

TACI mutation with invasive polyclonal CD8⁺ T-cell lymphoproliferation in a patient with common variable immunodeficiency

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Mutations of the gene encoding the TNF receptor family member transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI), *TNFSRF13B*, have recently been described in patients with common variable immunodeficiency (CVID). We report the case of a man with CVID in association with a heterozygous TACI gene mutation (C104R) who had a highly unusual, invasive, polyclonal CD8⁺ T-cell lymphoproliferation resulting in massive hepatosplenomegaly and causing renal impairment because of infiltration. Although lymphoproliferation is well described in CVID, the key features in this patient included the T-cell origin of the lymphoproliferation, its polyclonal nature, its infiltration into multiple organs, and the presence of the TACI gene mutation. (*J Allergy Clin Immunol* 2006;117:870-7.)

Key words: Transmembrane activator and calcium-modulator and cyclophilin ligand interactor, common variable immunodeficiency, CD8, lymphoproliferation

Abbreviations used

APRIL:	A proliferation-inducing ligand
BAFF:	B-cell activating factor belonging to the TNF family
BAFF-R:	B-cell activating factor belonging to the TNF family receptor
CT:	Computed tomography
CVID:	Common variable immunodeficiency
ICOS:	Inducible costimulator
IgAD:	IgA deficiency
IVIG:	Intravenous immunoglobulin
RR:	Reference range
TACI:	Transmembrane activator and calcium-modulator and cyclophilin ligand interactor
TCR:	T-cell receptor

CASE PRESENTATION

A man was given a diagnosis of common variable immunodeficiency (CVID) in 1981 at the age of 20 years after recurrent bronchitis, pneumonia, and skin infections in association with panhypogammaglobulinemia. There was no family history of immunodeficiency. He was treated initially with intravenous immunoglobulin (IVIG) for 8 years before deciding to discontinue it for personal reasons. His recurrent infections returned over the next 6 years, and radiologic changes of early bronchiectasis developed, such that in 1995, IVIG was recommenced. However, during the first infusion, he had an anaphylactic reaction associated with high-titer anti-IgA antibodies, and IVIG was subsequently withheld.

In 2003, he presented with anorexia, weight loss, fevers, and night sweats. Examination revealed hepatosplenomegaly (liver span of 20 cm and spleen 13 cm below the costal margin), and thoracic and abdominal computed tomographic (CT) scans showed mediastinal, hilar, and para-aortic lymphadenopathy with early bronchiectasis. Investigations showed mild pancytopenia and markedly abnormal liver function test results, with a prominent increase of serum alkaline phosphatase level. The IgG level had decreased further to 0.33 g/L. Subsequent investigations, including a lymph node biopsy, showed a predominance of CD8⁺ T cells in blood, lymph nodes, and bone marrow but no evidence of lymphoma.

An alternative preparation of IVIG was commenced without incident, and he initially improved clinically, but over the following 18 months, the hepatosplenomegaly progressed (liver span of 25 cm and spleen 20 cm below the costal margin), with the return of nocturnal fevers and malaise. In 2005, his liver function deteriorated further. He had progressive renal impairment, with the creatinine value peaking at 0.3 mmol/L, and he was admitted for investigation. An abdominal CT scan confirmed massive hepatosplenomegaly and showed bilaterally enlarged kidneys. Peripheral blood phenotyping demonstrated a marked $\alpha\beta$ T-cell receptor (TCR)-positive CD8⁺ lymphocytosis, which was also present on bone marrow aspiration (Table I). V β TCR expression analysis of blood by

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TABLE I. Cell-surface phenotype of lymphocytes from blood, spleen, bone marrow, and splenic hilar lymph node taken in 2005 and analyzed by means of flow cytometry

Marker	Blood	Spleen	Bone marrow	Splenic hilar lymph node
CD3	92% (3772/ μ L)	90%	90%	93%
CD2	—	96%	78%	—
CD4	12% (492/ μ L)	6%	10%	30%
CD8	80% (3280/ μ L)	83%	80%	62%
CD5	—	89%	75%	—
CD7	—	90%	61%	—
CD10	—	1%	1%	—
CD19	0%	1%	0%	—
CD20	—	1%	0%	3%
HLA-DR	—	56	87%	—
Kappa	—	0%	0%	1%
Lambda	—	0%	0%	1%
CD3 ⁺ /CD16 or CD56 ⁺ (NK cells)	6%			
CD3 ⁺ /CD16 or 56 ⁺	1%			

Values represent percentages of lymphocytes as defined by light-scatter characteristics. In blood absolute counts are shown in parentheses. NK, Natural killer.

means of flow cytometry, covering approximately 70% of known V β families, showed this T-cell population to be polyclonal (Table II).

Diagnostic splenectomy and liver, kidney, and splenic lymph node biopsies were performed (results detailed below).

DIFFERENTIAL DIAGNOSIS

This man with established CVID had progressive hepatosplenomegaly characterized by a polyclonal CD8 lymphocytosis in blood. This progressed despite IVIG replacement until finally resulting in renal impairment. The main diagnostic possibilities for the hepatosplenomegaly included (1) lymphoma, (2) granulomatous disease, (3) amyloidosis, and (4) infiltrative lymphoproliferation, possibly related to chronic viral infection. For the renal failure, the main considerations were (1) infiltrative lymphoproliferative disease, possibly lymphoma; (2) amyloidosis; and (3) obstruction caused by retroperitoneal lymphadenopathy. Although most cases of CVID are idiopathic, the differential diagnoses for genetic causes of CVID are listed in Table III.¹⁻¹³

LABORATORY AND OTHER TESTING-PROCEDURES

1981

Immunoglobulin levels were as follows: IgG, 1.8 g/L (reference range [RR], 7-16 g/L); IgA, less than 0.1 g/L (RR, 0.7-4.5 g/L); and IgM, 0.30 g/L (RR, 0.8-2.5 g/L).

TABLE II. Expression of TCR V β families in the peripheral blood, with the RR

V β family	Result (% of CD3 cells)	RR (%)
V β 1	8.2	1.89-11.7
V β 2	3.2	4.03-23.48
V β 3	1.8	0.52-15.71
V β 4	1.6	0.79-3.26
V β 5.1	2.9	3.19-14.93
V β 5.2	1.7	0.49-4.98
V β 5.3	0.9	0.37-2.98
V β 7.1	6.2	0.64-20.01
V β 7.2	2.2	0.05-5.45
V β 8	4.2	2.26-29.47
V β 9	2	1.1-9.3
V β 11	0.7	0.25-5.11
V β 12	0.9	1-4.76
V β 13.1	1.9	1.62-8.16
V β 13.2	3	0.8-5.28
V β 13.6	3.3	0.84-8.8
V β 14	5.1	1.33-8.03
V β 16	0.8	0.42-1.9
V β 17	11.1	2.28-12.61
V β 18	0.5	0.58-5.23
V β 20	3.5	0-9.73
V β 21.3	3.4	1.08-5.97
V β 22	5.1	1.99-9.89
V β 23	4.1	0.28-4.76
Total	78.3	

Seventy percent of the expected V β T-cell repertoire is covered by these reagents (IOtest Beta Mark PN IM3497; Beckman Coulter, Fullerton, Calif). No underexpression or overexpression of a specific V β TCR family was detected, which is consistent with a polyclonal T-cell proliferation.

TABLE III. Proteins in which mutations have been described in association with CVID

Protein	Gene
Btk	Bruton's tyrosine kinase ^{3,4}
SAP	SH2D1A ⁵⁻¹⁰
ICOS	ICOS ¹¹
TACI	TNFRSF13B ^{1,2}
BAFF-R	TNFRSF13C ¹²
CD19	CD19 ¹³

SAP, Signaling lymphocyte activation molecule (SLAM)-associated protein.

2003

The results of full blood count showed a hemoglobin level of 90 g/L, a white cell count of 3.1×10^9 /L, and a platelet count of 112×10^9 /L.

Liver function tests showed a bilirubin level of 13 μ mol/L (RR, 2-21 μ mol/L), an albumin level of 40 g/L (RR, 35-53 g/L), an alkaline phosphatase level of 795 U/L (RR, 25-110 U/L), a gamma glutaryl transferase level of 138 U/L (RR, 10-49 U/L), an alanine transaminase level of 40 U/L (RR, 10-47 U/L), and an aspartate transaminase level of 53 U/L (RR, 5-40 U/L).

Electrolytes, urea, and creatinine values were normal.

Immunoglobulin levels were as follows: IgG, 0.33 g/L; IgA, 0.07 g/L; and IgM, 0.27 g/L.

Flow cytometry on peripheral blood showed the following: CD8⁺ T cells, 75% of lymphocytes (1365/ μ L); CD4⁺ T cells, 16% (291/ μ L); CD19⁺ B cells, 1% (18/ μ L). B-cell phenotyping demonstrated the absence of CD27⁺ memory B cells and increased CD21⁺ B cells, which is consistent with CVID category Ia.¹⁴

Lymph node biopsy (right axilla) showed interfollicular and parafollicular histiocytic proliferation with admixed small lymphocytes, which is consistent with a reactive lymphadenitis. No granulomas were seen. No organisms, including acid fast bacilli, were identified or cultured. Results of PCR for *Toxoplasma gondii* was negative. Flow cytometry on the lymph node showed CD8⁺ T cells to constitute 60% of lymphocytes, with 17% CD4 cells and 14% CD19 cells. There was no B-cell monoclonality, with a normal kappa/lambda ratio.

Bone marrow aspirate and trephine biopsy showed no morphologic abnormality. Seventy-five percent of lymphocytes were CD8⁺ T cells, with 13% CD4⁺ T cells and 6% CD19⁺ B cells. There was no B-cell monoclonality.

2005

The results of full blood count showed a hemoglobin level of 89 g/L, a white cell count of 6.9×10^9 /L, a lymphocyte count of 4.1×10^9 /L, and a platelet count of 129×10^9 /L. Blood film showed lymphocytosis and confirmed thrombocytopenia in the absence of platelet aggregates. No large granular lymphocytes were seen.

Liver function tests showed a bilirubin level of 16 μ mol/L, an albumin level of 32 g/L, an alkaline phosphatase level of 1186 U/L, a glutaryl transferase level of 136 U/L, an alanine transaminase level of 32 U/L, and an aspartate transaminase level of 46 U/L.

CT of the abdomen-pelvis revealed massive hepatosplenomegaly, bilaterally enlarged kidneys (16 cm in length), no dilatation of the collecting system, and no renal calculi.

Peripheral blood phenotyping by means of flow cytometry demonstrated CD8⁺ lymphocytosis (3280 cells/ μ L, Table I). All (100%) CD3 cells were $\alpha\beta$ -TCR⁺. V β -TCR expression analysis demonstrated polyclonality (Table II).

Bone marrow aspirate and trephine biopsy showed hypercellular marrow with trilineage maturation and mild lymphocytosis without evidence of lymphoma. Flow cytometry showed an increased population of CD8⁺ cells (80%) expressing the activation marker HLA-DR (Table I).

Histopathology of liver, spleen, and kidney biopsy specimens revealed marked expansion of the white pulp of the spleen by a diffuse and nodular infiltrate of small lymphoid cells, with extensive spillover of these cells into the red pulp (Fig 1, A). A similar dense, nodular, and diffuse small cell lymphoid infiltrate was present in the liver, involving the portal tracts and lobules (Fig 1, C), and in the renal interstitium associated with architectural distortion of the parenchyma (Fig 1, E). These infiltrates all stained

strongly for CD8 on immunoperoxidase (Fig 1, B, D, and F). There was no evidence of granulomatous inflammation or amyloidosis on Congo Red staining.

Flow cytometry of spleen cells showed that CD8⁺ T cells comprised the majority of infiltrating cells and the expressed activation markers CD38 and HLA-DR, minimal CD71 and CD69, and no CD25 (Fig 2), which is consistent with a state of chronic activation.¹⁵

Flow cytometric analysis for expression of proteins possibly deficient in CVID showed that surface expressions of CD19 and B cell-activating factor belonging to the TNF family (BAFF) receptor (BAFF-R/BR3) were normal in comparison with those seen in healthy control subjects (data not shown). Expression of inducible costimulator (ICOS) by T cells could not be determined because the patient's lymphocytes failed to activate in response to PHA, possibly because of the immunosuppressive medication that he was taking at the time of the attempted analysis (see below).

For viral studies, PCR test results for EBV, cytomegalovirus, human herpes virus 6, hepatitis B virus, and hepatitis C virus in blood were negative. PCR test results for human herpes virus 8 in tissue sections of the spleen were also negative. Hepatitis B virus surface antigen was negative.

In genetic testing X-linked lymphoproliferative disease was excluded by sequencing cDNA from peripheral blood, which showed a normal *SH2D1A* gene (S. Tangye, personal communication). Sequencing of the transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI) gene, however, revealed a heterozygous cysteine to arginine mutation at amino acid 104 (C104R) identical to the one described by both Geha and Grimbacher (Fig 3).^{1,2}

DIAGNOSIS WITH DISCUSSION OF PATHOGENESIS AND MANAGEMENT PLAN

This patient has a polyclonal, invasive, CD8⁺ T-cell lymphoproliferative disease on a background of CVID associated with a mutation of the TACI gene. There were no compelling cytologic features of T-cell lymphoma, except for tissue infiltration, and the polyclonal nature of the CD8 T-cell lymphoproliferation did not support it. There was no evidence of granulomatous disease, which can often complicate this condition.¹⁶ The disorder was not a proliferation of large granular lymphocytes because the morphology was that of typical lymphocytes, and natural killer cell markers were negative (Table I).

The patient was subsequently started on oral prednisolone, 75 mg/d. His fevers and malaise immediately resolved, and his creatinine and alkaline phosphatase levels both decreased to 0.12 mmol/L and 454 U/L, respectively. He was started on azathioprine (3 mg/kg) to assist weaning of his steroid dose, and his renal and hepatic functions have stabilized. His CD8 count remains increased (1548 cells/ μ L) but is significantly lower than baseline. The

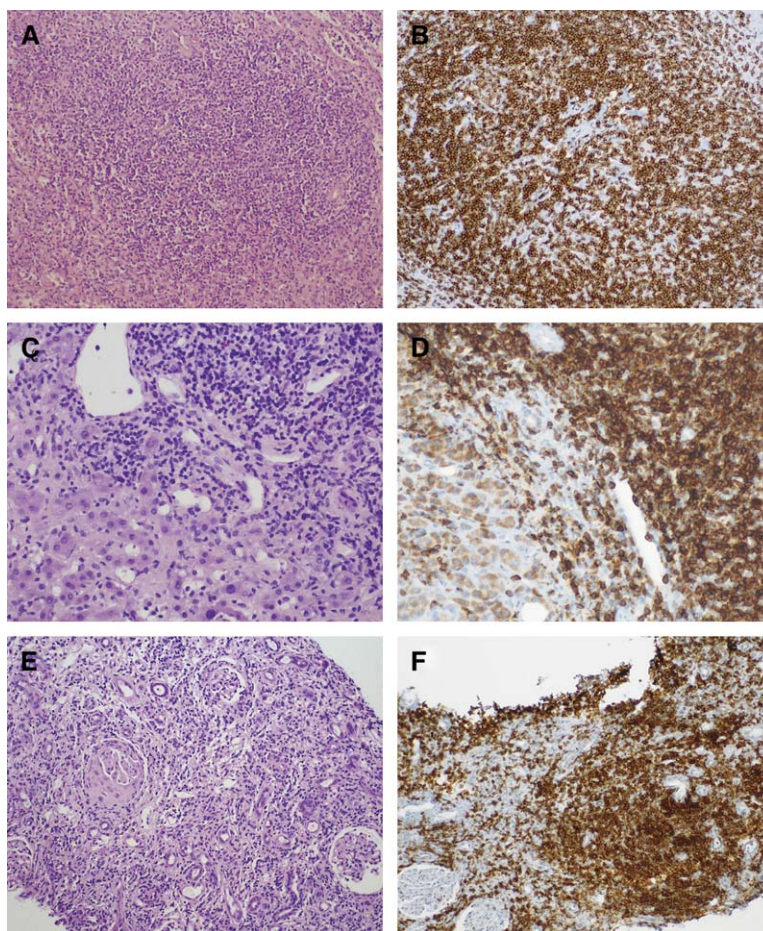


FIG 1. CD8⁺ T-cell infiltration of tissues stained with hematoxylin and eosin (**A**, **C**, and **E**) and with CD8 immunoperoxidase (**B**, **D**, and **F**). **A** and **B**: Spleen. Lymphoid aggregates composed of small to medium-sized CD8⁺ lymphoid cells. **C** and **D**: Liver. Dense CD8⁺ lymphoid infiltrate in portal tract (*upper right*), spilling over into the adjacent hepatic parenchyma. **E** and **F**: Kidney. Diffuse interstitial CD8⁺ lymphoid infiltrate with fibrous crescent in glomerulus on the *left*.

long-term plan of management is to control the end-organ effects of his lymphoproliferative disease, particularly the renal impairment, with immunosuppressive medications. Should these fail, consideration will be given to the use of mycophenolate, reserving traditional antilymphoma regimens as third-line therapy.

The key interest points in this case are the development of an infiltrative polyclonal CD8 T-cell lymphoproliferative disorder in association with CVID and the discovery of a mutation in the TACI gene in the same patient. Most cases of CVID are sporadic, whereas only a small proportion are familial.¹⁷ Of the familial cases, few have a clear-cut molecular explanation. It has been recognized that some cases of X-linked (Bruton's) agammaglobulinemia^{3,4} or X-linked lymphoproliferative (Duncan's) disease⁵⁻¹⁰ with mutations in the *Btk* and *SH2D1A* genes, respectively, can masquerade as CVID. These patients might present similarly to those with CVID, but they can be detected by means of direct sequencing of the relevant gene. Little was known of other genetic conditions that could be manifest as CVID until the last few years, during which

several mutations in proteins associated with B-cell activation have been discovered (**Table III**).

The first of these was a homozygous mutation of the ICOS gene,¹¹ an important costimulator for the activation of B cells by T cells.¹⁸ This mutation has only been described in 9 patients,¹⁹ and all possessed an identical mutation suggesting common ancestry. Recent reports have documented a further 2 apparently rare mutations associated with CVID, one involving BAFF-R and affecting a single patient¹² and the other involving the B cell-specific signaling protein CD19 in 3 siblings.¹³ In contrast, a third mutation, involving the TACI gene, has been demonstrated in a much greater proportion of patients with CVID,^{1,2} with estimates of 5% to 10% prevalence.² TACI, a member of the TNF receptor family, is thought to be important in mediating isotype switching in B cells by binding its ligands BAFF and a proliferation-inducing ligand (APRIL; **Fig 4**).^{1,20} Unlike the other genetic causes of CVID, TACI gene mutations are often heterozygous, and TACI surface expression seems preserved,^{1,2} except in the few cases of homozygous deficiency.²

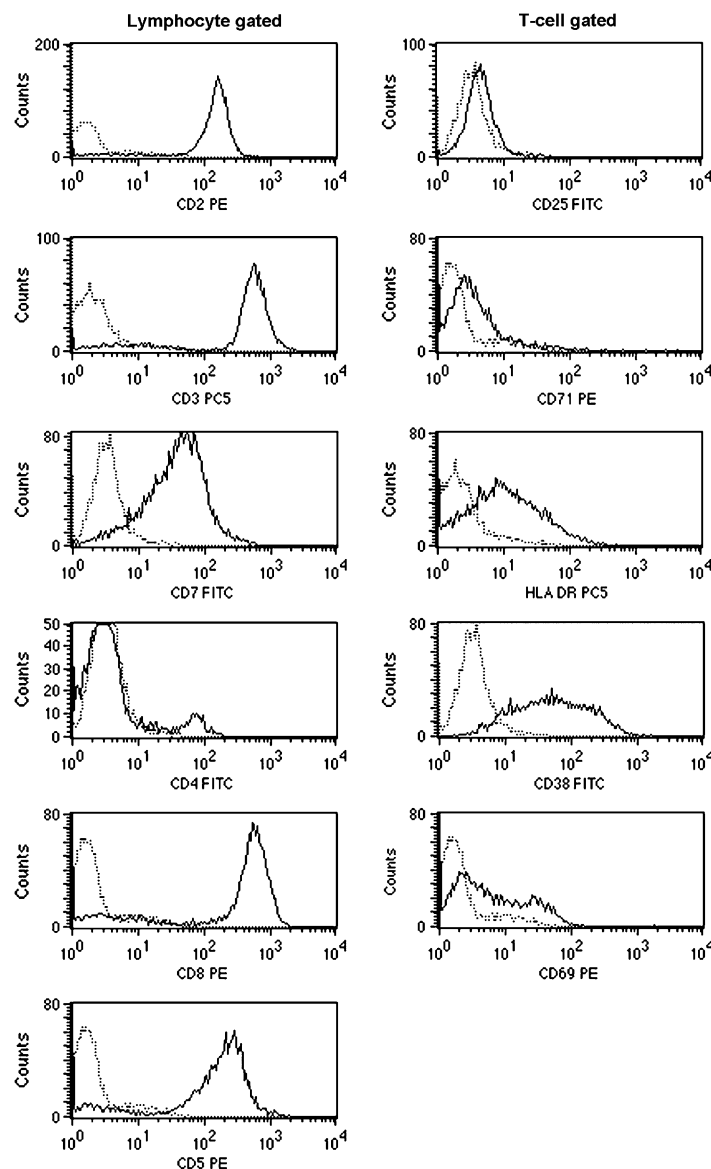


FIG 2. Flow cytometry of spleen cells showing expression of T-cell markers (*left histograms*, gated on lymphocytes by light scatter) and activation markers (*right histograms*, gated on T lymphocytes). Lymphocytes express all mature T-cell markers and are predominantly CD8⁺. T cells express the activation markers CD38 and HLA-DR but minimal expression of the other activation markers. Isotype controls are represented by *dotted lines*. PE, Phycoerythrin; FITC, fluorescein isothiocyanate; PC5, phycoerythrin-cyanin 5.

One fascinating observation made in both the reports linking TACI mutation with CVID was that the same mutation could also be found in patients with isolated IgA deficiency (IgAD), even within a CVID kindred.^{1,2} Furthermore, although the families reported by Castigli et al¹ showed a perfect correlation between mutations in the TACI gene and a personal history of either CVID or IgAD, the study by Salzer et al² revealed one case of a sibling who was free of humoral immunodeficiency, despite having a mutation in the TACI gene (a homozygous S144X mutation). Indeed, the C104R mutation in our patient was also detected in one of his 2 daughters, who nevertheless is presently asymptomatic and has normal

immunoglobulin levels and IgG subclasses. At this stage, the factors governing the phenotypic expression of the same mutation as CVID versus IgAD are completely unknown. Notwithstanding the observation that mutations within the TACI gene resulting in amino acid substitutions do not give rise to a monomorphic condition, there is an extremely convincing correlation with CVID and IgAD because extensive sequencing in healthy control subjects has failed to show the mutation,^{1,2} excluding the possibility that these mutations represent simple polymorphisms. It will be interesting to follow currently asymptomatic carriers for the possible evolution of immunodeficiency because most patients with CVID do not present until

adulthood. Thus although much more remains to be discovered regarding the clinical and biologic consequences of mutations of TACI, our report adds further weight to the hypothesis that mutations in the TACI gene are an important factor in CVID.

The pathogenesis of CVID in the context of TACI mutation remains speculative. Functional studies by Castigli et al¹ have shown that B cells from patients with the C104R mutation fail to produce either IgG or IgA in response to stimulation with APRIL but are able to produce IgG in response to BAFF stimulation, presumably through BAFF-R. This suggests that signaling through BAFF-R supports isotype switching to IgG, whereas activation of TACI is needed to switch to IgA secretion (Fig 4). One infers from this study that under normal circumstances, BAFF is able to bind both receptors and stimulate production of both IgG and IgA, whereas APRIL binds only to TACI and promotes IgA production. In this model dysfunctional TACI could account for IgAD, but the loss of IgG production characteristic of patients with CVID remains unexplained because BAFF stimulation through BAFF-R should not be affected. Further functional studies of B cells at all stages of development will be critical to our greater understanding of the pathogenesis of CVID in the setting of a TACI mutation and might provide an explanation for why it manifests in the heterozygous state.

Lymphoproliferative disorders are well documented in patients with CVID. There is an increased incidence of non-Hodgkin's lymphoma, usually of B-cell origin, although a case of T-cell lymphoma has also been documented.²¹ A study of 248 patients with CVID documented that 7.7% of the patients had non-Hodgkin's lymphoma over variable periods of time.²² The magnitude of this increase varies in different studies, with early estimates suggesting a risk of up to 438 times normal in women with CVID,²³ whereas a British study of 220 patients with CVID found 3 patients with lymphoma, resulting in a 30-fold increased risk of this disease.²⁴ A Danish-Swedish study found a somewhat lower risk, with 4 cases of lymphoma in 562 patients with CVID, resulting in a 12-fold increase in risk.²⁵ It is possible that some studies might have overestimated the true incidence of lymphoma, however, because tests of clonality were not always performed.²⁶

Benign lymphoproliferative disorders are more common than lymphoma in CVID. These range from reactive follicular lymphoid hyperplasia with preservation of lymph node architecture to atypical reactive lymphoid hyperplasia, in which lymph node architecture might be distorted by a polymorphic lymphocytic infiltrate.¹⁶ Extranodal lymphocytic infiltrates can also occur, including nodular lymphoid hyperplasia of the small intestine and lymphocytic infiltrates in the lung and bone marrow.²⁷ One US study of 30 nodal and extranodal lymphoid lesions from 17 patients with CVID found 14 cases of reactive lymphoid hyperplasia, 8 cases of atypical lymphoid hyperplasia, 6 cases of chronic granulomatous inflammation, and 2 cases of malignant lymphoma,¹⁶ although both lymphoma cases were diagnosed histologically without

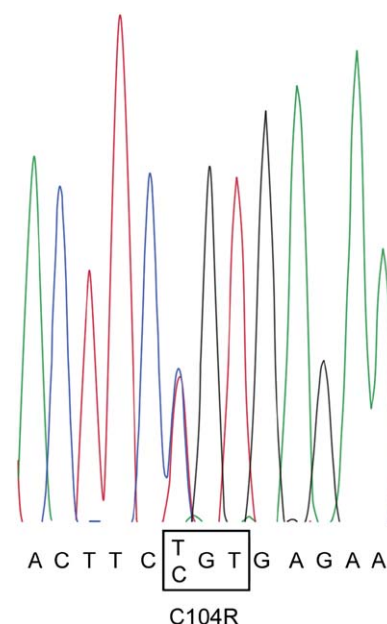


FIG 3. C104R heterozygous mutation in TACI gene exon 3. The T to C mutation in the sense strand is indicated, and the codon triplet is boxed. Exons were amplified by means of PCR, with primers described in Salzer et al² and sequenced with ABI Big Dye Version 3.1 (Applied Biosystems, Foster City, Calif) and an ABI Prism 3100 Genetic Analyser.

confirmation of clonality. Patients with atypical lymphoid hyperplasia had more widespread or massive disease, and several were initially given misdiagnoses of lymphoma on histology. Subsequent immunohistochemical analysis, immunophenotyping, and gene rearrangement studies demonstrated the infiltrate to be polyclonal, with expansion of both B- and T-cell compartments.¹⁶

The lymphoproliferation in the patient reported here displayed some characteristics that were typical of the benign lymphoproliferation reported in CVID but some that were most atypical. Our patient was in CVID category Ia, which is defined by a paucity of circulating CD27⁺ memory B cells and an increased proportion of immature CD21⁺ B cells,¹⁴ and this subgroup has been associated with benign lymphoproliferation.¹⁴ Furthermore, the prominence of circulating activated CD8⁺ T cells is well described in CVID, interestingly in association with splenomegaly.²⁸ However, in contrast to these reports, the clinical presentation in our patient with marked CD8⁺ T-cell proliferation involving the infiltration of multiple organs and resulting in parenchymal disruption and organ failure is highly unusual. There is only one reported case, to our knowledge, that had some similarities to ours,²⁹ a young female patient with CD8⁺ T-cell infiltration of the liver, spleen, and kidneys, along with renal failure. The authors suggested a diagnosis of T-cell lymphoma, although no clonal markers were performed to confirm this, and clinical progress and treatment were not reported. Lymphoma-like invasiveness by a proved polyclonal population of CD8⁺ T cells has not, to our knowledge, previously been documented in a patient with CVID.

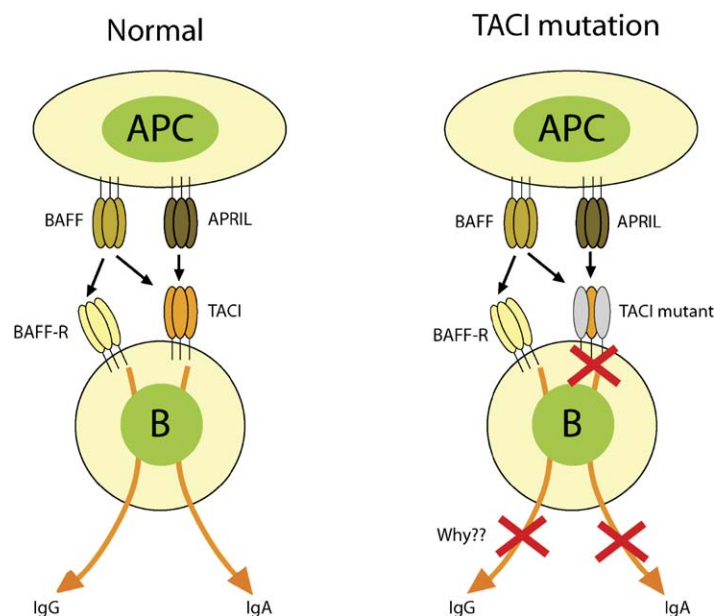


FIG 4. Speculative mechanism for the pathogenesis of CVID in the setting of the TACI mutation on the basis of experiments reported by Castigli et al.¹ TACI engagement seems important for B-cell isotype switching to IgA, although it is unclear why IgG production is affected in patients with CVID because BAFF-R engagement appears sufficient to promote IgG production *in vitro* (see text). APC, Antigen-presenting cell.

The link between the TACI mutation and the lymphoproliferation described in the patient here is unclear. Lymphoproliferation has been noted in the few reported patients with TACI mutations and CVID, with manifestations including splenomegaly (6/13) and tonsillar hyperplasia (5/13),² as well as one patient who had non-Hodgkin's lymphoma.¹ TACI-deficient mice have fatal lymphoproliferation, with splenomegaly and lymphadenopathy and frank lymphoma in up to 15%,³⁰ but the proliferation involves expansion of the B-cell compartment. These studies imply a role for TACI as a negative regulator of B-cell function in mice but do not carry immediate parallels to the patient reported here, who had marked T-cell expansion. Reports of the expression of TACI on activated T cells,³¹ although disputed by others,³² might be relevant, especially if TACI is shown also to be a negative regulator in T cells.

An alternate possibility for the CD8⁺ T-cell proliferation described here is that polyclonal T cells were responding to chronic infection. We think this is unlikely because the condition was very slowly progressive over several years, there was no specific V β clustering in what might be expected to be an oligoclonal response, and PCR results for likely viral candidates were negative. Nevertheless, because the few reported cases with TACI mutation have not at this stage shown the complication reported here, it is likely that another factor, be it environmental or genetic, is active.

SUMMARY STATEMENT

CVID is a heterogeneous disorder manifest by hypogammaglobulinemia and recurrent sinopulmonary infec-

tion. The cause is unknown in the majority of cases, although a family history in some patients suggests genetic influences. The latter remain largely unexplained, with the exception of rare deficiencies of various proteins with key roles in the B-cell activation and differentiation pathway (Table III). These deficiencies can often be readily detected by using simple flow cytometric assays, and identification of further cases of these rare disorders will aid our understanding of B-cell biology in CVID and related disorders and potentially pose novel methods of treatment.

The most exciting of these genetic causes of CVID (and IgAD) is the recent description of a mutation in the *TNFSRF13B* gene encoding the TACI protein, which might be present in up to 10% of patients.^{1,2} The higher prevalence compared with the other protein deficiencies might partly be explained by the dominant negative effect of the mutation, such that the majority of patients described are heterozygous, in contrast to most other immunodeficiency disorders, which are either X-linked or autosomal recessive. The patient reported here has CVID in association with a previously reported *TNFSRF13B* gene mutation but also demonstrated a marked infiltrative polyclonal CD8⁺ T-cell lymphoproliferative disorder. Although lymphoproliferation in CVID might be due to granulomatous disease, lymphoma, or pseudolymphoma, our patient was unique in that his CD8⁺ T cells infiltrated lymph nodes, blood, bone marrow, liver, spleen, and kidneys and resulted in organ disruption and renal failure. The relationship between the TACI mutation and the T-cell lymphoproliferative disorder is unclear, with further identification and follow-up of patients with such mutations needed to demonstrate the relationship between this biological abnormality and its clinical manifestations.

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