AN UPDATE ON ANGIOSTRONGYLOSIS

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Jane Eastwood looks at the effects the parasite can have on dogs, including life-threatening infections, and runs through diagnosis and treatment techniques

Summary

Angiostrongylus vasorum is a nematode parasite that can cause life-threatening infections in dogs. The aim of this article is to review the current knowledge regarding *Angiostrongylus* infection in dogs, especially with respect to the widening geographical range of the parasite, the complex and still poorly understood life cycle and the clinical challenge presented by cases. A synopsis of some referred clinical cases is included as well as advice on the range of clinical presentations, to help raise awareness of the infection. Clinical cases can present with acute or chronic syndromes, which can mimic a range of respiratory, coagulopathic or neurological diseases. Clinicopathological features are often very non-specific and unhelpful in reaching a diagnosis. Practical tips to help in-house diagnosis of the condition with the aim of rapid and appropriate treatment are included along with a review of available treatment options.

Key words

Angiostrongylus, dog, respiratory, coagulopathy, infection

THE main definitive hosts for *Angiostrongylus vasorum* are dogs and foxes, but natural infection has been documented in other animals relevant to the UK, including the ferret, otter, stoat and badger (Helm 2010, Simpson 2010).

Early case reports in the UK date from the 1980s and highlighted an endemic area in Cornwall and the south-west (Martin, 1992). Later studies suggested further hyperendemic areas were focused in the south-east of England (Chapman, 2004). Since then the geographic distribution of documented cases has widened to include northern England and Scotland (Helm, 2009; Yamakawa, 2009). Angiostrongylosis is considered to be an emerging disease in Europe. Reviewing the literature gives a blinkered view of disease incidence, as many clinical cases will have occurred without being published. The reported explosion in slug and snail populations in the cool, wet spring and summer of 2012 implies small animal vets in the UK could expect more *A vasorum* infections. This article reviews developments in the understanding and treatment of a complex and life-threatening disease where clinician awareness is key to prompt diagnosis and treatment.

Life cycle

A vasorum is a sophisticated parasite and aspects of the indirect life cycle are still poorly understood. Adult worms are found in the right side of the heart and/or pulmonary circulation of the definitive host.

Eggs hatch quickly, releasing L1 larvae, which migrate through capillary and alveolar walls and up the bronchial tree to be coughed up, swallowed and passed out in faeces. L1 larvae infect the intermediate host and undergo moults to become L3 stage larvae. The definitive host acquires L3 larvae by eating the intermediate host or possibly ingesting secretions from that host. Experimental studies showed L3 larvae can survive outside an intermediate host and this might be a significant route of infection. Paratenic hosts such as frogs could also bridge the gap between definitive and intermediate host.

Once L3 larvae are liberated in the intestinal tract of a definitive host, additional moults and migration via the abdominal lymph nodes, liver, and venous system culminate in L5 larvae reaching the right side of the heart.

The prepatent period, defined as the period between infection of a dog and the earliest time at which larvae can be recovered from that dog, is variable, with different studies identifying a range between 27 to 107 days. Untreated dogs may excrete larvae for prolonged periods and asymptomatic animals may provide a reservoir of infection. The relative contributions of newly hatched L1 larvae, L3 larvae or later larval and adult stages to the clinical disease syndromes are not yet fully understood.

Disease distribution

The geographic range for *A Vasorum* has expanded not only in the UK, but also through other European countries including Ireland, Denmark, Sweden, the Netherlands, Germany, Switzerland and Italy (Helm, 2010; Morgan, 2010). Infection in dogs has been reported in Newfoundland where

genetic testing indicates infection was introduced from Europe through dogs, foxes or intermediate hosts.

Although increased detection of infection could in part be explained by increasing awareness rather than true increased incidence of disease, this is unlikely to be enough to fully explain recent trends. Climate change could influence breeding patterns of intermediate hosts and changes in fox populations, such as increasing urbanisation, are well recognised.

Even without climate change the potential geographic range for *A vasorum* could easily include parts of North America, Japan, South Africa, Australia and New Zealand. Travelling pets could allow spread of infection to these currently non-endemic areas.

Risk factors

Recent reviews of *A vasorum* infection identified certain risk factors (Morgan, Jefferies et al 2010; Helm, 2010).

• Age

Dogs of any age are susceptible, but the clinical syndrome is more likely in young dogs, perhaps reflecting an immature immune system or inquisitive behaviour facilitating access to intermediate hosts. Those surviving either clinical or experimental infection are not necessarily protected from reinfection, suggesting acquired immunity is not solid.

• Seasonal variation

Subtle seasonal differences are reported, with higher diagnosis rates in winter and spring and a smaller peak in late summer/ early autumn. The variable pre-patent period and lag times before development of significant clinical disease could effectively blur any seasonal peaks. The full clinical impact of changes in intermediate host populations in the UK over the past 12 months may still be ahead of us.

• Breed predisposition

Breed susceptibility to disease is often difficult to assess due to popularity of individual breeds. Reports in the UK indicate cavalier King Charles spaniels and Staffordshire bull terriers might be at increased risk (Chapman, 2004). The author has found British bulldogs and boxers to be over-represented and other clinicians will have their own memorable breeds.

Clinical presentation (see Table 1)

The challenge with *A vasorum* infections lies in “expecting the unexpected”. While the majority of

infected dogs show respiratory signs, coughing is not always severe and dyspnoea is reported in only 12 per cent to 24 per cent of cases, despite frequent pulmonary changes including granulomatous pneumonia with thrombosis and fibrosis. In chronic infections, pulmonary hypertension and associated right-sided heart failure may cause exercise intolerance and syncope. Thoracic radiographs are often abnormal, even when respiratory signs are not part of the clinical presentation, and can prove invaluable in diagnosis (Figures 1a and 1b).

Another common manifestation of infection is haemorrhage. In a review of 23 UK cases, eight presented with unexplained bleeding (Chapman, 2004). While haemoptysis can feature in respiratory cases, sites of bleeding are often varied and sometimes dramatic. Signs include petechiation, ecchymoses, sublingual haemorrhage and haematomas, scleral, retinal or iris haemorrhage, haemoabdomen and haemothorax. Bleeding from elective surgical sites can be acute, severe and life threatening or a chronic, low-grade recurrent complication in dogs that seemed normal prior to surgery. The pathogenesis of the coagulopathy remains frustratingly unclear.

Disseminated intravascular coagulation has been proposed as the mechanism in some cases and, given the lack of a definitive test for disseminated intravascular coagulation, this remains a reasonable explanation. Other cases were reported to have secondary immune mediated thrombocytopaenia, acquired von Willebrand factor deficiency and factor five and eight deficiency. Interestingly, severity of bleeding does not correlate well with detectable coagulation abnormalities and coagulation profiles can be normal.

Neurological disease is another manifestation of infection with a worrying prognosis in some cases. Presentations vary and can mimic both primary spinal cord or intervertebral disc disease (with paresis or paralysis) and intracranial disease (with signs such as seizures, circling, ataxia, change in behaviour or mentation). The most likely explanation for neurological signs is damage due to haemorrhage and typical MRI changes have been described (Figure 2a). Inflammatory CNS disease associated with larval migration also occurs.

Not all dogs present with acute illness and clinicians may recognise low-grade chronic infections with vague signs such as weight loss, lethargy, poor appetite and vomiting/diarrhoea. Aberrant migrating larvae and ectopic adult worms have been identified in many sites including the eye, myocardium, skeletal muscle, liver, kidney, bladder and gastrointestinal tract. A range of non-specific signs would therefore not be unexpected.

Clinicopathological features

Biochemistry profiles and haematology/complete blood counts are appropriate tests to perform, but no pathognomonic findings are reported in clinical or experimental cases. The most common findings are markers for chronic inflammation including low-grade anaemia (possibly secondary to haemorrhage in some cases), neutrophilia, monocytosis, mild eosinophilia, thrombocytopaenia and

hyperglobulinaemia (Schnyder, 2010). Proteinuria is reported in some cases. Clinically significant hypercalcaemia is rare, but can occur secondary to dysregulated 1,25 dihydroxycholecalciferol production by macrophages in pulmonary granulomas. Clinicians should remember, however, that mild hypercalcaemia is a common insignificant finding in young dogs.

Diagnosis

The secret to success in diagnosing and managing infection is to be familiar with the clinical presentations and, therefore, to consider the disease early in appropriate cases.

Definitive diagnosis at present relies on identification of the organism. The traditional least invasive test is a faecal Baermann based on L1 larvae migrating and accumulating as sediment in a container. The test is generally read after eight hours, giving a two-day turnaround time at external laboratories. Tests may be positive after 30 minutes and a modified Baermann could be performed in-house (Morgan, 2010). Standard faecal flotation tests designed to detect parasitic cysts and ovae are not useful. In the author's clinic, a simple faecal smear is the first line test in suspected cases. This is a cheap and rapid test requiring only very basic skills and equipment. A rectal examination is performed to obtain a faecal sample for a Baermann test. Residual material adhering to the glove is mixed with a drop of tap water on a microscope slide and examined under a microscope (x 10 objective). A recent study showed compared with a Baermann, direct faecal smears have a sensitivity of up to 54 per cent (with an inexperienced assessor) or 61 per cent (with an experienced clinician) even with old samples (Humm, 2010). Specificity of the test was high, but inexperienced assessors gave an incorrect positive result 35 per cent of the time. In clinical cases, a fresh faecal smear is likely to reveal live motile larvae, which are easily identified even by untrained individuals. False negatives are, however, quite likely and a negative inhouse faecal smear should be confirmed by a Baermann test.

Although the Baermann test is currently the best diagnostic test available, intermittent excretion of L1 larvae means a single test might only detect 50 per cent of infected dogs. Pooled samples collected over three days compensate for this limitation, but increase the time to diagnosis (Koch, 2009).

Where the clinical index of suspicion is high, but a faecal smear and/or Baermann test is negative (or unacceptably delayed), then treatment without a confirmed diagnosis is justified. An attempt to reach a diagnosis should always be made, especially in complex cases. If the question is "what harm can treatment do" the answer would be that inappropriate treatment means the clinician might then not pursue appropriate investigations to reach the correct diagnosis. There are also potential risks of inducing parasite resistance.

Bronchoscopy and a bronchoalveolar lavage or tracheal wash are sometimes performed in respiratory cases without prior faecal testing for *A vasorum*. When collected samples or airway inspection reveal unexpected haemorrhage, in-house cytology to look for motile L1 larvae is

worthwhile. A faecal sample should also be collected if it has previously been overlooked in the diagnostic plan. It is rare for expectorated sputum to have any diagnostic value, but angiostrongylosis is the exception and direct microscopic examination can occasionally be diagnostic.

Recent research has developed blood tests using PCR and ELISA technology to detect parasite DNA and antigens, as well as serological tests to detect circulating antibody. These tests are likely to become commercially available for clinical diagnosis and will also improve epidemiological understanding of the infection (Jefferies, 2011).

A useful practical tip for the time being is that two-view thoracic radiography and an in-house faecal smear can be diagnostic and facilitate prompt treatment.

Treatment

A number of drugs have been used to manage angiostrongylosis, suggesting no single treatment is 100 per cent effective. In the author's opinion, treatment choice is hampered by lack of studies directly comparing different drugs and protocols in clinical cases. One product (moxidectin/imidacloprid) is licensed for treatment in the UK. Another product (milbemycin oxime) is available in the UK in combination with praziquantel but the manufacturer's recommendation is to use the monovalent product after the first treatment and this is not currently available. Useful treatments and/or preventives available in the UK and the evidence to support their use are outlined in Table 2

While all treatments substantially reduce worm burdens and attenuate associated pathology, no single treatment guarantees a cure. Continued monitoring and repeat treatments are recommended if residual infection is suspected. Optimal timing for follow-up tests is not known, but repeating a three-day Baermann after full resolution of clinical signs is good practice. A positive test at this stage could indicate treatment failure or reinfection. Treatment efficacy is, therefore, difficult to evaluate.

Additional supportive treatment is often required. Corticosteroids are sometimes advocated in cases with severe respiratory compromise to prevent anaphylaxis associated with rapid larval death. This advice may be drawn from experience in treating dirofilariasis, but anaphylaxis is rare in *A vasorum* infections. Corticosteroids may help minimise damaging inflammation in severe respiratory disease irrespective of the cause. Immune suppressive doses have been used to manage possible immune mediated thrombocytopaenia, but while the mechanism of any coagulopathy is unclear, this is controversial. Simple techniques, including oxygenation and cage rest, are often beneficial in critical respiratory cases. Although proof of bacterial involvement is rare, antibiotics are frequently used against opportunist infection in any compromised lung. It is hard to argue against prophylactic antibiotics, but polypharmacy may be best avoided.

Managing any coagulopathy associated with infection is problematic when the mechanism is so poorly understood. Coagulation profiles and a platelet count may help guide treatment, but treating the underlying cause (that is, appropriate anthelmintic treatment) is of paramount importance. Blood products including whole blood (for red cells and coagulation factors) or packed red cells and/ or fresh frozen plasma are sometimes indicated. Clinicians must be prepared to transfuse critical cases. Supportive care is often crucial to outcome in these cases and the prognosis can be excellent with the appropriate level of care.

Prevention

Prevention (rather than cure) would be an ideal solution to the clinical challenge of *A vasorum*, but is not always achievable. With more than 30 different slug species in the UK and reports that numbers doubled or tripled in the first half of 2012, attempts to prevent access are likely to fail. Promoting use of molluscicides could prove counterproductive by increasing risk of exposure to toxins such as metaldehyde.

The evidence for which anthelmintic treatment might best prevent infection is limited and based on experimental infection rather than clinical cases. Moxidectin/imidacloprid and milbemycin oxime are, in the author's view, both likely to be beneficial. Where a clinical case of infection has been confirmed, other dogs sharing the same environment will inevitably be at risk and reinfection rates could be high.

• Some of the drugs mentioned in this article are not licensed for use in dogs and are used under the cascade.n

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