Canine Pulmonary Fibrosis

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BACKGROUND

Idiopathic pulmonary fibrosis (IPF) is a well-recognised, sporadic interstitial lung disease of the dog, which is mainly seen in elderly West Highland white terriers, but can be seen in other breeds[1,2,3]. Affected dogs present in later middle age or older, with a prolonged history of respiratory signs including coughing, exercise intolerance and dyspnoea and distinct pulmonary crackles on auscultation[1,4]. Typically the dogs are otherwise well and there are no associated haematological or biochemical abnormalities. A diffuse increased interstitial lung pattern is seen on thoracic radiographs and the extent matches the severity of the clinical presentation. At least half of affected dogs will have evidence of pulmonary arterial hypertension and likely this contributes to their overall respiratory and exercise disability[5]. The presence of crackles on auscultation is a regarded as cardinal finding that increases suspicion of a diagnosis, but can also be associated with chronic bronchitis and pulmonary oedema[2]. While to what extent treatment slows progression is unknown there is no currently effective treatment that will arrest or reverse the disease. The geographical distribution of the disease is not known, but it appears to be present in the WHWT breed worldwide.

IDIOPATHIC PULMONARY FIBROSIS (OR SOMETHING ELSE ALTOGETHER)

Since the first comprehensive report in 1999[1] increasing amounts of information about this disease have emerged including data on high resolution computed tomography (HRCT) and some data on pathology[6,7,8]. From the outset the use of the term IPF, borrowed from the presumed analogous human condition, had been questioned, and some reports have preferred the less categorical term of “chronic pulmonary disease”, while still suggesting the likely analogy to human IPF[1]. Nevertheless, according to standardised disease nomenclature IPF is a condition defined by its pathological state and it is preferable that when using disease names, even across species, there is a level of consistency and clarity as to what disease is actually being described. IPF, in line with the guidelines issued by the American Thoracic Society and the European Respiratory Society (ATS/ERS), is defined as an interstitial lung disease where the pathology is consistent with “usual interstitial pneumonitis” (UIP) and where HRCT findings show less than 30% ground glass attenuation and distinct basilar honeycombing[9]. UIP pathology is characterised by a patchy sub-pleural distribution with adjacent honeycombing, and then adjacent areas of relatively normal lung. Within the fibrotic zones are characteristic distinct myofibroblastic foci. The distribution of the pathology matches what is seen on HRCT and the absence of ground glass opacity suggests minimal active inflammation. The most recent ATS/ERS consensus statement also further defines the rarer non-specific interstitial pneumonitis (NSIP) which can be confused with IPF[9]. In the case of NSIP this is now recognised as a distinct entity with HRCT findings of bilateral ground glass opacity and mosaic attenuation, occasional traction bronchiectasis, irregular reticular opacities and bronchiolectasis, but with no evidence of honeycombing[9,10]. On histopathology there is interstitial inflammation and fibrosis with uniform distribution, but honeycombing and myofibroblastic foci are absent[9]. On the basis of HRCT findings alone the major differential diagnosis for non-fibrotic NSIP in human patients is hypersensitivity pneumonitis, where mosaic attenuation is a common finding and associated with air-trapping. These patients typically have a history of exposure to organic antigens as seen with bird-fanciers- and farmers-lung, and the pathology in advanced disease can be confused with both NSIP and IPF[10].

With the greater availability of computed tomography in veterinary practice, which was not available when the disease was first described, there is increased information on HRCT findings associated with this disease in the dog[2,8]. Canine IPF is characterised by extensive ground glass opacity, mosaic attenuation, parenchymal bands and variable degrees of fibrosis, occasional traction bronchiectasis, but honeycombing is very rarely reported. In the earlier descriptions of the pathology of canine IPF variable, but severe septal fibrosis with alveolar epithelisation, chronic lymphocytic inflammation and type II pneumocyte proliferation were reported[1,11]. More recently two combined studies have examined the histopathology from a series of 18 WHWTs and compared to that seen with human UIP and NSIP[7,12]. Pathology consistent with NSIP was found in all dogs with changes associated with UIP in some, but there was complete absence of myofibroblastic foci in any of the dogs examined[7]. While the total amount of data for the dog cannot match that available for human patients with IPF, the more recent availability of HRCT coupled with the pathology reports available suggest that this disease is more analogous to human NSIP and not to IPF, an observation made in the recent review by Clercx et al[4].

TREATMENT

Treatment options for canine IPF are limited and have relied on trialling the patient on oral prednisolone at anti-inflammatory dose, and sildenafil with pimobendan to control secondary pulmonary hypertension[2]. Many dogs will show a partial response to prednisolone therapy, which is not seen with IPF in human patients, but will then loose benefit as the dose is tapered. Any improvement with prednisolone has previously been ascribed to control of concurrent chronic bronchitis rather than an effect on IPF itself. Many dogs are now maintained on inhaled steroids, with anecdotal reports of benefit, but there are no controlled studies reported. Many owners have also tried unconventional treatments such as cold laser therapy, but again there are no studies verifying any benefit. Irrespective of whatever treatment is used there is a predictable decline in respiratory function over months to years resulting in eventual respiratory failure. While one study reports the median survival of 18 months from the owners first noting clinical signs we do not know if survival is affected by treatment[1]. An additional confounding factor in predicting prognosis is with increased awareness, often informed by social media, owners and veterinarians likely are recognising respiratory disability earlier than previous.

For most owners management of this disease is more orientated towards extending survival times with “acceptable” levels of respiratory disability, which might not equate with veterinary criteria of acceptable quality of life.

In contrast to IPF NSIP in human patients is treated with prednisolone at immuno-suppressive doses and the cytotoxic drugs myocphenolate mofetil or azathioprine, with cyclophosphamide, cyclosporine and rituximab being reserved for patients that fail to respond[10,13]. While there are limited number of studies reported one found an 81% response to treatment with either the patient stabilising or improving on a corticosteroid alone or with an additional cytotoxic agent[14]. As the evidence suggests that canine IPF might be more analogous to human NSIP it would make sense to offer a treatment option incorporating prednisolone at immuno-suppressive doses with mycophenolate mofetil. Prednisolone/mycophenolate mofetil is widely used in dogs for a range of immune-mediated conditions and is well tolerated[15]. We are currently trialling this approach in Edinburgh primarily in dogs with HRCT findings consistent with the criteria for NSIP diagnosis in human patients. We are administering prednisolone at 1mg/Kg BID for 21 days, tapering off and removing over the subsequent 28 days, introducing mycophenolate on day 21 at 100mgh/kg BID for 35 days, and if there is clear benefit, changing to 250mg mycophenolate every other day thereafter. Discretionary omeprazole is admistered SID if there are any adverse gastro-intestinal signs. While numbers to date are small we are achieving promising results in particular a clear improvement in respiratory signs and exercise ability. To what extent this treatment will extend life is uncertain, but the experience so far would suggest this treatment approach enhances quality of life over and above current treatment regimens.

CONCLUSION

Canine IPF has proved an extremely difficult condition to treat and manage with an inevitable slow progression to respiratory failure in all affected dogs. Re-appraisal of the HRCT and pathology data from the dog and comparing that with interstitial lung disease in humans suggests a closer analogy to NSIP. As treatment options used to date are limited in their effectiveness a new strategy of treating as NSIP would appear to be worthwhile. Only in due course with the proper studies will the efficacy or not of this approach be determined.

REFERENCES

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