Equine Red Maple Toxicosis

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Introduction

The red maple tree (*Acer rubrum*) is a deciduous tree that occurs naturally across most of eastern North America. It exhibits the greatest north to south distribution range of all tree species along the East Coast; typically found in alluvial woods, along waterways, or on moist shady slopes (Burrows et al. 2012). Due to its brilliant fall red, orange or yellow foliage, red maple trees are a common addition to the average home landscape scheme and are often found in close proximity to pastures. Although beautiful, consumption of this plant can cause poisoning by the ingestion of wilted leaves by equids (Agrawal et al. 2013; Alward et al. 2006; George et al. 1982; Weber and Miller. 1997). The red maple receives most of the blame within literature; however, other maple tree species such as the sugar maple (*Acer saccharum*) and silver maple (*Acer saccharinum*) are also capable of producing toxicities (O'Callaghan et al. 2015). As a result of the ever-increasing abundance of these species, red maple toxicity may be a problem encountered with increasing frequency in the future (Fei and Steiner. 2007).

History and Presentation

No age, breed, or sex predilection has been identified, which makes exposure to red maple leaves the primary risk factor (George et al. 1982; Semrad 1993). Most horses develop clinical red maple toxicosis during the late summer and fall, as the leaves of these deciduous trees are shed in preparation for the coming winter. (Tennant et al. 1980; Divers et al. 1982; Alward et al. 2006). However, there are many case reports in which horses were exposed to wilted of dried red maple leaves after a storm (Witonsky et al. 2001) where broken tree branches can lead to development of wilted leaves out of season. These findings indicate that although there is a pattern associated with red maple toxicity, it can occur almost any time of year in which the tree bears foliage.

On presentation, horses with red maple toxicosis can exhibit a variety of clinical signs. The severity of symptoms is largely dependent on the volume consumed, the time elapsed since consumption, and potentially the time of year in which ingestion occurs (George et al. 1982;

McConnico and Brownie 1992). Two clinical syndromes of red maple toxicosis in horses have been described. The first is a peracute form resulting in death within 18 hours post ingestion due to severe methemoglobinemia, and hemolytic anemia with or without methemoglobinuria (Divers et al. 1982; McConnico and Brownie 1992). The second is an acute form where horses typically present 1-2 days after ingestion and most commonly exhibit depression, lethargy, inappetence, and colic signs (George et al. 1982; Witonsky et al. 2001; Alward et al. 2006). The most frequent physical exam and initial diagnostic findings of red maple toxicity include pale, muddy, or icteric mucous membranes, hemolytic anemia and hemoglobinuria or myoglobinuria (Witonsky et al. 2001). Heinz bodies (inclusions within erythrocytes composed of denatured hemoglobin) or eccentrocytes (erythrocytes with hemoglobin localized to part of the cell, leaving areas with little hemoglobin) (Stockham and Scott 2008) were noted in 33% of the initial blood samples (Alward et al. 2006).

Common blood work abnormalities include a hemolytic sample when centrifuged, anemia, azotemia, and hyperbilirubinemia. Packed cell volumes are often in the range of 10-20% at presentation, but continue to fall over a period of days due to a combination of intravascular and extravascular hemolysis (Adams 2011). Urinalysis findings commonly include signs of methemoglobinuria (brown or “chocolate” colored urine), isosthenuria, bilirubinuria, and tubular casts.

Severity of clinical signs can be dose dependent with the toxic dose range being approximately 1.5-3.0 grams of wilted leaves per kilogram of body weight. This means a toxic dose would be roughly one to two pounds of wilted leaves for the average horse (George et al. 1982; Adams 2011). Pathophysiology

Gallic acid is the best described culprit in red maple leaves leading to the classical signs of toxicosis. It acts as a strong oxidant, which is implicated in the oxidation of hemoglobin to methemoglobin in equine erythrocytes (Alward et al. 2006). Interestingly, experiments evaluating

the oxidative damage of gallic acid alone compared to that of red maple leaf extract revealed a significant variation in the damage produced. The red maple leaf extract caused significantly more severe oxidative damage to equine erythrocytes compared to that of gallic acid alone (Boyer et al. 2002; Alward et al. 2006). These findings suggest the oxidative damage of gallic acid is enhance by the presence of another, yet unidentified, agent in red maple leaves. This synergism of compounds leads to enhanced methemoglobin formation, resulting in reduced oxygen carrying capacity, subsequent tissue hypoxia, and ultimately organ damage (Boyer et al. 2002; Alward et al. 2006). It appears that a seasonal variation in A. *rubrum* leaf chemical composition may lead to differences in the oxidative damage produced and thus be the basis for the two distinct clinical patterns of methemoglobinemia and hemolytic anemia observed (George et al. 1982; Boyer et al. 2002).

Hemoglobin naturally contains ferrous iron (Fe2+) which serves to bind oxygen within red blood cells for transport and delivery throughout the body (Roder 2001). Oxidation of hemoglobin converts ferrous iron (Fe2+) to ferric iron (Fe3+). Hemoglobin containing ferric iron can no longer efficiently bind oxygen (methemoglobin), and subsequently the red blood cell loses its ability to provide oxygen to tissues (Roder 2001). This process of hemoglobin denaturation can then cause microscopically visible precipitate formation and attachment to the inner surface of red blood cell walls, known as Heinz body formation; or hemoglobin clumping, known as eccentrocyte formation (Witonsky et al. 2001). Due to the presence of Heinz bodies, and/or conformational changes in oxidized red blood cell surface morphology, these cells are more susceptible to destruction by fragmentation and osmotic lysis (intravascular hemolysis), and erythrophagocytosis (extravascular hemolysis) (Tennant et al. 1981; McConnico and Brownie 1992; Semrad 1993; Witonsky et al. 2001).

Glutathione acts as a scavenger of free radicals and is important in the protection of the cellular components from oxidation in most mammals; however, horses seem to be at a metabolic

disadvantage (Witonsky et al. 2001; Boyer et al. 2002). Although there is a single case report of red maple toxicosis in camelids (Dewitt et al. 2004), toxicity in cattle, sheep, goats and deer have not been described. This may be because horses are naturally deficient in an enzyme referred to as glutathione reductase, which in other species, allows glucose to serve as a defensive mechanism against oxidative damage (Robin and Harley 1967; Boyer et al. 2002). Due to this deficiency, the oxidant-induced damage to equine erythrocytes caused by free radicals (such as those produced by red maple toxins) leads to the rapid depletion of glutathione. Then hemoglobin undergoes oxidation to methemoglobin, globin denaturation leads to the appearance of Heinz bodies, and the weakening of cell membranes leads to membrane fragility and erythrocyte hemolysis (Boyer et al. 2002; O'Callaghan et al. 2015).

Differential Diagnoses

Differential diagnoses for acute hemolytic anemia in the horse include immune-mediated hemolytic anemias (drug-induced, neoplastic, idiopathic responsive), infectious anemias (equine infectious anemia, piroplasmosis), snake envenomation, hepatic failure, and red maple toxicosis (Divers et al. 1982; Corriher et al. 1999; Witonsky et al. 2001). Methemoglobinemia in the horse has been attributed to red maple toxicosis, phenothiazine toxicosis, onion (*Allium spp*) ingestion, congenital methemoglobinemia and flavin adenine dinucleotide (FAD) deficiency (Harvey et al. 2003; Alward et al. 2006). A detailed history is often key in definitively diagnosing red maple toxicosis (Alward et al. 2006).

Diagnostic Approach/Considerations

Although there are no pathognomonic disease features to diagnose red maple toxicosis, a diagnosis can be made based upon a combination of history of exposure to maple leaves, the presence of acute hemolytic anemia, Heinz body anemia, eccentrocytosis, methemoglobinemia, and ruling out of other potential causes of hemolytic anemia (Alward et al. 2006).

Treatment and Management Options

Treatment for red maple toxicosis is supportive, with the aim of promoting tissue perfusion and oxygenation (Boes et al. 2016). Whole blood transfusions and/or oxygen therapy may be indicated to increase oxygenation, along with intravenous fluids to increase tissue perfusion and combat dehydration, as well as non-steroidal anti-inflammatory medications to reduce pain and decrease systemic inflammation (Alward et al. 2006; Boes et al. 2016). Glucocorticoids are frequently used in red maple toxicosis; however, their efficacy is debatable (Alward et al. 2006; Boes et al. 2016).

Ultrapurified bovine hemoglobin (Oxyglobin®) has been shown to be safe in the treatment of red maple toxicosis by temporarily improving oxygen delivery to vital organ tissues (Vin et al. 2002).

It is suggested that treatment with ascorbic acid (vitamin C) may assist in nonenzymatic reduction of methemoglobin back to hemoglobin and also partially reduce severity of hemolytic anemia (Claro et al. 2006; O'Callaghan et al. 2015). This means vitamin C can help combat the oxidative damage induced by the red maple toxin (O'Callaghan et al. 2015). The dosage, route, and form of vitamin C in the horse can greatly affect its absorption and subsequent efficacy against oxidative principles (McConnico and Brownie 1992). Rosehip is a commercially available dietary supplement which comes from the base of a rose flower. It has been demonstrated to achieve protective serum concentrations of vitamin C capable of dramatically reducing oxidative damage in the equine patient with a fraction of previously used synthetic sources (Winther et al. 2012). Therefore, it may be used as a natural prophylactic agent against red maple toxicosis and potentially other illnesses and toxins which cause oxidative damage. In patients that present post ingestion, the recommended route of administration for vitamin C is intravenously, diluted in crystalloid fluids and given by constant rate infusion (McConnico and Brownie 1992). This

method of administration allows vitamin C to serve as a continuous oxygen free radical scavenger, optimizing therapeutic efficacy (McConnico and Brownie 1992).

Methylene blue is used to treat nitrite-induced methemoglobinemia in ruminants, but its use in horses should be avoided because of a lack of efficacy in promoting methemoglobin reduction in equine erythrocytes (Boes et al. 2016).

Expected Outcome and Prognosis

Due to horses' naturally occurring metabolic glutathione deficiency, determining methemoglobin levels in a horse suspected of red maple toxicity can potentially be both diagnostic and prognostic (Witonsky et al. 2001). Normal methemoglobin levels are typically less than 3%. Studies have shown that animals with methemoglobin levels >20% have a poor prognosis. This reveals the potential to use methemoglobin levels as a means to monitor a patient's daily progress (Tennant et al. 1981; McConnico and Brownie 1992; Semrad 1993; Witonsky et al. 2001).

Many variables must be taken into account when assessing potential outcomes in patients with red maple toxicity. Even among treated horses, the mortality rate associated with red maple toxicosis is high (60% to 65%) (George et al. 1982; Alward et al. 2006). It was originally thought that leaves consumed before September 15th might contain a less potent concentration of toxins than leaves consumed after that date (George et al. 1982; Boyer et al. 2002). However, a restrospective study on 32 horses did not associate a relationship between mortality and time of year at which horses developed red maple toxicity, implying that, although case numbers may increase at certain times of year, seasonal variance is not accompanied by an increase in case severity (Alward et al. 2006).

In contrast to previous suggestions that low PCV is a poor prognostic indicator (Corriher et al. 1999), in the retrospective study by Alward et al., a low PCV (16.5%) at presentation was not associated with mortality (Alward et al. 2006). However, the PCV values in this study could have been artificially increased in some patients because of dehydration or splenic contraction (Alward

et al. 2006). There was also no association found between detection of eccentrocytes or Heinz body formation with mortality (Alward et al. 2006).

Other Pertinent Information

Wildlife herbivory, especially by white-tailed deer (*Odocoileus virginianus*), has long been recognized as a vital component of the shaping of forest ecosystems (Kittredge and Ashton 1995; Long et al. 2007; Eschtruth and Battles 2008). Interestingly, white tailed deer have been shown to preferentially avoid browsing on red maple seedlings (Kittredge and Ashton 1995). If deer population densities persist, the forest composition could be one dominated by red maple (Kittredge and Ashton 1995). Increasing numbers of wildlife herbivores preying on non-*Acer* species could also be playing a role in this increase of *Acer spp.* abundance by decreasing competition. In 2007, a study by Fei and Steiner revealed a dramatic increase in red maple abundance. The species has also expanded the western portion of its range to occupy most of eastern North America (Fei and Steiner 2007). The reason behind this change is not fully understood. Wildlife and forest management practices, prescribed burn regimes, introduced species, invasive insects, or climate change could all potentially be playing a factor (Fei and Steiner 2007).

Conclusion

Red maple toxicosis is a serious illness with potentially deadly consequences. Rapid treatment is critical in order to minimize oxidative damage induced by the leaves' toxic principle(s) (McConnico and Brownie 1992). Horse owner education is a vital part of prevention of this condition. With a rising abundance of *Acer rubrum*, red maple toxicity may become a more frequent diagnosis, and practitioner awareness is of dire importance.

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