Marek’s Disease: A Mini-Review
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Summary: Marek’s disease is a lymphoproliferative disease principally of the domestic chicken known to be caused by herpesvirus i-e oncogenic (serotype 1) strains of Marek’s disease herpesvirus (MDV) that replicates in the lymphoid and epithelial tissues. Pathogenesis is complex, involving cytolytic and latent infection of lymphoid cells and oncogenic transformation of CD4+ T cells in susceptible chickens. Infection of a young susceptible chick with the alpha herpesvirus is followed after 4 to 7 days by a short period of virus replication in lymphoid cells and reticulum cells in thymus, spleen and bursa of fabriciaus. Following an early cell associated cytolytic infection of lymphocytes a switch to latent infection occurs at about 7 days. Latently infected T lymphocytes harbor the MDV genome with limited viral antigen expression and they carry the virus through the bloodstream to the visceral organs, peripheral nerves, and feather follicle epithelium (FFE). MDV replication in feather tissues results in shedding of cell-free virus with skin and feather debris, and this is the source of infection for other chickens. This virus presents a complex and variable pathological picture in which both neoplastic and inflammatory changes are observed. The most commonly affected organs and tissues are peripheral nerves, iris gonads, spleen, heart, lungs, liver and muscle. Paralysis is evident with ataxia for period of several days. Diagnosis is based on enlarged nerves, lymphoid tumors in viscera and confirmation is by demonstration of tumor – associated surface antigen on some of the individual cells by immunofluorescence. A real-time PCR method is developed, optimised and validated, to enable quantitation of Marek’s disease virus genomes. Vaccination is the principal method of control. Genetic resistance of chickens to the disease has been exploited in the laboratory to develop resistant breeds. Chemoprophylaxis is of little success.

History of Marek’s disease:
Marek’s disease is a fatal lymphoproliferative disease in domesticated chickens (Gallus domesticus) with its inception in 1907 by a renowned veterinarian Dr. Joseph Marek at department of Royal Hungarian veterinary school in Budapest. Initially the disease was described as ‘polyneuritis’ while studying four adult cockerels, which were affected by paralysis of wings and legs. He noted thickening of sacral plexus and spinal routes which were infiltrated by mononuclear cells [1]. Vilhelm Ellerman and Olaf Bang, two Danish scientists in 1908 were the first to show that leukemia of fowl was transmissible by cell free filtrates. Peyton Rous in 1910 working in Newyork reported that sarcoma of fowl was also caused by a filterable agent [2]. Both of these later turned out to be avian retroviruses i.e. Avian leukemia and Rous sarcoma viruses but important factor was the evidence of virally-induced tumors in man and chicken [2,3]. The first report of marek’s disease in united kingdom was made in a meeting at Royal society of medicine by Galloway in 1929. For another 40 years the etiology, nature of lesions and transmission was argued until period between 1962-1970 when herpesvirus was isolated from turkeys and vaccine being produced [4]. Before introduction of vaccination in 1970, marek’s disease caused annual losses of 150 million USD in United States and 40 million USD in United Kingdom [5].

Etiology: Marek’s disease is one of the most ubiquitous avian infections and is identified among flocks worldwide. Every flock except for those maintained under strict pathogen-free conditions are presumed to be infected. Clinical disease is however not always apparent in flocks [1,6]. The etiological agent is alphaherpesvirus also called Gallid herpesvirus 2. Three serotypes recognized in which serotype 1 and 2 designate virulent and avirulent chicken isolates and 3 are avirulent turkey herpesvirus. A classification system called ‘neuropathotyping’ is a statistical approach that was used to establish a new system of classification of Marek’s disease virus on the basis of neurologic responses [7]. Serotype 1 comprise pathogenic virus and their attenuated variants; serotype 2 are a group of non-pathogenic virus isolated from chickens, and serotype 3 is the herpesvirus of turkeys (HVT) which has
been used extensively as a vaccine against MD. All strains of chickens are susceptible to infection with MDV but genetic studies have shown that genes linked to the major histocompatibility (B) complex are associated with resistance to disease following infection with standard pathogenic strains [8]. Gallid herpesvirus 2, the causative agent is cell-associated in tumors and in all organs except in feather follicle where enveloped infectious virions egress from the body [9].

**Epidemiology:** The incidence of MD increased substantially from the 1930s to the 1950s with the expansion in poultry production and is found among flocks all over the world. By the 1960s MD caused significant problems with poultry health and welfare and a heavy financial burden on the poultry industry. Most chickens have antibodies to Marek’s virus by the time they are mature, infection persists and virus is shed from follicles along with desquamated cells. This dander can remain infective for several months in dust and litter in poultry houses [10]. Congenital infection does not occur and chicks are protected by maternal antibodies for first few weeks of life [5,6,10] Epidemics involve sexually immature birds 2-5 months old, high mortality rate about 80% soon peaks and then decline.[5] However the mortality rate may vary from 1% to 50% during the life span of chicken in the population.[9] The only significant factor with an effect on mortality from MD is rearing house pen. Because the pen within a rearing house can have a significant effect on mortality from MD, it is not unlikely that rearing house could also have a similar effect. The environment during the first 8 to 9 weeks of life is of greatest importance in determining the subsequent mortality from MD and the environment after this time had little or no influence.[11] Three factors are very important in determining whether infection leads to clinical disease are strain of virus, genetic constitution of host and age of host. [2]

**Pathogenesis:** Three phases are recognized 1) productive – restrictive infection. 2) Latent infection. 3) Neoplastic transformation [6]. Subclinical infection with virus shedding is common. Infection is acquired by inhalation of dander. Epithelial cells of respiratory tract are infected and contribute to cell-associated viremia involving macrophages. By sixth day there is productive infection of lymphoid cells in variety of organs including thymus, bursa of fabricius, bone marrow, spleen resulting in immunosuppression [5]. In Humoral immunity, primary and secondary antibody response is decreased in the body as described by Purchase et al. (1968) [12], while IgG level increases as previously noted by Howard et al (1967) [13]. In cellular immunity, median skin graft rejection time in infected birds was either normal or slightly delayed and hypersensitivity to tuberculin was slightly decreased in significantly depressed MD birds. The presence of infection may also increase the susceptibility of fowl to other diseases [14]. The production of cytokine mRNAs, in addition to viral DNA was quantified by quantitative reverse transcription – PCR in splenocytes during the course of Marek’s disease virus infection in susceptible and resistant inbred chicken lines. (Pete Kaiser et al.) IL – 6 and IL – 18 from splenocytes play a crucial role in driving immune responses in susceptible chicken lines resulting in lymphomas as there levels are elevated and in resistant inbred lines maintained MDV latency as IL – 6 and IL – 18 levels are low [15]. The MDV has the ability to establish latency within the chicken lymphocytes and transforms chicken CD4+ T-cells as described by Parcell et al (2003). Transformed T-cells are seen as skin leukosis or as lymphomas in visceral organs. During latency, MDV suppresses lytic gene expression and has evolved mechanisms for blocking the apoptosis of latently infected CD4+ T-cells. Of the genes expressed during MDV latency and in the transformed cell, the Meq (Marek’s EcoRI-Q-encoded protein) has been shown to block apoptosis and transactivate gene expression. Upon reactivation to lytic infection, the splice variants of Meq predominate and that these forms lack several of the domains important to Meq trans-activation and trans-repression. During early stages of reactivation rightward from the origin of replication, a family genes, including phosphoprotein 38 (pp38) are expressed. Three separate open reading frames (Hep, Mys, and pp38) are encoded by distinct transcripts from this region. (Hep = BamHI-H-encoded protein Mys =mystery protein) [16]. During 2nd week after infection, there is persistent cell – associated viremia followed by proliferation of T lymphoblastoid cells and a week later, death begins to occur [5].

**Clinical signs and Lesions:** Clinical signs include immunosuppression, polyneuritis and T- cell lymphoma formation in visceral and ectoderm-derived tissues. Paralysis is sometimes noted but birds show depression prior to death. Neurolymphomatosis is associated with an asymmetric paralysis of both legs and wings. Ocular lymphomatosis leads to graying of iris of one or both eyes. Cutaneous disease involves round,
nodular lesions up to 1cm in diameter particularly at feather follicles [5]. Main lesions observed are enlarged nerves mainly vagus, brachial, sciatic. Nodular and lymphoid tumors may be seen in various organs like liver, heart, lungs, spleen, kidney, muscle, proventiculus and gonads. Enlarged feather follicles termed ‘skin leukosis’ may be noted in broilers and is cause of condemnation during processing [6]. The principal histopathological changes of CNS by vvMDV consist of non-suppurative meningoencephalomyelitis and lymphomatous lesion, which are further categorized into two types, non-necrotizing and necrotizing. The main changes in the former type are perivascular cuffing of lymphoid cells of variable thickness. The most significant change in the latter type is necrotizing lymphomatous and, sometimes, non-suppurative inflammatory lesions (malacia). These malacic lesions are frequently accompanied by fibrinoid necrosis of blood vessels [17].

**Diagnosis:** Diagnosis is made histologically or by demonstration of tumor associated antigen (MATSA) on some individual cells by immunofluorescence [6]. Serum antibodies to Gallid herpesvirus 2 may be demonstrated using virus neutralization. Primers that can distinguish attenuated and wild type strains have been developed for PCR assays [10]. Feathers can be sampled readily from live birds and feather tip extracts are useful as a source of Marek’s disease virus DNA for polymerase chain reaction (PCR) amplification for detection of MDV antigens by ELISA [18]. However, compared with conventional PCR, real-time PCR is rapid, sensitive, reproducible, and has a wide dynamic range and, being a closed system requiring no post-amplification manipulation of the amplicon, reduced risk of carry-over contamination and enables the quantitation of Marek’s disease virus genomes as copy number per million host cells [19]. Real-time PCR assays used recently to quantify MDV do not have internal standards for calculation of MDV genome copy number per cell [15].

**Prevention and Control:** Several methods have been developed to prevent the disease. The variation of the innate susceptibility to chickens is exploited in laboratory and used to develop resistant lines. Genetic resistance to MD is associated with genes within the B locus, encoding the chicken major histocompatibility complex (MHC) [20]. The MHC of the chicken is composed of three classes of genes, B-F (class I), B-L (class II), and B-G (class IV). MHC-associated resistance to MD is mapped to the B-F region rather than to B-G region [21]. Although the influence of the chicken classical MHC in resistance to MD is well established, the role of the recently identified, genetically independent, MHC-like region known as Rfp-Y is unclear [22]. The contagious feature of the disease forces many to eradicate the disease. Chemoprophylaxis against Marek’s is of little success though a substituted benzimidazole appears to partly prevent tumor development but not the replication of virus. Prevention of marek’s by vaccination is possible and in United States the vaccine is cell associated virus and consists of HVT-infected live tissue culture cells preserved by dimethyl sulfoxide in liquid nitrogen [9]. MD vaccine viruses establish a persistent infection which reduces early viraemia, after subsequent exposure to pathogenic strains, and protects against tumour formation and hence mortality so infection has no economic consequences [23]. However, importantly, MD vaccines do not prevent super-infection by challenge viruses. Multiplication of the virulent challenge virus and its shedding from feather tissues still occurs. Moreover there is incidence of vaccine failure due to certain factors as in Fig 1 [24]. This has two major consequences. Firstly, virulent virus shed by vaccinated birds is still oncogenic to non-vaccinated birds. Secondly, there is continued evolution of field viruses towards pathotypes of greater virulence [25]. BAC (bacterial artificial chromosomes) clones of an attenuated MDV strain, CVI988, have been used to investigate various gene functions for studying MDV biology and pathogenesis. Viruses derived from the BAC clones are stable after in vitro and in vivo passages and showed characteristics and growth kinetics similar to those of the parental virus. These viruses induced 100 percent protection against infection by the virulent strain RB1B, indicating that BAC-derived viruses could be used with efficacies similar to those of the parental CVI988 vaccines. The construction of the CVI988 BAC is a major step towards understanding the superior immunogenic features of CVI988 and provides the opportunity to exploit the power of BAC technology for generation of novel molecularly defined vaccines [26].

Research on Marek’s disease (MD) has accomplished a great number of success within the last 50 years, such as the development of the first most widely used anticancer vaccine around the
world; the very efficient control of one of the most devastating diseases for the poultry; and the development of a technology that permits immunization of embryos against infectious poultry diseases. But in doing so the fact to be realized is that the vaccines that protect against the development of the disease do not stop the infection or transmission and are only a temporary solution that might drive the pathogen to higher virulence [27].

![Image](image_url)

**Fig 1.** Factors involved in vaccine failure [24].

**References:**


