



Review

History and current status of Marek's disease in turkeys

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Hafez M. Hafez

E-mail: hafez.mohamed@fu-berlin.de**Abstract**

Marek's disease (MD), caused by a highly contagious and oncogenic herpesvirus, causes immunosuppression and tumors in chickens. Although several reports on the occurring lymphomas (MD-like conditions) in turkeys have been published, less attention has been paid to the disease in this species. Recently, Marek's disease virus (MDV) has been demonstrated in lymphomatous tumors in commercial turkeys in several countries. The present review aimed to describe the past and recent situation of MD in turkeys, including clinical picture and methods used for diagnosis. Additionally, three hypotheses that might explain the emergence of MDV in turkeys, including virus evolution and evolution of MDV variants, modern hybrid turkeys, and raising of turkeys close to chickens, were discussed. The pathogenesis of MDV infection in turkeys remains unclear, and further investigations are necessary. Although herpesvirus of turkey (HVT) vaccine didn't protect turkeys against challenge with a virulent MDV, Rispens strain is effective, highlighting the need for further assessment of the effectiveness of MDV vaccines in turkeys.

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Marek's disease (MD) is a common lymphoproliferative and neuropathic disease of chickens, and occasionally in turkeys and quails. It was firstly described in 1907 by József Marek in cockerels as polyneuritis, due to paralysis of legs and wings. The disease is characterized by infiltration of mononuclear cells in peripheral nerves and various other organs and tissues, including iris and skin. Additionally, other non-neoplastic syndromes such as transient paralysis (Witter et al., 1999), arteriosclerosis (Minick et al., 1979; Fabricant et al., 1983), eye panophthalmitis (Ficken et al., 1991; Pandiri et al., 2008), and immunosuppression (Islam et al., 2002; Faiz et al., 2016) have been reported in chickens. Nowadays MD is a potential threat to the poultry industry worldwide due to direct economic losses as a result of lower feed conversion, loss of body weight, decreases in egg production, and condemnations of carcasses at slaughter, and indirect due to vaccinations costs and immunosuppression (Davison, 2010; Gimeno and Schat, 2018; Rozins et al., 2019; Walker et al., 2019; Yilmaz et al., 2020).

The disease is caused by Marek's disease virus (MDV), belonging to the genus *Mardivirus*, subfamily *Alphaherpesvirinae*, family *Herpesviridae* (Davison, 2010). Three MDV serotypes are recognized using polyclonal or monoclonal antibody tests, polypeptide pattern, and DNA analysis. Serotype 1 (Gallid alphaherpesvirus 2, MDV-1) contains weak and high oncogenic strains such as natural avirulent CVI988 adapted vaccine strain (Rispens et al., 1972). Serotype 2 (Gallid alphaherpesvirus 3, MDV-2) contains non oncogenic apathogenic and /or low pathogenic MDV strains isolated from apparently healthy chickens (Biggs and Milne, 1972; Cho and Kenzy, 1972). Serotype 3 (Meleagrid alphaherpesvirus 1, MDV-3) includes avirulent herpesviruses that were isolated from turkeys and represented by herpesvirus of turkey (HVT) strain being used as a vaccine against MD in chickens (Witter et al., 1970).

Despite vaccination against MD has been adopted since the 1960s, MDV became more virulent in chickens (Witter, 1997; Witter et al., 2005), and field viruses started to adapt by unknown mechanisms. New MDV

variants have been emerged due to the ongoing evolution of the virus, resulting in changes in the clinical consequences of the virus over time. Till now, four MDV pathotypes, namely, mild (m) MDV, virulent (v) MDV, very virulent (vv) MDV, and very virulent plus (vv+) MDV have been recognized, causing tremendous economic losses to the poultry industry.

Although several reports on naturally occurring MD in turkeys were published in the past, less attention has been paid to the disease in this species. It has been shown that experimental inoculation of pathogenic MDV can cause a lymphomatous disease in turkeys (Paul et al., 1977; Witter et al., 1974). Besides, experimental infection of turkeys with pathogenic MDV can induce persistent viremia (Elmubarak et al., 1981). The levels of detectable circulating MDV were generally lower in turkeys compared to infected chickens with the same strain. The most common gross lesions were seen in the liver and spleen. Peripheral nerves were involved infrequently, and the tumor formation was similar in chickens and turkeys. Furthermore, infection of chickens or turkeys with a virulent MDV resulted in immunosuppression. Witter and Solomon incidentally isolated a virulent MDV-like strain from a turkey (TK 809) (Witter and Solomon, 1971). In the present review we will shed light on the past and recent history, diagnosis, and control of MD in turkey.

History of MD in turkeys

Several reports on naturally occurring lymphomas (MD-like conditions) in turkeys were published in the past. In 1939, Downham suggested that young turkeys are particularly susceptible to MDV (Downham, 1939). The author reported three MD outbreaks in turkeys that were characterized by very high mortality rates (62-87%), blackhead lesions and lymphomatosis. Interestingly, turkeys were kept on a farm which had been previously used for turkeys and chicken rearing, suggesting horizontal transmission from chickens (Downham, 1939). In the same year, Andrew and Glover (Andrewes and Glover, 1939) reported an outbreak of partly paralyzed male turkeys on a small farm in Dorset, UK. The post-mortem examination revealed enlargement of the right sciatic nerve and thickening of the brachial plexuses. Histopathological examination exhibited neurolymphomatosis in conjunction with spleen and liver enlargement and cellular infiltration in these organs. Turkeys under investigation had no contact with chickens except that the latter had been kept in a nearby pen (Andrewes and Glover, 1939). Neoplasm in the liver lymphomatosis was demonstrated in the histopathological examination.

Later on lymphomatosis outbreaks were reported in turkeys (Simpson et al., 1957). Lesions resembling MD in chickens were also observed in two wild turkeys trapped in Florida during 1969-70 (Busch and Williams, 1970). During 1972 a high incidence of tumors in commercial flocks of meat-type turkeys was observed in the Netherlands (Voute and Wagenaar-

Schaafsma, 1974). The disease commenced at 8-12 weeks of age and was characterized by increased mortality, enlarged livers with foci, and histopathological changes similar to those seen in MD of chickens.

It has been shown that experimental inoculation of pathogenic MDV can cause lymphomatous disease in turkeys (Witter et al., 1974; Paul et al., 1977). Also, Elmubarak and others found that experimentally infected turkey poults with pathogenic MDV become persistently viraemic; however, the levels of detectable circulating MDV were generally lower in turkeys than in similarly inoculated chickens (Elmubarak et al., 1981). The infection of chickens and turkeys with a virulent MDV resulted in immunosuppression. (Witter and Solomon, 1971) incidentally isolated a virulent MDV-like strain from a turkey (TK809).

The virus seemed partially adapted to turkeys, growing better than chicken MDV strain in turkey cells *in-vivo* and *in-vitro* (Witter et al., 1974). When comparing the pathogenicity of TK809 strain with virulent MDV strains, it was found that this strain is oncogenic for both chickens and turkeys. However, the lesions incidence was greater overall in turkeys inoculated with TK809 strain than those inoculated with other MDV strains. Although the clinical manifestations of MD are similar in chickens and turkeys, it appears to be a fundamental difference in the mechanism of the disease induction by MDV in these two species. In chicken, MDV transforms T-cells, whereas in turkeys, B-cells are likely to be the target cells for transformation by MDV (Elmubarak et al., 1981; Nazerian et al., 1982). In contrast to these results, it was found that cell lines established from MDV-induced turkey tumors was T-lymphocytes (Powell et al., 1984). Additionally, the susceptibility of different turkey lines to MDV were investigated. It was found that small white Beltsville type seems to be resistant, while the commercial type (Nicholas) is moderately susceptible to develop MD lesions (Nazerian and Sharma, 1984).

In several experiments, the disease could be reproduced in turkeys by injection of blood from diseased turkeys. The agent was identified as a serotype 1 MDV with serotype-specific monoclonal antibodies (Coudert et al., 1995). Several reports on natural MDV outbreaks associated with tumors in commercial turkey flocks were described in several countries. In 1990, an increased MD incidence accompanied by high condemnation rates at slaughter was observed in broiler farms located in the southwest of France. Shortly after that, a high incidence of tumor cases was also detected in turkey farms located in the same area (Coudert et al., 1995). At the beginning of outbreaks, black turkey lines appeared to be more susceptible than others.

However, the situation was changed within a short period, and later also commercial BUT-type turkeys in other parts of France were affected (Kross-Landsman, 1998). From 1995 till now, several reports on natural MD outbreaks in meat turkey were described in Israel (Davidson et al., 1996); Germany (Voelckel et al., 1999; Hafez et al., 2002), England (Powell et al., 1984; Voelckel et al., 1999; Deuchande et al., 2012; Blake-Dyke

and Baigent, 2013), Ukraine (Powell et al., 1984; Hauck et al., 2020), Italy (Mescolini et al., 2020), Poland (2015–2018) (Kozdrun et al., 2020). Hauck and others reported two MD cases in backyard turkeys, which had been kept together with chickens (Hauck et al., 2020).

Clinical signs and histopathological lesions of MD in turkeys

Clinical signs of MD in turkeys are non-specific, mostly appeared between 12 to 30 weeks of age. Growth retardation, un-willingness to move, dehydration, lameness, and paralysis were observed (Coudert et al., 1995). In Germany, natural MD outbreaks were observed in small turkey flocks with mortality reached up to 60% at 20 weeks (Voelckel et al., 1999). Chronic pododermatitis and lameness of both legs were reported in backyard turkeys (Hauck et al., 2020).

The post-mortem examination revealed white foci and small white nodules in different organs (Figure 1), including liver, spleen, kidney, heart, lung, and proventriculus (Hafez et al., 2002). Histopathology showed neoplastic lymphocytic cells infiltration with multifocal locations of most organs. The infiltrating lymphoid cells consisted of a mixed population of small and medium lymphocytes, lymphoblasts, and plasma cells.

Diagnosis of MD in turkeys

Generally, laboratory diagnosis of MD is based on histopathology and molecular identification of MDV. The diagnosis is associated with some difficulties since the levels of detectable circulating MDV-1 in experimentally infected turkeys are generally lower than the levels in similarly inoculated chickens (Elmubarak et al., 1981). In some cases attempts to re-isolate the virus from experimentally infected turkeys were unsuccessful (Witter et al., 1970). MDV was successfully isolated on primary chicken embryo fibroblast (CEF) cell cultures prepared from 10-day-old specific-pathogen-free embryonated chicken eggs (Ozan et al., 2021). MDV developed characteristic cytopathic effects, including large round cells and formation of plaques after the third passage in primary CEF cells approximately 5 days post-inoculation.

For molecular identification of MDV various polymerase chain reaction (PCR) assays have been described. Conventional and real-time PCR assays with primers targeting different genes were developed for amplification of serotype 1 MDV (Reddy et al., 2000; Handberg et al., 2001; Islam et al., 2004). More PCR assays have been described to distinguish pathogenic and non-pathogenic serotype 1 MDV and vaccine viruses of MDV-serotypes 2 and 3 (Becker et al., 1992; Silva, 1992; Zhu et al., 1992). The real-time PCRs have also been developed to differentiate virulent MDV-1 and CVI988 vaccine viruses (Renz et al., 2013; Gimeno et al., 2014; Baigent et al., 2016). The loop-mediated isothermal amplification (LAMP) protocols have been established for rapid molecular detection of MDV (Wozniakowski et al., 2011; Angamuthu et al., 2012).

Control attempts

It is hypothesized that MDV spreads horizontally from infected chickens to turkeys when kept in proximity. Therefore, more attention to biosecurity and separation between chicken and turkey farms must be taken into consideration to minimize the risk of spreading. The HVT vaccine didn't protect turkeys against virulent MDV strain challenge (Elmubarak et al., 1981; Nazerian and Sharma, 1984). However, the Rispens strain vaccine is effective against MDV in turkeys. It has been used in France successfully since 1991 and in Switzerland since 1995 (Kross-Landsman, 1998). However, vaccination attempts under experimental conditions using the commercial CVI988 vaccine were ineffective against the MDV-1 challenge (Davidson et al., 2002).

Potential hypotheses for the emergence of MD in turkeys

Several hypotheses could explain the increase of MDV incidences in turkeys. Firstly, the evolution of MDV and the emergence of MDV variants that are oncogenic in turkeys. It has been found that the increase in the number of MD cases in turkeys goes hand in hand with the discovery of MDV strains (Witter, 1997). This could be the reason for a shift of infectivity and overcoming the turkey's natural resistance to MDV. Secondly, modern hybrid turkeys might be more sensitive to MDV. This hypothesis is based on the fact that different frequencies after experimental infection of genetically different turkeys with the same MDV strain are present (Witter et al., 1970; Nazerian and Sharma, 1984). So far, only a few experimental infection attempts of MDV in modern hybrid turkeys are known. In the attempt by (Coudert et al., 1995), only some of the turkeys infected with a very high oncogenic strain (RB1B) exhibited a clinical picture of the disease, while the animals infected with a high oncogenic strain (HPRS 16) remained healthy. For chickens, it is known that in addition to the virulence of the infecting MDV strain, the genetic constitution of an animal seems to have a part in determining the multiplication of MDV in the organism. High viremia titers are associated with increased MD mortality in chickens (Bertram, 1999). Thirdly, raising turkey together with chickens might contribute to the interspecies transmission of MD. Most documented MD cases were reported in turkeys that are reared with or close to chickens.

Conclusions

In conclusion, although several studies reported the susceptibility of turkeys to MDV, several aspects of MD infection pathogenesis in turkeys remain unclear, and further investigations are necessary. In addition, reliable scientific data on the efficacy of the vaccine in turkeys are required. We recommend strict isolation between chickens and turkey. Additionally, vaccination of day-old turkey chicks might be recommended in endemic areas.

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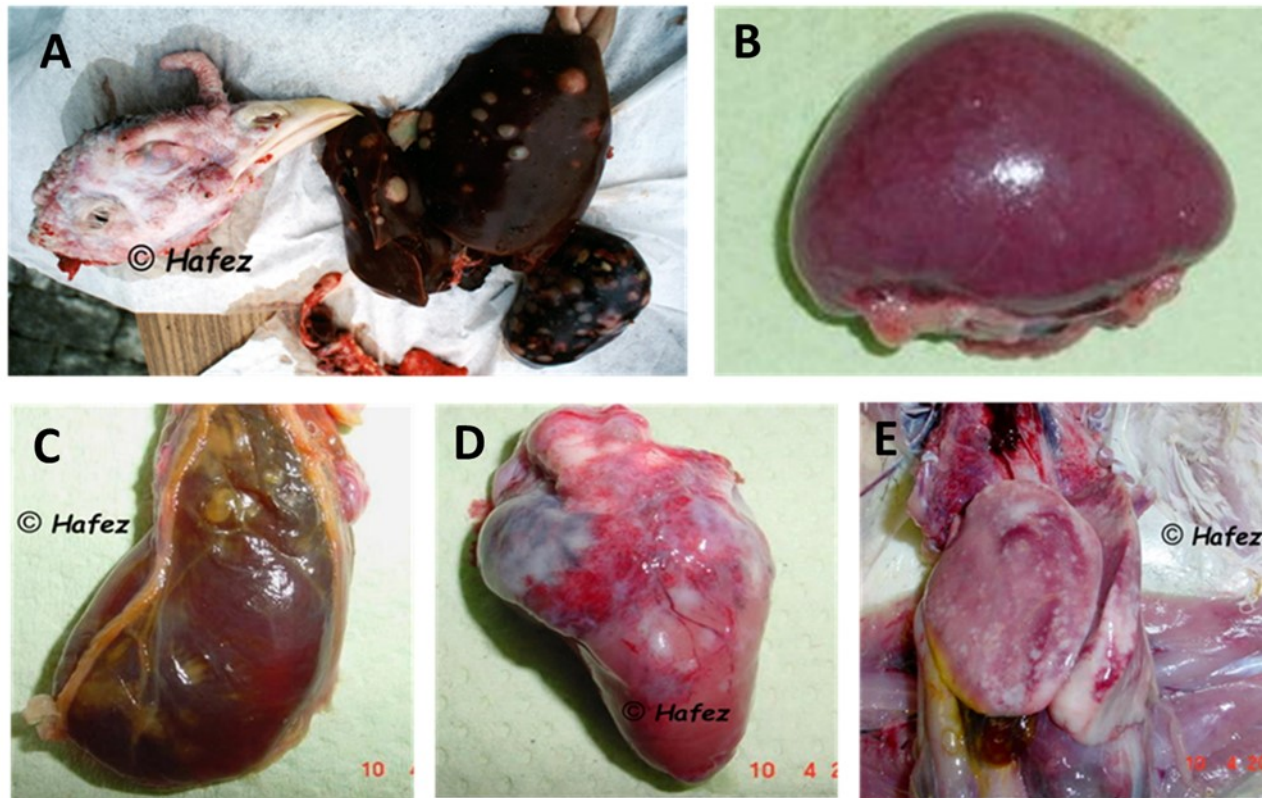


Figure 1: Post-mortem lesions of MD in small turkey flocks in Germany at nine weeks of age. On necropsy pale white nodules were found primarily in the lungs (A), spleen (B), gall bladder (C), heart (D), and liver (E). In this farm turkeys and broiler chickens were kept close to each other.

Conflict of Interest. The authors declare no conflict of interest.

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