin Immunol* 2005;116:1161–2. [PubMed: 16275393]
- [45]. Mrusek S, Marx A, Kummerle-Deschner J, Tzaribachev N, Enders A, Riede UN, Warnatz K, Dannecker GE, Ehl S. Development of granulomatous common variable immunodeficiency subsequent to infection with *Toxoplasma gondii*. *Clin Exp Immunol* 2004;137:578–83. [PubMed: 15320909]
- [46]. Wheat WH, Cool CD, Morimoto Y, Rai PR, Kirkpatrick CH, Lindenbaum BA, Bates CA, Ellison MC, Serls AE, Brown KK, Routes JM. Possible role of human herpesvirus 8 in the lymphoproliferative disorders in common variable immunodeficiency. *J Exp Med* 2005;202:479–84. [PubMed: 16103407]
- [47]. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. *N Engl J Med* 2007;357:2153–65. [PubMed: 18032765]

- [48]. Grunewald J, Eklund A. Role of CD4+ T cells in sarcoidosis. *Proc Am Thorac Soc* 2007;4:461–4. [PubMed: 17684290]
- [49]. Fehrenbach H, Zissel G, Goldmann T, Tschernig T, Vollmer E, Pabst R, Muller-Quernheim J. Alveolar macrophages are the main source for tumour necrosis factor-alpha in patients with sarcoidosis. *Eur Respir J* 2003;21:421–8. [PubMed: 12661995]
- [50]. Barnes PF, Fong SJ, Brennan PJ, Twomey PE, Mazumder A, Modlin RL. Local production of tumor necrosis factor and IFN-gamma in tuberculous pleuritis. *J Immunol* 1990;145:149–54. [PubMed: 2113553]
- [51]. Aly S, Laskay T, Mages J, Malzan A, Lang R, Ehlers S. Interferon-gamma-dependent mechanisms of mycobacteria-induced pulmonary immunopathology: the role of angiostasis and CXCR3-targeted chemokines for granuloma necrosis. *J Pathol* 2007;212:295–305. [PubMed: 17534845]
- [52]. Roach DR, Bean AG, Demangel C, France MP, Briscoe H, Britton WJ. TNF regulates chemokine induction essential for cell recruitment, granuloma formation, and clearance of mycobacterial infection. *J Immunol* 2002;168:4620–7. [PubMed: 11971010]
- [53]. Saunders BM, Tran S, Ruuls S, Sedgwick JD, Briscoe H, Britton WJ. Transmembrane TNF is sufficient to initiate cell migration and granuloma formation and provide acute, but not long-term, control of *Mycobacterium tuberculosis* infection. *J Immunol* 2005;174:4852–9. [PubMed: 15814712]
- [54]. Giovannetti A, Pierdominici M, Mazzetta F, Marziali M, Renzi C, Mileo AM, De Felice M, Mora B, Esposito A, Carello R, Pizzuti A, Paggi MG, Paganelli R, Malorni W, Aiuti F. Unravelling the complexity of T cell abnormalities in common variable immunodeficiency. *J Immunol* 2007;178:3932–43. [PubMed: 17339494]
- [55]. Cambronero R, Sewell WA, North ME, Webster AD, Farrant J. Up-regulation of IL-12 in monocytes: a fundamental defect in common variable immunodeficiency. *J Immunol* 2000;164:488–94. [PubMed: 10605046]
- [56]. Aukrust P, Lien E, Kristoffersen AK, Muller F, Haug CJ, Espevik T, Froland SS. Persistent activation of the tumor necrosis factor system in a subgroup of patients with common variable immunodeficiency--possible immunologic and clinical consequences. *Blood* 1996;87:674–81. [PubMed: 8555490]
- [57]. Cunningham-Rundles C, Radigan L, Knight AK, Zhang L, Bauer L, Nakazawa A. TLR9 activation is defective in common variable immune deficiency. *J Immunol* 2006;176:1978–87. [PubMed: 16424230]
- [58]. Ito T, Schaller M, Hogaboam CM, Standiford TJ, Chensue SW, Kunkel SL. TLR9 activation is a key event for the maintenance of a mycobacterial antigen-elicited pulmonary granulomatous response. *Eur J Immunol* 2007;37:2847–55. [PubMed: 17853411]
- [59]. Kalia S, Dutz JP. New concepts in antimalarial use and mode of action in dermatology. *Dermatol Ther* 2007;20:160–74. [PubMed: 17970883]
- [60]. Davies CW, Juniper MC, Gray W, Gleeson FV, Chapel HM, Davies RJ. Lymphoid interstitial pneumonitis associated with common variable hypogammaglobulinaemia treated with cyclosporin A. *Thorax* 2000;55:88–90. [PubMed: 10607809]
- [61]. Kahler CM, Heininger P, Loeffler-Ragg J, Vogelsinger H. Infliximab therapy in pulmonary sarcoidosis. *Am J Respir Crit Care Med* 2007;176:417. [PubMed: 17675452]author reply 417-8
- [62]. Wells AU. Infliximab in extrapulmonary sarcoidosis: tantalising but inconclusive. *Eur Respir J* 2008;31:1148–9. [PubMed: 18515552]
- [63]. Smith KJ, Skelton H. Common variable immunodeficiency treated with a recombinant human IgG, tumour necrosis factor-alpha receptor fusion protein. *Br J Dermatol* 2001;144:597–600. [PubMed: 11260023]
- [64]. Thatayatikom A, Thatayatikom S, White AJ. Infliximab treatment for severe granulomatous disease in common variable immunodeficiency: a case report and review of the literature. *Ann Allergy Asthma Immunol* 2005;95:293–300. [PubMed: 16200822]
- [65]. Zwerner J, Fiorentino D. Mycophenolate mofetil. *Dermatol Ther* 2007;20:229–38. [PubMed: 17970888]

- [66]. Le Guern V, Le Roux G, Martin A, Feuillard J, Cohen P, Poirer H, Raphael M, Guillevin L, Mouthon L. Lymphoma complicating common variable immunodeficiency with granulomatous disease: report of two cases. *Eur J Haematol* 2003;71:459–63. [PubMed: 14703697]
- [67]. Sharma OP. Hypercalcemia in granulomatous disorders: a clinical review. *Curr Opin Pulm Med* 2000;6:442–7. [PubMed: 10958237]

Figure 1.

The abdominal computed tomographic scan of subject # 15 who had a complex and mixed attenuation mass within the small bowel mesentery. This involved the spleen and surrounding tissues to the left of the midline. The arrow marks the left upper quadrant where the adhesive tissues in this area proved to be a collection of large granulomata. A splenectomy was performed.

Figure 2. Shows the spleen of subject # 19. She had a history of intractable AIHA and the splenectomy was done for this reason. The surface of the spleen revealed multiple white surface and interior lesions that were shown to be granulomas on histologic stains.

Figure 3.
Shows a histologic H&E stain revealing a solitary granuloma in the bone marrow of Subject # 26, done because she had ongoing ITP.

TABLE-1

Patients and Location of Granuloma

#	Sex	Age Dx (CVID)	Age Dx granuloma	Years with granulo ma	Location of Granuloma (Biopsy proven)	LIP *
1	F	2	8	2	Liver	-
2	F	5	7	2	Axillary lymph node	-
3	F	6	13	4	Lung	-
4	M	6	10	21	Cervical lymph node	-
5	F	11	11	4	Lung, lymph node, liver	Yes
6	F	11	10	20	Lung	-
7	M	12	15	29	Cervical lymph node	-
8	F	12	12	7	Lung	Yes
9	M	13	2	3	Liver, lymph node	-
10	M	14	33	4	Lung, liver	-
11	M	14	14	3	Skin, lymph node, kidney	-
12	F	16	12	16	Skin, cervical lymph node, retina (?)	-
13	F	16	19	7	Lung, liver	Yes
14	M	21	13	6	Lung	Yes
15	M	22	22	1	Spleen, bowel, lymph node	-
16	M	22	31	1	Skin with nerve infiltration	-
17	M	24	25	14	Liver	-
18	M	25	21	5	Lung	-
19	F	26	26	25	Lymph node, lung, liver, spleen	-
20	F	27	9	20	Lung, lymph node, skin, brain	-
21	F	27	23	3	Lung	-
22	F	29	33	5	Liver, spleen	-
23	F	30	13	10	Lung, inguinal lymph node	-
24	F	30	19	13	Lung, liver, spleen	-
25	F	31	?	20	Spleen, lymph node	-
26	F	32	43	9	Bone Marrow	-
27	F	35	30	3	Liver, brain	-
28	F	36	26	16	Lung	Yes
29	M	37	42	20	Lung, Lymph node, retina (?)	-

#	Sex	Age Dx (CVID)	Age Dx granuloma	Years with granulo ma	Location of Granuloma (Biopsy proven)	LIP *
30	M	37	28	7	Skin	-
31	F	38	33	6	Lung, liver	-
32	F	44	52	4	Lymph node, skin	-
33	F	48	30	25	Lung	-
34	F	50	51	10	Lung, bone marrow	-
35	F	50	51	18	Lung, liver	-
36	F	53	53	7	Lung	Yes
37	M	59	?	23	Lymph node, skin.	-

* LIP: lymphocytic interstitial pneumonia

TABLE-2
Laboratory Characteristics and Immunologic Functions

NUM	Sex	IgG*	IgA	IgM	% T	% B	CD4/CD8	Mitogen proliferation (cpm) *		
								PHA	CONA	PWM
1	F	169	<6.7	17.6	90.5	6.4	2.6	ND**	ND	ND
2	F	400	21	32	60	46	2.5	ND	ND	ND
3	F	420	2	18	82.0	10.0	ND	13856	14791	1915
4	M	395	0	118	46.0	7.0	0.7	20129	8919	1796
5	F	25	6	23	84	8.0	2.2	15460	7390	1310
6	F	246	10	46	65.0	5.0	2.2	11000	5210	5781
7	M	109	0	1	72.0	7.0	2.14	22535	13743	8994
8	F	295	0	30	ND	8.7	ND	ND	ND	ND
9	M	390	0	11	74.0	13.0	0.8	30770	7740	2150
10	M	310	2	51	71	7	1.12	76%	42%	56%
11	M	7	0	<7	84	32.0	1.2	ND	ND	ND
12	F	149	<6.7	35	89	1.7	0.2	ND	ND	ND
13	F	164	5	20	59.0	25.0	2.7	reduced	reduced	reduced
14	M	32	<7	<20	68	10	2.6	30%	21%	17%
15	M	33	<7	4	84	1.0	1	2100	1350	289
16	M	317	<6	<4	87	<1	2	3200	1600	2200
17	M	250	25	4	82.0	6.0	0.8	27750	26650	5600
18	M	222	10	12	69.5	3.5	ND	14268	9206	10697
19	F	60	7	20	68.0	1.0	ND	3515	2668	1388
20	F	<33	<7	<4	85	3.0	1.08	69%	43%	62%
21	F	78	10	12	86.0	6.0	3.2	33180	21273	7993
22	F	169	<7	12	44	<1	0.4	ND	ND	ND
23	F	8	5	0	90.0	0.0	1.45	21355	12378	16665
24	F	299	30	150	73.0	7	3.2	370	570	110
25	F	343	47	54	58	31.7	2.76	ND	ND	ND
26	F	415	19	15	60	9.0	1.5	22500	9500	2200
27	F	417	<22	59	89	7.0	2.28	51%	81%	66%
28	F	46	7	17	78	<5	5.5	4510	298	679

NUM	Sex	IgG*	IgA	IgM	% T	% B	CD4/CD8	Mitogen proliferation (cpm)*		
								PHA	CONA	PWM
29	M	223	<22	<17	92	0.0	0.418	reduced	reduced	reduced
30	M	210	0	35	91.0	4.0	2.2	34095	19097	6985
31	F	76	0	7	87.5	7.0	ND	7318	5250	1265
32	F	440	33	185	ND	ND	ND	ND	ND	ND
33	F	460	<43	44	74.0	21.0	2.05	44006	24427	18129
34	F	37	0	15	47.0	25.0	3.33	1038	1438	3830
35	F	50	14	43	38.0	5.0	1.5	8402	11029	7459
36	F	149	6.7	20.9	85.0	4.0	2.3	reduced	Normal	reduced
37	M	250	<5	30	78	7	4.1	56922	22841	18261

Mitogens: Under lined values are reduced. Normal ranges: PHA: 20,000- 90,000; CON A= 7,500-45,000; PWM = 2,500-30,000 or more than 80% of normal controls

* Serum IgG= 600-1600 mg/dl; IgA = 90-300 mg/dl; IgM

** ND= not done.

Table 3
Autoimmunity, Splenectomy and Treatment

number	Autoimmunity	Splenectomy/Reason	Other Treatments	Reason
1	-	-	Monthly IV methylprednisolone;	liver granuloma; also for sinusitis
2	AIHA/ITP	-	2 years prednisone, varying doses, rituximab once course	Autoimmunity
3	RA	-	?	-
4	AIHA	-	2 weeks prednisone for AIHA	AIHA
5	-	-	Pulse oral steroids	Granuloma
6	-	-	Several years prednisone , hydroxychloroquine	Lung granuloma
7	ITP	-	2 weeks of prednisone	ITP
8	AIHA	-	Cyclosporine 100 mg BID, several years of prednisone ; IV steroids for AIHA	Lung granuloma; AIHA
9	-	-	Pulse (monthly) steroids	Granuloma
10	ITP	-	Oral prednisone and IV steroids	ITP
11	ITP/AIHA	-	Oral and IV (monthly)steroids	Lung granuloma
12	-	Yes/enlarged	Prednisone for ITP in the past; now 20 mg/day every few months for uveitis	ITP /Uveitis
13	ITP	Yes/enlarged	6-9 months of prednisone	ITP and uveitis
14	-	-	Chronic prednisone 20 mg/day	Lung granuloma and hypercalcemia
15	-	Yes/ mass lesion	none	-
16	-	-	none	-
17	ITP	Yes/AIHA	6 months of prednisone	ITP
18	-	-	?	-
19	ITP/AIHA	Yes/AIHA	One year prednisone (20 mg /2 days)	ITP/ AIHA
20	-	-	Oral prednisone for 12 months	Lung granuloma
21	AIHA	-	IV Steroids for AIHA/Oral prednisone x 12 months for lungs	AIHA/Lung granuloma
22	ITP	Yes/ITP	Chronic oral prednisone , imuran, MTX [*]	ITP/Liver granuloma
23	AIHA	-	One month oral prednisone	AIHA
24	-	-	Trial Infliximab, hydroxychloroquine 200 mg BID x 15 years	Lung granuloma
25	ITP	Yes/ITP	One month prednisone	ITP
26	ITP	-	none	-
27	-	-	Imuran 100 mg/day x 6 months , daily prednisone 20 mg/ day x one year	Brain granuloma
28	ITP	Yes/ITP	MTX [*] 7.5 mg once a week x 6 months ; Cyclosporine, chronic prednisone	Lung granuloma
29	ITP/AIHA	-	Chronic prednisone (10 mg/2 days)	Cytopenia prevention
30	ITP	-	Two weeks prednisone for ITP; Two weeks for skin	ITP; Skin granuloma
31	-	-	Unknown doses oral steroids	Lung granuloma
32	-	-	Chronic prednisone , MTX7.5 mg once a week x 12 months , hydroxychloroquine 200 mg BID; , etanercept	Lung and skin granuloma
33	-	-	none	-
34	AIHA	Yes/AIHA	Years of prednisone , Hydroxychloroquine 200 mg BID x 5 years	AIHA; lung disease

number	Autoimmunity	Splenectomy/Reason	Other Treatments	Reason
35	ITP		Years of oral steroids (10 mg/ 2 days)	Lung granuloma; also gastrointestinal malabsorption
36	-	-	One week oral (5 mg day) steroids, Cox ₂ inhibitor	Lung granuloma
37	-	-	none	-

* MTX = methotrexate

TABLE-4**Mortality**

NUMBER	Sex	Age Dx (CVID)	Age Died	Reason of Death
6	F	11	34	Respiratory failure; post-op lung transplantation
8	F	12	27	Acute hemolytic anemia
15	M	22	26	Pneumonia
16	M	22	34	PML * and pneumonia (Pseudomonas)
21	F	27	30	Pneumonia, respiratory failure
23	F	30	43	Respiratory failure
24	F	30	41	Pulmonary hypertension, respiratory failure
28	F	36	48	Pneumonia, respiratory failure
34	F	50	69	Cirrhosis, acute liver failure
35	F	50	65	Respiratory failure, Pneumonia

* Progressive multifocal leukoencephalopathy