Malignant Catarrhal Fever

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Malignant catarrhal fever (MCF) is a serious, globally distributed viral disease syndrome of certain susceptible ruminant species that has an intricate and as yet poorly understood epidemiology and pathogenesis. It is of greatest economic importance in domestic cattle breeds, but also can inflict serious losses in exotic and wild ruminants on game farms and in zoos. Certain other ruminant species are well adapted to the causative viruses, and serve as subclinical sources of transmission to susceptible species. The two most prominent reservoirs for MCF viruses are domestic sheep and wildebeest.

Etiology

There are at least two, and probably more, closely related viruses that are etiologically associated with MCF. They are classified in the subfamily Gammaherpesvirinae, the group that contains other important lymphotrophic herpesviruses such as Epstein-Barr virus of man and Herpesvirus saimiri of primates. Sheep and wildebeest (subfamily Acelaphinae) provide the source of virus for most outbreaks of MCF in cattle. These sources represent the reservoir for the two major MCF viruses, which are closely related antigenically and genetically. However, their genomes can be readily distinguished by polymerase chain reaction (PCR) or restriction enzyme digestion, and the “lifestyles” of the two viruses within their respective reservoir hosts (sheep and wildebeest) appear to differ significantly from one another.1-2 Nevertheless the signs and lesions induced by these two strains of virus are indistinguishable.

The virus that is endemic in wildebeest can be isolated and propagated in vitro.3 Considerably more is therefore known about this agent than about the one in sheep, which has never been successfully propagated. It was named acelaphine herpesvirus 1 (AHV-1) in reference to the wildebeests' subfamily. The agent that is endemic in sheep, though never isolated, has nevertheless been designated ovine herpesvirus 2 (OHV-2) on the basis of its antigenic and base sequence relatedness to AHV-1. It is referred to herein as the sheep-associated MCF virus (SA-

MCFV). The envelopes of these viruses are fragile, and thus close contact and cool, moist weather maximize the efficiency of transmission.

Epidemiology

Most ruminant species are susceptible to infection with MCF virus.4 The nature and impact of that infection, however, are variable, ranging from totally subclinical in well-adapted reservoir species, to rapidly lethal in species of high clinical susceptibility.

Reservoir Hosts

Almost all adult domestic sheep and wildebeest that are living under natural flock or herd conditions are infected.3,5 Though these two groups represent the source of most cases of MCF, other species are now known to harbor the virus, but the nature of the infection and the ability to transmit the virus are generally unclear. Exceptions include certain exotic species of sheep such as mouflons, and domestic goats, for which considerable evidence exists to implicate them in disease transmission. In the wildebeest, although transplacental infection occasionally occurs, AHV-1 usually passes from the dam to the newborn calf shortly after birth. Infection ensues, which results in active viral shedding to the environment in naso-ocular secretions, primarily during the first 3 months or so of life. Shedding ceases thereafter, presumably due to the emergence of an effective antiviral immune response. The calves are responsible for most cases of transmission to cattle.

The epizootiology of the sheep agent is somewhat controversial at present. Some reports suggest it is very similar to the wildebeest, in that infection occurs during the perinatal period.6 Conversely, data from our laboratories indicate that the pattern varies somewhat from the wildebeest, in that most lambs appear not to be infected during the perinatal period, but several months later.7 Recent data have shown that lambs weaned and removed from the flock at a sufficiently young age escape infection, and remain free of virus as long as they are not exposed to an infected sheep.8 Infection of lambs is predominantly horizontal, between flockmates. The site of viral shedding is apparently the nasopharynx, as it is in the wildebeest. More studies are needed in this area, to clarify the epidemiology of the infection in sheep.

Clinically Susceptible Hosts

These include many species belonging to the subfamilies Bovinae (cattle, buffalo, bison, gaur), Cervinae and Odocoilinae (deer, moose, elk, and reindeer, as well as duikers), and several other ruminant species. Only the basic outlines of the epizootiology of MCF are understood at present. Although the kinetics of some outbreaks can be explained, the frequent occurrence of puzzling epizootiologic patterns9 is a humbling reminder of the meagerness of our current knowledge.

MCF is usually sporadic, with only one to a few cases occurring at a given time. Severe outbreaks with heavy losses are, however, not uncommon.10-11 Whether transmitted from sheep or from wildebeest, the majority of, though not all, cases in cattle occur around the time of lambing or calving. The epizootiology of SA-MCF is as yet less well understood than that of wildebeest-associated MCF. Secretions from the neonatal wildebeest clearly are the predominant source of virus, but lambs have not yet been proved definitively to be the source of virus for most cases of SA-MCF. The ewes themselves or placent tissues are also potential viral sources. Clarification of
this issue needs further study. Transmission is considered to be mostly due to direct contact with infected secretions or fluids, either by direct animal interaction or via fomites, including feeders, common water sources, birds, and caregivers. Direct contact, however, is not absolutely necessary, as transmission sometimes occurs over short to moderate distances. Claims of aerosol transmission exist but are difficult to evaluate.

In addition to clustering during lambing season, significant numbers of cases of SA-MCF are also seen in late summer and fall, several months after the end of lambing season. Further, following removal of all sheep from the premises to quell outbreaks, cases may continue to occur for the next 3 or 4 months. Cases such as these apparently represent recrudescence of infections established earlier. Occasional transplacental transmission from cows to their fetuses has been reported with AHV-1. The preponderance of the evidence suggests that clinically susceptible animals are dead-end hosts and do not transmit the virus horizontally to herdmates. What sometimes appear as epizootics of MCF probably represent multiple cases from common-source exposures.

Inapparent infections are not uncommon among clinically susceptible ruminants. Surveys have shown that a minimum of 4% to 13% of cattle with no history of MCF-like disease are seropositive, as are similar percentages of whitetail and mule deer, elk, bison, and captive moose. These latent infections, under conditions not yet understood, sometimes reactivate, leading to acute disease. No figures are available on the probability of recrudescence or factors influencing its occurrence. In the absence of recrudescence, antibody can wane in these latently infected, clinically susceptible species until it can no longer be detected by current assays.

PREVALENCE AND CASE FATALITY RATE

MCF is a significantly underreported disease. Probably 70% or more of bovine MCF cases are misdiagnosed, escape detection, or are simply not reported to laboratories. Recent detailed investigations in Switzerland revealed that only about 20% to 25% of cases of MCF are actually recognized (U. Müller-Dobles, personal communication, 1996). Lethal cases of MCF are readily diagnosed clinically or by histopathology, but the subacute and chronic cases, which occur with some frequency, often are never diagnosed, particularly if the animal recovers. Most descriptions of MCF include a very high case fatality rate. Published estimates are based primarily on studies using parenterally inoculated AHV-1 virus, and are probably too high for SA-MCF that is acquired by natural exposure. Improved diagnostic tools have recently enabled recognition of "atypical" cases that have historically gone undetected, allowing a more realistic estimate of MCF lethality. A case fatality rate for SA-MCF of 50% to 70%, rather than the traditional 95% or greater is probably more accurate.

CLINICAL SIGNS

Clinical expression of MCF is quite variable, both as regards organ involvement and rapidity of progression. Classic descriptions of acute MCF divide the syndrome into "forms," for example, head and eye, alimentary, encephalitic, skin form, and so forth. These are arbitrary classifications, reflecting little of a fundamental nature. In significant outbreaks, several forms can often be seen on a single premise. Incubation periods are highly variable, ranging from 18 to over 100 days. Leukopenia may occur early in the disease but can be easily missed. MCF is basically lymphoproliferative, involving hyperplasia and perivas-
DIAGNOSIS

Typical acute cases of MCF can often be diagnosed clinically. A combination of high fever, salivation, profuse purulent nasal discharge, enlarged lymph nodes, and the characteristic bilateral corneal edema can be quite diagnostic. Often, however, the animals succumb before diagnostic signs develop, particularly in highly susceptible cervid species. On necropsy, one may observe swollen, hemorrhagic lymph nodes, tonsils, and Peyer's patches, erosions of the alimentary or nasal mucosa, or contrarily, few gross lesions may be found. In these cases, histopathologic study often reveals the widespread lymphoproliferation and vasculitis, which may be highly indicative of MCF. Frequently, however, further criteria are needed to rule out bovine virus diarrhea (BVD) and mucosal disease, infectious bovine rhinotracheitis (IBR), or epizootic hemorrhagic disease (EHD) of deer. Morphologically, BVD in cattle, and EHD and bluetongue in deer can be particularly difficult to differentiate from MCF. The presence of florid necrotizing arteritis in medium-caliber vessels within multiple organs is, however, strongly suggestive of MCF.

Tests available for laboratory confirmation consist of serology, PCR, and viral isolation. Viral isolation is of little practical use in field diagnosis. Only the wildebeest strains can be cultivated in vitro; at present the sheep strains cannot. Moreover, isolation is too unreliable and takes too long to be of topical usefulness. However, efficient laboratory diagnostic tests are now available to detect the DNA of both AHV-1 and OHV-2 strains of MCF virus, and to measure anti-MCF antibody. Acute cases in susceptible species such as cattle are best confirmed by detecting viral DNA in the blood. All animals with acute MCF have high levels of viral DNA in circulating lymphocytes, which readily can be detected by PCR, using appropriate primers. The clinician should inform the laboratory as to which virus strain is suspected, sheep or wildebeest, so that the laboratory can use appropriate primers, many of which are strain-specific. Submitting anticoagulated blood allows the laboratory to test both for DNA in the cells and for antibody in the plasma. At necropsy, the best tissue to submit for PCR is lymph node or spleen, although virtually any organ from acutely ill animals will yield positive results. PCR can also be conducted on DNA extracted from formalin-fixed, paraffin-embedded tissues, which is particularly useful for retrospective studies.

Antibody testing in acutely ill animals can also be diagnostically useful. Serology is available at selected laboratories around the world. Polyclonal antibody assays such as immunofluorescence and conventional enzyme-linked immunosorbent assay (ELISA) are in use in some laboratories. They are useful, but suffer somewhat from a relative lack of specificity. Highly specific assays based on monoclonal antibodies have recently become available, representing a marked improvement in the reliability of MCF serology. One should hear in mind when interpreting serologic results that between 5% and 10% of normal cattle (and slightly lower percentages of deer, bison, and other susceptible species) are seropositive, and that about 25% of cattle with acute MCF die before producing detectable levels of antibody. Thus the presence of antibody is proof of infection but not of etiology. One must also bear in mind that the significance of both serology and conventional PCR must be carefully interpreted in carrier species, in which a high proportion are naturally infected.

TREATMENT

As with most veterinary viral diseases, there is no specific treatment for MCF. General support with antibiotics, fluids, electrolytes, and topical treatment of corneal lesions may improve the recovery rate. In addition, a few reports exist of
Corticosteroids will induce widespread necrosis in proliferating lymphoid populations in MCF. The benefits and cost-effectiveness of intensive treatment with corticosteroids, alkylating agents, antibiotics, or Vinca alkaloids have not been studied systematically owing to the difficulty and expense of reproducing the disease experimentally.

CONTROL

There is no vaccine for MCF; none of the published attempts to produce one have been successful. Physical separation of carrier species (sheep, goats, wildebeest) from susceptible species is the only proven control measure available at present. The potential for recrudescence is always present in latently infected cattle or other susceptible species. Inclusion of a specific serologic examination for MCF antibody in a routine prepurchase examination to identify apparently infected cattle, bison, or other susceptible species should be considered, to minimize the possibility of recrudescence cases. However, since there is little evidence that susceptible species shed infectious virus, even during active disease, the decision to remove all recovered or latently infected animals from the herd is difficult to justify.

REFERENCES