Infectious Leukemias in Domestic Animals

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Introduction

Viruses have been regarded as substantial candidates for the aetiology of cancer in man since the demonstration that the prime factors in the pathogenesis of naturally occurring leukemias in certain domestic animals were viruses of what is now known as the retrovirus group. Early in this century leukosis in domestic poultry was shown experimentally to be infectious and enzootic bovine leukosis was long considered by many veterinarians in continental Europe to be transmissible on epidemiological grounds. Later the discovery of feline leukemia virus added further substance to the suggestion that leukemia in most, if not all, animal species might be caused by viruses. Since then viruses have been isolated from spontaneous leukemia in captive gibbons but no further leukemogenic viruses have been isolated from any other domestic animal and the evidence for viral aetiology of leukemia in man is still equivocal.

Obviously it is naive to consider that the natural history of leukemia in all species might be the same: That virus might be isolated from each case of neoplasia as easily as it is found in leukemia in chickens or that the thread of transmission might be followed as easily as in cats. There is, however, a great deal to be learnt from the epidemiological studies which have been carried out in these species which is relevant to studies of leukemia in man. In this brief review I will discuss some of the evidence from which we derive our interpretation of the natural occurrence of virus-induced leukemias in animals and will outline similarities and differences between the disease in each species. Where appropriate the relevance to human leukemia will be discussed.

Avian leukosis

Avian leukosis was the first malignant disease shown to be infectious. The disease has always occurred among laying birds in poultry flocks throughout the world with an incidence of about 4–10% of all deaths. The most common form is lymphoid leukosis in which the cells involved are lymphoblasts derived from the bursa of Fabricius in which the initial transformation event occurs. During the first years of this century leukosis was transmitted to chickens using cell-free material derived from spontaneous tumours [1]. Much later as methods for demonstrating the avian leukosis viruses (ALV) and anti-viral

antibodies were developed, the extent of infection in chicken flocks became obvious [2,3]. The virus is present in all commercial chicken flocks and almost all members of the flock become infected before they reach sexual maturity. ALV is maintained in chickens by a cycle of transmission in which virus is transmitted epigenetically through the egg. If the egg is free of maternal antibody the growth of virus is unrestricted in the developing embryo and the newly hatched chicken becomes persistently infected. No antiviral immune responses are detected in such birds, which develop into hens producing eggs of which, again, a high proportion will contain virus. Thus the cycle is complete. It is in these viraemic, non-immune birds that leukosis occurs.

Immunity is, indeed, the major factor determining the proportion of hens which are at high risk of developing disease. Some viraemic hens in a flock have in addition to the virus, virus-neutralising antibodies which are also transmitted in the egg. The proportion of eggs from these birds which contain virus is much lower than in non-immune birds. Further, maternal antibody appears to restrict early replication of virus in congenitally infected chicks so that they are not rendered tolerant to viral antigens and, like their dams, develop antibodies.

It is considered that contact transmission is of little relevance in the natural history of ALV or in the pathogenesis of leukosis. Undoubtedly horizontal transmission does occur but present evidence suggests that this results mainly in immunity [4].

Bovine Leukosis

A form of leukemia known as enzootic bovine leukosis has been known for many years to be prevalent in cattle in Europe. Leukosis in cattle is a lymphosarcoma which occurs in four forms: adult multicentric, adolescent thymic, calf multicentric and a skin type. The adult multicentric form predominates in herds affected by enzootic leukosis. Typically in these herds multiple cases of the disease occur so that time-space clusters are evident; the incidence of the disease may be as high as 10% of the population at risk per annum [5].

During the early part of the century it became clear that enzootic leukosis was spreading westwards from eastern Europe. By the time the disease reached Denmark and Sweden more detailed prospective epidemiological observations were made from which it was concluded that the disease spread from hight to low incidence areas following the importation of cattle [6,7]. German and Danish veterinarians showed that haematological changes occurred in cattle in multiple case herds [6,8]. In particular a persistent lymphocytosis was established in many cows which was considered to be a pre-leukemic sign.

Enzootic leukosis is now found throughout eastern Europe, in Sweden, Germany, France and Italy, and North America. The British Isles were free of the disease until very recently when it was diagnosed in cattle imported into Scotland from Canada. In countries and certain areas within countries in which the enzootic disease has not been found, a sporadic form of lymphosarcoma is also seen which is discussed below.

The major factor in the occurrence of enzootic leukosis is undoubtedly the presence in members of the herd of bovine leukemia virus (BLV). Early experiments on transmission of leukosis by cell-free extracts were unsuccessful although transplantation of cells reproduced the disease. Attempts to visualise a virus in tumours by electron microscopy met with little success. The virus was eventually found when short term cultures of leukocytes from cattle with leukaemia were examined in the electronmicroscope [9]. Subsequently permanent virus producing cell cultures were established and antibodies were detected which reacted with viral antigens in the cells using immunofluorescence.

The epidemiological studies which followed the development of these tests revealed that BLV infection is common among cattle in multiple case herds with a prevalence of between 30 and 95% but does not occur in leukaemia-free herds [10]. In this system the presence of antiviral antibodies is strongly correlated with the isolation of virus. That virus is spread horizontally between cattle is suggested by the finding that newborn calves have no serological evidence of BLV but the age of 48 months most have developed antibodies.

Feline Leukemia

Leukemia is the most frequently diagnosed neoplasm in domestic cats [11]. Involvement of lymphoid cells is most common but myeloid and erythroid leukemias are seen quite frequently. The lymphoid malignancies occur in four main clinico-pathological forms: thymic, multicentric and alimentary lymphosarcoma and lymphatic leukemia. Feline leukemia virus (FeLV) is isolated from 90% of the thymic, 70% of the multicentric but only 33% of the alimentary cases. Investigation of communities with a high prevalence of active infection (see below) as well as experimental studies have revealed that FeLV also causes other diseases: aplastic and haemolytic anaemia, immunosuppression and early foetal death [12].

FeLV is transmitted by contact and congenitally [12]. Infection of young kittens by inoculation of FeLV experimentally or by contact with cats excreting the virus in the saliva, often results in a persistent viraemia which is prodromal to the development of leukemia often after a latent period of several years. Congenital transmission of FeLV is also common. All of the kittens born of viraemic dams are persistently infected. These, and kittens experimentally infected within the first 10–12 weeks of life, never show a detectable immune response to the virus.

The incidence of feline leukemia is related to epidemiological situation. In populations of free range urban and suburban cats, exposure to FeLV is widespread based on the prevalence of antibody to FOCMA (feline oncornavirus-associated cell membrane antigen) which is present on the surface of FeLV transformed leukemic cells. In urban Glasgow, about 50% of all adult cats have antibody [12]. The prevalence of these antibodies is related to the degree of roaming, young cats having the lowest prevalence and older stray

cats the highest. In spite of the frequency of exposure very few cats (less than 5%) have an active persistent viraemia [14] and consequently the incidence of lymphosarcoma is low (estimated at 0,05%). Whether the virus which induces persistent viraemia in these cats is obtained by horizontal or congenital transmission is not known owing to problems of tracing contacts and even parents.

A very different situation is observed in cats in closed multicat households in which FeLV is enzootic [12]. There the prevalence of anti-FOCMA antibodies is high but in contrast to free range cats there is a large proportion of viraemic cats (30–40%). Virus neutralising antibodies are also common among these cats (40%). As might be expected the incidence of lymphosarcoma is high, the disease occurring most frequently in cats which have been viraemic, often for long periods.

It is believed that the differences between these patterns is a reflection of the dose of virus to which the cats were exposed: free range cats have frequent intermittent contact with other cats, a few of which will be excreting FeLV so that the virus dose is low and will tend to immunise. Susceptible cats in closed households, on the other hand, are exposed to large, frequent doses of virus from carrier cats and tend to develop persistent viraemia with greater frequency.

Immunity is again a major determinant of the outcome of FeLV infection in individual cats. There is a marked correlation between the presence of virus neutralising antibodies and the absence of viraemia suggesting that these antibodies are important to the abrogation of FeLV infection [12]; and also between the possession of high titres of anti-FOCMA antibodies and protection from leukemia [15].

Virus-Negative Leukemias

Most investigations of leukemia in poultry, cattle and cats have not unnaturally been concerned with those cases in which a virus is involved. However, from many cases of leukemia in cattle and cats no virus may be isolated and recently virus-free cases of avian leukosis have been described.

In areas in which enzootic bovine leukosis is not encountered the occurrence of lymphosarcoma in cattle is sporadic and many more cases of the adolescent thymic and calfhood multicentric types are seen. These do not typically occur in multiple case herds and BLV has not been isolated from any such case.

As mentioned above, virus-negative leukemias are common in cats: in our series half are virus-free and these are mainly from the free range population. This reflects the proportion of alimentary lymphosarcomas only one third of which yields virus. As far as is known the clinico-pathological findings in virus-negative and virus-positive cases are identical although detailed analysis of the cell types and their surface markers have not yet been made.

The importance of the virus-negative leukemias, especially in cats, is that they may be analogous to leukemia in man: And because it is possible to study the relationship with a known leukemogenic virus. The evidence for

the involvement of FeLV in the pathogenesis of virus-negative lymphosarcoma in cats is equivocal. There is some serological evidence of FeLV exposure in a proportion of these cases. We have evidence that cases of FeLV-negative leukemia occur in households where FeLV is not present; M. Essex and his colleagues have, however, found clusters of virus-free cases in the same households where virus-positive cases also occur. Further evidence that FeLV may be involved is that FOCMA, which is present on the surface of FeLV-positive leukemic cells, is also found in virus-negative tumours [16]. However, FeLV-specific proviral DNA in excess of the level found in normal, uninfected cat cells has not been found in virus-free tumours [17].

Conclusions

The features which are common to avian, bovine and feline leukemia are: many cases are associated with virus which is isolated from the blood; the viruses are contagious; a persistent virus infection may be established; the latent period from infection to clinical disease is long and the disease characteristically occurs after sexual maturity; and animals are often healthy during the latent period and may continue to excrete virus.

There are, however, sufficient differences between the host responses in these species to introduce a note of caution in extrapolating findings from any one to leukaemia in another species. For example, the presence of virus in individual cats, hens or cattle indicates a certain risk of developing leukemia; but the interpretation of the presence of antibody is different in each species: in cattle it means that the animal has an active virus infection; in cats virus neutralising antibody is related to the abrogation of virus infection and resistance to challenge, and anti-FOCMA antibodies protect against leukemia; while in chickens, virus and neutralising antibodies often occur together.

A question which concerns epidemiologists studying human leukemia is whether epidemiological investigations of the distribution of cases can determine whether leukemia in man is likely to be an infectious disease. In cats, chickens and cattle, time-space clusters of the disease were found, the nature of which strongly suggested that leukemia was infectious. In man the evidence for clustering is not strong. However, it is important to note that even in cats, epidemiological studies based on cancer registry returns failed to produce evidence of contagious spread [18]; some clustering was found but it was concluded that this might have been due to chance. Of course subsequent serological and virological studies established the infectious nature of the disease. This was most apparent in closed communities of cats. It would not be possible to demonstrate that leukemia was infectious in free range cats despite the observation that FeLV is widespread in this population.

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