The Pharma Innovation Journal 2023; SP-12(7): 1129-1137

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277-7695
ISSN (P): 2349-8242
NAAS Rating: 5.23
TPI 2023; SP-12(7): 1129-1137

www.thepharmajournal.com
Received: 04-04-2023
Accepted: 09-05-2023

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Histocompatibility influence, vulnerability and immunity to RSV infection of layer (CARI-Priya) chicken

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Abstract
We examined the influence of histocompatibility on the outcome of infection of Layer CARI-Priya strain with Rous Sarcoma Virus (RSV). Before inoculation, we conducted genomic analysis of the virus using ALV AE(326bp), ALV A(229bp), and MDV(583bp) primers. The introduction of RSV-A into CARI-Priya chicks resulted in the development of tumours with progressive or regressive phenotypes, exhibiting varying tumour profile index (TPI). A considerable increase in TPI scores (5 or 6) in a subset of chicks revealed their vulnerability to RSV-A. 90% of the chicks had metastatic disease, which was a mixture of Myxosarcoma and fibro sarcoma.

Keywords: CARI-Priya chicken, histocompatibility, Rous sarcoma virus, metastases

1. Introduction
Rous sarcoma virus (RSV) is an oncogenic retrovirus. Rous (1911) described tumour growth in chickens that could be transmitted by a cell-free filtrate of tumours. The tumours were transmitted in barred Plymouth Rock chickens. Repeated transmission of the tumour filtrate increased the growth rate and reduced the latent period. The virus eventually identified was named in his honour (RL Taylor Jr., 2004) [14]. Positive evaluations (Svoboda, 1986) [18], (Plachy and Hejnar, 2002) [13] of the RSV are present and are outside the range of this conversation. The virus has 4 genes. The gag gene encodes structural proteins, pol produces reverse transcriptase, and env generates the viral envelope. The v-src oncogene changes cells to the cancerous phenotype. The first 3 genes are necessary for viral reproduction while the src gene is necessary for transformation but not reproduction.
The virus enters a cell through a receptor specific to each viral subgroup. Inheritance of the receptor is dominant to the absence of the receptor (Collins and Zsigray, 1984) [2]. Therefore, chickens homozygous for cellular resistance to a particular viral subgroup cannot be infected by that virus. A genetic replica of the viral RNA is created using the retrovirus-specific reverse transcriptase enzyme. This genetic material becomes a part of the host's genetic makeup and is later transcribed to generate viral particles that emerge from the cell membrane (Svoboda, 1986) [18]. Tumour development might be regressive, in which the tumour diminishes in size over time and might entirely vanish, or might be progressive, in which the tumour size escalates over time resulting in significant fatality (Collins and Zsigray, 1984) [2].
Thirteen erythrocyte alloantigen systems in chickens were identified by (Briles, *et al.* 1950). One of these systems, B, had extensive polymorphisms compared with most other alloantigen. Rapid skin graft rejection in donor and recipient chickens mismatched for the B blood group revealed this system to be the major histocompatibility complex (MHC) (Schierman and Nordskog, 1961) [17]. Comprehensive investigation has demonstrated a resemblance in structure and function between the B complex and the MHC of other organisms. For instance, a collaboration between T helper cells and B cells or macrophages to produce an antibody response is limited by MHC, indicating that the interacting cell types need to have the same MHC (Vainio, *et al.* 1987) [20]. This requirement for identity is also essential for T cytotoxic cell elimination of target cells (Maccubbin and Schierman, 1986) [12]. Two classes of chicken MHC molecules are homologous to those found in mammals. B-F compounds, the class I homologue found on all nucleated cells, govern self/nonself recognition. These substances are essential for responses against cancer cells or cells infected with viruses. Nucleated chicken red blood cells also showed the B-F antigen (Dietert, *et al.* 1991) [6].

The type II substances, B-L, are found on B cells, macrophages, and other cells that present antigens. The B-L products control the regulatory interactions among immune system cells. Another group of substances in the B complex, B-G class IV, is found only in chickens. Previously thought to be present only on red blood cells, polymorphic B-G substances are found on various cell types. The exact function of B-G is unknown, but a recent hypothesis suggests a role in the selection of immunoglobulins (Salomonsen, *et al*. 1991) [15]. Major histocompatibility complex haplotypes have different associations with disease. In mammals, there are only weak associations between MHC haplotype and the response to pathogens. Some human autoimmune diseases have strong associations with the MHC haplotype. The relative risk for ankylosing spondylitis, autoimmune inflammation of the spine, is > 100× for individuals having the HLA-B27 haplotype (Kaufman and Salomonsen, 1997) [10]. Chickens exhibit a strong connection between B complex haplotype and their reaction to various pathogens such as cancer-causing viruses, non-cancer-causing viruses, parasites, and bacteria. Two perfect illustrations of B complex regulation are Marek's disease, which is caused by a cancer-causing herpes virus, and RSV (Dietert, *et al*., 1991, Kaufman and Salomonsen, 1997) [6, 10].

Avian leucosis or lymphoid leucosis is the most common form of neoplastic disease observed in chicken and other avian species (Witter RL, *et al.* 2000) [22] Most of the neoplastic diseases have a viral aetiology and are caused by avian retroviruses of genus Alpha retrovirus of Retroviridae family (Van Regenmortal-MH, *et al*. 2000) [21]. These illnesses result in substantial financial damages in commercial laying hens and breeding flocks because of tumour fatalities and additional reproductive issues like postponed sexual maturation, decreased fertility and hatching rates, and a decline in egg output (Gao Y, *et al.* 2012) [7]. Moreover, avian leucosis virus (ALV) is present in commercial chickens and eggs, thus exposing human beings on a consistent basis. To this day, as there are no commercial vaccines accessible for managing ALV infection, enhancing the genetic characteristic to combat disease is the optimal method for ensuring long-term control of ALV infectious diseases in poultry. Disease resistance studies in the Rous sarcoma virus have allowed new findings on related mechanisms and the genes involved (RL Taylor Jr., 2004) [14]. Analysis of inbred lines, their crosses, congenic lines, and non-inbred populations have revealed the anti-RSV response of many B complex haplotypes (RL Taylor, Jr, 2004) [14]. Particular MHC genotypes decide RSV tumour reduction or advancement and depending on the degree of tumour growth, a tumour profile indicator (TPI) was designated (Collins WM, *et al.* 1977) [3].

The variation in the resistance/ susceptibility of CARI Priya a Layer strain of India to RSV-A has not been studied so far. Therefore, this study was designed to explore the prevailing MHC haplotypes/ genotypes in the CARI Priya a Layer strain and their association with resistance and susceptibility to RSV-A. The MHC haplotypes of the CARI Priya layer were determined using genomic DNA as a template before challenging the chicks with RSV-A. Genotyping was accomplished using the PCR markers.

2. Materials and Methods

2.1 Virus

Bryan Typical variant of Rous sarcoma virus (Rous linked virus-1), (BS-RSV (RAV-1), hereafter to be called RSV-A, was employed for the current investigation. Freeze-dried ampoules of RSV-A (Rous sarcoma virus) obtained from Tumor Immunology Lab, IVRI, Izatnagar were used for the fresh preparation of RSV. Each freeze-dried ampoule was reconstituted in 0.5 ml of Normal saline solution (NSS). 9 to 11-day-old fertilized chicken eggs obtained from Experimental Layers Farm, CARI, Izatnagar were used to assess the concentration of Rous Sarcoma Virus (RSV) using the chorioallantoic membrane (CAM) test following the procedure of (Groupe V, *et al*. 1957) [8]. The infectivity concentration of the virus was determined to be 1x103 pock-forming units (P.F.U.) / ml. The virus was managed in accordance with biosafety level 2 facilities.

2.2 Chicks management practices

The protocols involving the care and use of animals for these experiments were in accordance with the rules of the Animal Ethics Monitoring Committee of the Institute, Government of India. 8 days-old chicks, belonging to Priya a Layer Strain of India, were obtained from Central Avian Research Institute (CARI), Izatnagar Uttar Pradesh (UP), India. The checks were moved to test barns at the Indian Veterinary Research Institute (IVRI), Izatnagar, UP, India, where they were exposed to Rous sarcoma virus (RSV-A). The birds were housed in battery brooders and were maintained under standard management and nutrition. The chicks were brooded under controlled warm conditions and were fed properly.

They have been given unrestricted get admission to meals and water. Each chick used to be given a wing band for identification. At the identical time, a separate team of healthy chicks used to be saved in the same facility.

2.3 Tumor induction

23 days old CARI Priya chicks were subcutaneously infected with Rous Sarcoma Virus (2000 P.F.U/0.2 mL of RSV-A suspension per chick) in the left wing-web and reared in the Challenge Sheds, IVRI, Izatnagar under contained facilities. The droppings, dead and necropsied birds, and other discards were disposed of through incineration. Chicks were observed regularly for the appearance of tumours at the primary site, as well as in other organs. Uninfected control birds were maintained separately, observed daily, and sacrificed by cervical dislocation at the end of the experiment.

2.4 Categorization of Chicks

The growth pattern of the primary tumours induced by the Rous sarcoma virus was observed every day, and chicks were categorized according to the magnitude of the growth of the tumour. The scoring was conducted to assign a tumour profile index (TPI) (16) using the following: TPI-1 = No detectable tumour; TPI-2= complete reversal by 42 or 56 days; TPI-3= complete reversal by 70 days, a decreasing slope, or complete reversal by 56 days followed by recurrence; TPI-4 = tumour covering > half the wing web area, but < Entire wing web; TPI-5 = tumour filling the whole wing web; or TPI-6 = large tumour extending beyond the wing net and spreading to other organs. Chicks with a TPI rating of 1 were considered non-responders, 2 or three have been regressors, and 4, 5, and 6 were progresses.

2.5 Gross pathological examinations

The increased pattern of the initial growths at the wing membrane that was caused by the Rous sarcoma virus was evaluated by calculating the size of initial growth with the

assistance of vernier callipers each day. Deceased chicks were examined for obvious pathological discoveries in various organs of the body and the locations of obvious injuries were documented.

2.6 Histopathological examinations

2.6.1 Collection of samples for histopathology

The experimental chicks were sacrificed by cervical dislocation and tissue samples *viz*., primary tumour tissue, lung, liver, spleen, heart, kidney, neck, and leg muscle were collected from progressor birds and fixed in 10% neutral buffered formalin solution for histopathological studies.

2.6.2 Histopathological procedure

Tissue pieces were micro-sectioned into 2-3 mm and washed overnight with running water. The samples were then dehydrated with ascending grades of ethanol starting from 70% ethanol to 80%, 90%, and 95%, absolute ethanol for 1 hour at each grade. Following dehydration, the tissues were cleared in three changes of xylene for 1 hour for each change. The tissue pieces were embedded in paraffin and sections were cut at 4 microns. These micro sections were fixed on slides and the sections were stained with Hematoxylin and Eosin (H&E).

2.6.3 Hematoxylin and Eosin (H & E) staining procedure

Sections were deparafinized in three changes of Xylene for 10 min, for each change. The sections were rehydrated in descending grades of ethanol (90%, 80%, 70%) and finally brought to water. The sections were stained with H & E stains and finally mounted in DPX (Distyrene Plasticizer Xylene). Sections were examined under a compound microscope.

2.7 Statistical analysis

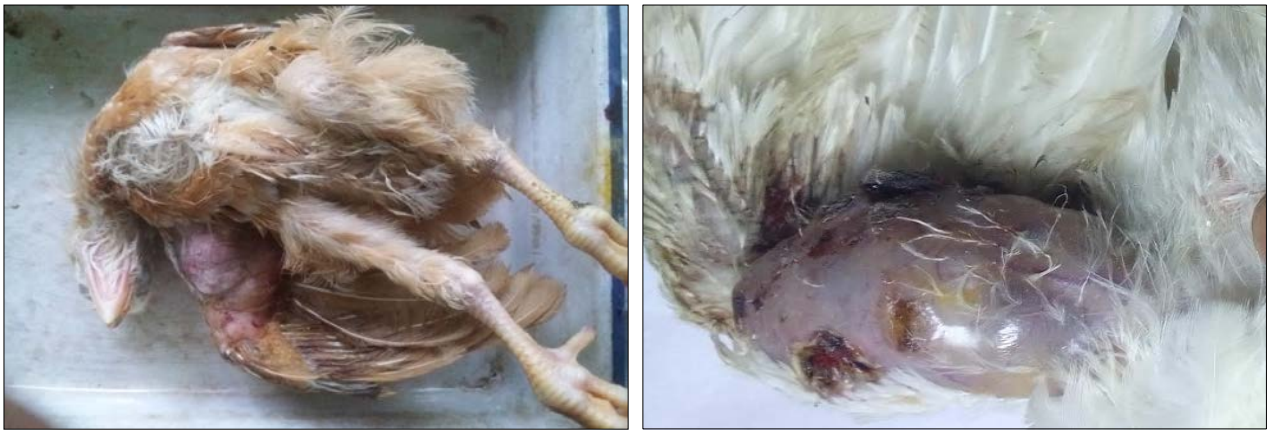
2.7.1 Effects of MHC-genotypes on tumour profile index (TPI)

The impact of MHC genotypes on TPI was assessed using SPSS version 16.0. The MHC genotypes were encoded and examined using the following model: Y ij = μ + Gi + e ij Where Yij = TPI for the itch genotype μ = Overall average Gi = Effect of the ith MHC-genotype e ij=Random error distributed with an average of 0 and a variance of s 2

3. Results and Discussions

3.1 Gross Pathology

The inoculation of CARI Priya chicks with RSV-A resulted in the appearance of a primary tumour at the site of inoculation between 10–12 days post-infection. The tumour could be seen as a single nodule the size of a pinhead or as multiple beads that later coalesced to form a single tumour mass (Fig. 1). The bird's ability to move was restricted as the tumour rapidly grew to encompass the entire wing web. From a soft, palpable mass to a stable, hard nodular mass, tumours vary in consistency. The reddish-brown, slick, tenacious cloth and foul-smelling fluid were inside soft, palpable tumours. The stable tumour mass was covered in tacky white-coloured material, and in some tumour masses, concentric rings could be seen when the mass was cut crosswise. In addition to the primary tumour, some chicks also developed metastatic tumours on their skin and in specific body organs. The following are actual photos of various types of tumours.



A B

Fig 1: Primary solid tumour (A). Multiple nodules on wing web (B) Covering the whole wing web

A B & C D

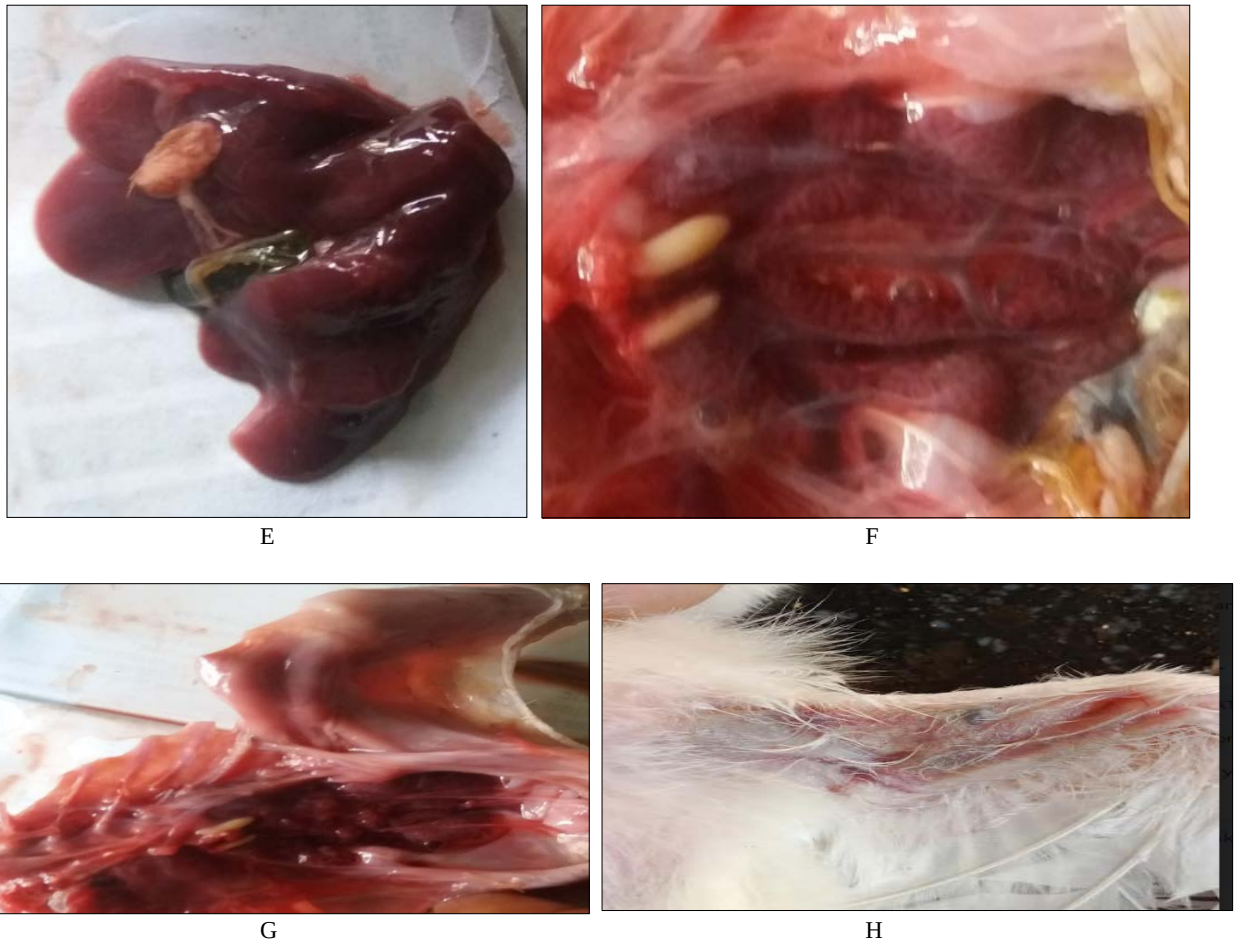


Fig 2: Representative tumour lesions metastasized to (A), Lung (B), Jaws (C), Neck (D), Heart (E), Liver (F), Spleen (G), and Kidney (H). Skin

Post-mortem reports revealed metastasis in the mandibular region, covering the jaw, tongue, neck, and thymus, the area between the rib bones and chest muscle, and leg muscle. Pearl-like white nodules were seen on the surface of the lung, liver, spleen, heart, and kidney (Fig2). Multiple friable, soft, pearl-like lesions ranging in size from 1 mm to 5 mm were present in the liver and spleen. They were white in colour. Small, pinpoint white foci could be seen in the lung, heart, and kidney. Due to cell proliferation, the chest, neck, and leg muscles thickened. Additionally impacted and displaying micro-foci on their surfaces were the proventriculus, gizzard, and caecum.

The percentage of chicks showing metastasis in different organs is shown in the following table (Table-1). In the present study, the incidence of metastasis was mostly observed in the lung, Pancreas, liver, and heart (42-45%), followed by the spleen and kidneys (18%), Leg and Ribs & Chest (19%). The least affected organs were the Neck (11%) and Jaws (4%). Splenomegaly and hepatomegaly was also observed.

Table 1: Percentage of Chicks Metastasis in different organs

Sl. No.	Organs	Percentage (%) of Chicks
1.	Jaws	4%
2.	Neck	11%
3.	Leg	19%
4.	Ribs & Chest	19%
5.	Lungs	45%
6.	Kidneys	18%
7.	Pancreas & Liver	42%
8.	Spleen	18%
9.	Heart	43%

3.2 Histopathology

Histopathological analysis typically revealed two types of tumours which were fibro sarcoma and Myxosarcoma. Fibrosarcoma consisted of immature fibroblasts, loosely arranged in irregular interwoven bundles, with a moderate amount of collagen. Myxosarcoma was characterized by stellate–like or fusiform-shaped tumor cells, with extended cytoplasm. The tumour cells were homogenous, with slightly basophilic mucinous contents. However, in a few birds, myxofibrosarcoma was also observed.

3.3 Progresso birds

3.3.1 Primary Tumor

At the site of inoculation, the tumours appeared as fibrosarcoma. In most cases, a typical fibrosarcoma had degeneration of tissues in the centre and pronounced

infiltration of mesenchymal cells at the periphery. The cancer cells were spindle-shaped and multidirectional, with no set pattern. At some locations, the cancer cells were compact and at other locations, they appeared myxomatous. The cancer invaded muscle tissue, causing atrophy. The primary tumours were highly vascularized, containing numerous and highly engorged blood vessels, as well as extensive haemorrhages. There was degeneration and necrosis of cells. The tumour stroma was infiltrated with neutrophils, mononuclear cells, and plasma cells. There was a proliferation of cells around hair follicles but the epidermis and skin were intact. Neoplastic cells were found in bundles (Fig 3).

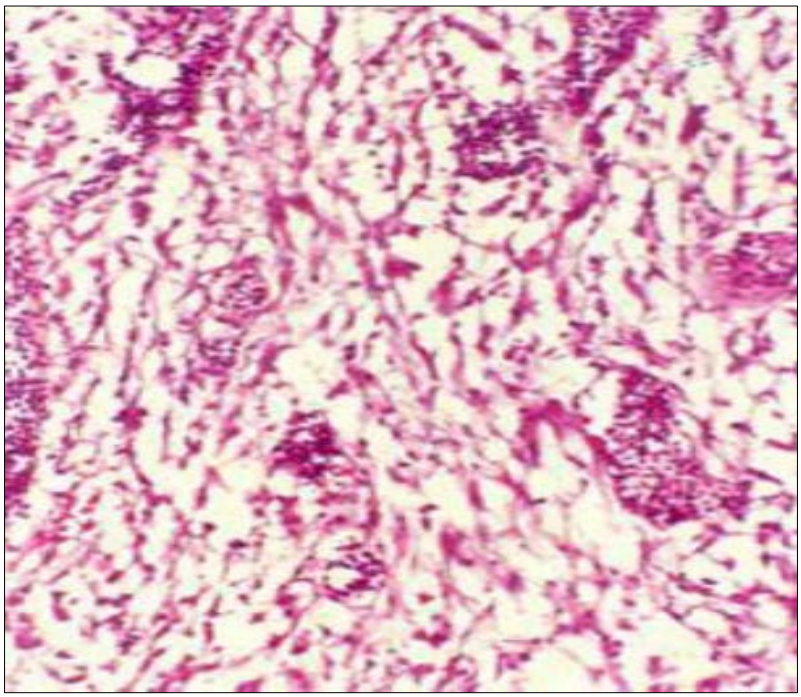


Fig 3: Primary tumour showing severe haemorrhage and presence of dense fibro-sarcoma (H & E:20X).

3.3.2 Leg muscle

Neoplastic cells proliferated widely, replacing muscle fibres and causing them to atrophy. Due to the presence of erythrocyte-rich, edematous fluid between the muscle fibres, fibrosarcoma significantly harmed the underlying muscle, causing the fibres to rupture and separate. The cancerous cells had various patterns. They were found in compact, long spindle-shaped cells or loosely arranged with different orientations. There were whorl formations with no specific direction. The cancerous cells were oval in shape in a few spots and had a high degree of vascularization, extensive myxomatous growths, and only a few remnants of muscle fibres. In some locations, it was clear that the muscle cells had died and been infiltrated by inflammatory cells (Fig 4).

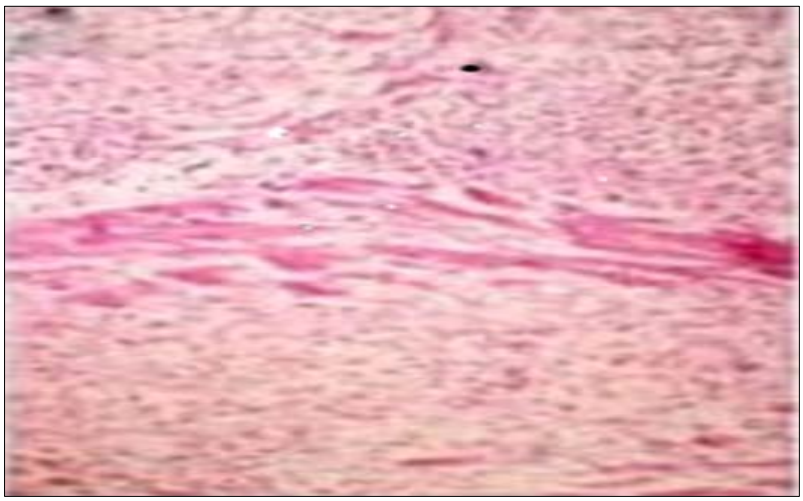


Fig 4: Leg muscle exhibiting myxomatous cells that are loosely arranged and have different orientations, as well as the proliferation of cancerous cells that is causing atrophy of muscle fibres (Hand E:20X).

3.3.3 Chest muscle

The chest muscles were completely replaced by neoplastic cells. Cells were oval-shaped and loosely arranged with myxomatous tissues in between the cells. Neoplastic cells were rarely of the fibrosarcomatous type. Groups of secretory cells were present in myxomatous tissues. The nature of the cells suggested the presence of an advanced stage of cancer (Fig 5).

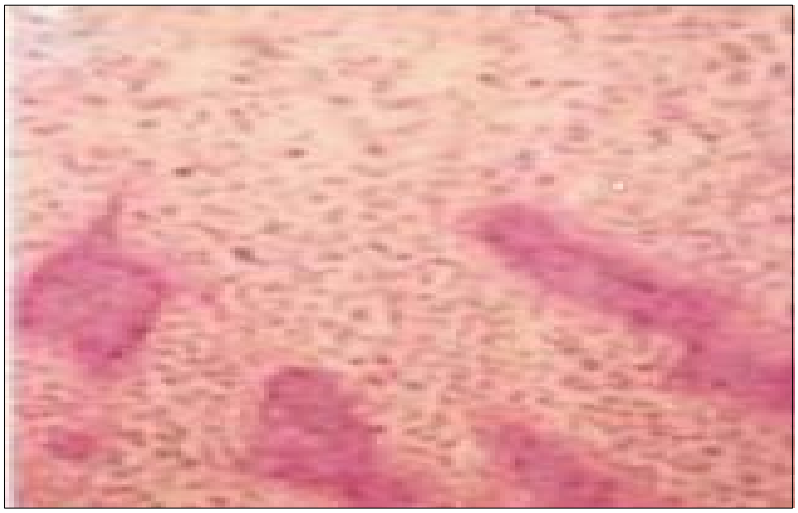


Fig 5: Chest muscle showing myxomatous cancerous cells with an oval shape and loose arrangement (H & E:20X)

3.3.4 Lung

Lymphoid cell proliferation was seen along with the histopathological manifestations of both fibro sarcoma and Myxosarcoma. A whirling pattern was present among the loosely arranged, elongated, lost-of-orientation cutaneous cells found in the tumour cells. Myxosarcomatous tissues occasionally had cells clumped together into a mass or clump of nuclei (Fig. 6).

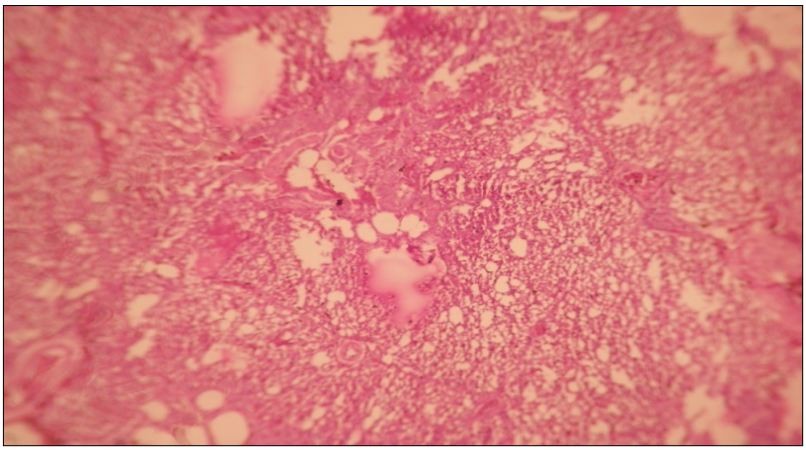


Fig 6: Lungs showing the presence of both fibro-sarcoma and myxosarcoma, proliferation of lymphoid cells, and elongated cutaneous cells that are loosely attached with loss of orientation in lungs (H & E:20X)

3.3.5 Liver

Moderate to extensive tumour growths of varying sizes were present and replaced the normal hepatic parenchyma. Degenerative tissues, vacuolations, lymphocytic infiltration, and haemorrhages were seen in the liver parenchyma. The perivascular area had mononuclear cell and fatty cell infiltration. There was a proliferation of cutaneous cells, which were loosely arranged. Fibrosarcoma could be seen as well as shown in the picture (Fig 7).

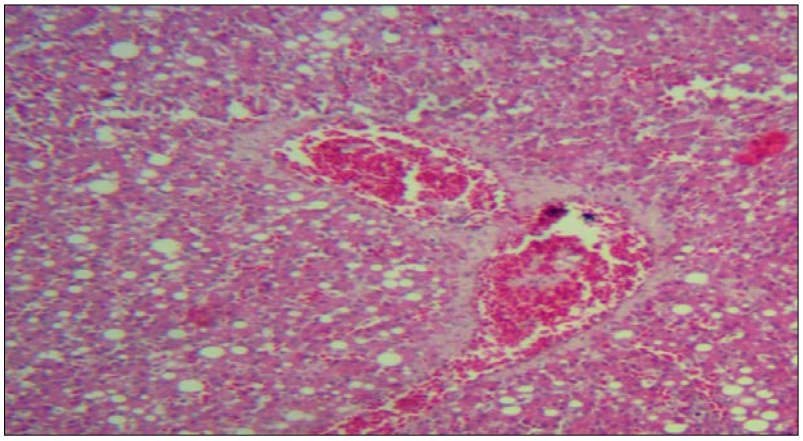


Fig 7: Liver showing fibro sarcoma with degenerative changes, vacuolations lymphocytic infiltration, and haemorrhages in parenchyma and proliferation of loosely arranged cutaneous cells (H & E:20X)

3.3.6 Spleen

Unorganized lymphoid cells were present throughout the spleen. The compact mass of cells that could be seen was a fibrosarcoma, and concentrated sarcomatous tissues could be seen (Fig. 8).

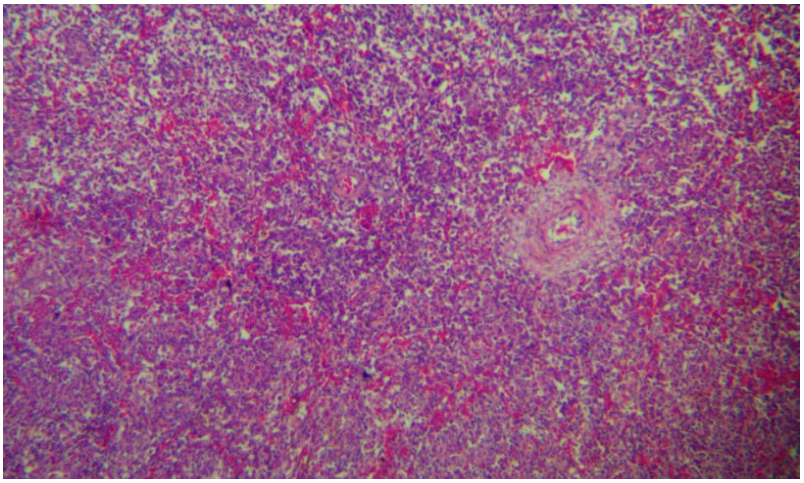


Fig 8: Spleen showing compact cells of fibro-sarcoma and proliferation of loosely arranged lymphoid cells (H & E:20X)

3.3.7 Kidney

There was degeneration of the kidney tubules and glomeruli. Ruptured RBC and debris were deposited in the center of the glomeruli (Fig 9).

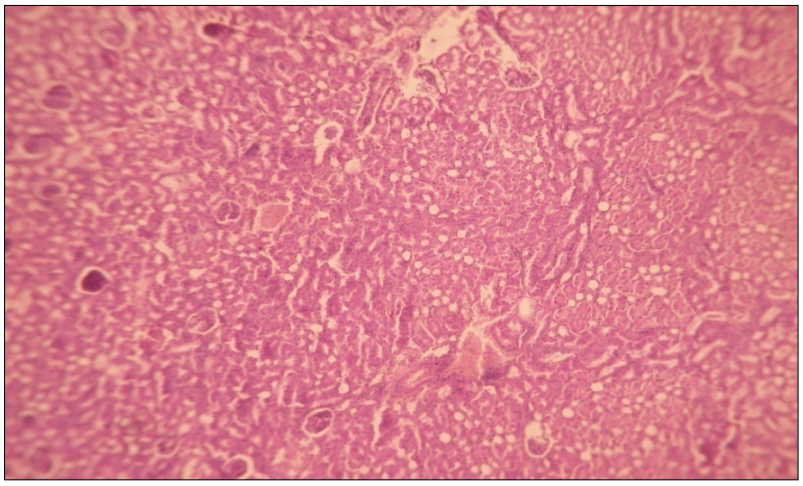


Fig 9: Kidney showing degeneration of kidney tubules and glomeruli and rupturing of RBCs with deposition of debris at the center (H & E:20X)

3.3.8 Heart

The myocardial fibres were separated and showed degenerative changes due to the infiltrating tumour. A mixed type of cellular infiltration, with mononuclear cells and heterophils, was present (Fig 10).

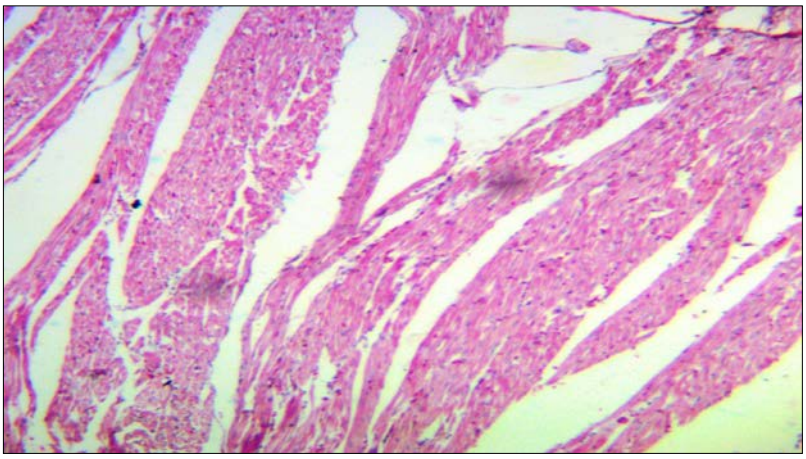


Fig 10: Heart showing degeneration of myocardial fibres and degenerative changes occurring due to infiltration of tumour cells, mononuclear cells, and heterophyllous (H & E:20X)

3.4 Non-Responder and uninfected control birds

Non-Responder and uninfected control birds also did not show any tumour formation in different the organs *viz.* Lung, liver, spleen, heart, kidney, and the site of inoculation.

The present investigation was designed to determine the histocompatibility impact susceptibility and resistance to RSV infection of layer (CARI-PRIYA) Chicken. At first, we analyzed the virus Gnomically with the help of ALV AE(326bp), ALV A(229bp), MDV (583bp), and Primer before inoculation in the Chick. The overall Tumor growth pattern was observed, and a Tumor Profile Index (TPI) score was determined. A higher TPI indicated greater Progression of Tumor Growth, and thus greater susceptibility to the Rous sarcoma virus (RSV). Conversely, a lower TPI indicated resistance towards the virus as demonstrated by either no induction or regression of the tumor. Similar results were reported by (R.L. Taylor, *et al.* 2004) [14] and (Lukacs, *et al.* 1989) [11]. We examined the gross pathology of the tumours and noted that primary tumours first appeared as single pin-head size nodules that grew and became extensive, covering the whole wing wave. Based on the TPI score, it was noted that CARI-PRIYA Chicks had a lower TPI score.

Halpern, *et al*, 1984 [9] also found RSV - induced tumours highly enlarged, which reflected both tumour cell proliferation and viral replication generating new tumour cells. In the present study, the lung, liver, and heart were the most affected organs, followed by the spleen and kidney and the least affected organs were proventriculus, gizzard, and intestine. Similar findings were reported by (Collins, *et al.* 1984) [2], where the incidence of metastatic tumours in the heart and the pericardial sac was 27%, followed by the liver and pancreas (18%), gastrointestinal tract (15%) and the least affected organ was the kidney (2%).

Comparing the histopathological 1984 lesions in different organs of chicks, two types of sarcomas were encountered in progressor birds; however, the regressor, non-responder, and uninfected control did not show a tumour in any of the organs studied. Mostly the tumours found in progress or birds were fibro sarcoma and to a lesser extent, the Myxosarcoma were found. Primary tumors had extensive fibrosarcoma's, with compact to lose architecture in the proliferating neoplastic cells. Metastatic organs indicated a variable degree of infiltration of fibro and myxo sarcomatous tissues, causing atrophy of adjoining areas and replacing the original parenchyma, leaving only remnants of normal structure. In (Halpern, *et al.* 1984) [9] additionally discovered fibro sarcomas, which were mainly made up of immature fibroblasts arranged erratically in irregular bundles. As stated by (Arshad *et al.* as well as Sastri, *et al.*, 1997, 1964) [1, 16] were not observed in this study, which might be because of a difference in the viral strain used for the subgroup.

Conclusions

The current study showed that Layer CARI-Priya Chickens exhibited resistance to or susceptibility to RSV. The absence of tumour induction also shows a homozygous state, resistant haplotypes became more resistant to RSV, whereas homozygosity in susceptible haplotypes increased susceptibility. Between homozygous genotypes that are susceptible and resistant to tumour growth, heterozygous genotypes showed intermediate tumour growth. As a result, we draw the conclusion that tumour regression is more successful in the heterozygous condition than in the homozygous condition. When compared to the homozygotes that make up their component heterozygotes, genetic complementation improved the response. Although the precise mechanism of genetic complementation is unknown. The anti-tumour response was described by as a complex response to various viral and tumour antigens in [21]. Comparing them to their component homozygote heterozygotes may be able to recognize a wider range of antigenic determinants from RSV. Understanding the mechanisms of genetic complementarity can therefore aid in the creation of genetically resistant breeds. In their natural environment, the CARI-Priya stock may have an advantage due to the higher variability at the Histocompatibility Complex proteins in the heterozygous condition.

Acknowledgements

The facilities provided by the Hon'ble Director Dr. Triveni Dutt, IVRI, Izatnagar, Ex-Head of the Department of Immunology IVRI, Dr. Alka Tomar, My Guide Dr. Jayanta Kumar Chatterjee, Associate Professor and Head, Visva Bharati University and I also thankfully acknowledged Professor S.K. Mukhopadhyay and Dr. R.N. Hansda, for assistance in the pathological experiment and overall guidance.

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