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Long-term remission rates after splenectomy in adults with Evans syndrome compared to immune thrombocytopenia: A single-center retrospective study

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Abstract

Objective: Evans syndrome, the combination of immune thrombocytopenia (ITP) and autoimmune hemolytic anemia (AIHA) or autoimmune neutropenia, is associated with a high rate of relapsed/refractory disease. There are limited data on the efficacy of splenectomy for this condition. We reviewed patient outcomes after splenectomy for Evans syndrome compared to ITP at our institution.

Methods: We performed a retrospective analysis of patients who underwent splenectomy for autoimmune cytopenias over a 23-year period with the intention of comparing disease relapse rates after splenectomy in patients with Evans syndrome and in those with ITP.

Results: During the study period, 77 patients underwent splenectomy for ITP and seven underwent splenectomy for Evans syndrome. In the Evans cohort, splenectomy led to an 85.7% initial response rate with a 42.8% rate of relapse within one year and a long-term (one-year) response rate of 42.8%. In the ITP cohort, the initial response rate was 90.9% with a long-term response rate of 70.1%.

Conclusion: Our data suggest that long-term remission rates after splenectomy are lower in adults with Evans syndrome compared to those with ITP, although splenectomy may still be an

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AUTHOR CONTRIBUTIONS

EDS involved in paper draft and data compilation. VR took part in paper draft, critical revision of manuscript, data formatting. JJS participated in critical revision of manuscript and data analysis. JZR involved in critical revision of manuscript, data formatting, and data analysis. TW participated in critical revision of manuscript and data analysis. BCS involved in critical revision of manuscript and approval of the submitted and final versions. TGD took part in critical revision of manuscript and approval of the submitted and final versions.

CONFLICT OF INTEREST

The authors have nothing to disclose.

DISCLAIMERS

None.

acceptable treatment for certain patients with Evans syndrome. Our findings underscore the need for further research and development of additional therapeutic strategies for this patient population.

Keywords

thrombocytes; red cell disorders

1 | INTRODUCTION

Evans Syndrome is an uncommon disease defined by the presence of immune thrombocytopenia (ITP) with autoimmune hemolytic anemia (AIHA) and/or autoimmune neutropenia.¹ The traditional first-line therapies for this condition include glucocorticoids and intravenous immunoglobulin (IVIG).¹ When effective, these treatments suppress immune-mediated cell destruction and allow for prolonged survival of circulating blood cells, thereby reducing the burden of end-organ dysfunction and symptoms experienced by patients. Unfortunately limited data series have suggested a high rate of relapsed or refractory disease after first-line medical treatment.² Splenectomy has been shown to produce robust five-year response rates in ITP and AIHA, but the data on its efficacy in Evans syndrome have been lacking.^{3–5} Some hypothesize that Evans syndrome represents a more advanced state of immune dysregulation than ITP and limited studies have demonstrated that splenectomy in Evans syndrome may produce long-term response rates of around 40%.^{6,7} We sought to evaluate outcomes in patients at our institution who underwent splenectomy for Evans syndrome in comparison with those with ITP.

2 | METHODS

We performed a retrospective analysis of all adult patients at our center who underwent splenectomy between the years of 1994 and 2017 for autoimmune cytopenias. In total, seven patients underwent splenectomy for Evans syndrome and 77 underwent splenectomy for ITP during the study period. All patients received at least one course of medical therapy prior to splenectomy for refractory cytopenias; the first-line treatment for all of these patients was corticosteroids, while subsequent lines of therapy varied between patients.

There were no major surgical complications in the patients with Evans syndrome. Primary outcomes assessed included initial response rate (RR), relapse rate within the first year after surgery, and long-term response rate, defined as a sustained response at the one-year mark. Response was defined as improvement in hematocrit and platelet count to within normal laboratory limits and loss of response as a sustained decrease to below the reference range. Long-term sequelae of splenectomy were not able to be measured with the data available.

3 | RESULTS

In the cohort with Evans syndrome (Table 1), six patients (85.7%) experienced immediate recovery of the hematocrit percentage to within normal range after splenectomy, and this response persisted through the follow-up period. Six patients (85.7%) had an increase in platelet counts to within normal limits after splenectomy, but three (42.8%) of these

demonstrated a loss of response within the first year, necessitating additional medical therapy. Three patients (42.8%) had long-term response in both hematocrit and platelet count after splenectomy, and one patient was lost to follow-up.

In the ITP cohort, 70 patients (90.9%) had an initial correction of platelet count to within normal range after splenectomy. Eleven patients (14.3%) experienced relapse within 1 year, while 54 (70.1%) entered long-term remission.

Two patients in the Evans cohort had a history of hematologic malignancy. One patient had a distant history of Hodgkin lymphoma that had been treated with BEACOPP chemotherapy—consisting of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone—leading to lymphoma remission 5 years prior to diagnosis of Evans syndrome. This patient's Evans syndrome remains in remission after splenectomy. The second patient had chronic lymphocytic leukemia (CLL) and was treated with corticosteroids, pentostatin, rituximab, and cyclophosphamide prior to splenectomy. This patient ultimately received mycophenolate mofetil 2 years after surgery for Evans relapse and then six cycles of rituximab and bendamustine for CLL progression. One additional patient was diagnosed with hepatitis C virus (HCV) infection during a hospital admission for Evans syndrome, with a quantitative HCV viral load of 5.2 million IU/mL. No treatment for this patient's infection was initiated during the hospitalization, and the patient was lost to follow-up after discharge.

4 | DISCUSSION

Our retrospective review of patients treated with splenectomy for Evans syndrome and ITP suggests that patients with both conditions experience similar initial response rates (90.9% vs 85.7%) after surgery, but those with Evans syndrome have significantly higher rates of relapse within 1 year after splenectomy than those with ITP. In particular, the rate of recurrent thrombocytopenia after splenectomy in patients with Evans syndrome was 42.8%, although interestingly there was no documented recurrence of autoimmune anemia in any of these patients. The etiology of the higher rate of relapse in Evans syndrome is unclear, although this condition may represent a more advanced state of immune dysregulation than ITP alone, and may therefore be more often refractory to therapy. Recurrence of thrombocytopenia but not of other autoimmune cytopenias after splenectomy has also been observed in patients with autoimmune lymphoproliferative syndrome (ALPS), consistent with their shared pathophysiologic mechanism.⁸ Our findings are broadly consistent with the limited existing literature on the efficacy of splenectomy in patients with Evans syndrome; for instance, an older retrospective series found that 60 percent of patients required additional medical therapy after splenectomy.⁶

Splenectomy is generally a safe procedure when performed for hematologic disorders,^{9,10} and there were no documented postoperative complications in our limited cohort of patients with Evans syndrome. However, the potential for surgical morbidity, including bleeding and arterial or venous thrombosis, must be taken into account when considering treatment options for patients with autoimmune cytopenias.¹¹ Moreover, splenectomy is an invasive and irreversible procedure and patients may express a preference to avoid it.

It has also been suggested that patients with Evans syndrome may have a higher rate of postsplenectomy infection than other groups. In pediatric cohorts, ALPS has been shown to heavily overlap with Evans syndrome and is associated with significant asplenia-associated morbidity. One retrospective series of patients with ALPS found that 30% of those who underwent splenectomy developed invasive bacterial infections, primarily with *Streptococcus pneumoniae*, and nearly half of these patients died as a result of infection.¹² Similar rates of invasive bacterial infections in asplenic ALPS patients have been recorded in other studies.^{13,14} Indeed, one large-scale review found the rate of bacterial sepsis exceeded 40 percent in ALPS patients after splenectomy and that risk of severe infectious complication, primarily involving encapsulated organisms, persisted for many years after surgery,⁸ suggesting that this is an important long-term complication that may not have been adequately captured in our data. The cause for the higher than expected rate of invasive bacterial infections in this patient population is unknown, but may be related to the more advanced state of immune dysregulation in these patients leading to heightened infectious risk.

Conversely, certain patients with medically refractory disease may view splenectomy as preferable to long-term immunosuppression, particularly those with comorbidities or lifestyles that are adversely affected by chronic medical management. Steroidsparing therapies such as splenectomy may significantly improve the quality of life of some patients. It is therefore crucial to review medical and surgical treatment options, and the risks and benefits of each approach, with the patient prior to approaching this clinical decision.

There are currently several accepted medical therapies that are used with varying degrees of success in patients with ITP; these include IVIG, targeted anti-CD20 therapies (particularly rituximab), mammalian target of rapamycin (mTOR) inhibitors, and a splenic tyrosine kinase inhibitor, fostamatinib. Thrombopoietin receptor agonists such as eltrombopag and romiplostim are also used with varying degrees of success. Current guidelines recommend use of these agents along with splenectomy, when clinically appropriate, in patients with steroid-refractory or relapsed ITP.^{1,4,15,16} However, the high cost of these medications, need for long-term therapy, and unpredictable response rates may make splenectomy an attractive therapeutic alternative in certain patients. Although there is a paucity of data to recommend these agents in Evans syndrome, primarily due to the rarity of this disease, there has been some evidence for their use in other autoimmune hematologic disorders.¹

While our data suggest that splenectomy may not lead to durable remission in a significant proportion of patients with Evans syndrome, additional information is needed to weigh the potential costs and benefits of surgical versus medical management. Our analysis should be considered in the context of its limitations, including small sample size and single-center involvement. It is important to recognize that Evans syndrome is an uncommon condition and most published cohorts are therefore small, although drawing clinical conclusions from such limited data can be challenging. While such data are informative and should be considered in approaching this clinical scenario, they do highlight the need for large-scale, multicenter studies to guide decision-making in this context.

In summary, our retrospective review at a single academic medical center suggests that splenectomy may produce an initial clinical response in patients with Evans syndrome, but that the durability of this response is often limited, as opposed to the long-lasting remissions frequently attained in patients with ITP. A significant proportion of patients who underwent splenectomy for Evans syndrome at our institution ultimately required additional postoperative medical management for refractory disease. The rarity of Evans syndrome, which has historically limited the amount of data available to guide treatment decisions, and the limited effective therapeutic options make further research into the management of this condition imperative.

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TABLE 1

Patients with Evans syndrome treated with splenectomy

Patient	Pharmaceutical therapies		Hematologic parameters			
	Presplenectomy	Postsplenectomy	Platelets (x10 ⁹ /L)	Hemoglobin (g/dL)	Hematocrit (%)	
23 F 1° Evans	Dexamethasone Prednisone IVIg anti-D globulin	Danazol IVIg	Presurgery postsurgery	6.8 -	20.7 -	
33 F 1° Evans	Dexamethasone IVIg	Dexamethasone IVIg	Presurgery Postsurgery	- -	- -	
51 F 1° Evans	Dexamethasone Rituximab	Cyclophosphamide Prednisone mycophenolate	Presurgery postsurgery	10.3 12.2	30.9 35.7	
69 M CLL 2° Evans	Dexamethasone Prednisone IVIg Rituximab cyclophosphamide Pentostatin	Prednisone Mycophenolat	Presurgery Postsurgery	3.6 9.1	9.8 24	
31 M Hodgkin lymphoma 2° Evans	Prednisone	-	Presurgery Postsurgery	5.9 9.5	16	
24 F Hepatitis C infection 2° Evans	Dexamethasone Prednisone IVIg	Prednisone	Presurgery Postsurgery	10.2 -	32.6 -	
25 F 1° Evans	Dexamethasone IVIg	Prednisone IVIg Cyclophosphamide Vincristine Rituximab	Presurgery Postsurgery	2 7	6.9 23	

Note: A total of seven patients with Evans syndrome underwent splenectomy. The medical therapies used before surgery and those used postoperatively are listed, along with preoperative count nadir and postoperative count peak after surgery. Several patients had complete responses documented in their charts without quantified platelet and hematocrit numbers recorded in our electronic medical record.