Clinical Commentary

Equine multinodular pulmonary fibrosis: New, emerging or simply recently described?

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Equine multinodular pulmonary fibrosis (EMPF) was described in 2007 by a group of investigators who found an association between EMPF and a somewhat unique equine gammaherpesvirus, equine herpesvirus type-5 (EHV-5) (Williams et al. 2007). The initial description primarily consisted of pathological, histopathological, microbiological and molecular findings in a group of horses considered to have EMPF when compared to a control group. It is the histopathological finding of well-demarcated nodular regions of pulmonary interstitial fibrosis, mixed inflammatory cell infiltration, and type II pneumocyte hyperplasia that currently sets the ‘gold standard’ for definitive diagnosis of EMPF. Identification of intranuclear inclusion bodies, while not guaranteed, is a helpful histological finding (Williams et al. 2007). A second manuscript describing the clinical findings, treatment and outcome in a group of 5 horses diagnosed with EMPF based on histopathological findings appeared early in 2008 (Wong et al. 2008). Here, a more cohesive clinical picture of EMPF began to appear, particularly the physical, historic, clinicopathological and imaging results, which are somewhat characteristic. The most recent description (Hart et al. 2008), albeit a single horse report, highlights how much we have yet to learn about this condition, in that it indicates a potential role for EHV-5 in immunosuppression in these patients. In the report of Wong et al. (2008), 3 of 5 cases had mild to moderate lymphopenia and a few had mild anaemia at some point in their clinical courses but none presented with the relatively pronounced pancytopenia described in the case report of Hart et al. (2008), where the horse had fairly severe anaemia, leucopenia - characterised by neutropenia and lymphopenia - and thrombocytopenia, although a regenerative neutrophil response was apparent as the band neutrophils were present. Ante and post mortem bone marrow samples were PCR positive for EHV-5, with the typical inclusion bodies of EHV-5 noted in some of the cells in the ante mortem samples, obtained prior to therapy.

EMPF has been clinically recognised prior to its complete pathological description in 2007 and has been known as ‘idiopathic pulmonary fibrosis’, amongst other names, prior to that initial description. Some of the case material used in that initial paper was obtained in the 1990s, and this author has been involved in cases that were probably EMPF since 1991. That said, the reader is cautioned that not all cases of pulmonary fibrosis in the horse are EMPF. Cases of equine pulmonary fibrosis have been described in association with various toxins (O’Sullivan 1979; Breeze and Carlson 1982; Breeze et al. 1984), allergens (Mansmann et al. 1975) and inhalation of irritants, including silica (Berry et al. 1991). Pulmonary fibrosis may also appear as a final stage of acute respiratory distress syndrome and in many cases an underlying inciting cause is never determined (Buergelt et al. 1986; Buergelt 1995; Donaldson et al. 1998).

Clinically distinguishing EMPF from other causes of respiratory disease requires a somewhat thorough investigation. It is not unusual for cases to have been treated for heaves or bacterial pneumonia prior to complete evaluation and complaints of exercise intolerance, tachypnoea, tachycardia and variable fever typically exist. For the clinician, the initial index of suspicion is provided once thoracic radiographs have been obtained, demonstrating the somewhat typical multifocal nodular pattern, frequently overlying a more generalised parenchymal interstitial pattern. The nodular radiographic pattern has historically been associated with the 2 primary differentials of either neoplasia or fungal pneumonia, with many clinicians and radiologists still unfamiliar with the radiographic appearance of EMPF. Thoracic ultrasonography is another useful imaging tool that will frequently reveal parenchymal ‘nodules’ or ‘masses’ of variable echogenicity if these lesions are present near the visceral pulmonary pleural surface. Pulmonary neoplasia remains a rather rare event in equine medicine and fungal pneumonia frequently has a somewhat reliable geographic distribution. However, for treatment and prognostic purposes, these diseases must be differentiated and the best means for distinguishing them is lung biopsy. Lung biopsy is best performed using ultrasonographic guidance and should be aimed at obtaining tissue from the nodular lesions. Spring-loaded or automatic biopsy 14 gauge or larger needles work best in this circumstance and should obtain a core sample of
22 mm in length. In this authors’ experience, because of the usual general distribution of the lesions, if a nodule can be biopsied in the more caudal dorsal region of the lung, complications from the procedure are minimal. Multiple biopsy samples should be obtained and examined using histopathological, PCR and microbiological techniques in order to differentiate between tumour, fungal infection and EMPF. Consultation with the pathologist and associated laboratories assisting in the diagnosis should be performed prior to biopsy to ensure proper sample handling.

The clinical investigation of respiratory disease in these cases usually, and should, involves obtaining transtracheal aspirates for cytology and culture and sensitivity and bronchoalveolar lavage in order to obtain samples for cytology and other microbiological investigations, including EHV-5 PCR and perhaps virus isolation. Typically, cytological evaluation of these fluids reveals suppurrative inflammation characterised by nondegenerate neutrophils and a lack of identified infectious agents, particularly helpful in ruling out fungal pneumonia. In the clinical case series of 5 horses by Wong et al. (2008) several horses had bronchoalveolar lavage fluid (BALF) obtained prior to institution of treatment while one had BALF obtained after treatment had been ongoing for a period of weeks. All BALF samples from horses obtained prior to treatment were PCR positive for EHV-5; BALF obtained after treatment was negative, as were 7 BALF samples obtained from horses with respiratory disease but without EMPF. These findings are intriguing and may suggest that BALF EHV-5 PCR may be useful in the future as a less invasive test for EMPF than biopsy, but much work remains to be done to demonstrate the utility of this test in assisting accurate diagnosis of EMPF. It is important to remember that not all pulmonary fibrosis diseases of the horses are EMPF and there are likely other, as yet fully clarified or defined, pulmonary fibrosis syndromes in the horse.

The identification of EHV-5, an equine gammaherpesvirus, in association with EMPF has been interesting, to say the least. Gammaherpesviruses are an emerging family of herpesviruses that are also lymphotropic, but tend to favour latent infections with minimal cell lysis (Roizman and Pellett 2001; Ackermann 2006). EHV-2 and EHV-5 are currently the best characterised equine gammaherpesviruses and acknowledged to be widespread within the equine population, although isolation of EHV-5 without special effort is uncommon (Telford et al. 1993; Franchini et al. 1997; Craig et al. 2005; Ackermann 2006; Bell et al. 2006). The pathogenic role of EHV-2 or -5 in equine respiratory disease is currently incompletely understood. Infection with EHV-2 has been associated with upper (pharyngitis) and lower (pneumonia) respiratory disease, lymphadenopathy, keratoconjunctivitis, general malaise and poor performance (Wilks and Studdert 1976; Schlocker et al. 1995; Nordengrahn et al. 2002). However, experimental infection with EHV-2 has produced variable results and the virus can be isolated from a high percentage of sick and healthy horses worldwide (Blakeslee et al. 1975; Roeder and Scott 1975; Fu et al. 1986; Schlocker et al. 1995; Murray et al. 1996; Franchini et al. 1997). Unfortunately, even less is known about EHV-5 and its role in causing disease. One of the earliest reports in which EHV-5 was isolated was from horses suffering from upper respiratory disease in Australia (Browning and Studdert 1987). Subsequently, EHV-5 has been detected in horses in Switzerland, Germany, New Zealand, England and the United States (Franchini et al. 1997; Borchers et al. 1999; Dunowska et al. 1999, 2000; Nordengrahn et al. 2002; Bell et al. 2006) The prevalence of EHV-5 appears to be variable depending on the specific region being tested. None of the peripheral blood leucocytes of 40 adult horses and 10 foals from Sweden were positive to EHV-5 via PCR. In contrast, EHV-5 was detected in peripheral blood leucocytes in 4 of 27 (15%) foals from Hungary whereas 5 of 21 adult horses (24%) and 3 of 3 foals from England were positive to EHV-5 (Nordengrahn et al. 2002).

A recent report demonstrated an association between 2 novel herpesviruses, asinine herpesvirus-4 (AHV-4) and asinine herpesvirus-5 (AHV-5), and interstitial pneumonia in donkeys (Kleboeker et al. 2002). Nucleotide sequencing and phylogenetic analysis place these viruses within the Gammaherpesvirinae subfamily and indicates that they are most closely related to EHV-2 and 5. Grossly, the lung in affected donkeys failed to collapse upon opening of the thoracic cavity and had primarily cranioventral distributed areas of discoulouration. However, the lung in one donkey in the series was characterised by numerous multifocal to coalescing, 1–3 mm diameter, tan nodules throughout the majority (>90%) of the lung parenchyma, similar to EMPF. Histological findings in donkeys that were PCR positive for herpesviruses (11/17 donkeys) varied from mild, lymphohistiocytic and suppurrative bronchiolitis with peribronchial interstitial inflammatory cell infiltrates to marked, diffuse accumulations of histiocytes and neutrophils with areas of interstitial fibrosis and necrotising bronchiolitis and interstitial pneumonia with syncytial cells as a prominent microscopic finding. While the report in donkeys has some similarities with EMPF, pathological features are distinct between the 2 disease processes (Williams et al. 2007; Wong et al. 2008).

The Epstein Barr virus (EBV) has been found in association with interstitial lung disease in humans with infectious mononucleosis. An early study found EBV DNA in interstitial pulmonary fibrosis patients using immunohistochemistry and nested PCR techniques (Stewart et al. 1999). A form of EBV with a specific genomic rearrangement termed WZhet was found in lung biopsy specimens and the buffy coat of patients with idiopathic (cryptogenic) pulmonary fibrosis; WZhet was not found in the buffy coat of immunosuppressed lung transplant patients and in only one normal control of 24 (Kelly et al. 2002). WZhet DNA was also found in BALF of affected patients, supporting the association between and EBV, at least in some cases, and providing evidence that BALF is an alternative for the detection of viral DNA in patients with interstitial pulmonary fibrosis. However, further investigation is required concerning the aetiology of idiopathic pulmonary fibrosis in man (Manika et al. 2007).

It appears that evidence is gathering to strengthen the association of gammaherpesviruses in association with...
pulmonary fibrosis diseases. What exact role these viruses play in disease development remains to be elucidated. The potential role of gammaherpesviruses in potential immunosuppression (Hart et al. 2008), needs additional consideration and points out another potential presentation for EMPF in horses.

So, is EMPF new, emerging or simply recently described? It is probably not new or emerging, as cases have been identified from close to 20 years ago. The development of newer and better imaging techniques and the fact that more horses with respiratory disease seem to be referred for better evaluation may have increased our ability to recognise the disease. The definitive diagnosis is due to the diligence of pathologists who recognised the unique presentation of the histopathology of the disease, and recognised the presence of herpes-like inclusion bodies within those lesions (Williams et al. 2007). Now that the disease is at least partially understood, more cases are being recognised as the ability to diagnose the disease has increased. Further work in the area of specific treatment needs to be undertaken and the potential of BALF analysis for ante mortem diagnosis also demands attention (Wong et al. 2008).

References


