Treatment Of Pancytopenia in a Dog with Western Herbal Medicine

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Abstract

A 12-year-old female speyed Jack Russell Terrier was diagnosed with pancytopenia prior to a Tibial Plateau Levelling Osteotomy Procedure in December 2023. The canine had been scavenging horse feed mixed with TMPS® powder (Trimethoprim Sulphadimidine) in the two weeks prior to surgery. Drug related bone marrow suppression was the most likely cause for the pancytopenia. The patient was monitored for two months to assess recovery. A haemogram in February 2024 confirmed no improvement with a borderline anaemia and moderate leukopenia remaining and a bone marrow aspirate and biopsy was the next diagnostic step. The canine was treated with herbal medicine using blood tonics and immune stimulants which normalised the red blood cell and white blood cell counts within seven weeks.

History

The patient had been experiencing severe lumbar pain and intermittent non weight bearing on the right hindlimb for six weeks. Radiography of the right stifle, lumbar/lumbosacral spine and a CT scan were conducted under general anaesthesia (GA) on the 12th of December 2024. The patient had previously had a left hindlimb TPLO surgery in March 2020, and the plate removed one year later. Mild synovial effusion with secondary osteoarthrosis was discovered on mediolateral and cranial-caudal radiographic views of the right stifle which suggested "emerging" cruciate disease although no obvious cranial draw was present under GA. No abnormalities were reported in the lumbar and lumbosacral spine. A CT scan of the spine from T3 to S3, using contrast agent, was also carried out and only subtle evidence of right cruciate disease was found. Pre-anaesthesia blood tests revealed a moderate pancytopenia with a low HCT 0.31 L/L (0.37-0.55), absolute reticulocyte count 5.28 x 10 ^9/L (0-60), leukopenia WBC 2.6 x 10^ 9/L (6-15) and borderline low platelets 159 x 10^9/L (165-500) (Table one). Biochemistry showed a low globulin of 19 g/L (23-52), and no evidence of renal or hepatic disease. There were no suspicious changes on a blood smear and no autoagglutination. The canine was active and had been in good health. Following the pancytopenia diagnosis complete analysis of reconstructed CT images of the thorax, abdomen, spine and pelvis was conducted and no significant changes found. A discovery by the dog's guardian found that the dog had been having daily access to an unknown amount of horse feed for two weeks that was mixed with trimethoprim sulphadimidine powder (TMPS®, Dechra) at a dose of 2.5 scoops daily for a 500kg horse. Sulphonamides have been reported to cause aplastic anaemia in dogs and bone marrow recovery occurs when the medication is stopped (Weiss & Adams, 1987). Initially the dog was going to be reassessed for her lameness and pancytopenia in one month but she completely ruptured her right cranial cruciate ligament two days later. A haemogram on the 19th of December showed resolution of the anaemia but the patient still had leukopenia, 5.0 x10^9/L (6.0-15.0). On the 21st of December she had a GA and epidural for a right TPLO. Her anaesthesia and recovery were smooth. She was sent home on five days of Amoxicillin and Clavulanate Potassium (Clavulox®) 125mg PO BID, paracetamol 250mg (Panadol®) PO BID and Meloxicam 0.1mg/kg PO SID (Metacam®, Boehringer) (Table two). To assist her recovery and rehabilitation the patient had laser therapy and physical rehabilitation for the next six weeks. Her energy and weight bearing were excellent. At six weeks post-op she had sedation and radiography which confirmed healing of her osteotomy site. A repeat haemogram showed

borderline anaemia and leukopaenia: HCT 0.39 L/L (0.37-0.55); absolute reticulocytes 17.99 x 10 9/L (0-60) and WBC 3.8 x 10 9/L (6.0-15.0). There had been no further access to TMPS powder. The specialist planned to reassess another haemogram in four weeks. At that stage it was still considered the sulphonamide antibiotic was having a lingering effect on bone marrow suppression, leading to a type of aplastic/hypoplastic anaemia. A bone marrow aspirate/biopsy was the next step.

Clinical signs: Western diagnosis

The patient had not shown any clinical signs suggestive of pancytopenia at the time of her first haemogram. Her biochemistry was normal apart from a slightly low globulin count. Renal disease was ruled out as a cause of myelosuppression. The patient had had no other complete blood count or biochemistry in the last 12 months. A blood smear taken on the 12th of December showed poikilocytes, adequate numbers of platelets, no autoagglutination and no evidence of Ehrlichia or Babeisa (not endemic in NZ). Views of her thorax, abdomen and pelvis were reconstructed on the CT following the pancytopenia diagnosis but no abnormalities were found. The vertebral column/spine showed mild spondylosis deformans within the lumbar spine. The thorax was unremarkable. The liver and biliary tree were normal. A collection of cholecystoliths (up to 7mm diameter) were found within the gall bladder. The spleen was subjectively mildly diffusely enlarged and contained multiple small mildly enhancing nodular foci most typical of benign extramedullary haematopoiesis. No long bone abnormalities were identified. Moderate left osteoarthrosis was seen consistent with her previous TPLO. A haemogram on the 19th of December showed improvement. That day the HCT was 0.51 L/L and WBC 3.8x10^9/L. Surgery then went ahead.

The presumptive western diagnosis was bone marrow suppression (aplasia/hypoplasia) secondary to trimethoprim sulphadimidine ingestion with decreased production of haematopoietic cell lines. Due to the mild to moderate non-progressive leukopenia and borderline anaemia, and no clinical symptoms, the patient was treated with conservative management and monitoring. If there was no improvement a bone marrow aspirate/biopsy was the next step.

Integrative Clinical examination: 22 February 2024

The patient had a serious medical event in 2019 when she became ill with an idiopathic polyradiculoneuritis. She recovered over five weeks with physical rehabilitation and was left

with only a subtle bilateral hindlimb tremor when overexercised. She went back to full activity as a farm dog. After her six-week post TPLO radiograph the patient had diarrhoea for two days after which she became inappetent in the mornings, had flatulence and borborygmus and was passing drier, smaller stools. Her energy was also reduced, she seemed anxious and was seeking out warmer places. She had always been prone to digestive issues following treatment with drugs. Since her left hindlimb TPLO in 2020 she was supplemented with 4CYTE Epitalis forte® for arthritis, boswellia 400mg SID (Natures Way®) and omega 3 1.5ml divided daily (Orthoplex Bioactive lipids®). Multispectrum probiotics 2gm daily (ProN8ure®) were mixed with her freeze-dried raw food (Ziwipeak®) diet and steamed vegetables.

On examination the patient seemed more subdued. She was moving very well and weight bearing fully on the right hindlimb at a stance and walk. Her body condition score was 4/9 and she had been maintaining her weight well. Her coat was shiny. Her tongue was pale pink and slightly dry while her pulse was floating and slightly empty to palpate. Her vitals were within normal limits. Her abdomen was soft to palpate with no organomegaly. Her ears, paws and dorsal spine were cool to palpate. Her musculoskeletal examination revealed mild hypertonus and spasm of lumbar epaxials, bilateral iliopsoas and gluteal muscles. Her left stifle had reduced flexion, crepitus and osteophytosis. Her right hindlimb had complete range of motion and was comfortable to palpation. She showed some reactivity to palpation of her Back Shu Spleen point, Bladder 20.

The patient's clinical signs of low vitality, increased muscle tone/spasm, anxiety, cool extremities and tongue and pulse changes were indicative of blood deficiency (Wynn & Fougere, 2007). Her leukopenia and borderline anaemia were also objective findings of this. Her digestive disturbance and slow recovery from her recent sedation showed suboptimal liver and digestive function and a dysbiosis. Given she had been administered three anaesthetics in the last two months, CT contrast agent, antibiotics, analgesics, TMPS powder and had to recover from major surgery her ability to detoxify and eliminate these "toxins" had been a major stress to her system (Table two).

Conventional (Western treatment)

Post surgery the patient was given five days of Amoxicillin and Clavulanate Potassium 125mg PO BID to prevent secondary infection. Possible treatment options for pancytopenia based on a complete diagnosis include antibiotics, transfusions, immune suppressants, bone

marrow stimulation and bone marrow transplantation but she was not administered any specific treatment (Kearns & Ewing, 2006).

Integrative Treatment

The primary goal of treatment was to alleviate her blood deficient symptoms with the use of blood tonics, which stimulate haematopoiesis. Herbs with immune stimulant actions were also needed to improve overall immune function and prevent secondary infections. Adaptogen herbs were used to improve the patient's vitality, resist stress and enhance convalescence. Digestive function was enhanced with bitter tonics, carminatives, demulcents, mild laxatives and anti-inflammatories alongside probiotics. Enhancing overall organ function to improve detoxification and elimination also improves vitality and hepatics, cholagogues, laxatives and diuretics were used to achieve this. Nervines were included to reduce her anxiety.

A liquid herbal formula combination of *Withania somnifera, Echinacea purpurea, Glycyrrhiza glabra* and *Matricaria recutita* was prepared using Phytomed herbal tinctures (Table three). The patient was given 0.95ml diluted in water, orally twice daily. *Silybum marianum* was given as standardised Silymarin 85mg orally once daily (Mediherb). The owner was instructed to continue probiotics and add in fermented foods such as kefir to improve her microbiome.

Herbs were selected for the following actions. *Withania somnifera* is a tonic, adaptogen, nervine, anti-anaemic, anti-inflammatory and immune modulator (Bone, 2006). In one study the administration of *Withania somnifera* extract to mice treated with cyclophosphamide significantly reduced the leukopenia that was seen to develop in the control mice. Analysis of bone marrow from the femurs of the Withania treated mice showed a significant increase in the number of cells as it strongly stimulated stem cell proliferation in bone marrow (Davis & Kuttan,1998). Similarly, Withania extract was also found to be protective to bone marrow and white blood cell count in a study where neutropenia was induced in mice given paclitaxel (Gupta et al, 2001). *Echinacea purpurea* is an immune stimulant, antimicrobial and anti-inflammatory (Wynn & Fougere, 2007). It also has myelostimulatory activity. Echinacea was found to inhibit the reduction in white blood cells after exposure to radiation (Mishima et al, 2004) and significantly reversed low red blood cell and white blood cells counts in immunocompromised rats treated with cyclosporine (Khattab et al, 2019; Ramasahayam et al, 2011). The granulocyte/macrophage colony forming cells in the bone marrow of rats given

Echinacea were doubled compared to rats in the control group in the cyclosporine study, proving myelopoiesis stimulating activity (Ramasahayam et al, 2011). *Glycyrrhiza glabra* is a demulcent, antispasmodic, laxative, immune modulator and adaptogen (Wynn & Fougere, 2006). *Matricaria recutita* has anti-inflammatory, carminative, cholagogue, spasmolytic, sedative, anti-inflammatory and bitter tonic actions (Wynn & Fougere, 2006). Alongside *Glycyrrhiza glabra*, *Matricaria recutita* was used to enhance digestive function. *Silybum marianum* is a hepatic tonic, choleretic, cholagogue and antioxidant and was used to enhance detoxification and elimination and help with improving biliary function related to the cholecystolithiasis found on her CT (Bone, 2006). The formula was given for four weeks and the patient then reassessed. A haemogram at her regular vet was carried out three weeks later.

Follow up appointment 25 March 2024

The patient was doing well, her vitality had improved, and all digestive issues had resolved. Her tongue was pink and her pulses toned. Her extremities were warmer to palpate. A haemogram taken on the 13th of March showed the anaemia had fully resolved, HCT 0.53 l/L, with a significant reticulocyte response 33.76 x 10^9/L but she was still mildly leukopenic, WBC 4.8 x 10^ 9/L. *Angelica sinensis* was added to her formula. *Matricaria recutita* was removed given her digestive problems had resolved. *Silybum marianum* was continued. The dose of the new formula was 0.95ml PO BID and was to be given over the next six weeks.

Angelica sinensis is a blood tonic, mild laxative and anti-inflammatory (Bone, 2006). It strongly stimulates haematopoiesis through its ability to promote the synthesis of haematopoietic growth factor (Li et al, 2017). Polysaccharide-enriched fractions from the root of *Angelica sinensis* were shown to significantly enhance the recovery of platelets, blood cells, haematopoietic progenitor cells and colony forming units of the myeloid, erythroid and megakaryocytic lineages in mouse models of myelosuppression with radiotherapy (Liu et al, 2010). Significant recovery of red blood cell counts and white blood cell counts were shown from day seven of treatment with Angelica following radiotherapy and bone marrow in the mice showed an increase of 70% cellularity compared to controls by day 21.

Follow up appointment 19 April 2024:

A haemogram taken on the 11th of April showed no further anaemia or leukopenia: HCT 0.52 L/L, absolute reticulocyte count 52.14 x 10^9/L and WBC 6.0 x 10^ 9/L. The patient had good energy and at 16 weeks post-TPLO she was back to normal activity. There were no further digestive issues and her anxiety was alleviated. Her tongue was pink and her pulses

toned. Muscle tension in her hindlimbs and lumbar area had resolved. The formula was continued for a further month with a repeat haemogram recommended monthly for two further months to ensure continued progress.

Discussion

Pancytopenia is considered a decrease in all circulating marrow cell lines: myeloid, erythroid and megakaryocytic. Clinical signs are nonspecific but include lethargy and petechiation. In this canine, pancytopenia was found incidentally on pre-anaesthetic blood tests. Her initial pancytopenia involved moderately low red cells, a low reticulocyte response, moderately reduced white blood cells and borderline low platelets. Pancytopenia can result from the peripheral destruction of cells or due to a primary insult to the bone marrow (Kearns & Ewing, 2006). Peripheral destruction of cells can be due to either sepsis, immune mediated disease, hemophagocytic syndrome or hypersplenism. Diagnostically this was ruled out. The patient's biochemistry and CT scan were also unremarkable apart from mild splenomegaly indicative of benign extramedullary haematopoeisis. Where there is decreased haematopoietic cell production a bone marrow aspirate and/or core biopsy is needed for a definitive diagnosis. Due to the mild nature of her cytopenias a conservative approach with repeated monitoring was taken. Various causes of decreased haematopoietic cell production include aplastic or hypoplastic marrow, marrow necrosis, myelodysplasia, marrow fibrosis/sclerosis and myelopthisis (Kearns & Ewing, 2006). In a retrospective study of canine pancytopenia in 51 dogs, eleven different disease processes were identified (Weiss & Evanson, 1999). More commonly chemotherapy, neoplasia (such as malignant histiocytosis, multiple myeloma), idiopathic aplastic anaemia and immune mediated disease were found. Given the degree and non-progressive course of pancytopenia in this canine, drug exposure to trimethoprim sulfadimidine causing an aplastic or hypoplastic anaemia seemed most possible. Destruction of stem cells and progenitor cells is recognised as a cause of marrow hypoplasia or aplasia and is the proposed method many drugs, toxins and infectious agents act to suppress bone marrow (Kearns & Ewing, 2006). In aplasia, all marrow haematopoietic cells become markedly reduced or absent and the haematopoietic space is replaced by adipose tissue. Various documented causes of aplasia and hypoplasia include sources of estrogen, infectious disease (parvovirus, babesiosis), chemicals, radiation treatment, and drugs such as phenylbutazone, chemotherapeutics, albendazole and trimethoprim sulfadiazine among others (Kearns & Ewing, 2006). Approximately 67% of aplastic anaemia are idiopathic with no known cause (Brazzell & Weiss, 2006). Once the bone marrow suppressing agent is removed

cytopenias should begin to resolve in 10 to 14 days but chronic aplastic anaemias feature haematopoietic stem cell injury and recovery can be unpredictable and lengthy, if at all (Kearns & Ewing, 2006). Sulphonamides have been documented to cause bone marrow suppression with various haematological findings of aplastic anaemia, granulocytopenia and thrombocytopenia (Weiss & Klausner, 1990). In one case study a dog with aplastic anaemia following trimethoprim sulfadiazine recovered promptly after treatment was discontinued (Weiss & Klausner, 1990). Given that it took longer for the leukopenia to resolve in this patient there may have been more significant injury to the myeloid stem cells. Definitive diagnosis required a bone marrow aspirate and biopsy but the dog's guardian preferred to investigate herbal medicine for treatment.

With the use of haematopoeitic herbal medicine, also known as blood tonics, the patient returned to a substantial red cell count within three weeks and a normal white cell count within seven weeks. She had shown a poor regenerative response for the two months prior to herbal treatment. *Withania somnifera* and *Angelica sinensis* were key blood tonic herbs used. With the use of blood tonics, the patient recovered from her overall systemic imbalance of blood deficiency. Withania strongly stimulates stem cell proliferation in bone marrow and was shown to resolve the borderline anaemia within three weeks as well as stimulating white blood cell recovery. To further support regeneration of white blood cells *Angelica sinensis* was introduced at four weeks and this led to a strong response with complete recovery of the white blood cell count on the 11th of April. *Angelica sinensis* is shown in studies to stimulate haematopoietic progenitor cells and colony forming units in myelosuppression models. *Echinacea purpurea* further added myelostimulatory activity to assist bone marrow recovery and stimulated immune function to avoid infections. Physiological enhancement included supporting her digestive function, adaptogenic support and enhancing detoxification and elimination with the use of *Glycyrrhiza glabra, Matricaria recutita* and *Silybum marianum*.

Haematopoeitic herbs were proven to resolve the lingering borderline anaemia and leukopenia in this canine patient which was a likely hypoplastic/aplastic anaemia secondary to bone marrow suppression from trimethoprim sulphadimidine in scavenged horse feed. Recovery of white blood cells and red blood cells was expected to occur within 21 days of stopping access to the drug but this did not occur. Over a seven week period, treatment with herbs resulted in a strong regeneration of red and white blood cells. Haematopoietic herbal tonics should be considered for improving bone marrow recovery in drug induced pancytopenias.

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Appendix

Table One

Date:	**11 April 2024**	**13 March 2024**	**07 Feb 2024**	**19 Dec 2023**	**13 Dec 2023**	**Units**	**Ref interval**
RBC	6.86	6.62	5.29 L	6.68	4.06 L	X10^12/L	5.50-8.20
Haemoglobin	181 H	181 H	136	178	105 L	g/L	120-180
HCT/PCV	0.52	0.53	0.39	0.51	0.31 L	L/L	0.37-0.55
MCV	75	80 H	74	77	76	fl	60-78
MCH	26 H	27 H	26 H	27 H	26 H	pg	20-25
MCHC	351	340	346	346	339	g/L	320-360
Abs retic	52.14	33.76	17.99	21.38	5.28	X10^9/L	0-60.00
Retic %	0.8	0.5	0.3	0.3	0.1	%	
WBC	6.0	4.8 L	3.8 L	5.0 L	2.6 L	X10^ 9/L	6.0-15.0
Neutrophil%	71	74	75	71	72	%	
NeutrophilAbs	4.2	3.6	2.8 L	3.5 L	1.9 L	X10^ 9/L	3.6-11.5
Lymphocyte %	19	21	17	19	19	%	
LymphocyteAb	1.1	1.0	0.6 L	0.9 L	0.5 L	X10^ 9/L	1.0-4.8
Monocytes %	-	2	4	2	3	%	
MonocytesAbs	-	0.1 L	0.2 L	0.1 L	0.1 L	X10^ 9/L	0.2-1.5
Eosinophils %	10	3	4	8	6	%	
EosinophilsAbs	0.6	0.1	0.2	0.4	0.2	X10^ 9/L	0.1-0.5
Platelets	225		162		159 Low	X10^9/L	165-500

Table Two: Medication for Procedures Administered and Post Op

Procedure and date	Medication administered
12 December 2023 CT T3-S3 Radiography pelvis and RHL	Methadone 0.3mg/kg and Acetylpromazine 0.01mg/kg intramuscular Propofol 4mg/Kg iv (Fresofol 1%) Maintenance with isoflurane/oxygen
21 December 2023 Right hindlimb TPLO	Premedication: Methadone 0.3mg/kg and Medetomidine 0.003mg/Kg intramuscular Induction: Ketamine 2mg/Kg and Propofol 4mg/kg intravenously Fentanyl bolus 2 mcg/Kg iv followed with constant rate infusion Maintenance: Isoflurane and oxygen During operation: 10mcg glycopyrrolate intravenously Cefazolin 22mg/Kg intravenously Epidural: 0.1mg/Kg of 5mg/mL sterile and preservative free morphine mixed in 0.5mg/Kg of 0.5% bupivicaine Post op medication: Amoxicillin/clavulanate (Clavulox®) 12.5mg/kg subcutaneously Meloxicam 0.1mg/kg injection
21 December 2023 Medication post op at home	Meloxicam 0.1mg/kg PO SID (Metacam, Boehringer) for 14 days Paracetemol 1.2 tablet PO TID (Paracetemol 500mg tablets) for 11 days Amoxicillin/Clavulanate Potassium 125mg PO BID Clavulox® 25Omg, ½ tablet twice daily)
08 February 2024 Six week post operative radiographs of the right hindlimb	Butorphanol (Butorphic®) 0.17ml and Medetomidine 0.09ml intramuscular Propofol 4mg/Kg intravenously Isoflurane/ Oxygen maintenance Antisedan reversal 0.15ml IM

Table Three: Formula 22 February 2024 using Phytomed Herbal Tinctures

Herbal medicine	Dose per day	Amount
Withania somnifera 1:2	0.6ml per day	18ml
Echinacea purpurea 1:2	0.5ml per day	15ml
Glycyrrhiza glabra 1:2	0.4ml per day	12ml
Matricaria recutita glycetract 1:3	0.4ml per day	12ml
	1.9ml per day	57ml

Table Four: Formula 25th of March 2024 using Phytomed Herbal Tinctures

Herbal medicine	**Dose**	**Amount**
Withania somnifera 1:2	0.6ml per day	18ml
Echinacea purpurea 1:2	0.5ml per day	15ml
Glycyrrhiza glabra 1:1	0.3ml per day	9ml
Angelica sinensis 1:2	0.5ml per day	15ml
	1.9ml per day	57ml