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Review Article

## CARCINOMA OF THE MUCOSA OF THE ETHMOID IN DOMESTIC ANIMALS

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### Résumé

CARCINOME DE LA MUQUEUSE DE L'ETHMOÏDE CHEZ LES ANIMAUX DOMESTIQUES. — L'adénocarcinome de l'éthmoïde est décrit depuis longtemps chez tous les mammifères domestiques mais en particulier en Inde chez les bovins et chez les porcs. La masse tumorale s'étend à partir de l'éthmoïde dans la cavité nasale et bloque le conduit respiratoire d'où les manifestations cliniques observées. Les ganglions rétropharyngés et parotidiens sont le siège de métastases. La transformation tumorale touche les cellules sécrétoires et les cellules non différenciées. Le diagnostic précoce peut être réalisé par examen des cellules dans le mucus nasal. La maladie est reproduite par instillation d'extraits acellulaires. La présence de divers virus a été décrite dans les tissus de la tumeur. Chez le porc, on trouve une corrélation entre l'incidence de la maladie et la consommation d'aliment contaminé par l'aflatoxine. Il s'agit d'un problème de troupeau mais ni les facteurs génétiques, ni les agents microbiens ne sont connus. Diverses interventions peuvent ralentir l'évolution de la tumeur en particulier le renforcement des défenses immunitaires et l'éradication.

The carcinoma of the mucosa of the ethmoid in cattle was reported to occur in an endemic form in Scandinavian countries in the beginning of this century (Stenstrom 1915, Magnusson 1916). It probably does not occur in that country (Cohrs 1966). Occurrence of this tumour in various species of animals has also been reported from many other parts of the world (Jackson 1936, Young *et al* 1961, Amaral and Nesti 1963, Rubaj and Woloszyn 1967, Tokarnia *et al* 1972, Inada *et al* 1973, Yonemichi *et al* 1978, Njoku *et al* 1978, Pospichil *et al* 1979, Giauffret *et al* 1984).

The tumours of the mucosa of the ethmoid was first recorded in cattle in Kerala, India, in 1960 (Rajan *et al* 1972). It has also been reported from Andhrapradesh (Narayana 1960, Sastri and Rao 1964), Tamilnadu (Damodaran *et al* 1974), Karnataka (Balasubramaniam 1975) and Orissa (Nayak *et al* 1979). Since the first record of the tumour in Kerala in 1960 the incidence of the tumour is on the increase and now it has established itself in an endemic form. In Kerala in the Department of Pathology since the last few years a project is in operation to make an in-depth study of the problem.

During the period 1960 to 1985, Rajan and Ramachandran (ICAR Scheme report 1985) recor-

ded 628 cases in domestic animals and made a detailed study of these cases. There are only cases which were examined in detail and there may be many cases which have not been brought to the notice of the veterinarians in the state. This included cattle (369), buffaloes (61), pigs (119), goats (75), and domestic deer (4). Among cattle cross-breds (351), non-descript (6), and pure bred (12) were found to be affected. The tumours were recorded from all the districts of the state. Viraraghavan *et al* (1980) recorded 234 neoplasms in cattle in Tamilnadu and pointed out that there is a hereditary predisposition for the development of the tumour.

A detailed account of the tumour in goats and pigs was given by Rajan *et al* (1980, 1981). Nayak *et al* (1979) recorded nine cases of the tumour in cattle from Orissa. The symptoms described by various authors were intermittent nasal discharge, epistaxis, respiratory difficulty characterised by snoring, unilateral or bilateral exophthalmos, swelling of the forehead, difficulty in swallowing and occasionally circling movements (Fontaine *et al* 1983). Most of the animals were in the first or second trimester of pregnancy when they manifested the symptoms of the disease (Rajan *et al* 1972). Sreekumaran and Rajan (1983a) described the epidemiological features of

the tumour in Kerala. They concluded that this tumour has established itself in an endemic form in Kerala and there appears to be no species barrier. Although, the incidence was seen in all breeds of cattle including non-descript cattle the incidence was high in cross-bred Jersey cattle. There was no sex specificity. There was no seasonal incidence as the cases were recorded throughout the year. Pregnancy was found to exacerbate clinical symptoms and the incidence was high in the age group of 6-10 years.

Rajan (1980) reported the gross features of the tumour in detail. The tumour was found to arise from the mucosa of the ethmoid and it extended down into the nasal cavity and often blocked the nasal passage. Posteriorly, it occasionally extended into the brain perforating the horizontal plate of the ethmoid and invaded into the brain. Downward, the tumour extended into the pharynx and blocked it. Anteriorly, the tumour invaded into the frontal bone, perforated it and bulged out as a tumour mass into the subcutaneous tissue.

Gross description of the tumour was given by different workers (Rajan *et al* 1972, Damodaran *et al* 1974, Nayak *et al* 1979, Viraraghavan *et al* 1980, Jose *et al* 1985). The tumour was found to arise invariably from the mucosa of the ethmoid as a pedunculated mass and filled the nasal cavity and extended into the pharynx, frontal sinus, maxillary sinus, and rarely into the palatine sinus. The tumour mass rarefied the nasal septum and turbinate scrolls. Rarefied bony spicules were seen embedded in the tumour mass. After rarefaction of the ethmoid bone in certain cases, the tumour invaded the brain and formed adhesion with the brain. The head lymphnodes showed metastatic foci in 32 % of cases (Rajan 1980). The pathology of the lymphnodes draining the tumour was described by Sreekumaran and Rajan (1984). Retropharyngeal and parotid lymphnodes were more frequently involved. Pulmonary and bronchial lymphnodes were involved in 5 % of cases.

Histological and histochemical features of the tumour were described in detail by Sreekumaran and Rajan (1983b). It was demonstrated that the tumour was a primary growth arising specifically from the olfactory mucosa of the ethmoid region. The primary tumour was considered as an adenocarcinoma and it was clarified that it progressed through a transitional stage to squamous cell carcinoma. Histologically, the tumours encountered by Rajan and Ramachandran (ICAR Scheme Report 1985) were classified as adenocarcinoma (317), transitional cell carcinoma (90), squamous cell carcinoma (165) and undifferentiated carcinoma (56). There was no difference in the histological types of the tumours encountered in different species of animals. The serum protein pattern in tumour bearing animals was also described (Sree-

kumaran and Rajan 1982a). They observed an increase in gammaglobulin, hypoalbuminaemia and decrease in albumin: globulin ratio. Tokarnia (1973) suggested that the histogenesis of the tumour is from the Bowman's gland of the olfactory mucosa. Yonemichi *et al* (1978) studied the ultrastructure of the cell. Pospichil *et al* (1979) and Krishnan Nair (1980) also studied the fine structure of the tumour cell. The neoplastic cells were either well differentiated secretory structures or undifferentiated ones. Desmosomes and tight junctions were seen between epithelial cells. Tonofibrils were described in some. Structures similar to basement membrane were also described. Prominent rough surfaced endoplasmic reticulum was a common finding and they were dilated and contained flocculent electron dense materials.

For the early diagnosis of the tumour exfoliative cytology with Papanicolou's stain was employed and the diagnostic criteria were perfected (Vijayan and Rajan 1982). They described the methods for collection and processing of nasal discharge for exfoliative cytology. Masillamony *et al* (1980) observed that staining with acridine orange and indirect fluorescent technique were of value in diagnosing ethmoid carcinoma early. Efficacy of Ehrlich test for the diagnosis of the tumour was evaluated by Rajan and Vijayan (1981) but was not found to be very satisfactory. Sulochana and Rajan (1981) did not find the agar gel diffusion test and passive haemagglutination test as useful for tumour diagnosis.

Cohrs (1952, 1953) reproduced the tumour in sheep by intranasal instillation of aqueous extracts of emulsified tumour material or cell free filtrates. Jayaraman *et al* (1979) observed genetic predisposition in bovines for tumour development in Tamilnadu. Young *et al* (1961) and Duncan *et al* (1967) observed viral particles but could not establish a hereditary predisposition to this condition. Yonemichi *et al* (1978) observed viral particles which were morphologically similar to Visna-Maedi virus in the tumour tissue by electronmicroscopy. Krishnan Nair *et al* (1981) observed budding viral particles and enveloped virus in the tumour tissue by electronmicroscopy, and they suggested further studies to clarify the aetiological role of this virus in causing the disease. Sulochana *et al* (1980) isolated seven haemagglutinating agents from the tumour tissue by chicken embryo inoculation. The occurrence of several cases in particular farm, the appearance of clinical cases in previously healthy herds after introduction of affected animals from affected farm (Stenstrom 1915, Yonemichi *et al* 1978), the enzootic nature of the disease and reports of successful transmission studies (Cohrs 1952, 1953) suggest the possible association of an infectious agent.

Transmission studies using cell free extracts and tumour tissue as such were attempted in rats, mice, guinea pigs, calves, goats, and pigs with and without immunosuppression by Rajan *et al* (1980) without success. However, Rajan and Karkae (1985) succeeded in establishing the tumour growth by the injection of cell free extracts at a remote site in the tumour bearing host. Efforts were made by them to grow the tumour cells *in vitro* using different media. There was adherence of tumour cells and the growth was seen for about a week, subsequently the cells died. But different results have been reported by others (Torres 1984).

Rajan *et al* (1972) and Pospichil *et al* (1979) reported simultaneous occurrence of ethmoid carcinoma in animals and mycotoxins in feed. They pointed out that the role of mycotoxins has to be assessed in causing the tumour though direct evidence for the involvement of the toxin was lacking. However, in pigs there was a direct correlation, between the incidence of the tumour and consumption of aflatoxin contaminated groundnut cake (Rajan *et al* 1981).

The immunological background of the tumour bearing animals was assessed employing different immunological markers. The cell-mediated immune response in tumour bearing animals was assessed using 2-4 dinitrochlorobenzene and phytohaemagglutinin (Sreekumaran and Rajan 1982b, Reddi and Rajan 1983a, 1983b, 1984a, 1984b) and leucocyte migration inhibition test (Sulochana *et al* 1982). The macrophage function

in tumour bearing animals was assessed (Reddi and Rajan 1983b). It was observed that tumour bearing animals were immunologically competent in early stages of tumour growth but the animals were immunologically unresponsive in late stages (Reddi and Rajan 1984a). Immunomodulation was attempted with BCG, Freund's adjuvant and tumour antigen (Reddi and Rajan 1982a, 1982b, 1982c). There was significant immunostimulation in stage I and stage II cases and this was characterized by disappearance of clinical symptoms and prolongation of survival period. This was evidenced by the histological proof of immunologically mediated tumour tissue destruction (Reddi and Rajan 1985). Pathology of the adrenal gland and spleen in tumour bearing cattle was described by Rajan and Reddi (1981) and Reddi and Rajan (1982d).

Beneficial effects were reported by Rajan *et al* (1983) following cobalt radiation therapy in goats bearing ethmoid carcinoma. Chemotherapy with endoxan (cyclophosphamide) was found to be of value in early stages of tumour growth. Local injection of anacarcin was found to be of value in treating ethmoid cancer (ICAR Scheme Report 1983). Surgery, chemotherapy and immunotherapy were also tried with encouraging results (ICAR Scheme Report 1983).

The studies conducted so far suggested the involvement of a virus in the causation of this tumour. The observations made also suggested that aflatoxin may have a direct or indirect role in causing the tumour.

## Abstract

The carcinoma of the mucosa of the ethmoid was reported in all domestic animals but specially in cattle and pigs in India. The tumour mass extended from the ethmoid to the nasal cavity and obturated the respiratory tract hence the clinical manifestation reported. Retropharyngeal and parotid lymph nodes showed by metastases. The tumoral transformation was observed in the cells of the ethmoid mucosa. An early diagnosis could be done by sampling of cells in the nasal mucus. The disease was reproduced by instillation of cellular extracts. Several viruses have been isolated from the tumour tissue. In pigs there was a correlation between the incidence of tumour and the use of aflatoxin contaminated feed. This was an enzootic problem for the herd but neither genetics or microbial factors are determined. Various attempts were made to control the tumour growth.

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