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CASE REPORT

Companion or pet animals

Aplastic anaemia treated using eltrombopag in a dog

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Abstract

A 2-year-old, neutered, female beagle was presented to a referral hospital for investigation of pancytopenia. The patient had a history of recurrent infections and, on previous blood tests, anaemia, leukopenia and thrombocytopenia were detected. At the time of presentation, the patient had been treated for 2 weeks with omeprazole, amoxicillin-clavulanic acid, marbofloxacin and gabapentin, and for 3 months with prednisolone, in decreasing doses. A bone marrow aspirate and core biopsy were performed. Hypoplastic bone marrow was observed. Once underlying infectious diseases and exposure to toxins were ruled out, a diagnosis of aplastic anaemia was made. The patient was treated with eltrombopag, a thrombopoietin receptor agonist that stimulates primitive haematopoietic stem cells, used for the treatment of aplastic anaemia in humans. One week after starting eltrombopag treatment, all the affected cellular lines were recovered. The patient continued in remission 7 months after treatment.

KEYWORDS

aplastic anaemia, bone marrow, eltrombopag, pancytopenia

BACKGROUND

Eltrombopag is a thrombopoietin (TPO) receptor agonist traditionally used to increase the platelet number in circulation in human patients with immune thrombocytopenia (ITP).[1,2] Multiple studies have demonstrated that the use of eltrombopag in humans with aplastic anaemia (AA) produces a multilineage response, achieving an increase in red blood cells (RBC), white blood cells (WBC) and platelets (PLT).[3–6] Recent studies have shown that the use of eltrombopag as a monotherapy improves haematopoiesis in patients with myelodysplastic syndrome.[7,8] The mechanism by which eltrombopag elicits a multilineage stimulation is not well understood. The main hypotheses suggest that it exerts this effect as TPO is a critical regulator of haematopoiesis.[9] Thrombopoietin receptor c-mpl is expressed on the surface of the haematopoietic stem cells,[10] and with the support of TPO and other cytokines, stem cells proliferate.[5] By this mechanism, eltrombopag may produce a direct stimulation on primitive haematopoietic stem and progenitor cells.[6]

In human medicine, acquired AA is generally caused by an immune-mediated destruction of haematopoietic stem and progenitor cells.[5] Traditionally, the treatment for severe AA has been based on intensive immunosuppression therapy,[5] consisting of antithymocyte globulin and cyclosporine with other immunosuppressive agents, with response rates around 60%[11] and relapse rates of approximately 30%–40%.[5] The response rate is increased up to 94% if eltrombopag is added to standard immunosuppression therapy.[5] Given the lack of studies in veterinary medicine, when other causes of pancytopenia (such as infectious agents, drugs and toxins) are excluded, immunosuppression has been recommended for the treatment of this condition.[12,13]

Only two case reports have been published on the use of eltrombopag in dogs.[14,15] In the first one, eltrombopag was used in combination with prednisolone and cyclosporine for the treatment of a dog with idiopathic aplastic anaemia (IAA), with a complete remission achieved.[14] In the second study, eltrombopag was used in combination with granulocyte colony-stimulating factor for the treatment of lomustine overdose in a dog.[15]

CASE PRESENTATION

A 2-year-old, neutered, female beagle was referred to the internal medicine service for investigation of pancytopenia. The patient was correctly vaccinated. The last vaccination (against rabies, canine distemper virus, canine adenovirus type 1, canine parvovirus, canine parainfluenza and canine adenovirus type 2) was administered 6 months before the consultation. It had not received preventive medications in the 3 months before the consultation. Three months before presentation, the patient was diagnosed with moderate lymphoplasmacytic enteritis during investigation of intermittent diarrhoea. The diagnosis was made following endoscopic

intestinal biopsies. The patient was treated with a hydrolysed protein diet (Hill's z/d), prednisolone (started at 1 mg/kg twice daily [BID] for 3 weeks, then tapered to 0.5 mg/kg BID for the next 3 weeks, 0.25 mg/kg BID during the next 3 weeks and, finally, 0.25 mg/kg once daily [SID] for 3 weeks) and omeprazole (1 mg/kg BID). After starting the new diet and treatment with prednisolone, the gastrointestinal signs improved and the patient had no more diarrhoea. One month after starting treatment, a complete blood cell count (CBC) was performed (Table 1), where a severe, mildly hypochromic and regenerative anaemia was detected, with haematocrit (HCT) of 8.5% (37.3%–61.8%), total RBC 1.22 M/μL (5.65–8.87 M/μL), mean cell haemoglobin concentration (MCHC) 31.8 g/dL (32–37.9 g/dL), total reticulocyte count 238.9 K/μL (10–110 K/μL) and severe thrombocytopenia with 39 K/μL PLT (148–484 K/μL). There was no melena detected by the owner or the referring veterinarian; however, a faecal occult blood test was not performed. No other sources of bleeding were detected. A transfusion of packed RBC was performed.

One month after the transfusion, a new CBC was performed (Table 1), showing a moderate normocytic normochromic and regenerative anaemia, with HCT of 19%, RBC 2.96 M/μL, total reticulocyte count 321.5 K/μL, moderate leukopenia with 4.68 K/μL WBC with severe neutropenia 0.09 K/μL (2.95–11.64 K/μL) and severe thrombocytopenia with 8 K/μL PLT. Treatment with weekly subcutaneous injections of cobalamin was started (unknown dose). Prednisolone dose at this point was tapered (from 0.5 mg/kg BID to 0.25 mg/kg BID). One week later, the patient presented with an abscess in the zygomatic region, with fistulisation to the oral cavity. It was suspected to be secondary to a foreign body, and was treated with amoxicillin-clavulanate (20 mg/kg BID for 4 weeks). Two weeks before referral, the patient developed a subcutaneous abscess in the left shoulder region. It was treated by the referring veterinarian with marbofloxacin (4 mg/kg SID) and amoxicillin-clavulanate (20 mg/kg BID), with complete resolution of clinical signs.

TABLE 1 Complete blood counts of the patient before referral

Haematologic variable	Two months before consultation	Three weeks before consultation	Reference interval
Red blood cells (M/μL)	1.22	2.96	5.65–8.87
Haematocrit (%)	8.5	19	37.3–61.7
Haemoglobin (g/dL)	2.7	6.3	13.1–20.5
Mean cell volume (fL)	69.7	64.2	61.6–73.5
Mean cell haemoglobin (pg)	22.1	21.3	21.2–25.9
Mean cell haemoglobin concentration (g/dL)	31.8	33.2	32.0–37.9
Red cell distribution width (%)	28	25.6	13.6–21.7
Reticulocytes (K/μL)	238.9	321.5	10.0–110.0
White blood cells (K/μL)	5.4	4.68	5.05–16.76
Neutrophils (K/μL)	3.81	0.09	2.95–11.64
Lymphocytes (K/μL)	1.09	4.31	1.05–5.10
Monocytes (K/μL)	0.5	0.28	0.16–1.12
Eosinophils (K/μL)	0	0	0.06–1.23
Basophils (K/μL)	0	0	0.00–0.10
Platelets (K/μL)	39	8	148–484
Mean platelet volume (fL)	10.8	16.4	8.7–13.2

Note: The first complete blood count (CBC) was performed when the patient was on treatment for the lymphoplasmacytic enteritis. At the time, it was receiving prednisolone at a dose of 0.5 mg/kg twice a day (BID). No blood smear was performed at this point. The second CBC, was performed before the diagnosis of the subcutaneous abscess located on the left shoulder region. At that time, the patient was on treatment with prednisolone at a dose of 0.5 mg/kg BID and amoxicillin-clavulanate (unknown dose).

LEARNING POINTS/TAKE-HOME MESSAGES

- For the diagnosis of idiopathic aplastic anaemia, it is important to rule out other causes of pancytopenia such as infectious diseases, drugs, toxins or radiation.
- Eltrombopag is a potential treatment for aplastic anaemia in dogs.
- Use of eltrombopag in dogs seems to be safe.

At presentation, the patient was on treatment with amoxicillin-clavulanate (20 mg/kg BID), marbofloxacin (4 mg/kg SID), omeprazole (1 mg/kg BID), prednisolone (0.25 mg/kg SID) and gabapentin (10 mg/kg three times a day [TID]).

On clinical examination, the dog was alert and responsive, with a bodyweight of 10 kg and a body condition score of 4 out of 9. Pale mucous membranes were noticed, with normal capillary refill time. Peripheral lymph nodes palpation was normal, and thoracic auscultation was unremarkable. No abdominal pain was detected, and the left shoulder abscess was no longer palpable. Rectal temperature was within normal limits, and no abnormalities were found at the neurological examination.

INVESTIGATIONS

Haematology revealed a moderate, mildly regenerative normocytic, hypochromic anaemia with an HCT of 26.9% (37.3–61.7%), total RBC count of 2.41 M/μL (5.65–8.87 M/μL) and reticulocyte count of 158.8 K/μL (10.0–110.0 K/μL), moderate leukopenia with 2.83 K/μL WBC (5.05–16.76 K/μL), mild neutropenia with 1.48 K/μL (2.95–11.64 K/μL), mild lymphopenia 0.83 K/μL (1.05–5.1 K/μL) and severe thrombocytopenia with 5 K/μL PLT (148–484 K/μL) (Table 2). The blood smear showed no signs of haemolysis and no haematic parasites, the RBCs appeared hypochromic, the neutrophil manual count confirmed the neutropenia and the PLT manual count was within 12–16 K/μL, without PLT clumps. Serologies for *Ehrlichia* spp., *Anaplasma* spp., *Dirofilaria immitis*, *Borrelia burgdorferi* (SNAP 4Dx, IDEXX Laboratories) and *Leishmania* (SNAP Leishmania, IDEXX Laboratories) were negative. No abnormalities were detected on abdominal ultrasound examination or on thoracic radiographs.

A Coombs' test was performed (Alvedia LabTest DAT), with a negative result. A genetic test for pyruvate kinase deficiency was also performed, with a negative result. At this point, all medications the patient was receiving were stopped except omeprazole. Treatment with sucralfate was added at standard dosage (500 mg/dog TID).

TABLE 2 Complete blood count on the day of the consultation and 1 week later

Haematologic variable	Consultation	One week after consultation	Reference interval
Red blood cells (M/μL)	4.02	3.93	5.65–8.87
Haematocrit (%)	26.9	25.7	37.3–61.7
Haemoglobin (g/dL)	8.2	8.2	13.1–20.5
Mean cell volume (fL)	66.9	65.4	61.6–73.5
Mean cell haemoglobin (pg)	20.4	20.9	21.2–25.9
Mean cell haemoglobin concentration (g/dL)	30.5	31.9	32.0–37.9
Red cell distribution width (%)	23.1	21.1	13.6–21.7
Reticulocytes (K/μL)	136.7	23.2	10.0–110.0
White blood cells (K/μL)	2.83	2.52	5.05–16.76
Neutrophils (K/μL)	1.48	0.89	2.95–11.64
Lymphocytes (K/μL)	0.83	1.96	1.05–5.10
Monocytes (K/μL)	0.47	0.54	0.16–1.12
Eosinophils (K/μL)	0.04	0.03	0.06–1.23
Basophils (K/μL)	0.01	0	0.00–0.10
Platelets (K/μL)	5	2	148–484
Mean platelet volume (fL)	14.7	14.8	8.7–13.2

One week later, a new CBC was performed. The anaemia (HCT 25.7%, total RBC count 3.93 M/μL) was non-regenerative at this point (total reticulocytes count 23.2 K/μL), the neutropenia had worsened (neutrophils count 0.89 K/μL) and severe thrombocytopenia was still present (PLT count 2 K/μL) (Table 2). On examination of the blood smear, mild anisocytosis was observed, and no PLT clumps were detected. The patient continued on treatment with omeprazole (1 mg/kg BID) and sucralfate (500 mg/dog TID).

Bone marrow aspirate and core biopsy were performed. The aspiration cytology showed a hypocellular bone marrow. Scarce hypocellular medullary spicules were observed, where small- and medium-sized adipocytes were distinguished, and the cellularity was predominantly composed of mature erythroid precursors with a ratio of approximately 0.21. Very few metarubricytes and pinucleated rubricites were observed. Among the total number of cells observed, 12% were small lymphoid cells and 11% were plasma cells. No megakaryocytes were observed. The cytological diagnosis was marked bone marrow hypoplasia with mild erythroid hyperplasia and ineffective erythropoiesis. At the core biopsy, well-organised, mature bone trabeculae were observed. Within the marrow spaces, a predominance of adipose tissue was detected, with decreased presence of haematic precursors and occasional plasma cells, fibroblasts and fibrocytes. The haematic precursors were mainly mature erythrocytes and, in less proportion, immature erythrocytes and segmented neutrophils. Scattered plasma cells and histocytes were also observed.

A semi-quantitative determination of iron deposits in the bone marrow was performed by Perls staining, which revealed an increase in pigment consistent with grade 3 (moderate) haemosiderin/iron deposits according to the Pawsat's classification,[16] where iron deposits in bone marrow can be classified as none (grade 0), very slight (grade 1), slight (grade 2), moderate (grade 3), moderately heavy (grade 4), heavy (grade 5) and very heavy (grade 6).

The histological diagnosis was marked bone marrow hypoplasia with mild to moderate fibrosis and megakaryocytic aplasia.

Leishmania spp., *Anaplasma* spp. and *Ehrlichia* spp. PCRs were performed on bone marrow tissue, with negative results.

DIFFERENTIAL DIAGNOSIS

AA is a clinical syndrome characterised by bicytopenia or pancytopenia in the blood and replacement of bone marrow by adipose tissue.[17] IAA is considered one of the most frequent causes of AA in dogs.[18] Other causes of AA are infectious agents (parvovirus,[19] *Ehrlichia canis*,[20] *Leishmania* spp.[21]), certain drugs (antineoplastics, estrogens, phenylbutazone, meclofenamic acid, carprofen, azathioprine, naproxen, chloramphenicol, cephalosporin, sulphonamides, phenobarbital, phenytoin, levamisole, albendazole, metronidazole, fenbendazole, amitraz, amiodarone, captopril, quinidine gluconate, acetaminophen, aspirin, phenacetin, benzocaine, methylene blue, diphenylhydrazine, human erythropoietin/darbepoetin, mitotane, colchicine),[22] heavy metals intoxication (lead, mercury, arsenic)[22] and radiation.[17] When these causes are ruled out in a patient with bone marrow hypoplasia/aplasia, a diagnosis of IAA is established.

In this patient, infectious causes were ruled out by serology and, subsequently, by bone marrow PCR. Drug and toxins were considered to be less likely based on previous history. Although it is true that the patient had received several drugs before the onset of the haematological alterations, none of these drugs has been previously described as causing pancytopenia/bone marrow aplasia.

Other extramedullary causes for the different cytopenias cannot be completely ruled out in this patient.

The patient showed anaemia after starting glucocorticoid therapy following the diagnosis of lymphoplasmacytic gastroenteritis. The appearance of digestive bleeding is an adverse effect produced on many occasions after the administration of glucocorticoids, and many patients do not show clinical signs associated with bleeding.[23] As anaemia, most of the time, has been hypochromic and regenerative, this option cannot be ruled out. However, at the time the bone marrow aspiration and core biopsy were performed, the patient had a non-regenerative anaemia, so in that clinical context, the diagnosis provided by the pathologist was a severe bone marrow hypoplasia. Also, at the Perls staining, no iron deficiency was detected in the bone marrow. In patients with anaemia secondary to gastrointestinal bleeding, iron stores in the bone marrow are usually decreased,[24] which makes anaemia secondary to gastrointestinal bleeding less likely in this patient.

The abscesses that the patient developed could be secondary to both the neutropenia detected before referral and/or the immunosuppression induced by the previously administered glucocorticoids. The presence of the abscesses could even be secondary to the patient's immunosuppression produced by the doses of glucocorticoids it had received. Nevertheless, no other justification was found for the neutropenia

TABLE 3 Complete blood counts from Day 0 onwards of eltrombopag treatment

Haematologic variable	Day 0	Day 7	Day 21	Day 24	Day 115	Day 236	Reference interval
Red blood cells (M/μL)	2.41	5.58	6.96	7.92	8.1	8.61	5.65–8.87
Haematocrit (%)	17.3	40.4	46.3	51.9	51.7	54.0	37.3–61.7
Haemoglobin (g/dL)	5.3	12.2	14.4	15.9	17.4	17.9	13.1–20.5
Mean cell volume (fL)	71.8	72.4	66.5	65.5	63.8	62.7	61.6–73.5
Mean cell haemoglobin (pg)	22	21.9	20.7	20.1	21.5	20.8	21.2–25.9
Mean cell haemoglobin concentration (g/dL)	30.6	30.2	31.1	30.6	33.7	33.1	32.0–37.9
Red cell distribution width (%)	29.3	20.1	20.5	22.2	19.8	20.4	13.6–21.7
Reticulocytes (K/μL)	158.8	252.2	70.3	188.5	89.1	172.2	10.0–110.0
White blood cells (K/μL)	4.99	6.02	7.81	7.18	11.75	6.18	5.05–16.76
Neutrophils (K/μL)	1.74	2.93	5.01	3.48	5.52	2.95	2.95–11.64
Lymphocytes (K/μL)	2.56	2.39	2.09	3.01	4.68	2.47	1.05–5.10
Monocytes (K/μL)	0.64	0.61	0.54	0.49	0.71	0.40	0.16–1.12
Eosinophils (K/μL)	0.04	0.09	0.15	0.2	0.77	0.35	0.06–1.23
Basophils (K/μL)	0.01	0	0.02	0	0.07	0.01	0.00–0.10
Platelets (K/μL)	21	297	376	307	317	268	148–484
Mean platelet volume (fL)	15.6	13	11.3	11.5	10.8	10.5	8.7–13.2

that the patient presented at the time of the consultation and in the re-examination carried out a week later, as the tests performed did not find any source of infection.

As no megakaryocytes were observed in the bone marrow cytology and biopsy, no causes other than aplasia or immune-mediated destruction could be established for the thrombocytopenia.

At this point, the most common endemic infectious agents that can potentially cause medullary aplasia were ruled out (*Leishmania* spp. and *Ehrlichia* spp.). Neoplastic and radiation causes were ruled out as well. Toxic causes could not be completely ruled out, as the dog had received several treatments before referral, although the anaemia and thrombocytopenia were detected before receiving most of the drugs (Table 1).

The most probable diagnosis was AA of unknown cause, without being able to completely rule out the presence of digestive bleeding as a contributing factor to the anaemia

TREATMENT

With these results, the dog was treated with eltrombopag (Revolade 12.5 mg, Novartis; at a dose of 1.25 mg/kg SID). The owner refused to use immunosuppressive treatments such as prednisolone and cyclosporin. The administration of omeprazole and sucralfate was also continued, as digestive bleeding could not be ruled out with the tests performed. Due to a confusion on the part of the owner, during the first 7 days of treatment, the owner administered to the patient twice the dose that was recommended: administering one tablet of 12.5 mg of eltrombopag BID instead of one tablet SID. At this point, a CBC was performed, showing an improvement in all the cellular lineages (Table 3). The HCT, leukocytes and PLT counts were within the reference ranges.

OUTCOME AND FOLLOW-UP

Eltrombopag dose was tapered to the recommended dose (half of a tablet of 25 mg SID). Treatment was continued for a further 14 days and then stopped. On the last day of treatment, CBC was performed that showed mild hypochromia, with all the other parameters within the reference range (Table 3).

Periodic medical re-examinations were performed, with no major changes on CBC (Table 3). The last re-examination was made 7 months after eltrombopag treatment, with all the parameters on CBC within the reference range.

DISCUSSION

Bone marrow hypoplasia, also called AA, is a clinical syndrome characterised by two or three cytopenias in the blood.[17] Different aetiologies have been identified, including infectious agents, drugs, toxins and radiation. When other causes of AA are ruled out, a diagnosis of IAA is established. In a retrospective study evaluating bone marrow specimens from a veterinary teaching hospital in the United States, AA was identified in 2.4% of the samples, most of them being IAA (1.7%).[18] In another study of 64 dogs with pancytopenia, IAA was identified in 9% of the bone marrow samples.[25] Most patients with IAA are young adults (mean age of 2.9 years), with no sex or breed predisposition.[18]

In human patients, an immune-mediated mechanism has been identified as the cause of this process, with implication of CD4 cells, CD8 cytotoxic T cells, regulatory T cells, Th17 cells and natural killer cells.[26,27] In veterinary medicine, no study has identified the mechanism of IAA. Response to immunosuppressive therapy in the few cases reported in the literature[12,13,18,28,29] also suggests an immune-mediated mechanism as the main cause of the disease.

Eltrombopag is now widely used in human medicine for the treatment of AA in combination with immunosuppressive therapy,[5] although there are case reports in which eltrombopag has been used as monotherapy with clinical response.[30,31] In those patients, the response was delayed in comparison with patients treated with a combination of eltrombopag and immunosuppressive agents.

In veterinary medicine, only two case reports describe the use of eltrombopag in dogs, one of them for the treatment of IAA[14] and the other one for the treatment of pancytopenia secondary to lomustine overdose.[15] In both studies, eltrombopag doses were extrapolated from the starting dosage used in children and the smallest tablet size available. The duration of treatment in veterinary patients has not been studied, while in human medicine, eltrombopag is used in combination with immunosuppressive drugs (cyclosporin and antithymocyte globulin) for a minimum of 3 months if remission is achieved.[1]

The maximum dose of eltrombopag indicated in human medicine is 150 mg per day, which is about 2.14 mg/kg in a 70 kg bodyweight adult. In this case, it was decided to use a similar dose to that published in the previous case reports. In the present case, the owner mistakenly administered twice the dose during the first week of treatment. This dose exceeded the maximum dose indicated for humans. The most frequent adverse effects of this drug are an increase in liver enzyme levels, increase in reticulin deposition in the bone marrow, or renal toxicity.[4] The dose was then immediately reduced to that initially prescribed. In this patient, clinical and haematological adverse effects were not identified after inadvertent administration of a 2.8 mg/kg SID dose. In this case, it was not possible to determine if there were variations in biochemical parameters, because no re-evaluations were performed as the patient was clinically stable.

A fast recovery of haematological parameters was detected in this patient, with the HCT, WBC and total PLT within the normal range only 7 days after initiating eltrombopag. This is a much earlier response when compared with the case by Kelly et al.[14], where a complete haematological response was found 33 days after starting treatment with eltrombopag.

The decision to not use immunosuppressive drugs was made because the owner rejected the use of prednisolone or cyclosporine. The owner was convinced that the clinical deterioration of the patient and the appearance of the abscesses was related to the previous administration of glucocorticoids. This, coupled to the poor prognosis associated with idiopathic aplastic pancytopenia in dogs despite treatment with immunosuppressants,[13,29,32] led us to investigate possible alternative treatments, such as the use of eltrombopag.

The length of the treatment with eltrombopag in this patient was 21 days. This was decided because continuing treatment would have been prohibitively expensive for the owner. Duration of treatment with eltrombopag in veterinary patients should be established. The case presented by Kelly et al.[14] received eltrombopag for 2 months based on a previous study in human patients.[1] In human patients, eltrombopag is usually administered for 6 months or more.[33]

We cannot prove that the use of eltrombopag was responsible for the improvement on all cell lineages. As previously mentioned, a toxic cause for the cytopenias cannot completely be ruled out and, in patients with pancytopenia secondary to myelotoxicity, the recovery of the cell counts is described to be fast.[27,34] The first available CBC was performed while the patient was on omeprazole and prednisolone. At that time, the patient had regenerative anaemia and thrombocytopenia. The thrombocytopenia was maintained despite withdrawal of prednisolone treatment, and was maintained until administration of eltrombopag. Omeprazole treatment was not withdrawn at any time, and the patient still recovered its haematological values, so it is unlikely that omeprazole was related to the patient's cytopenias. This, together with the fact that the other medications used subsequently have not previously been associated with myelosuppression in any case published in the literature, leads us to strongly believe that eltrombopag has contributed to improve the recovery of the cell lineages.

In this case, it is difficult to determine the specific effect of eltrombopag on the recovery of the different cell lines. It is possible that eltrombopag acted by stimulating PLT production, and the improvement of PLTs stopped possible occult gastrointestinal bleeding in the patient, which in turn contributed to the improvement of the erythrocyte line. However, as the bone marrow showed no evidence of iron deficiency, occult gastrointestinal bleeding as a cause of anaemia was considered less likely.

Also, it cannot be determined if the rapid remission detected in this patient was produced by the high dose administered during the first 7 days.

The case described by Kelly et al.[14] received cyclosporin and prednisolone at the same time as eltrombopag, making it difficult to establish if the response was secondary to the eltrombopag or a combination of eltrombopag with immunosuppressive drugs. In the case described by Aspinall et al.[15], a granulocyte-macrophage colony-stimulating factor was used in combination with eltrombopag. In that case also, it was difficult to know whether the patient's recovery was related to the use of eltrombopag, as the pancytopenia was caused secondary to a lomustine overdose and it was not idiopathic.

In this case report, there are several limitations. It was not possible to rule out if digestive bleeding could contribute to the anaemia of the patient. Also, bone marrow toxicosis could not be completely ruled out due to the previously administered drugs. Another limitation was that serum chemistry was not performed on each follow-up visit. Serum chemistry was performed on day 115 after treatment with eltrombopag, with all the parameters within the reference range. One last limitation of this case report is that a repeat bone marrow aspirate and core biopsy were not performed when the patient was in remission, as is recommended in human patients. This was not performed due to strong ethical reasons.

Eltrombopag can be used as part of the treatment for AA in dogs, but further clinical studies evaluating its use are needed, as its use could improve the poor prognosis of this disease. Ideal doses and optimal treatment duration should be established in future studies.

AUTHOR CONTRIBUTION

Alfredo Rodriguez-Cobos: case management, writing and editing of manuscript. Sabela Atencia: case management, editing and review and final review of manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

ETHICS STATEMENT

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to.

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MULTIPLE-CHOICE QUESTION

Aplastic anaemia is a clinical syndrome characterised by bicytopenia or pancytopenia in the blood and replacement of bone marrow by adipose tissue. Idiopathic aplastic anaemia is considered one of the most frequent causes of aplastic anaemia in dogs. What are the other causes of aplastic anaemia?

POSSIBLE ANSWERS TO MULTIPLE-CHOICE QUESTION

1. Infectious agents
2. Drugs
3. Neoplasia
4. Radiation
5. Answers 1, 2, 3 and 4 are all correct.
6. Answers 1, 2 and 4 are correct.

CORRECT ANSWER

6) Answers 1, 2 and 4 are correct.

Various drugs (such as griseofulvin, oestradiol, phenylbutazone), infectious agents (parvovirus, *Ehrlichia canis*, *Leishmania chagasi*) or exposure to radiation have been associated in the literature with the development of aplastic anaemia.