A 7 year old neutered male neuter domestic shorthair cat was presented to the Internal Medicine Service for investigation of two generalised tonic-clonic seizures that occurred within four hours of each other 10 days prior to presentation. The cat was otherwise well with a normal appetite, urination and defecation, but had been lethargic and dull in these 10 days. Initial blood tests before referral showed a markedly elevated PCV of 86%.

The cat had a good body condition and appeared bright and alert with no neurological defects identified on an examination. A grade 1-2 parasternal systolic murmur was identified, but there was no audible evidence of a dysrhythmia and no pulse deficits. The cat became very relaxed during his examination and laid in lateral recumbency, which was reported to be unusual. A retinal examination showed a small area of haemorrhage in the right eye dorsally. Hypertension of 190mmHg was repeatedly recorded when the cat was relaxed.

1) What are your differential diagnoses for polycythaemia in a cat?
2) What diagnostic evaluations would you perform in this cat to investigate this?
3) Which of the clinical and laboratory findings could be secondary to the polycythaemia?
4) How would you treat this cat?
1) What are your differential diagnoses for polycythemia in a cat?

An increase in red cell concentration may result from a relative or absolute increase in erythrocytes.

Relative
This type of polycythemia is secondary to dehydration, which may occur for several reasons. Dehydration rarely results in a PCV >60% in cats.

Transient absolute polycythemia
This may occur with excitement when splenic contraction releases red cells into circulation. The high result would not be persistent so the PCV from resampling at a second time point should be lower.

Absolute polycythemia- Secondary
Driven by increase erythropoietin (EPO) production/presence:

- Due to systemic hypoxia
  - Cardiac conditions: Anatomical (tetralogy of Fallot, reverse patent ductus arteriosis), or an appropriate physiological response to left sided or biventricular heart failure.
  - Chronic Pulmonary conditions: Diffuse conditions resulting in low oxygen transport such as chronic bronchitis or allergic airway disease, primary infections such as Bordetella, Mycoplasma, lung worm or infiltrative/diffuse neoplasia. Severe obesity could also reduce alveolar ventilation because of fat accumulation in the thorax.

- Due to local renal hypoxia: e.g. a mass or thrombus reducing renal blood flow or a mass, cyst or hydronephrosis within the kidney again reducing oxygenation.

- Due to a specific neoplasm of the renal tissue producing erythropoietin or an extra-renal tumour producing EPO or EPO-like substance.

- Excessive exogenous erythropoietin or darbepoetin.

- Due to hyperthyroidism: direct effect of thyroid hormone stimulating red cell precursors. Erythropoietin production may also be increased.

Absolute polycythemia- Primary inappropriate
A rare condition in cats – There is a primary proliferation in red blood cells as a neoplastic or pre-neoplastic condition. Often the PCV is above 65% and other cells lines (leukocytes and thrombocytes) can be high. EPO is normally low or normal.

2) Diagnostic investigations included:

- Routine haematology and serum biochemistry
In-house PCV was markedly elevated at 78%, with normal total solids (70g/dL). Laboratory
haematology revealed similarly increased red blood cells. The reticulocytes were also increased but other cell lines were within reference ranges. A blood smear evaluation did not reveal any evidence of neoplastic cell changes. Serum biochemistry was largely unremarkable apart from a low glucose at 2.4mmol/l (3.3 – 5), which was repeatedly low, measured directly from the cat (there was no period of storage). Total t4 was within the reference range.

- An FeLV and FIV snap test was negative
- Echocardiography excluded a cardiac cause for the polycythemia, although this did identify hypertrophic cardiomyopathy.
- SpO2 was 96% (pinna measurement).

Before further investigations, for patient safety a therapeutic blood draw (see later details) was completed.

- Whole body computed tomography was completed with a mild sedation. No diffuse pulmonary changes or abdominal masses were identified. The renal architecture was normal with no contrast enhancement. There was a 1cm lesion within the lungs, suspected to be a benign mucus plug or artefact, but a neoplasm could not be excluded.
- An arterial PO2 (measured with the aid of the same sedation) during the polycythemia (now 65%) was 80. This result was high enough to exclude hypoxia as a cause of the polycythemia.
- Erythropoietin (EPO) was elevated at 42mIU/ml (new laboratory reference 10-30)

The diagnosis for this cat therefore was absolute polycythemia secondary to inappropriate production of erythropoietin. The source of the erythropoietin has yet to be confirmed and the pulmonary mass is not in a position that can be safely sampled.

3) Which of the clinical and laboratory findings could be secondary to the polycythemia?

**Hypertension:** Increased blood viscosity can cause a systemic high blood pressure.

**Retinal Haemorrhage:** Both secondary to the hypertension, but this can also occur purely with increased capillary blood viscosity. This was resolving at revisits.

**Mental dullness and seizures:** Reduced oxygen delivery to the cerebrum due to blood viscosity. Both haemorrhage and increased clotting would also predispose to vascular events. The hypoglycaemia would also theoretically result in neurological signs, including seizures, but historically cats with polycythemia have not been reported to suffer from clinical manifestations of this side effect.

**Hypoglycaemia:** Previous reports of stored polycythemic blood have shown significant decreases in glucose after as little as 2 hours storage, due to RBC usage of glucose. Theoretically this is the mechanism for this patient without storage.

**Cardiac Murmur:** This could be both due to increased blood viscosity and the hypertrophic cardiomyopathy (HCM). The HCM is likely a physiological response to increased blood viscosity requiring increased ventricular pressure to maintain cardiac output, but other causes cannot be excluded.
4) How would you treat this cat?

An intravenous catheter was paced when the cat was admitted before further procedures, so that any further seizure activity could be acted on. A small blood sample from this placement served to allow blood analysis without jugular puncture.

**Emergency treatment- Therapeutic phlebotomy:**

- Clip and EMLA both the left and right jugulars as preparation. Using a 20-21g butterfly catheter, and several 5-10ml syringes remove a calculated amount.

Different references advise different amounts 10ml/kg/day OR an aim of 15% reduction/day and also different finishing PCVs 50-60% are advised (Javinsky, 2012) and (Ettinger(2010)).

We aimed for a 15% reduction per day to achieve 50% final PCV. Removing 20ml/kg of blood reduces the PCV by approximately 15% (BSAVA Manual (2012)) so this was calculated and removed.

- To avoid hypovolaemia a 10ml/kg bolus of crystalloid fluid was provided and the total volume removed was replaced with crystalloids over the next 4 hours.

- A second blood draw was required to reach the goal PCV.

This was performed the following day after the cat had received appropriate fluid therapy. The cat was much livelier after the first blood draw so sedation was required for this and again intravenous fluid therapy was provided. A measurement following the second period of fluid therapy was 55%.

**Continued treatment**

If the polycythaemia is secondary, then treatment should also be aimed at the underlying cause if possible after emergency phlebotomy.

Ideally future blood draws should be considered once the PCV increases above 65% or sooner if clinical signs develop. Each case is individual for the continued requirement for therapeutic blood draws. Some reports suggest an average of once per month, but if this is more frequently required then additional therapies should be considered.

Hydroxyurea might be considered in this cat if phlebotomies are required more than once a month and no cause of the elevated EPO can be determined.

**Hydroxyurea**

The exact mechanism is unknown, but this drug works in primarily neoplastic conditions by interfering with DNA synthesis. It can be used in polycythemia vera mg/kg once a day or 10 – 15 mg/kg twice daily PO for 1-2 weeks (for PV until hematocrit is below 60%) and then every other day (for PV tapered to lowest effective dosage frequency) (Watson et al., 1994, Plumb, 2015).

**Leeches**
There are some reports of using leaches for a gradual and low stress phlebotomy, especially for cats where viscosity is too high to allow for phlebotomy (Nett et al., 2001). Calculations are available for this along with leech disposal kits. Most blood is lost through the anticoagulated wounds left by the leaches and hospitalisation and fluid therapy are still advised.

**PHLEBOTOMY TIPS**

1. Jugulars should be reserved as much as possible as if for a blood donation cat as repeated attempts or several days of blood draws may be needed.

2. Try not to use small gauge needles for jugular puncture as the phlebotomy will take a long time due to increased viscosity.

3. Use small syringes 5-10ml to reduce the negative pressure on the jugular and reduce venous collapse.

4. Prepare for phlebotomy to take a long time- get multiple helpers for 30 minutes.

5. Use of an anticoagulant (heparin or citrate) in the butterfly catheter and line helps reduce the blood clotting inside the butterfly catheter during the phlebotomy.

6. Our hospital has found that arnica cream helps to reduce bruising post venepuncture.

**Discussion**

We re-evaluated this cat 1-week post phlebotomy and his PCV was still 55%. He was very bright and back to his normal behaviour at home with no further seizures. The hypoglycaemia and hypertension had resolved and the retinal haemorrhage was improving.

There is uncertainty for this cat’s final diagnosis. The first reason for this is the division between polycythaemia vera and secondary conditions is based on excluding other primary causes, but also on the EPO level. This level is not well established in cats with only small numbers (n = 11 to 30) with values from 9 to 38 mU/mL (median, 18 mU/mL), (Cook and Lothrop, 1994).

There have also been reports of cats with primary polycythaemia vera with elevated EPO (Cook and Lothrop, 1994). Secondary polycythaemia may occur as a paraneoplastic condition in people without measurable elevations in EPO though this has not yet been reported in cats.

The association of the lung lesion to the polycythaemia is unknown, and no pulmonary lesions have been reported to cause paraneoplastic polycythaemia in cats or dogs, but have been identified in people (Liu et al., 2009). Ideally cytology or histology would be completed. This may be a benign lesion and as this risk of pneumothorax with fine needle aspiration is high thus has not been advocated. Histology would require thoracoscopic removal of the affected lung lobe or a thoracotomy, and again the risk of this procedure have currently precluded this.

No renal lesions were seen with mouse trap CT, but given the EPO result has returned as elevated, renal imaging will be repeated in the future with abdominal ultrasound.

Hydroxyurea will only be used if necessary as there are significant side effects, of which not all have been reported in cats;
• gastrointestinal side effects (anorexia, vomiting, diarrhoea),
• stomatitis
• sloughing of nails
• alopecia
• dysuria
• bone marrow depression (anaemia, thrombocytopenia, leukopenia)
• pulmonary fibrosis

The prognosis for primary polycythemia is guarded as many cases will develop either treatment side effects, progress to leukaemia or develop myelofibrosis. There are some reports of cats surviving for more than 6 years with this condition. The prognosis for secondary polycythemia depends on the underlying cause.

References