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Outcomes of splenectomy in patients with common variable immunodeficiency (CVID): a survey of 45 patients

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Summary

Splenectomy has been used in patients with common variable immunodeficiency disorders (CVID), mainly in the context of refractory autoimmune cytopenia and suspected lymphoma, but there are understandable concerns about the potential of compounding an existing immunodeficiency. With increasing use of rituximab as an alternative treatment for refractory autoimmune cytopenia, the role of splenectomy in CVID needs to be re-examined. This retrospective study provides the largest cohesive data set to date describing the outcome of splenectomy in 45 CVID patients in the past 40 years. Splenectomy proved to be an effective long-term treatment in 75% of CVID patients with autoimmune cytopenia, even in some cases when rituximab had failed. Splenectomy does not worsen mortality in CVID and adequate immunoglobulin replacement therapy appears to play a protective role in overwhelming post-splenectomy infections. Future trials comparing the effectiveness and safety of rituximab and splenectomy are needed to provide clearer guidance on the second-line management of autoimmune cytopenia in CVID.

Keywords: autoimmune cytopenia, common variable immunodeficiency, splenectomy, splenomegaly

Introduction

Common variable immunodeficiency disorders (CVID) is a heterogeneous group of disorders characterized by recurrent infections, hypogammaglobulinaemia and poor response to vaccination. Splenomegaly is a common feature in CVID, but neither its causes nor its consequences are well understood [1]. This clinical observation is associated closely with certain clinical presentations such as lymphadenopathy, granulomatous inflammation and autoimmune cytopenia [1,2], and is more prevalent among those with reduced class-switched memory B cells ($CD19^+CD27^+IgD^-IgM^-$) and increased $CD21^{lo}$ B cells [3–5].

The spleen is the largest secondary lymphoid organ and plays vital roles in the immune response. Due to its unique structure and vascularization, the spleen is essential in the removal of various blood-borne pathogens [6]. The innate and adaptive immune systems co-operate closely in the marginal zone of the spleen where the highly specialized monocyte–macrophage system captures pathogens by a set of unique surface receptors [7,8]. In humans, the severe reduction of marginal zone-like B cells in the peripheral blood following splenectomy indicates an important role for the spleen in the development or maintenance of this B cell population [9]. These B cells are thought to be crucial for the immune response to polysaccharides of encapsulated bacteria; therefore, CVID patients with decreased numbers of $CD27^+IgM^+IgD^+$ marginal zone-like B cells may have an increased burden of infections [10]. Thus the spleen, via several complementary mechanisms, supports defence especially against encapsulated bacteria. These unique functions of the spleen are illustrated clearly by the increased life-long risk of severe infections such as meningitis and septicaemia after splenectomy [11].

Despite the potential of compounding an existing immunodeficiency, splenectomy has been used in CVID patients mainly in the context of refractory autoimmune cytopenia and suspected lymphoma. There are understandable concerns about this approach, but unfortunately there are limited published data to guide these clinical decisions. Resnick and colleagues have reported recently that splenectomy was not associated with reduction in survival in CVID patients [12], but significant post-operative complications and infections have been shown in earlier reports [1,13]. With the increasing use of rituximab as an alternative treatment for refractory autoimmune cytopenia in immunocompetent individuals [14,15], the role of splenectomy needs to be re-examined in immune-incompetent patients.

Therefore, on behalf of the European Society for Immunodeficiencies (ESID) Clinical working party and EUROpean-Primary Antibody Deficiency network (EUROPADnet), a multi-centre retrospective clinical survey was set up to investigate the prevalence, indications for and outcomes of splenectomy in patients with CVID.

Patients and methods

Data collection

A retrospective survey was distributed among the European Society for Immunodeficiencies (ESID) Clinical Working Party and EUROPADnet between June and December 2010. The survey was also available for download on the ESID website during that period. Other centres were contacted based on a literature search of published case reports and through personal communications. Further details and clarifications were obtained by e-mail communication following submission of the survey.

Data of all splenectomized CVID patients, both alive and deceased, were collected from 16 centres in seven European countries: the Czech Republic, Italy, Germany, Spain, Sweden, Turkey and the United Kingdom. CVID patients were identified by individual centres in accordance with the ESID criteria (http://www.esid.org). Where splenectomy was performed > than 3 years prior to the formal diagnosis of CVID, the co-existing diagnosis of CVID was verified by the presence of (i) laboratory evidence of hypogammaglobulinaemia at the time of splenectomy, or (ii) a significant infection history predating splenectomy and a clinical history compatible with CVID. Patients who were diagnosed with a haematological malignancy during this window period were excluded from the study.

We defined splenomegaly as a palpable spleen on clinical examination, ultrasound caudal measurement of greater than 13 cm [16] or an actual weight greater than 400 g. Granulomatous complication was defined if granulomas were identified at any site, including the spleen, in a given patient. Autoimmune cytopenia included idiopathic thrombocytopenic purpura (ITP), autoimmune haemolytic anaemia (AIHA), Evan's syndrome (including trilineage cytopenia) and autoimmune neutropenia.

Criteria for response in autoimmune cytopenia to splenectomy or other treatments

Attempts to determine the therapeutic response of autoimmune cytopenia according to the recent international workshop [17] failed, due mainly to the loss of historical data. Therefore, treatment response was divided broadly into responder and non-responder based on the treating physician's judgement and the need for further therapies. Responders included those who were described as having complete or partial responses and who required no further treatment except for low-dose maintenance corticosteroid. Non-responders included patients who were described as having poor and no responses or who required subsequent alternative treatment. A partial response with multiple relapses following splenectomy was classified as a non-responder.

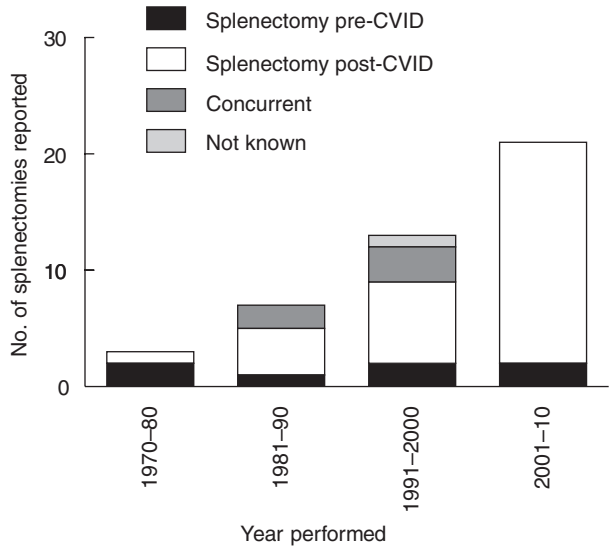

Fig. 1. Number of splenectomies performed on common variable immunodeficiency disorders (CVID) patients within Europe between 1972 and 2010 in relation to the timing of CVID diagnosis.

Defining severe infection after splenectomy

Meningitis and bacterial septicaemia were defined as overwhelming post-splenectomy infections (OPSI). Opportunistic infections and any infections resulting in death were also noted. The follow-up time in months was used as time denominator to calculate the rate of infection. Due to the potential confounding effects of lymphoma and chemotherapy on morbidity and mortality, patients ($n = 5$, patients 1, 5, 6, 21 and 31) with lymphoma were not included in this analysis.

Results

Patient characteristics

Forty-eight splenectomies were reported among 1211 CVID patients (4·0%; 12 deceased) between 1972 and 2010 (Fig. 1). No details other than alive/deceased status were available from three patients, so these were excluded from further evaluation. The indications for splenectomy are shown in Fig. 2.

The characteristics of the remaining 45 patients (male/female = 18/27) are summarized in Table 1 (also see Fig. 2). The ages at diagnosis of CVID ranged from 5 to 68 years [mean ± standard deviation (s.d.) = 30·5 ± 17·5]; patient 24 was excluded from the calculation because no data in this field were provided. The ages at splenectomy ranged from 8 to 74 years (32·8 ± 16·7) (patient 30 excluded). Thirteen splenectomies were performed prior to or at the diagnosis of CVID, 31 splenectomies with the knowledge of CVID and one unknown (year of CVID diagnosis not clear).

Of the CVID patients, 39 (86·7%) patients had splenomegaly, 36 (80%) autoimmune cytopenia, 29 (64·4%) lymphadenopathy, 20 (44·4%) liver disease, 20 (44·4%) gastrointestinal disease excluding iron deficiency, 20 (44·4%) granulomata and nine (20%) interstitial lung disease. Five lymphomas, including one T cell lymphoma, were reported. Organ-specific autoimmune diseases reported were scleroderma (one) and autoimmune diabetes (one). One patient had basal cell carcinoma.

Effectiveness of splenectomy in CVID

Splenectomy in autoimmune cytopenia. Splenectomy appears to be an effective treatment in autoimmune cytopenia in CVID. Evaluable data were available from 24 patients with autoimmune cytopenia (11 ITP, seven Evan's syndrome, five AIHA and one unclassified; 20 of 23 were splenectomized for refractory autoimmune cytopenia, four of seven for a combination of reasons). All patients except for patients 18, 19, 24, 40 and 42 had diseases refractory to corticosteroids, high-dose intravenous immunoglobulin (IVIG) or both. A summary is shown in Table 2. Eighteen of 24 patients (75%) were classified as responders and six patients (25%) were classified as non-responders. The use of both splenectomy and rituximab was noted in five patients. Patient 6 initially achieved a partial response after rituximab and then went into complete remission after splenectomy. Patient 17 failed to respond to splenectomy

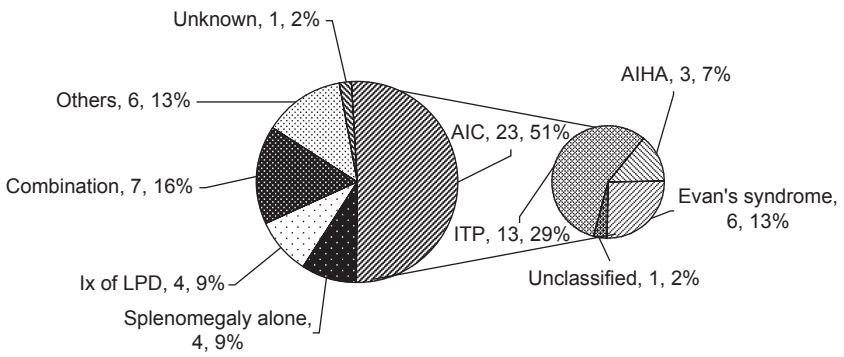

Fig. 2. Reasons for splenectomy. LPD: lymphoproliferative disorder; AIC: autoimmune cytopenia; ITP: idiopathic thrombocytopenic purpura; AIHAL autoimmune haemolytic anaemia.

Table 1. Patients' characteristics.

Patient no.	M/F	Age of CVID diagnosis	Age of splenectomy	Timing of splenectomy (before/after CVID diagnosis)	Splenomegaly	Other clinical phenotypes	Reason for splenectomy	Alive / deceased
1	M	22	44	After	Yes	Granulomatous, NHL	Splenomegaly, splenitis, atypical mycobacterium	A
2	F	12	14	After	Yes	–	Evan's syndrome	A
3	M	18	8	Before	Yes	Evan's syndrome, GI symptoms	–	A
4	M	53	53	Concurrent	Yes	Granulomatous, gastric carcinoma, pancreatic insufficiency	Part of gastrectomy	A
5	F	42	52	After	Yes	Pancreatic insufficiency, lymphoma	Evan's syndrome, suspected lymphoma	D
6	F	45	48	After	Yes	Chronic diarrhoea, liver disease, lymphadenopathy, lymphoma	AIC	D
7	M	35	36	After	Yes	Granulomatous, chronic diarrhoea	Suspected lymphoma	A
8	M	11	13	After	Yes	Granulomatous, lymphadenopathy, enteropathy, ILD	Evan's syndrome	A
9	F	47	49	After	Yes	Lymphadenopathy, malabsorption, ILD, liver disease	Evan's syndrome	A
10	F	17	16	After	Yes	Lymphadenopathy	Evan's syndrome	A
11	F	8	9	After	Yes	Lymphadenopathy, liver disease	Suspected lymphoma	A
12	F	30	43	After	Yes	Lymphadenopathy, gastritis with intestinal metaplasia, basal cell carcinoma	Suspected lymphoma	A
13	F	68	74	After	Yes	Granulomatous, lymphadenopathy, ILD, liver disease	Splenomegaly	A
14	F	62	66	After	Yes	Granulomatous, lymphadenopathy, ITP, chronic diarrhoea, liver disease	Splenomegaly	A
15	F	30	39	After	Yes	GI symptoms. ITP, liver disease	Trauma	A
16	F	17	22	After	Yes	Granulomatous, lymphadenopathy, enteropathy, liver disease	ITP	A
17	F	28	40	After	Yes	Granulomatous, lymphadenopathy, gastritis, liver disease	ITP	A
18	M	25	25	Concurrent	Yes	Granulomatous, lymphadenopathy, liver disease	ITP	A
19	F	22	23	After	No	Granulomatous, lymphadenopathy	ITP	A
20	M	31	31	Concurrent	No	Granulomatous, lymphadenopathy, ILD	ITP	A
21	M	65	61	After	Yes	Lymphadenopathy, ITP, ILD, liver disease, lymphoma	Splenomegaly, suspected lymphoma	A
22	F	5	20	After	Yes	Granulomatous, lymphadenopathy, ITP, ILD, liver disease, iron deficiency	Splenomegaly	A
23	F	35	35	Concurrent	No	Granulomatous, liver disease	ITP	A
24	M	–	18	Unknown	No	Lymphadenopathy, liver disease	Evan's syndrome	A
25	F	41	33	Before	No	Chronic diarrhoea, AIHA, autoimmune diabetes	ITP	A
26	F	43	20	Before	Yes	–	ITP	A
27	M	11	11	After	Yes	Granulomatous, lymphadenopathy, ILD	Evan's syndrome	A
28	M	13	15	After	Yes	Lymphadenopathy	ITP	A
29	F	22	35	After	Yes	Lymphadenopathy, malabsorption, liver disease	AIHA	A
30	M	35	–	After	Yes	Lymphadenopathy, AIHA, malabsorption, liver disease	Lymphoproliferative syndrome	D
31	F	37	48	After	Yes	Granulomatous, lymphadenopathy	T cell lymphoma	D
32	F	59	57	Before	Yes	Lymphadenopathy, ILD	AIHA	D
33	M	10	15	After	Yes	Chronic diarrhoea	ITP	A
34	F	20	26	After	Yes	Granulomatous, chronic diarrhoea	Evan's syndrome, splenomegaly	D
35	M	15	12	Before	Yes	Lymphadenopathy, enteropathy, AIN	ITP	A
36	F	28	31	After	Yes	Granulomatous, lymphadenopathy, liver disease	ITP, splenomegaly, suspected lymphoma	A
37	F	10	16	After	Yes	Lymphadenopathy, colitis, scleroderma	Splenomegaly	A
38	F	8	11	After	Yes	Granulomatous, lymphadenopathy, Evan's syndrome	Retroperitoneal bleeding following splenic biopsy	A
39	F	51	70	After	Yes	Lymphadenopathy, Evan's syndrome	Suspected lymphoma	A
40	M	7	17	After	Yes	–	ITP	A
41	M	61	68	After	Yes	Liver disease	AIHA	D
42	M	28	27	Before	Yes	Lymphadenopathy, granulomatous, enteropathy, iron deficiency, liver disease	Hepatosplenomegaly, AIHA	D
43	M	32	35	After	Yes	Liver disease.	Splenomegaly, AIHA	D
44	F	38	30	Before	No	Iron deficiency, liver disease	ITP	A
45	F	45	51	After	Yes	Lymphadenopathy, granulomatous, enteropathy, ILD, iron deficiency, liver disease	Systemic granulomatous disease	D

NHL: non-Hodgkin's lymphoma; AIC: unclassified autoimmune cytopenia; ITP: idiopathic thrombocytopenic purpura; AIHA: autoimmune haemolytic anaemia; AIN: autoimmune neutropenia; ILD: interstitial lung disease; CVID: common variable immunodeficiency disorders; GI: gastrointestinal; M/F: male/female.

Table 2. Outcome of splenectomy in autoimmune cytopenia.

Patient no.	Autoimmune cytopenia	Previous treatment	Outcome of splenectomy	Final treatment
6	Unclassified	Corticosteroid, rituximab	Responder	–
8	Evan's syndrome	Corticosteroid, high-dose IVIG	Responder	–
9	Evan's syndrome	Corticosteroid	Responder	–
10	Evan's syndrome	Corticosteroid, high-dose IVIG	Responder	–
17	ITP	Corticosteroid, cyclosporin	Non-responder	Rituximab, vincristine, cyclophosphamide
18	ITP	Unknown	Responder	–
19	ITP	Unknown	Responder	–
20	ITP	Corticosteroid, high-dose IVIG	Responder	–
24	ITP	Unknown	Non-responder	Rituximab
25	Evan's syndrome	Corticosteroid, high-dose IVIG, rituximab	Responder	–
26	ITP	Corticosteroid, high-dose IVIG, azathioprine, cyclosporin, cyclophosphamide	Responder	Rituximab (23 years later)
27	Evan's syndrome	Corticosteroid, high-dose IVIG	Responder	–
28	ITP	Corticosteroid, high-dose IVIG	Non-responder	Unknown
29	AIHA	Corticosteroid, high-dose IVIG	Responder	–
32	AIHA	Corticosteroid, high-dose IVIG, other immunosuppressants	Responder	–
33	ITP	Corticosteroid	Responder	–
34	Evan's syndrome	Corticosteroid, high-dose IVIG	Responder	–
35	ITP	Corticosteroid, high-dose IVIG	Responder	–
36	ITP	Corticosteroid	Responder	–
40	Evan's syndrome	None	Responder	–
41	AIHA	Corticosteroid, deoxycoformicin, azathioprine, chlorambucil	Non-responder	Corticosteroid, azathioprine
42	AIHA	None	Responder	–
43	AIHA	Corticosteroid	Non-responder	Corticosteroid
44	ITP	Corticosteroid	Non-responder	Bleomycin, azathioprine

AIHA: autoimmune haemolytic anaemia; ITP: idiopathic thrombocytopenic purpura; IVIG: intravenous immunoglobulin.

and cyclosporin, but achieved a partial response to combined therapy with rituximab, vincristine and cyclophosphamide. Patient 24 did not respond to splenectomy, but was treated successfully with rituximab and maintenance prednisolone 15 years later. Patient 25 had no response to rituximab, but went into complete remission after splenectomy. Finally, patient 26 went into complete remission for 23 years following splenectomy, and was treated successfully with rituximab upon relapse.

Splenectomy for suspected lymphoma. The diagnosis of lymphoma by splenectomy in CVID was low in this cohort (two of seven). Including those with a combination of reasons, seven patients underwent splenectomy as a diagnostic procedure for suspected lymphoma. Only patients 5 and 21 were diagnosed with lymphoma by splenectomy. Patient 5 had isolated splenic high-grade non-Hodgkin's lymphoma.

Adverse effect of splenectomy

Severe infection following splenectomy. When patients with lymphoma were excluded ($n = 5$), nine episodes of OPSI including eight cases of bacterial meningitis (two meningococcal, two pneumococcal, one *Haemophilus influenzae* and three not stated) and one case of pneumococcal sepsis were reported among 40 patients. IgG trough levels were available for 36 of 40 patients (mean = 8·46 g/l). Six episodes of OPSI occurred prior to Ig replacement therapy, as CVID was not yet diagnosed; one patient made a personal choice not to commence replacement therapy until a later date. Seven of the nine (77·8%) episodes of OPSI occurred within 3 years of splenectomy, two (22·2%) occurred between 4–6 years and none beyond. The annual risk of OPSI was calculated at 2·47% (nine episodes × 12/4375 months of follow-up × 100%).

Six episodes of cytomegalovirus (CMV) reactivation, five fungal infections, one enteroviral meningoencephalitis, one septic arthritis, one enterococcal peritonitis, one *Proteus mirabilis* septicaemia and one *Escherichia coli* pneumonia were also reported.

Surgical complication following splenectomy. Surgical complications were uncommon in this cohort. Two of 45 patients (patients 4 and 9) experienced non-fatal surgical complications (one subdiaphragmatic abscess and one portal vein thrombosis).

Mortality of splenectomized patients. A total of 10 deaths were reported in this cohort, of which the cause of death

Table 3. Summary of 26 histological reports.

Histological findings	Frequency (of 26)
Granulomatous inflammation	13
Congestive red pulp	8
Lymphoma/lymphoma-like	Highly malignant B cell NHL × 1 Plasmoblastic lymphoma × 1 Low-grade B cell lymphoma × 1 Castleman's disease-like × 1
Follicular hyperplasia	3
Atrophic germinal centres/white pulp	3

NHL: non-Hodgkin's lymphoma.

was available for nine patients. Four patients died from unusual infections (*E. coli* septicaemia, fungal septicaemia, disseminated CMV and *Pneumocystis jirovecii* pneumonia). Two of those four patients had received long-term immunosuppression for autoimmune cytopenia. The remaining deaths are thought to be unrelated to splenectomy. Three patients died from a combination of lymphoma, chemotherapy and secondary infections, one died from a sustained seizure secondary to existing neurological disease (no infection mentioned) and one died from uncontrolled bleeding following a lung biopsy. There were no reported deaths from OPSI. The overall risk of mortality, excluding patients with lymphoma, was 1·6% per patient year ($6 \times 12/4375 \times 100\% = 1{\cdot}6\%$).

Splenic histology

Histological descriptions of spleen were available from 26 patients and are summarized in Table 3. More than one finding was noted in some reports. Granulomas were reported in 13 (50%) patients, while congestive red pulp, lymphoid malignancy, follicular hyperplasia and atrophic germinal centres/white pulp were noted in eight (30·1%), four (15·3%), three (11·5%) and three (11·5%) patients, respectively.

Discussion

This report represents the largest cohort to date describing the outcome of splenectomy in CVID including treatment response in autoimmune cytopenia (Table 4). Splenectomy in CVID was described in a few reports, but detailed descriptions of outcomes were not always available [1,18–22]. The majority of splenectomies in our cohort were performed for refractory autoimmune cytopenia in the presence of splenomegaly, followed by investigational splenectomy for suspected lymphoma.

Effectiveness of splenectomy in CVID

Splenectomy is regarded as 'the most effective and best-evaluated' second-line therapy for AIHA that is refractory to corticosteroids [17]. However, while similar success was demonstrated in some reports of CVID-associated autoimmune cytopenia [1,13], the results from other studies were less convincing and relapses were common even if the initial responses were adequate (Table 4) [18,19,23]. Within our cohort, sustained responses of >1 year were seen in at least 17 of the 18 responders (17 of 24 = 70·8%), and nine of 16 (56·3%) remained in remission for 8 years or more. Our finding clearly supports previous studies reporting a high success rate of splenectomy in refractory autoimmune cytopenia [1,13]. Of note, a number of patients still required long-term oral corticosteroids (prednisolone 4–15 mg) following their splenectomies, but were able to avoid critical levels of cytopenia (data not shown). One patient remained on prednisolone 20–30 mg for granulomatous lung disease.

Rituximab is being used increasingly as an alternative in refractory autoimmune cytopenia in CVID [23–27]. A recent study reported an 85% success rate at 1 year and 50% at 39 ± 30 months, including four patients treated for relapse post-splenectomy. At the same time, three rituximab non-responders were treated successfully with splenectomy [23]. Another study also reported two patients requiring splenectomy after rituximab [12]. While in most autoimmune diseases rituximab use is followed by restoration of B cell populations [28,29], it is uncertain whether this is also true of its use in hypogammaglobulinaemic patients, and deaths have been reported following rituximab in these patients [23,30].

Both splenectomy and rituximab appear to be equivalent in their efficacy in autoimmune cytopenia in CVID. The follow-up after splenectomy has been longer than for rituximab, although splenectomy is irreversible. Therefore, decisions regarding these therapies should be made on an individual basis following careful risk/benefit assessments.

CVID patients carry an up to 12-fold increase risk of B cell lymphoma [31,32]. The diagnosis requires histological verification, which in some patients may lead to a splenectomy. In this survey, lymphoma was identified in only two of seven patients, and one patient also had lymph node involvement. Isolated splenic lymphoma was rare in this series, and in this case splenectomy is the diagnostic and therapeutic procedure of choice. However, all other means, including positron emission tomography (PET) scanning, should be exploited before resorting to splenectomy.

Histological findings

Splenic granulomata were noted in half the histological reports in this series. While splenic granulomata are rare and have been described mainly in sarcoidosis, lymphoma and tropical infections [33–35], the spleen is the third most common site after the lungs and lymph nodes in CVID [21,36–38].

Table 4. Summary of literature on splenectomy in common variable immunodeficiency.

Reports	No. of splenectomies	Surgical complication	Severe infection	Response for refractory AIC	Mortality in splenectomized patients
Hermaszewski & Webster 1993	14	1 Pulmonary embolism	Total = 5 2 meningitis, 3 pneumococcal infection resulting in death	Unknown	3 from infections, 1 from pulmonary embolism, 1 from lymphoma
Cunningham-Rundles & Bodian 1999	16	1 LUQ abscess and bowel obstruction, 1 draining fistula, 1 collection of fluid	Total = 2 2 pneumococcal sepsis	7/8 responses	None
Michel *et al*. 2004	6	None	Total = 1 1 *Toxoplasmosis gondii* uveitis (but also received multiple immunosuppressants)	4/6 responses	None
Seve *et al*. 2005	12	None	Total = 6 4 life-threatening pneumococcal infections, 2 *Neisseria meningitidis*	7/7 responses (4 relapses after 14 years)	None
Wang & Cunningham-Rundles 2005	11	Not mentioned	Not mentioned	5/7 responses (Evan's syndrome not included)	Not mentioned
Resnick *et al*. 2012	39	2 portal hypertension 2 fistulae	Total = 1 1 post-operative bacterial sepsis	15/19 responses (2 after rituximab)	Not applicable
ESID Clinical Working Party 2012	45	2/45	Total = 24 8 meningitis, 1 pneumococcal septicaemia, 5 fungal infections, 5 CMVs, 1 septic arthritis, 1 bacterial peritonitis, 1 enteroviral meningoencephalitis, 1 *Escherichia coli* pneumonia and 1 *Proteus sepsis*	18/24 responses (2 after rituximab)	4 from infections, 3 from lymphoma + chemotherapy + sepsis, 2 from unrelated causes, 1 unknown
Approximate estimation	143	10/132 = 7·6%	Not applicable	56/71 = 78·9%	Not applicable

LUQ: left upper quadrant; CMV: cytomegalovirus; ESID: European Society for Immunodeficiencies.

Adverse effects of splenectomy in CVID

The risk of procedure-related early complications following splenectomy in CVID is low and comparable to those in non-CVID cohorts (Table 4) [39,40]. The two reported complications in our cohort were non-fatal and treatable.

None of our patients suffered from septicaemia or meningitis prior to their splenectomies, suggesting that these infections were related, in part, to their procedures. Despite being treated adequately with Igs, the annual OPSI risk (2·47%) in our cohort is higher than that reported in non-CVID splenectomized patients (0·23–2·3%) [41,42]. However two-thirds of our OPSIs occurred when patients were not receiving Igs, suggesting that Ig replacement therapy may play a role in preventing these infections in CVID. This protective role of Ig replacement therapy is supported by the low infection rate also reported by Resnick and colleagues, in which all except one patient were on Ig replacement therapy at the time of their splenectomies [12]. As reported in non-CVID patients [43], the highest risk of OPSI lies within the first 3 years of splenectomy, as nearly 80% of the episodes occurred during this period. However, the life-long risk of OPSI as suggested by Waghorn was not demonstrated, but this could be secondary to the limited size of our cohort.

A fifth of our cohort suffered from unusual infections, such as CMV reactivation and fungal infections. Our result may be skewed by the high number of patients receiving maintenance corticosteroids and other immunosuppressants for autoimmune cytopenia. Unfortunately, we could not collect enough immunophenotypical data for any meaningful analyses, and the impact of splenectomy on the manifestation of opportunistic infection remains to be understood.

Data from the Northern European Database showed that the annual mortality rate associated with CVID patients with no disease-related complications, with autoimmune cytopenia, with lymphadenopathy or with enteropathy were 0·6, 2·3, 2·4 and 3·1%, respectively [44]. In agreement with other previously published data [2,12], non-infectious complications of CVID are associated with higher mortality. Given the high prevalence of non-infectious complications within our cohort, a mortality rate of 1·6% per patient year is lower than one would expected and does not suggest a higher mortality among splenectomized CVID patients.

Limitations of this study

These data are observational, and no direct comparison can be made with other published data in CVID or other diseases. The data were submitted voluntarily, and there is a risk that this would bias towards a higher apparent rate of splenectomy in CVID. Older data may be less complete because of the difficulty in capturing events from older records, and long-deceased patients may not be identified. Data returns were often incomplete, and the submitting centres were contacted to obtain clarification wherever possible. Where incomplete data were analysed, this is noted in the text.

Conclusion

Our data suggest that splenectomy represents an effective treatment for autoimmune cytopenia in most CVID patients who are refractory to steroids, and even rituximab. As in AIHA, there are currently no directly comparable data on the long-term efficacy and side effects of rituximab and splenectomy. Both therapies appear to be equivalent in their efficacy, but given the invasive and irreversible character of splenectomy, the sequential use of rituximab before splenectomy seems appropriate. Ig replacement therapy may have a protective role in overwhelming post-splenectomy infections in CVID and therefore, if possible, CVID patients should aim to achieve stable therapeutic IgG trough levels prior to splenectomy. Future trials investigating the role of prophylactic antibiotics, in particular during the early years, and a head-to-head comparison between splenectomy and rituximab would be invaluable for the care of CVID patients with refractory autoimmune cytopenia.

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Disclosure

The authors declare no conflicts of interest.

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