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Splenectomy in the management of primary immune-mediated hemolytic anemia and primary immune-mediated thrombocytopenia in dogs

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Abstract

Background: Current reports about the use of splenectomy for the management of immune-mediated hemolytic anemia (IMHA) or immune-mediated thrombocytopenia (ITP) or both in dogs are limited.

Objectives: To retrospectively describe the use of splenectomy as part of the management for IMHA, ITP, and concurrent IMHA and severe thrombocytopenia (CIST) in dogs. It was hypothesized that splenectomy would be beneficial in allowing for reduction of dose of immunosuppressive drugs or discontinuation in 1 or more of these groups.

Animals: Seventeen client-owned dogs (7 with IMHA, 7 with ITP, and 3 with CIST) were identified across 7 UK-based referral hospitals from a study period of 2005 to 2016.

Abbreviations: AIHA, autoimmune hemolytic anemia; ANA, antinuclear antibodies; BUN, blood urea nitrogen; CIST, concurrent immune-mediated hemolytic anemia and severe thrombocytopenia; CT, computed tomography; DAT, direct antiglobulin test; FE, female entire; FN, female neutered; FNA, fine needle aspirates; IMHA, immune-mediated hemolytic anemia; ITP, immune-mediated thrombocytopenia; ME, male entire; MN, male neutered; MRI, magnetic resonance imaging; N/A, not applicable; NAD, no abnormalities detected; PIMA, precursor-targeted immune-mediated anemia; PLT, platelet; RVS, referring veterinary surgery; SAT, saline agglutination test; TED, thromboembolic disease; TEG, thromboelastography; US, ultrasound.

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Methods: Data were collected retrospectively via questionnaires and included information about diagnosis, management and treatment response before and after splenectomy. Based on clinical outcome, treatment with splenectomy as part of the management protocol was classified as either successful or unsuccessful.

Results: Six of 7 dogs with ITP were managed successfully with splenectomy as part of their management protocol (3 complete and 3 partial responses), although 1 subsequently developed suspected IMHA. Of the 7 dogs with IMHA, splenectomy was part of a successful management protocol in 4 dogs (2 complete and 2 partial responses). In the CIST group, 1 case (1/3) responded completely to management with splenectomy as part of the management protocol.

Conclusions and Clinical Importance: Splenectomy was considered successful and well tolerated in most cases of isolated ITP. Whether there is a benefit of splenectomy in cases of IMHA and CIST could not be determined in the current study.

KEYWORDS
AIHA, autoimmune, IMHA, ITP, spleen

1 | INTRODUCTION

Immune-mediated hemolytic anemia (IMHA) and immune-mediated thrombocytopenia (ITP) are common causes of anemia and thrombocytopenia, respectively, in dogs.[1,2] Nonassociative/primary disease is diagnosed if infectious, neoplastic, or toxic causes cannot be identified.[3] Mainstay treatment is medical management with glucocorticoids, often alongside adjunctive immunomodulatory therapies.[1,4] Concurrent IMHA and severe thrombocytopenia (CIST) can occur.[5] This is commonly called "Evans syndrome," a term first used in human medicine describing concurrent autoimmune hemolytic anemia (AIHA) and ITP without an identified cause.[6] In dogs with IMHA, concurrent immune-mediated destruction of platelets is often suspected but infrequently proven.[5,7]

Platelet or erythrocyte destruction is mediated through autoantibody binding,[3] promoting destruction via the complement cascade or hepatic/splenic monocyte phagocyte system. In human ITP, splenic plasma cells produce anti-platelet antibodies.[8] Therefore, the spleen represents a potential therapeutic target.

In humans with ITP or AIHA, as in dogs, glucocorticoids represent first-line treatment.[9,10] Splenectomy is performed in chronic, refractory ITP, with two thirds discontinuing medical treatment by 5 years after splenectomy.[11] Despite increased use of rituximab (monoclonal antibody targeting CD20) and thrombopoietin receptor agonists, splenectomy remains an important treatment option for human ITP,[12] and immune-mediated hematological disorders are a common reason for nontraumatic elective splenectomy.[13] In human AIHA, splenectomy might theoretically be more beneficial when Fc-mediated phagocytosis is the predominant mode of erythrocyte destruction (compared to complement-mediated phagocytosis or intravascular hemolysis) but, overall, outcome after splenectomy is variable and unpredictable.[14]

Published response and relapse rates for dogs with IMHA, ITP, and CIST treated medically are variable. Response rates of ~80% are reported with the use of prednisolone alone in IMHA,[4,15-19] with relapse rates of ~11% to 24%.[15,18,20] With ITP, 1 study reported that 89.6% of dogs survived to discharge, with a 41% relapse rate.[21] Little data is available for the long-term follow-up of CIST treated medically: 1 study reported that only ~24% of dogs treated medically were alive at 30 days from hospital admission,[5] and another that 75% of dogs survived to discharge.[7] Splenectomy could be an attractive option in cases poorly responsive to medical treatment, or where sustained medical treatment is cost prohibitive, produces adverse effects or is unavailable.

Only small case series about splenectomy as treatment for immune-mediated hematological disorders in dogs are published,[22-25] making drawing conclusions difficult; however, splenectomy appears well tolerated. Our experience is that splenectomy is usually offered either as a "last resort" in cases refractory to immunosuppressants, or where splenic abnormalities are identified. Anecdotally, some of these cases appear to respond favorably, often despite failing multiple prior treatment modalities. The objective of this retrospective study was to describe the clinical outcomes of dogs with IMHA, ITP, and CIST that underwent splenectomy. We hypothesized that splenectomy would be beneficial in allowing for immunosuppressive drug dose reduction or discontinuation.

2 | MATERIALS AND METHODS

2.1 | Study groups

Thirteen referral centers in the United Kingdom (UK) were invited to contribute via personal communication. Collaborators searched their clinical databases for dogs diagnosed with nonassociative IMHA, ITP, or CIST that underwent splenectomy during treatment between 2005 and 2016; 1 center included cases from 2001 to 2016. For dogs in all 3 groups, minimum diagnostic investigations required for inclusion

were hematology, biochemistry, and thoracic and abdominal imaging, to rule out inciting causes. Infectious disease screening was not an inclusion criteria and was performed at the clinician's discretion; when performed these details were collected. Dogs with evidence of a disease trigger were excluded. Benign splenic histopathological changes, including extramedullary hematopoiesis or lymphoid hyperplasia, were not excluded.

Clinical details were acquired via questionnaires, capturing signalment, vaccination status, travel history, diagnostic tests performed, and concurrent treatment (before, during, and after splenectomy). Questionnaires requested information about clinical reasoning behind splenectomy, histopathology, complications, and subsequent hematological values, and invited clinicians to subjectively assess splenectomy success. Data regarding the presence of negative prognostic indicators were collected: hyperbilirubinemia and high serum BUN concentrations for IMHA,[26] and melena and high serum BUN concentrations for ITP.[25] Available follow-up information from the referral centers' and referring veterinarians' clinical records was also requested.

IMHA was diagnosed on the basis of anemia (PCV <35%), alongside at least 1 of: positive direct antiglobulin test (DAT; Coombs' test); positive saline agglutination test (SAT); or spherocytosis (determined by blood smear review at a reference laboratory). Where anemia was persistently (>5 days) nonregenerative, the diagnosis of precursor-targeted immune-mediated anemia (PIMA) did not require positive DAT, SAT or spherocytosis, and was based on finding ineffective erythropoiesis (erythroid hypercellularity or maturation arrest), with or without evidence of erythroid precursor phagocytosis, on bone marrow aspirate or biopsy. Secondary causes of PIMA were ruled out as for cases of IMHA and ITP.

A diagnosis of primary ITP was made on the basis of moderate to severe thrombocytopenia ($<50 \times 10^9$/L) without an identified underlying cause. CIST was diagnosed when a dog met the diagnostic criteria for both non-associative IMHA/PIMA and ITP.

One of the authors (JB) compiled the questionnaires. Two authors (JB and JW) reviewed all available case data and classified the success of splenectomy, as part of a management protocol, for each case as per the following categories:

- Successful – Complete response: The dog experienced complete clinical remission (normalization of hematocrit/PCV, platelet count, or both) after splenectomy allowing all immunosuppressive therapy to be tapered and discontinued.
- Successful – Partial response: The dog's immunosuppressive therapy (or blood transfusion dependency) was reduced and the anemia/thrombocytopenia improved, although discontinuation of medical treatment was not possible.
- Unsuccessful: Splenectomy did not appear to result in clinical benefit and the dog's condition/treatment remained similar to, or worse than, before splenectomy. Where definitive or suspected detrimental adverse effects occurred as a result of splenectomy, this was highlighted.

2.2 | Data/statistical analysis

Data were collected in questionnaires and collated/analyzed using proprietary software (Word and Excel 2011, Microsoft). Descriptive statistics were calculated using Excel.

2.3 | Ethics

This study was approved by the Ethics Committee of the Animal Health Trust (approval number: 51-2015).

3 | RESULTS

Eighteen cases were submitted from 7 centers: Animal Health Trust, Queen's Veterinary School Hospital (University of Cambridge), Queen Mother Hospital for Animals (Royal Veterinary College, University of London), Pride Veterinary Centre, Anderson Moores Veterinary Specialists, Small Animal Teaching Hospital (University of Liverpool), and Langford Vets Small Animal Referral Hospital (University of Bristol). Data were collated and analyzed by 2 authors (JB and JW) at the Animal Health Trust.

One case was excluded because of concurrent diagnosis of renal neoplasia. After review of the submitted data, the remaining 17 dogs were considered to have nonassociative/primary disease; 7 dogs with IMHA, 7 dogs with ITP, and 3 dogs with CIST. No dogs had travel history outside the UK. Individual dogs in the text and tables are referred to by unique codes, as defined in Tables S1 to S6, Supporting Information according to their disease process and a number (eg, IMHA1).

3.1 | IMHA group

3.1.1 | Group characteristics and diagnostic testing

Signalment and major clinicopathological findings, including PCV at the time of diagnosis and splenectomy, are summarized in Table 1. Ancillary diagnostic tests used to exclude associative IMHA are summarized in Table S1. All dogs with IMHA (7/7) underwent abdominal imaging before splenectomy: CT (1/7) or ultrasound (6/7). Five of the ultrasound examinations were conducted at the referral center and 1 at the primary care practice. The notable findings reported were frequently related to the spleen (Table 1). All dogs had thoracic imaging performed (4/7 radiographs; 3/7 CT); the results were either unremarkable or considered clinically unimportant (Table S1). Four dogs underwent screening for infectious diseases, all of which were negative (Table S1). Of the 7 IMHA cases, 4 (4/7; 57%) were hyperbilirubinemic and 2 (2/7; 29%) had abnormally high serum BUN at presentation (Table 1). One of these dogs (IMHA2) exhibited both abnormalities.

TABLE 1 Summary of clinical findings, treatment and outcome in dogs with IMHA undergoing splenectomy as part of their management protocol

Rating of success		All IMHA cases	Successful – Complete response	Successful – Partial response	Unsuccessful
Number of dogs		7	2/7 IMHA3, IMHA6	2/7 IMHA5, IMHA7	3/7 IMHA1, IMHA2, IMHA4
Breed (number if >1)		Maltese Terrier, Crossbreed, Labrador Retriever (2), Standard Poodle, English Springer Spaniel (2)	Labrador Retriever (2)	English Springer Spaniel (2)	Maltese Terrier, Crossbreed, Standard Poodle
Age [years] (median; range)		7; 3-12	11.5; 11-12	5.5; 5-6	7; 3-12
Sex (ME/MN/FE/FN)		1/2/1/3	1/0/0/1	0/1/0/1	0/1/1/1
PCV [%] at diagnosis (median; range; number of dogs data available for)		15; 12-29; 7/7	19; 15-23; 2/2	20.5; 12–29; 2/2	13; 13-25; 3/3
PCV [%] at splenectomy (median; range; number of dogs data available for)		21; 12-34; 7/7	20.5; 15-26; 2/2	16.5; 12-21; 2/2	24; 16-34; 3/3
Negative prognostic indicators at presentation	BUN above the reference range	2/7	0/2	1/2 IMHA5	1/3 IMHA2
	Serum total bilirubin above the reference range	4/7	1/2 IMHA3	1/2 IMHA7	2/3 IMHA2, IMHA4
Abnormal imaging of the spleen immediately before splenectomy		6/7	2/2 IMHA3: Suspected splenic rupture at referring practice IMHA6: Splenic masses	2/2 IMHA5: Splenic nodules IMHA7: Splenomegaly	2/3 IMHA1: Splenomegaly and nodules IMHA4: Splenic nodule
Time from diagnosis to splenectomy [days] (median; range)		6; 1-528	1; 1	267; 6-528	11; 4-37
Splenic histopathology performed		7/7	2/2 IMHA3: Performed but report unavailable IMHA6: Splenic hematoma	2/2 IMHA5: Erythrophagocytosis, hemosiderosis, neutrophilic infiltration (concomitant neutrophilia) IMHA7: Extramedullary hematopoiesis, lymphatic ectasia, hemosiderosis	3/3 IMHA1: Extramedullary hematopoiesis IMHA2: Necrosis and fibrin deposition IMHA4: Necrosis, hemorrhage, hemosiderosis
Possible splenectomy-related complications		3/7	1/2 IMHA3: Portal vein thrombus on CT at referral after splenectomy; dog asymptomatic	0/2	2/3 IMHA2: Death 4 days after splenectomy because of cardiorespiratory arrest secondary to suspected thromboembolic disease IMHA4: Euthanized 8 days after splenectomy because of clinical deterioration (pyrexia, heart murmur, and declining PCV)

TABLE 1 (Continued)

Rating of success	All IMHA cases	Successful – Complete response	Successful – Partial response	Unsuccessful
Treatment before splenectomy				
None	2/7	2/2 IMHA3, IMHA6	0/2	0/3
Glucocorticoids +1 second-line	2/7	0/2	1/2 IMHA7	1/3 IMHA2
Glucocorticoids +2 second-line	3/7	0/2	1/2 IMHA5	2/3 IMHA1, IMHA4
Reason for splenectomy				
Inadequate response to initial (<30 days) medical treatment	2/7	0/2	1/2 IMHA7	1/3 IMHA4
Inadequate response to sustained (>30 days) medical treatment	2/7	0/2	1/2 IMHA5	1/3 IMHA1
Concern about splenic lesions	2/7	2/2 IMHA3: Referring vet suspected splenic rupture IMHA6: Splenic histopathology – splenic hematoma	0/2	0/3
Other	1/7	0/2	0/2	1/3 IMHA2: Exploratory laparotomy to remove peritoneal foreign body (wooden stick) provided opportunity for therapeutic splenectomy

Abbreviations: BUN, blood urea nitrogen; CT, computed tomography; FE, female entire; FN, female neutered; IMHA, immune-mediated hemolytic anemia; ME, male entire; MN, male neutered; PCV, packed cell volume.

TABLE 2 Summary of clinical findings, treatment, and outcome in dogs with ITP undergoing splenectomy as part of their management protocol

Rating of success		All ITP cases	Successful – Complete response	Successful – Partial response	Unsuccessful
Number of dogs		7	3/7 ITP1, ITP3, ITP5	3/7 ITP2, ITP6, ITP7	1/7 ITP4
Breed (number if >1)		English Springer Spaniel, English Cocker Spaniel, Miniature Dachshund, Golden Retriever, crossbreed (3)	English Springer Spaniel, Miniature Dachshund, Crossbreed	English Cocker Spaniel, Crossbreed (2)	Golden Retriever
Age [years] (median; range)		4; 3-10	3; 3-10	4; 3-5	10; –
Sex (ME/MN/FE/FN)		1/2/2/2	0/2/0/1	1/0/1/1	0/0/1/0
PLT count [$\times 10^9$/L] at diagnosis (median; range; number of dogs data available for)		3; 0-39; 7/7	3; 0-6; 3/3	29; 1-39; 3/3	1; –; 1/1
PLT count [$\times 10^9$/L] at splenectomy (median; range; number of dogs data available for)		50.5; 1-140; 6/7	50.5; 24-77; 2/3	87; 15-140; 3/3	1; –; 1/1
Negative prognostic indicators at presentation	BUN above the reference range	1/5	1/2 ITP5	0/2	0/1
	Presence of melena	5/7	2/3 ITP3, ITP5	2/3 ITP2, ITP6	1/1 ITP4
Abnormal imaging of the spleen immediately before splenectomy		5/7	2/3 ITP1: Splenic masses ITP5: Splenomegaly	2/3 ITP6: Splenic nodules ITP7: Splenomegaly	1/1 ITP4: Splenomegaly
Time from diagnosis to splenectomy [days] (median; range)		104; 3-622	113; 20-519	104; 66-622	3; –
Splenic histopathology performed		4/7	2/3 ITP1: Lymphoid hyperplasia ITP3: Performed but report unavailable	2/3 ITP6: Lymphoid hyperplasia ITP7: Extramedullary hematopoiesis	0/1
Possible splenectomy-related complications		1/7	0/3	1/3 ITP7: Suspected IMHA developed after splenectomy	0/1
Treatment before splenectomy					
None		1/7	0/3	1/3 ITP7	0/1
Glucocorticoids +1 second-line		2/7	1/3 ITP3	0/3	1/1 ITP4
Glucocorticoids +2 second-line		4/7	2/3 ITP1, ITP5	2/3 ITP2, ITP6	0/1
Reason for splenectomy					
Inadequate response to initial (<30 days) medical treatment		2/7	1/3 ITP5	0/3	1/1 ITP4
		3/7	1/3	2/3	0/1

TABLE 2 (Continued)

Rating of success	All ITP cases	Successful – Complete response	Successful – Partial response	Unsuccessful
Inadequate response to sustained (>30 days) medical treatment		ITP3	ITP2, ITP6	
Concern about splenic lesions	2/7	1/3 ITP1: Splenic histopathology – lymphoid hyperplasia	1/3 ITP7: Splenic histopathology – extramedullary hematopoiesis)	0/1

Abbreviations: BUN, blood urea nitrogen; FE, female entire; FN, female neutered; IMHA, immune-mediated hemolytic anemia; ITP, immune-mediated thrombocytopenia; ME, male entire; MN, male neutered; PLT, platelet.

3.1.2 | Splenectomy details

Reasons for splenectomy are detailed in Table 1, the most common being inadequate response to sustained (>30 days) medical treatment (2/7; 29%), inadequate response to initial (<30 days) medical treatment (2/7; 29%) and concern about splenic lesions (2/7; 29%). Concerning the latter cases, IMHA3 had splenectomy performed before referral because of suspicion of splenic rupture, which was ruled out at surgery; and, with IMHA6, possible splenic neoplasia prompted splenectomy, although this was excluded via histopathology. One dog (IMHA2) underwent splenectomy as an additional procedure while undergoing celiotomy to remove a peritoneal foreign body. There was a lack of associated peritoneal reaction associated with this finding both on imaging and intraoperatively; therefore, it was clinically considered to be chronic and incidental to the acute diagnosis of IMHA.

The median time from diagnosis to splenectomy was 6 days (range: 1-528; Table 1).

Three dogs had possible postoperative complications (Table 1). The dog that underwent splenectomy before referral (IMHA3) had subclinical portal vein thrombus reported on CT after splenectomy, although its relationship to surgery was unknown. Two dogs (IMHA2 and IMHA4) died within 10 days of surgery.

3.1.3 | Outcomes

Table 1 summarizes medical treatment before splenectomy and clinical outcome. Details of medical treatment after splenectomy is summarized in Table S2. Splenectomy was considered successful as part of the management of 4 dogs (4/7; 57%). Of these, 2 had a complete response and 2 a partial response after splenectomy (Table 1).

Both complete responders (IMHA3 and IMHA6) had splenectomy performed 1 day after diagnosis, because of abnormal splenic appearance on imaging. At the time of last follow-up, 537 days after splenectomy, IMHA3 was in receipt of no immunosuppressive treatments. IMHA6 was treated with splenectomy alone and the dog's PCV had normalized by 16 days after splenectomy. Splenic histopathology was performed in both cases, but was unavailable for review in the case of IMHA3. In the case of IMHA6, histopathology was consistent with a splenic hematoma.

Both IMHA5 and IMHA7 showed partial responses after splenectomy. IMHA5 demonstrated an improved and stabilized PCV after splenectomy, allowing for reduced doses of immunosuppressive drugs but was lost to follow-up at 33 days after splenectomy. IMHA7 was euthanized 980 days after splenectomy because of a nonhealing surgical wound after anal sacculectomy. At this time, the dog was still in receipt of prednisolone but at lower doses, and without second-line immunosuppressants, compared to before splenectomy.

In 3 dogs, splenectomy was considered to be unsuccessful as part of their management protocol. IMHA1 was euthanized 15 days after the procedure because of worsening anemia. IMHA2 and IMHA4 died soon after splenectomy. Despite stabilization of the dog's PCV

TABLE 3 Summary of clinical findings, treatment, and outcome in dogs with concurrent IMHA and severe thrombocytopenia undergoing splenectomy as part of their management protocol

Rating of success		All CIST cases	Successful – Complete response	Unsuccessful
Number of dogs		3	1/3 CIST1	2/3 CIST2, CIST3
Breed (number if >1)		Siberian Husky, Crossbreed, Rottweiler	Siberian Husky	Crossbreed, Rottweiler
Age [years] (median; range)		8; 5-11	8; –	8; 5–11
Sex (ME/MN/FE/FN)		0/1/0/2	0/0/0/1	0/1/0/1
PCV [%] at diagnosis (median; range; number of dogs data available for)		12; 9-27; 3/3	12; –; 1/1	18; 9–27; 2/2
PCV [%] at splenectomy (median; range; number of dogs data available for)		28; 24-29; 3/3	28; –; 1/1	26.5; 24–29; 2/2
PLT count [$\times 10^9$/L] at diagnosis (median; range; number of dogs data available for)		30; 1-36; 3/3	1; –; 1/1	33; 30-36; 2/2
PLT count [$\times 10^9$/L] at splenectomy (median; range; number of dogs data available for)		42; –; 1/3	42; –; 1/1	–; –; 0/2
Negative prognostic indicators at presentation	BUN above the reference range	1/3	0/1	1/2 CIST3
	Serum total bilirubin above the reference range	2/3	0/1	2/2 CIST2, CIST3
Abnormal imaging of the spleen immediately before splenectomy		2/3	0/1	2/2 CIST2: Splenic myelolipomas CIST3: Splenomegaly and splenic mass
Time from diagnosis to splenectomy [days] (median; range)		50; 5-56	50; –	30.5; 5–56
Splenic histopathology performed		3/3	1/1 CIST1: Performed but report unavailable	2/2 CIST2: Extramedullary hematopoiesis, congestion, moderate hemosiderosis CIST3: Multifocal thrombosis with necrosis
Possible splenectomy-related complications		3/3	1/1 CIST1: Bruising at surgical site	2/2 CIST2: Wound dehiscence and evisceration (14 days after surgery) prompting euthanasia CIST3: Surgical wound infection (proven on cytology, treated with empirical antibiotic therapy)
Treatment before splenectomy				
Glucocorticoids +1 second-line		2/3	1/1 CIST1	1/2 CIST3
Glucocorticoids +2 second-line		1/3	0/1	1/2 CIST2
Reason for splenectomy				
Inadequate response to sustained (>30 days) medical treatment		2/3	1/1 CIST1	1/2 CIST2
Concern about splenic lesions		1/3	0/1	1/2 CIST3: Splenic histopathology – Multifocal thrombosis with necrosis

Abbreviations: BUN, blood urea nitrogen; CIST, concurrent immune-mediated hemolytic anemia and severe thrombocytopenia; FE, female entire; FN, female neutered; ME, male entire; MN, male neutered; PCV, packed cell volume; PLT, platelet.

immediately after surgery, IMHA2 died after cardiorespiratory arrest (suspected secondary to thromboembolic disease [TED]) 4 days after splenectomy. IMHA4 was euthanized 8 days after splenectomy because of the onset of pyrexia and recommencement of PCV decline.

3.1.4 | TED/antithrombotic therapy

Six of 7 dogs (86%) were treated with antithrombotic therapy (Table S2), consisting of aspirin, clopidogrel, or both; 2 only received treatment after splenectomy (1 in the face of suspected TED [IMHA2]), with the others receiving therapy both before and after splenectomy (Table S2).

3.2 | ITP group

3.2.1 | Group characteristics and diagnostic testing

Table 2 outlines signalment and major clinicopathological findings. All dogs with ITP had abdominal ultrasound performed at a referral center. One (ITP6) also underwent abdominal and thoracic CT. All dogs had thoracic imaging (6/7 radiographs; 1/7 CT), the results of which were either unremarkable, or of equivocal clinical relevance (Table S3). The most noteworthy findings reported were related to the spleen (Table 2). Six of the 7 dogs within the ITP group underwent infectious disease screening, which was negative in all (Table S3). Serum BUN concentrations at presentation were available for 5 dogs (5/7); 1 was abnormally high (1/5; 20%; Table 2). Five had melena at presentation (5/7; 71%; Table 2), including the dog with abnormally high serum BUN (ITP5).

3.2.2 | Splenectomy details

Table 2 outlines the reasons for, and outcomes after, splenectomy. The most common reason for splenectomy was inadequate response to sustained (>30 days) medical management (3/7; 43%). One of the dogs (ITP1) that underwent splenectomy for possible splenic lesions (subsequently ruled out with histopathology), had secondary drivers for splenectomy: inadequate response to initial (<30 days) medical management and concurrent gastrotomy to remove a gastric foreign body (plastic carrier bag), providing an opportunity for splenectomy.

The median time from diagnosis to splenectomy was 104 days (range: 3-622; Table 2).

No definitive splenectomy-related complications were reported (Table 2). However, 1 dog (ITP7) developed suspected IMHA after splenectomy. This dog was initially presented with moderate, asymptomatic thrombocytopenia and mild, regenerative anemia. Coombs' test was negative, and spherocytes were not evident. Splenectomy was performed before medical treatment was instigated owing to an abnormal splenic appearance. The thrombocytopenia responded rapidly to splenectomy but anemia worsened, despite no observed hemorrhage. The anemia subsequently improved with immunosuppressive therapy.

3.2.3 | Outcomes

Table 2 gives a summary of medical treatment before splenectomy, alongside clinical outcome. Further details on medical treatment after splenectomy can be found in Table S4. Splenectomy was considered successful in the management of 6 of the 7 dogs with ITP.

Three dogs achieved complete response: ITP1 had a normal platelet count at 50 days after splenectomy in the absence of medical treatment. The dog was euthanized 112 days after splenectomy because of generalized epileptic seizures; there was no evidence of systemic bleeding or neurological deficits. ITP3 and ITP5 were able to have immunosuppressive treatment discontinued, were clinically well, and were receiving no medications at 345 and 810 days after splenectomy, respectively.

A further 3 dogs achieved partial response after splenectomy: ITP2 and ITP6 both had long-term follow-up (1142 and 566 days after splenectomy, respectively), with documented normal platelet counts after splenectomy, and lower immunosuppressive drug doses compared to before splenectomy. ITP7 experienced resolution of ITP but development of suspected IMHA, requiring the use of immunosuppressive drugs, as discussed above.

One of the 7 dogs was deemed to have an unsuccessful outcome after splenectomy. ITP4 was euthanized 3 months after splenectomy and was splenectomized only 3 days after diagnosis because of clinician/owner preference. A normal platelet count was documented 7 days after splenectomy. However, the dog suffered a suspected relapse 60 days after surgery, prompting a prednisolone dose increase, which resulted in an improvement in the platelet count. A further relapse occurred after a further 31 days, with collapse, mucous membrane pallor and abdominal distension. At that time, euthanasia was performed with no further investigations.

3.3 | CIST group

3.3.1 | Group characteristics and diagnostic testing

Table 3 outlines signalment and major clinicopathological findings. All (3/3) dogs underwent bicavitary imaging (Table S5), reported to be unremarkable apart from splenic appearance in CIST2 and CIST3 (Table 3). Infectious disease screening was negative in all cases (Table S5). One case (CIST1) was diagnosed with PIMA and ITP. Two were hyperbilirubinemic (CIST2 and CIST3) and 1 also had abnormally high serum BUN (CIST3) at presentation.

3.3.2 | Splenectomy details

Two dogs underwent splenectomy because of inadequate response to sustained (>30 days) medical treatment (2/3) while the other had surgery performed because of suspected splenic neoplasia (1/3), which was ruled out with histopathology (Table 3).

The median time from diagnosis to splenectomy was 50 days (range: 5-56; Table 3).

All 3 dogs experienced surgical complications (Table 3). One, for which splenectomy was considered completely successful, suffered mild bruising at the surgical site (CIST1). Surgical site infection occurred in another case (CIST3), which alongside worsening anemia and transfusion dependence prompted euthanasia. One reported complication was severe: wound dehiscence and evisceration 14 days after surgery, resulting in euthanasia (CIST2). For both of the latter 2 dogs, splenectomy was ultimately considered unsuccessful as part of their management protocol.

3.3.3 | Outcomes

A summary of medical treatment alongside outcome is shown in Table 3. Further details on medical treatment after splenectomy can be found in Table S6. Splenectomy as part of a treatment protocol was considered completely successful in 1 dog (1/3) and unsuccessful in 2 (2/3). Both dogs for which splenectomy was considered unsuccessful experienced potential or definitive detrimental effects and were euthanized, as above.

The successful case (CIST1) had concurrent PIMA and severe thrombocytopenia. This dog was treated, unsuccessfully, with multiple immunosuppressive medications and intravenous administration of human immunoglobulin before splenectomy. After splenectomy, the dog's platelet count normalized but anemia persisted prompting the introduction of azathioprine and subsequently mycophenolate mofetil, although all immunosuppressive medications were ultimately tapered and discontinued, with the dog remaining in remission.

4 | DISCUSSION

This case series represents the largest published group of dogs undergoing splenectomy for immune-mediated hematological disorders, adding to the data available about its utility and complications. In this series, improvement was observed most consistently after splenectomy in dogs with isolated ITP, lending support to the hypothesis that splenectomy might be beneficial in allowing for immunosuppressive drug dose reduction or discontinuation in isolated ITP.

Although contributors were asked to supply prognostic indicator data for IMHA and ITP, we recognize that the strength of evidence supporting the use of these parameters is poor[26] and that the small cohort sizes make it impossible to draw firm conclusions. However, it is notable that in the ITP group 5/7 had 1 or more negative prognostic indicators; all 5 of these dogs (71%) had melena at presentation, compared to just 15/73 (21%) at presentation in a previous study.[25] Overall, 6/7 dogs within the ITP group (71%) of the current study failed to respond adequately to either initial or sustained medical therapy before splenectomy, much higher than would be expected from previous reports.[21] Despite this, 6/7 ITP cases had partial or complete disease response after splenectomy and the platelet count at the time of splenectomy in 3 of these 6 dogs was >50 $\times$ 10^9/L. Along with the timing of splenectomy in many cases, this is consistent with the surgery being performed in the chronic stage of the disease, after initial medical management, as recommended in human medicine.[27] This is also echoed in 1 early case series where 5 dogs with relapsing ITP, despite prolonged medical management, were treated with splenectomy; 4/5 dogs achieved a complete and sustained response to splenectomy.[23]

Two cases of note, ITP4 and ITP5, had splenectomy performed early in the disease course, at 3 and 20 days, respectively, making assessment of response to initial medical therapy difficult. Nevertheless, both had negative prognostic indicators at presentation, suggesting they might have represented severe cases. ITP4 was not successfully managed, being euthanized 90 days after splenectomy because of suspected disease relapse despite continued treatment with 2 immunosuppressants. Initial robust clinical response was demonstrated by a normal platelet count 7 days after splenectomy but it is difficult to know if this represented a direct response to splenectomy, medical treatment (started before splenectomy) or both. As the spleen appeared homogeneous at ultrasound and had a normal gross appearance, histopathology was not performed in this case; therefore, relapse of diffuse neoplasia cannot be completely excluded. In humans with ITP, platelet counts often increase rapidly in those responding to splenectomy; however, as seen in the case of ITP4, not all human responders achieve a long-term response.[28] ITP5 experienced a complete response having failed to respond to therapy 20 days after diagnosis, which although being a short time after diagnosis, is longer than the majority of dogs take to respond to medical treatment.[21]

Another dog (ITP1) was euthanized without further investigations, 112 days after splenectomy because of seizures, despite a normal platelet count documented at 50 days after splenectomy in the absence of ongoing medical treatment. Normal intracranial magnetic resonance imaging had been obtained before splenectomy because of the onset of acute onset vestibular signs (diagnosis: idiopathic vestibular syndrome). Neurological manifestations of ITP are uncommon in dogs and signs of intracranial hemorrhage would typically be expected alongside other clinical evidence of bleeding (ie, petechiae and ecchymoses),[29-31] so the seizures were considered unrelated to relapse of ITP or the splenectomy procedure performed 112 days prior.

The most unexpected response after splenectomy was seen in ITP7. Despite resolution of the thrombocytopenia after surgery, management with splenectomy was only considered partially successful, because of progression of a previously stable, mild, regenerative anemia. Although not described in dogs, development of hemolytic anemia after splenectomy for thrombocytopenia has been reported in humans.[32] Additionally, humans with Evans syndrome often have ITP

and AIHA diagnosed at separate times, with cytopenias occurring asynchronously in 45.5% of cases.[33] The dog, however, was included in the ITP group as the diagnostic criteria for CIST was not met at the time of splenectomy. Given the timeline, splenectomy appears relevant to the progression of the anemia, perhaps through the loss of compensatory splenic erythropoiesis, but it remains possible that this was coincidental or only indirectly related (eg, perioperative adverse drug reaction or unrecognized hemorrhage).

Evidence for the use of splenectomy as management for ITP in dogs is scarce, with the authors only aware of 10 dogs previously reported. In 1 study, 3 dogs with ITP showed improvement in platelet counts after splenectomy, with no immediate adverse effects, and all dogs were alive 1 year later.[22] A later study described a complete response (platelet count >200 000 $\times$ 10^9/L without medical treatment) in 4/5 dogs that underwent splenectomy because of relapsing ITP, despite prolonged medical therapy before splenectomy.[23] A retrospective study examining treatment and prognostic indicators in dogs with ITP included 2 cases, but no outcome information was included.[25] Taken together, these results suggest that splenectomy might be useful in the treatment of dogs with ITP that show inadequate or nonsustained response, or where medical therapy is not tolerated.

Unlike the ITP group, most dogs in the IMHA group had splenectomy performed in the acute phase of the condition. The IMHA complete responders both had splenectomy as initial therapy because of splenic abnormalities; it is possible that these responses reflected less severe disease that would have responded to medical therapy. However, these limitations are likely to reflect real-world clinical settings where multiple treatment strategies (ie, immunosuppressive therapy and splenectomy) might be employed simultaneously. Furthermore, it is perhaps unsurprising that splenectomy was performed earlier in the course of disease in IMHA compared to ITP. This could be because of fewer effective adjunctive therapies in the acute disease phase of IMHA in contrast to ITP (ie, vincristine[34,35] and intravenous administration of immunoglobulin[36,37] for ITP) and lower relapse rates in IMHA compared to ITP,[15,18,20,21] meaning that splenectomy might more likely be sought in the initial treatment of IMHA versus the chronic stage/at time of relapse for ITP. Additionally, widely available, effective blood products for management of anemia (ie, red cell transfusion) compared to thrombocytopenia,[38] might allow faster stabilization of dogs with IMHA, enabling earlier anesthesia and splenectomy. An unpublished prospective study described dogs with IMHA treated with either medical therapy alone or medical therapy with early splenectomy (most within 48 h of presentation).[39] A more rapid hematocrit recovery and increased survival at 6 months was reported in the splenectomy group, suggesting that splenectomy might be beneficial in the acute phase of IMHA.

As with ITP, evidence for the use of splenectomy as management for IMHA in dogs is limited; we are aware of 13 cases from 2 peer-reviewed publications in addition to the unpublished study cited above.[39] One reported 100% survival in 3 dogs with 2 dogs in complete remission and 1 dog in partial remission after 1 year.[22] Horgan et al reported that 9 of 10 dogs (90%) survived to 30 days, with 4 of these not receiving any immunosuppressive medications.[24] That study is limited by the lack of follow-up beyond 30 days, but did demonstrate that beneficial effects on anemia could be seen within 3 days. As with the current study, complications directly attributable to splenectomy were uncommon. Two dogs (IMHA2 and IMHA4) died, or were euthanized, shortly after surgery but their deaths were likely as a result of their underlying disease rather than splenectomy, with suspected TED and progressive anemia, respectively.

While hyperbilirubinemia and high BUN have been associated with poor prognosis in IMHA,[26] the authors are unaware of data documenting the frequency of these findings in dogs with IMHA to compare our cohort to. Subjectively, we believe that the frequency of 5/7 dogs in the IMHA group having 1 or both above reference range, including 3/4 with inadequate response to medical therapy, is likely consistent with a severely affected cohort.

Although 1 previous study reported case fatality rates for dogs with CIST similar to dogs with either isolated IMHA or ITP,[7] 2 other studies reported poorer outcomes.[5,40] With 1 successful and 2 unsuccessful cases, and with all dogs experiencing splenectomy-related complications, our study observations are comparable to those in the latter studies. Feldman et al described 3 cases with reported Evans syndrome treated with splenectomy; after 1 year, 2 dogs showed complete remission and 1 partial remission.[22]

Risks associated with splenectomy in humans include overwhelming postsplenectomy infection (including sepsis and some vector-borne diseases [eg, babesiosis and malaria]), hemorrhage and TED (particularly within the splenoportal system).[41,42] Beyond perioperative complications, including hemorrhage or surgical site infections, little information exists about risks associated with splenectomy in dogs.[43,44] Increased risk of sepsis has not been demonstrated in dogs; the greatest infectious disease risk is likely to be related to vector-borne diseases, including infection with *Babesia* spp.,[45,46] *Mycoplasma haemocanis*,[47,48] and *Ehrlichia canis*.[49] The current cohort were UK residents (without travel history), where vector-borne infectious diseases are uncommon. Most dogs were screened for a limited panel of infections. The importance of such screening, for the purposes of detecting secondary ITP/associative IMHA and assessing risk of splenectomy, would be higher where specific infections are endemic, and the risk of splenectomy might outweigh potential benefits in such environments. The recent identification of *Babesia canis* in the UK[50] and changing geographical distributions of vector-borne diseases mean that clinicians should be alert to changing risk profiles in their area. Gastric dilation-volvulus has been reported as a complication of splenectomy,[51] although other studies have refuted this link,[52] and it was not recognized in this cohort.

Thromboprophylaxis is used in clinical practice in dogs with IMHA as increased risk of TED is well recognized.[53,54] Furthermore, thromboembolic complications are reported in humans after splenectomy for hematologic diseases.[55-57] Two IMHA cases developed definitive or suspected TED. Given that TED is common in IMHA, it could have occurred because of underlying disease in these dogs, although the risk could have been increased by splenectomy. There is inadequate evidence to determine the most effective thromboprophylaxis in dogs

with IMHA. Evidence supports the use of individually tailored dosing of unfractionated heparin,[58] or antiplatelet therapy using clopidogrel +/− aspirin.[20,59] In the current study, antiplatelet drugs (aspirin/clopidogrel) were used in the majority of cases; anticoagulant use was not reported. Subjectively, in our experience, no more thromboembolic events occurred than would be expected with non-splenectomized IMHA cases. Four of 7 IMHA cases received thromboprophylaxis before splenectomy but both dogs that developed suspected TED had not, perhaps suggesting that instigating this treatment before surgical intervention might be valuable. Small animal guidelines for the rational use of antithrombotics suggest that their use intraoperatively balances the risk of bleeding with the risk of thrombosis.[60] However, a recent consensus statement on the treatment of IMHA in dogs advised thromboprophylaxis is stopped or lowered to a minimum dose before splenectomy.[4]

The main limitations in the current study are those often inherent in retrospective case series: small case numbers, incomplete and inconsistent quality of clinical data and follow-up for individual dogs, variable treatment protocols, and a lack of control group. Retrospective case collection could have introduced selection bias; however, contributors were encouraged to search the clinical databases in an unbiased fashion, and include cases irrespective of outcome. The strength of the multicenter approach is that we captured data from as large a number of cases as possible; however, the fact that only a few cases were identified in each center, each with several in-charge clinicians, means that the clinical approaches were highly variable.

As case recruitment began before to its publication, inclusion criteria for cases of IMHA was less demanding than that proposed by the ACVIM consensus statement for the diagnosis of IMHA.[61] However, dogs within the IMHA group met the criteria for suspicion of IMHA as a minimum (3/7 met criteria for being diagnostic, 3/7 supportive, and 1/7 suspicious of IMHA), and were managed under the supervision of board-certified internists confident in the diagnosis of nonassociative IMHA.

Splenic histopathology was available for most dogs. In the cases where it was absent, in light of the otherwise available clinical data, this was not thought to represent a serious limitation. Splenic histopathology was performed but the report was unavailable for 3 cases: One dog within each of the 3 groups (IMHA3, CIST1 and ITP 3). Given the available follow-up for these dogs, it is known that the clinicians determined the histopathological findings to be clinically unimportant. Three dogs (ITP2, ITP4, and ITP5) did not have splenic histopathology performed. The reason for this is unknown but it could have been a clinical decision based on the gross appearance of the spleen (all unremarkable or mild splenomegaly on imaging). Long-term follow-up was available for ITP2 and ITP5, 1142 and 810 days respectively, with a positive outcome in both cases. This suggests that the presence of a malignant neoplastic process within the spleen is unlikely. This assumption is more difficult to make in the case of ITP4, which was euthanized 90 days after splenectomy, as discussed above.

It has been recommended that splenectomy should not be performed until bone marrow biopsy has confirmed hyperplasia of the relevant cell line (erythroblasts or megakaryocytes),[62] excluding bone marrow failure compensated by splenic extramedullary hematopoiesis. However, the authors' experience is that this is not routinely performed. In this cohort, bone marrow biopsy was inconsistently performed (5/17 dogs), mainly for the diagnosis of non-regenerative anemia; where performed, relevant cellular hyperplasia was always reported, making it impossible to assess the validity of this recommendation. It remains possible that some unsuccessful cases, particularly with lineage specific deteriorations (ITP7), would have benefited from bone marrow assessment before splenectomy.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL USE

Specific off-label use of antimicrobials did not form part of this retrospective study. However, off-label use of antimicrobials could have occurred in the management of some of the cases as deemed appropriate by the attending clinician on a case-by-case basis.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER REGULATORY BODY APPROVAL

The study was approved by the Ethics Committee of the Animal Health Trust (project number: 51-2015).

HUMAN ETHICS APPROVAL

The authors declare that human ethics approval was not needed for this study.

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SUPPORTING INFORMATION

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